SUPPORTING INFORMATION

Leucettinibs, a class of DYRK/CLK kinases inhibitors inspired by the marine sponge natural product Leucettamine B

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1. General information

Reactions were performed using oven-dried glassware under inert atmosphere of argon. Unless otherwise noted, all reagent-grade chemicals and solvents were obtained from commercial suppliers and were used as received. Reactions were monitored by thin-layer chromatography with silica gel 60 F254 pre-coated aluminum plates (0.25 mm). Visualization was performed under UV light at 254 or 312 nm or, when necessary, with appropriate TLC stains including: phosphomolybdic acid, $KMnO_4$, ninhydrin, CAM, vanillin, *p*-anisaldehyde.

^1H NMR analyses (400 or 500 MHz) and ^{13}C NMR spectra (101 MHz) were recorded with a Bruker ULTRASHIELD 500 or 400 spectrometer. Processing and analyses of the spectra were performed with MestReNova. Data appear in the following order: chemical shifts in ppm which were referenced to the internal solvent signal, multiplicity, number of protons, and coupling constant *J* in Hertz. **Note**: all final compounds were analyzed at 300, 323 and 343K, with D1 = 1 or 30s (relaxation time). The temperature giving the best result (minimization/coalescence of tautomeric forms) was the one retained for the interpretation of ^1H NMR's.

Microwave experiments were conducted in an Anton Paar Monowave 400® microwave reactor. The experiments were conducted in a monomode cavity with a power delivery ranging from 0 to 850 W, allowing pressurized reactions (0 to 30 bars) to be performed in sealed glass vials (4 to 30 mL) equipped with snap caps and silicon septa. The temperature (0 to 300 °C) was monitored by a contactless infrared sensor and calibrated with a ruby thermometer. Temperature, pressure, and power profiles were edited and monitored through a touch-screen control panel. Times indicated in the various protocols are the times measured when the mixtures reached the programmed temperature after a ramp period of 3 min.

Sealable round flasks were purchased from Chemglass (https://chemglass.com/) and equipped with screwable PTFE caps and PTFE O-ring, with volumes ranging from 60 mL to 1L (60 mL, 220 mL, 420 mL or 1L) capable of withstanding pressures up to 10 bar (5 bar for the 1L version).

Both sealable tubes (Biotage) and sealable round flasks (Chemglass) were heated using Drysyn heating systems equipped the appropriate adapters.

Chromatographic purifications of compounds were achieved on an automated Interchim Puriflash XS420 equipped with 30 µm spherical silica-filled prepacked columns as stationary phase.

HPLC/MS and UPLC/MS analyses were carried out by Atlanchim Pharma (3 rue Aronnax, 44800, Saint-Herblain, France, www.atlanchimpharma.com).

- Intermediate compounds were analyzed using an Acquity Waters UPLC/MS equipped a UV detector (Diode Array Detector), a simple quadrupole SQD2 mass detector (ionization: 3.5 kV ESI, desolvation temperature: 400 °C) and a reverse-phase column (NUCLEODUR C18 Gravity-SB 50/2, 1.8µm). Samples (0.2 to 0.6 mg) were solubilized in a ACN/DMSO (9/1) mixture, and filtered on a 0.2 µm syringe filter prior to injection. Conditions: A= H_2O + 0.1%

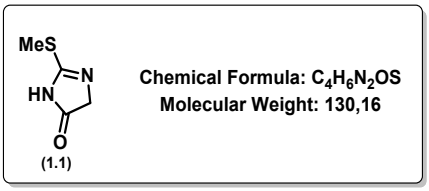
(v/v) HCO_2H; B= CH_3CN + 0.1% (v/v) HCO_2H, flow rate : 0.65 mL/min, injection volume: 2 µL. elution: A/B: 95/5 to 5/95 in 5 min.

- Final compounds were analyzed using an Ultimate 3000 ThermoScientific HPLC equipped with a WPS-3000RS autosampler, a UV detector (DAD-3000 Diode Array Detector), a TCC-3000RS column oven and a reverse-phase column (Waters XTERRA RP18 150x4.6mm 3.5µm). Samples (0.2 to 0.6 mg) were solubilized in a ACN/DMSO (9/1) mixture, and filtered on a 0.2 µm syringe filter prior to injection. Conditions: A= H_2O + 0.1% (v/v) HCO_2H; B= CH_3CN + 0.1% (v/v) HCO_2H, flow rate: 1 mL/min, injection volume: 2 µL. elution: A/B: 95/5 to 5/95 in 20 min. MS determination of the final compounds was carried out by direct infusion with the UPLC/MS system described above.

The nomenclature of the following compounds was generated using Chemdraw. To avoid any confusion, the "(±)" symbol added to designate a racemic mixture; "*cis"* and "*trans"* prefixes were also used to assign the relative stereochemistry of two adjacent chiral centers.

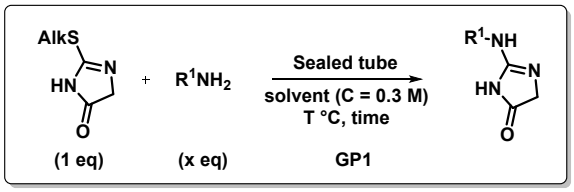
2. NMR descriptions and synthetic protocols of *N*2-functionalized aminoimidazolones

Synthesis of 2-methylsulfanyl-1,4-dihydroimidazol-5-one (1.1)



MeI (51.4 mL, 0.827 mol, 4 eq) was slowly added dropwise to a stirred suspension of 2-thiohydantoin (24 g, 206.6 mmol, 1 eq), DIPEA (72 mL, 413.2 mmol, 2 eq) and DMAP (10.096 g, 82.64 mmol, 0.4 eq) in DCM (413 mL) maintained at 0 °C. The resulting mixture was stirred 6h at 0 °C. A precipitate gradually appeared. Upon completion (TLC), the precipitate was filtered on a fritted glass funnel. The resulting solid was adsorbed on silica and purified by FC on silica gel (elution : cyclohexane/AcOEt/DCM 70/30/3 to 0/60/40). The volume of the collected fractions was reduced to approximately an eighth of its initial volume, until yellow crystals started to appear. The mixture was stirred 30 min at 0 °C and the solid was collected by filtration on a fritted glass funnel to yield 2-methylsulfanyl-1,4-dihydroimidazol-5-one (15.368 g, 118.1 mmol, 57%) in analytically pure form. Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.24 (br s, 1H, NH, D_2O exchanged), 4.01 (s, 2H), 2.47 (s, 3H). MS (ESI$^+$): $[M+H]^+$ 131.0.

General Protocol 1 - Addition of aliphatic amines on 2-alkylsulfanyl-1,4-dihydroimidazol-5-ones (GP1)



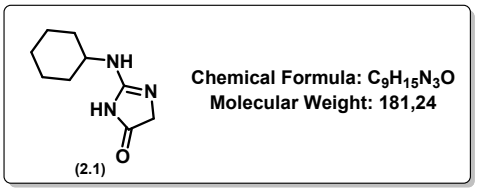
GP1: the appropriate amine (x eq) was added to a stirred solution of the appropriate 2-alkylsulfanyl-1,4-dihydroimidazol-5-one[(a)] (1 eq) in the adequate solvent (C = 0.3 M/isothiourea) in a sealed tube or sealed round flask (heating block). The mixture was thoroughly purged with vacuum/argon cycles and heated at the appropriate temperature for the indicated time (see details below). Upon completion (followed by consumption of the isothiourea on TLC), the mixture was brought back to room temperature.

- **GP1-A: direct precipitation of the desired product:** The reaction medium was stirred 1h at 0 °C. The precipitated solid was filtered off on a fritted glass funnel. High purity may be achieved after filtration by washing, reprecipitation, trituration, or recrystallization.

- **GP1-B: the product failed to precipitate**: the reaction mixture was concentrated *in vacuo*, adsorbed on silica, and purified by FC. High purity may be achieved after purification by washing, reprecipitation, trituration, or recrystallization.

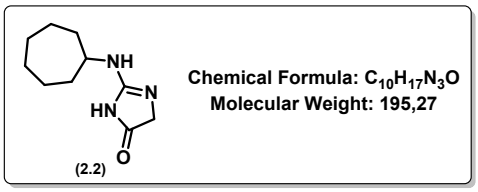
- (a) May require activation with AcOH

Synthesis of 2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (2.1)



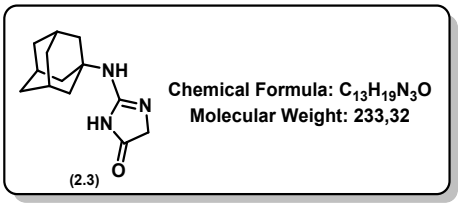
Compound (**2.1**) was synthesized according to **GP1-A** : reaction carried out in THF, on a 8.91 mmol scale of intermediate (**1.1**) and 4 eq of cyclohexylamine, at 120 °C (sealable round flask, heating bock), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Off-white solid, 35% (571 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 7.41 (br s, 1H, NH, D_2O exchanged), 6.95 (br s, 1H, NH, D_2O exchanged), 3.61 (s, 2H), 3.39 – 3.23 (m, 1H), 1.88 – 1.75 (m, 2H), 1.74 – 1.62 (m, 2H), 1.61 – 1.51 (m, 1H), 1.33 – 1.03 (m, 5H). MS (ESI$^+$): $[M+H]^+$ 182.0.

Synthesis of 2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (2.2)



Compound (**2.2**) was synthesized according to **GP1-A** : reaction carried out in THF, on a 11.52 mmol scale of intermediate (**1.1**), with 4 eq of cycloheptylamine, at 120 °C (sealable round flask, heating bock), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Off-white solid, 64% (1.429 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 7.42 (br s, 1H, NH, D_2O exchanged), 6.88 (br s, 1H, NH, D_2O exchanged), 3.86 – 3.68 (m, 1H), 3.59 (s, 2H), 1.89 – 1.76 (m, 2H), 1.70 – 1.32 (m, 10H). MS (ESI$^+$): $[M+H]^+$ 196.0.

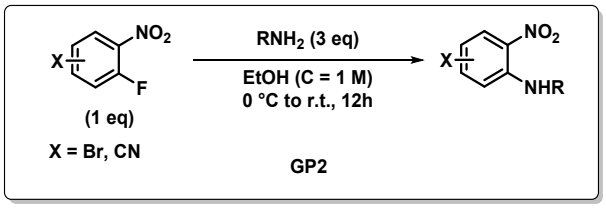
Synthesis of 2-((adamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (2.3)



Compound (**2.3**) was synthesized according to **GP1-B** : reaction carried out in dioxane, on a 3.073 mmol scale of intermediate (**1.1**), with 3 eq of adamantan-1-amine and 4 eq of AcOH, at 150 °C (heating block), for 16h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 9/1). The final product required a trituration in DCM at 0 °C. Beige solid, 35% (254 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 7.18 (br s, 1H, NH, D_2O exchanged), 6.73 (br s, 1H, NH, D_2O exchanged), 3.52 (s, 2H), 2.03 (s, 3H), 1.96 (s, 6H), 1.62 (s, 6H). MS (ESI$^+$): $[M+H]^+$ 234.2.

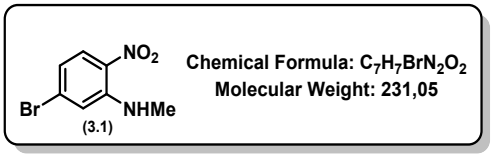
3. NMR descriptions and synthetic protocols for heteroarylcarboxaldehydes and their precursors

General Protocol 2: aromatic substitution of *o*-fluorinated nitro-anilines (GP2)



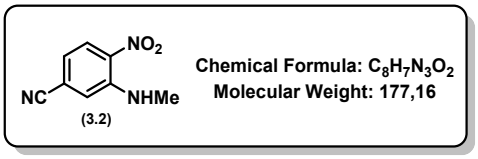
GP2: The appropriate amine (3 eq) was added dropwise to a stirred solution of the suitably substituted *o*-fluoro-nitro-benzene (1 eq) in EtOH (C = 1 M) maintained at 0 °C. The resulting mixture was stirred 1h at 0 °C, brought back to room temperature and stirred another 12h. Upon completion (TLC), the mixture was partially concentrated *in vacuo* and poured onto water. The precipitated solid was filtered off on a Büchner funnel and thoroughly dried *in vacuo*. The resulting solid was reprecipitated from DCM/pentane at 0 °C to yield the desired product in analytically pure form.

Synthesis of 5-bromo-*N*-methyl-2-nitroaniline (3.1)



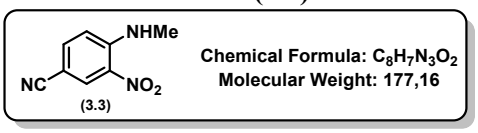
Compound (**3.1**) was synthesized according to **GP2** : reaction carried out on a 68.18 mmol scale of 4-bromo-2-fluoro-1-nitro-benzene, with $MeNH_2$ (2 M solution in MeOH or 33% w/w in EtOH, 3 eq). Bright orange solid, 87% (13.763 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.30 – 8.20 (m, 1H, NH, D_2O exchanged), 7.98 (d, J = 9.1 Hz, 1H), 7.16 (s, 1H), 6.82 (d, J = 9.1 Hz, 1H), 2.94 (d, J = 5.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 146.3, 130.9, 130.1, 127.9, 117.7, 116.4, 29.8. MS (ESI$^+$): $[M+H]^+$ 232.8.

Synthesis of 3-(methylamino)-4-nitrobenzonitrile (3.2)



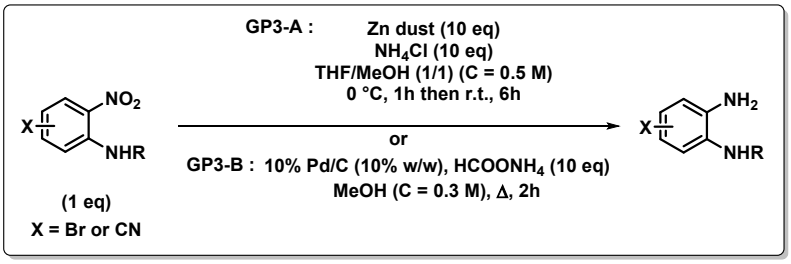
Compound (**3.2**) was synthesized according to **GP2** : reaction carried out on a 150.5 mmol scale of 3-fluoro-4-nitro-benzonitrile, with $MeNH_2$ (2 M solution in MeOH or 33% w/w in EtOH, 3 eq). Bright orange solid, 97% (25.917 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.25 (d, J = 5.3 Hz, 1H, NH, D_2O exchanged), 8.18 (d, J = 8.7 Hz, 1H), 7.51 (s, 1H), 7.01 (dd, J = 8.8, 1.7 Hz, 1H), 2.97 (d, J = 5.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 145.2, 132.9, 127.4, 119.4, 118.1, 117.7, 116.4, 29.9. MS (ESI$^+$): $[M+H]^+$ 178.0.

Synthesis of 4-(methylamino)-3-nitrobenzonitrile (3.3)



Compound (**3.3**) was synthesized according to **GP2** : reaction carried out on a 181 mmol scale of 4-fluoro-3-nitrobenzonitrile, with $MeNH_2$ (2 M solution in MeOH or 33% w/w in EtOH, 3 eq). Bright yellow solid, 99% (31.799 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.71 – 8.58 (m, 1H, NH, D_2O exchanged), 8.50 (d, J = 1.8 Hz, 1H), 7.84 (dd, J = 9.1, 2.0 Hz, 1H), 7.11 (d, J = 9.1 Hz, 1H), 3.00 (d, J = 5.0 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 147.5, 137.6, 131.7, 130.7, 118.3, 115.6, 96.0, 29.9. MS (ESI$^+$): $[M+H]^+$ 178.0.

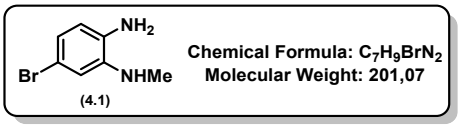
General Protocol 3 – Reduction of *o*-amino nitro-anilines (GP3)



GP3-A (X = Br): NH_4Cl (10 eq) was carefully added portionwise over 30 min to a stirred solution of the appropriate bromo-*N*-alkyl-2-nitro-aniline (1 eq) and zinc dust (10 eq) in a THF/MeOH mixture (1/1) (C = 0.5 M) maintained at 0 °C. When the addition ended, the mixture was stirred another hour at 0 °C (until the orange color fully disappeared) and gradually brought back to room temperature. The reaction medium was stirred another 6h at room temperature. Upon completion (TLC), the mixture was filtered off on a pad of celite. The celite was rinsed with MeOH. The filtrate was concentrated *in vacuo*, adsorbed on silica and purified by FC on silica gel (elution : cyclohexane/AcOEt : 8/2 to 1/1) to yield the desired bromo-*N*-alkyl-benzene-1,2-diamine in analytically pure form.

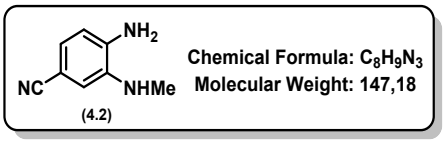
GP3-B (X = CN): 10% Pd/C (10% w/w) was carefully added portionwise to a stirred solution of the appropriate cyano-substituted *N*-alkyl-nitroaniline (1 eq) and ammonium formiate (10 eq) in MeOH (C = 0.3 M). The resulting mixture was refluxed 6h. Upon completion (TLC), the mixture was filtered off on pad of celite. The celite was rinsed with MeOH. The filtrate was concentrated *in vacuo*, the resulting crude was partitioned between AcOEt and sat. $NaHCO_{3(aq)}$. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with water and brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting solid was reprecipitated from DCM/pentane at 0 °C to yield the desired product in analytically pure form.

Synthesis of 5-bromo-*N*1-methylbenzene-1,2-diamine (4.1)



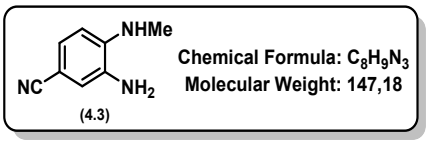
Compound (**4.1**) was synthesized according to **GP3-A** : reaction carried out on a 17.31 mmol scale of intermediate (**3.1**). Brown oil, 81% (2.83 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 6.52 (dd, J = 8.1, 2.2 Hz, 1H), 6.44 (d, J = 8.1 Hz, 1H), 6.40 (d, J = 2.2 Hz, 1H), 4.88 (bs, 1H), 4.61 (bs, 2H), 2.68 (d, J = 3.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 138.8, 134.4, 118.4, 114.6, 110.9, 108.8, 29.9. MS (ESI$^+$): $[M+H]^+$ 201.1.

Synthesis of 4-amino-3-(methylamino)benzonitrile (4.2)



Compound (**4.2**) was synthesized according to **GP3-B**: reaction carried out on a 146.2 mmol scale of intermediate (**3.2**). Beige solid, 87% (18.764 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 6.85 (dd, J = 8.0, 1.8 Hz, 1H), 6.61 – 6.52 (m, 2H), 5.48 (br s, 2H, NH, D_2O exchanged), 5.01 (q, J = 5.0 Hz, 1H, NH, D_2O exchanged), 2.72 (d, J = 4.9 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 140.4, 136.4, 122.2, 121.4, 112.2, 110.4, 97.3, 29.9. MS (ESI$^+$): $[M+H]^+$ 148.1.

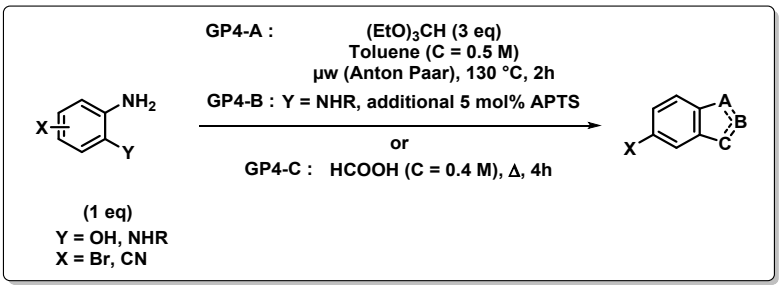
Synthesis of 3-amino-4-(methylamino)benzonitrile (4.3)



Compound (**4.3**) was synthesized according to **GP3-B**: reaction carried out on a 179.5 mmol scale of intermediate (**3.3**). Brown solid, 90% (23.777 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 6.94 (dd, J = 8.1, 1.6 Hz, 1H), 6.76 (d, J = 1.8 Hz, 1H), 6.41 (d, J = 8.2 Hz, 1H), 5.56 (q, J = 4.9 Hz, 1H, NH,

D_2O exchanged), 4.88 (br s, 2H, NH, D_2O exchanged), 2.76 (d, J = 4.8 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 141.1, 135.1, 123.0, 121.1, 114.5, 108.1, 96.4, 29.5. MS (ESI^+): $[M+H]^+$ 148.0.

General protocol 4: cyclization of brominated 2-aminophenols and *N*2-methylbenzene-1,2-diamines with triethyl orthoformate (GP4)

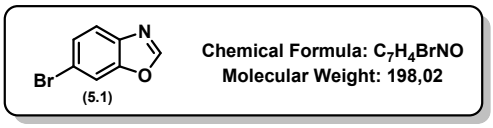


GP4-A (Y = OH and X = Br): a solution of the appropriate 2-amino-bromo-phenol (1 eq) and $(EtO)_3CH$ (2 eq) in toluene (C = 0.5 M) was irradiated at 130 °C for 2h. Upon completion (TLC), the mixture was cooled down room temperature, directly adsorbed on silica, and purified by FC on silica gel using the appropriate gradient of solvents (elution : cyclohexane/AcOEt : 1/0 to 6/4) to yield the desired bromo-1,3-benzoxazole in analytically pure form.

GP4-B (Y = NHR and X = Br): a solution of the appropriate 4-bromo-*N*-methyl-benzene-1,2-diamine (1 eq), $(EtO)_3CH$ (2 eq), and APTS.H_2O (5 mol%) in toluene (C = 0.5 M) was irradiated at 130 °C for 2h. Upon completion (TLC), the mixture was partitioned between AcOEt and sat. $NaHCO_{3(aq)}$. The aqueous layer was extracted three times with AcOEt. The combined organic layers were washed with brine and water, dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The resulting brown solid was dissolved in DCM at 0 °C and precipitated from pentane. The precipitated light beige solid was filtered off on a Büchner funnel, thoroughly rinsed with pentane, and dried *in vacuo* to yield the desired bromo-1-methyl-benzimidazole in analytically pure form.

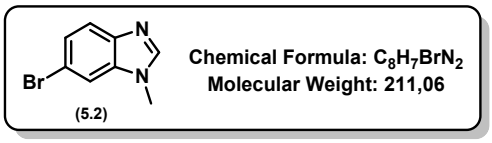
GP4-C (Y = NHR and X = CN): a solution of cyano-substituted *N*2-methylbenzene-1,2-diamine (1 eq) was refluxed in HCOOH (C = 0.4 M) for 4h. Upon completion (TLC), the mixture was brought back to room temperature, and concentrated *in vacuo*. The resulting crude was carefully treated with sat. $NaHCO_{3(aq)}$ to neutral pH. The precipitated solid was filtered on a Büchner funnel. The solid was solubilized in DCM and washed with water, sat. $NaHCO_{3(aq)}$, dried over $MgSO_4$, filtered and concentrated *in vacuo* to yield the desired solid in analytically pure form. Higher purity may be achieved by reprecipitation from DCM/pentane at 0 °C.

Synthesis of 6-bromo-1,3-benzoxazole (5.1)



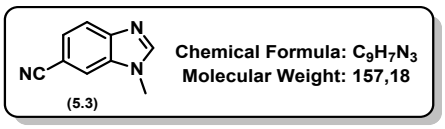
Compound (**5.1**) was synthesized according to **GP4-A** : reaction carried out on a 21.27 mmol scale of 2-amino-5-bromo-phenol. Light beige solid, 89% (3.745 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.79 (s, 1H), 8.12 (s, 1H), 7.77 (d, J = 8.4 Hz, 1H), 7.58 (d, J = 8.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 154.8, 150.0, 139.1, 127.8, 121.5, 117.7, 114.5. MS (ESI$^+$): $[M+H]^+$ 199.7.

Synthesis of 6-bromo-1-methyl-benzimidazole (5.2)



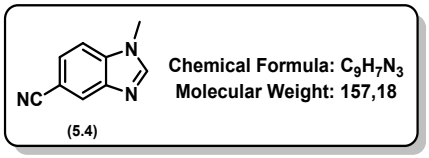
Compound (**5.2**) was synthesized according to **GP4-B** : reaction carried out on a 10.94 mmol scale of intermediate (**4.1**). Light beige solid, 79% (1.815 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.21 (s, 1H), 7.86 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.33 (d, J = 8.4 Hz, 1H), 3.83 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 145.6, 142.4, 135.8, 124.3, 121.0, 114.7, 113.3, 30.8. MS (ESI$^+$): $[M+H]^+$ 212.8.

Synthesis of 1-methyl-1*H*-benzo[*d*]imidazole-6-carbonitrile (5.3)



Compound (**5.3**) was synthesized according to **GP4-C** : reaction carried out on a 127.5 mmol scale of intermediate (**4.2**). Beige solid, 94% (18.829 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.46 (s, 1H), 8.24 (s, 1H), 7.82 (d, J = 8.4 Hz, 1H), 7.59 (dd, J = 8.3, 1.6 Hz, 1H), 3.90 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 148.1, 146.2, 134.3, 124.8, 120.4, 119.9, 115.9, 104.0, 31.1. MS (ESI$^+$): $[M+H]^+$ 158.1.

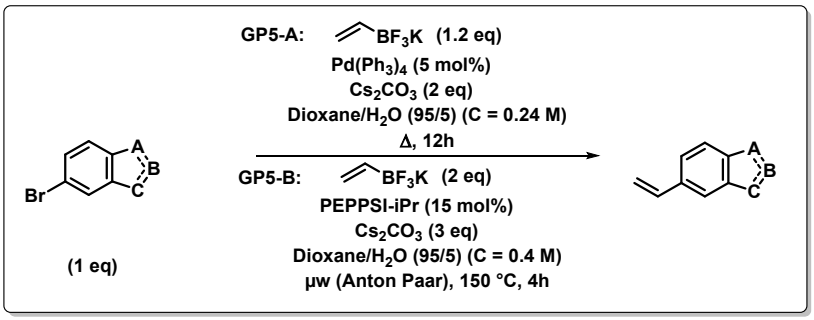
Synthesis of 1-methyl-1*H*-benzo[*d*]imidazole-5-carbonitrile (5.4)



Compound (**5.4**) was synthesized according to **GP4-C** : reaction carried out on a 156.3 mmol scale of intermediate (**4.3**). Beige solid, 73% (17.895 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.43 (s, 1H), 8.20 (d, J = 1.4 Hz, 1H), 7.79 (d, J = 8.4 Hz, 1H), 7.67 (dd, J = 8.4, 1.5 Hz, 1H), 3.89 (s, 3H). ^{13}C

NMR (101 MHz, DMSO-d_6, 300K) δ_C 147.4, 142.8, 137.5, 125.6, 124.4, 119.9, 111.9, 103.7, 31.0. MS (ESI^+): $[M+H]^+$ 158.0.

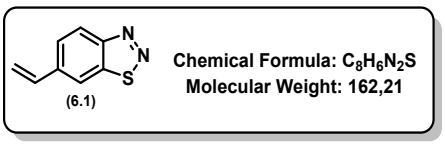
General Protocol N°5: palladium-catalyzed vinylation of heteroarylbromides (GP5)



GP5-A: a mixture of the appropriate heteroarylbromide (1 eq), potassium vinyltrifluoroborate (1.2 eq), Cs_2CO_3 (2 eq), and $Pd(PPh_3)_4$ (5 mol%) in dioxane/H_2O (95/5) (C = 0.4 M) was thoroughly purged with vacuum/argon cycles. The mixture was brought to reflux and heated for 12h. Upon completion (^1H NMR), the mixture was partitioned between H_2O and AcOEt. The aqueous layer was extracted three times with AcOEt. The combined organic layers were dried over $MgSO_4$, filtered, concentrated *in vacuo*, adsorbed on silica, and purified by FC on silica gel using the appropriate gradient of solvents (see details below for each compound) to yield the desired vinylheteroaryl in analytically pure form.

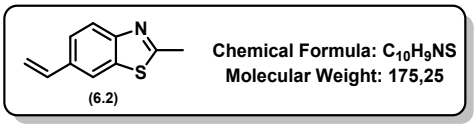
GP5-B : In a sealed tube thoroughly purged with vacuum/argon cycles, a mixture of the appropriate heteroarylbromide (1 eq), potassium vinyltrifluoroborate (2 eq), Cs_2CO_3 (3 eq), and PEPPSI-iPr (15 mol%) in dioxane/H_2O (95/5) (C = 0.4 M) was irradiated for 4h at the adequate temperature (see details below for each compound). Upon completion (^1H NMR), the mixture was cooled down room temperature, directly adsorbed on silica, and purified by FC on silica gel using the appropriate gradient of solvents (see details below for each compound) to yield the desired vinylheteroaryl in analytically pure form.

Synthesis of 6-vinylbenzo[*d*][1,2,3]thiadiazole (6.1)



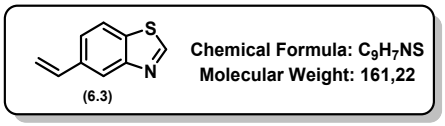
Compound (**6.1**) was synthesized according to **GP5-B** : reaction carried out on a 15.38 mmol scale of with 6-bromo-1,2,3-benzothiadiazole. Purification by FC: elution: cyclohexane/AcOEt: 98/2 to 8/2. Brown oil, 59% (1.466 g). ^1H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.66 (d, J = 8.7 Hz, 1H), 8.45 (s, 1H), 7.93 (d, J = 8.7 Hz, 1H), 6.97 (dd, J = 17.6, 10.9 Hz, 1H), 6.13 (d, J = 17.6 Hz, 1H), 5.55 (d, J = 10.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 157.4, 141.4, 138.3, 135.5, 125.5, 123.3, 118.5, 117.8. MS (ESI^+): $[M+H]^+$ 163.1.

Synthesis of 2-methyl-6-vinylbenzo[*d*]thiazole (6.2)



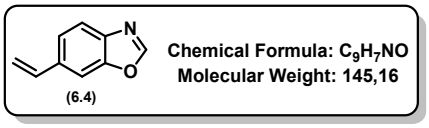
Compound (**6.2**) was synthesized according to **GP5-A** : reaction carried out on a 8.77 mmol scale of 6-bromo-2-methylbenzo[*d*]thiazole. Purification by FC : elution : cyclohexane/AcOEt : 95/5 to 7/3. Brown oil, 70% (1.073 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.12 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.60 (dd, J = 8.4, 1.8 Hz, 1H), 6.83 (dd, J = 17.6, 10.9 Hz, 1H), 5.91 (d, J = 17.6 Hz, 1H), 5.31 (d, J = 10.9 Hz, 1H), 2.79 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 167.3, 152.7, 136.2, 135.8, 134.0, 124.2, 121.9, 119.6, 114.7, 19.8. MS (ESI$^+$): $[M+H]^+$ 176.0.

Synthesis of 5-vinylbenzo[*d*]thiazole (6.3)



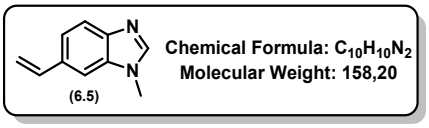
Compound (**6.3**) was synthesized according to **GP5-A** : reaction carried out on a 14.01 mmol scale of 6-bromobenzo[*d*]thiazole. Purification by FC: elution : cyclohexane/AcOEt : 99/1 to 7/3. Pale yellow oil, 79% (1.794 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 9.39 (s, 1H), 8.16 (s, 1H), 8.13 (d, J = 8.4 Hz, 1H), 7.65 (d, J = 8.4 Hz, 1H), 6.90 (dd, J = 17.7, 11.0 Hz, 1H), 5.99 (d, J = 17.7 Hz, 1H), 5.34 (d, J = 11.0 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C ^{13}C NMR (101 MHz, DMSO) δ 156.8, 153.6, 136.3, 135.7, 133.0, 123.4, 122.5, 120.7, 115.0. MS (ESI$^+$): $[M+H]^+$ 161.9.

Synthesis of 6-vinylbenzo[*d*]oxazole (6.4)



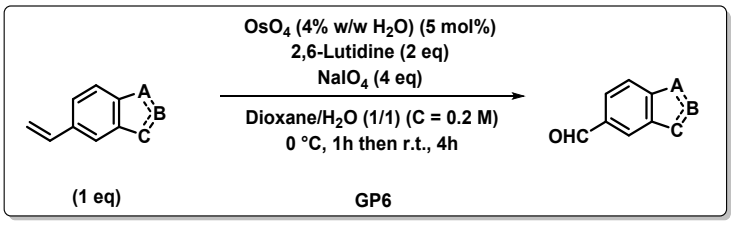
Compound (**6.4**) was synthesized according to **GP5-A** : reaction carried out on a 40.70 mmol scale of intermediate (**5.1**). Purification by FC: elution : cyclohexane/AcOEt : 99/1 to 8/2. Brown oil, 74% (4.345 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 8.73 (s, 1H), 7.90 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 7.53 (d, J = 8.2 Hz, 2H), 6.86 (dd, J = 17.7, 11.0 Hz, 1H), 5.94 (d, J = 17.6 Hz, 1H), 5.33 (d, J = 10.9 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 154.7, 149.9, 139.5, 136.2, 135.3, 123.2, 119.9, 115.0, 108.4. MS (ESI$^+$): $[M+H]^+$ 145.9. (N.B. : (6.4) has nearly identical Rf as starting material (5.1) in cyclohexane/AcOEt : 8/2).

Synthesis of 1-methyl-6-vinyl-1*H*-benzo[*d*]imidazole (6.5)



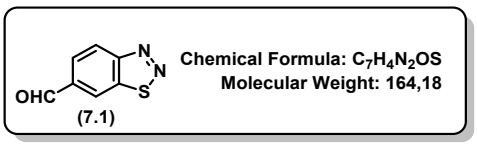
Compound (**6.5**) was synthesized according to **GP5-B** : reaction carried out on a 4.26 mmol scale of intermediate (**5.2**). Purification by FC : elution : DCM/MeOH : 99/1 to 94/6. Brown oil, 82% (551 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 300K) δ_H 7.87 (s, 1H), 7.74 (d, J = 8.3 Hz, 1H), 7.49 – 7.33 (m, 2H), 6.86 (dd, J = 17.5, 10.9 Hz, 1H), 5.79 (d, J = 17.5 Hz, 1H), 5.26 (d, J = 10.9 Hz, 1H), 3.85 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ_C 144.2, 143.8, 137.3, 135.0, 133.2, 120.8, 120.2, 113.2, 107.3, 31.1. MS (ESI$^+$): $[M+H]^+$ 159.1.

General Protocol N°6: Synthesis of heteroarylcarbaldehydes from vinylheteroaryls – Osmium-catalyzed Lemieux-Johnson oxidation (GP6)



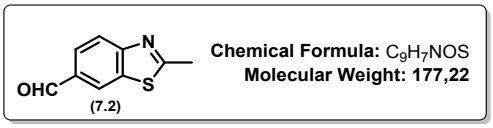
GP6: $NaIO_4$ (4 eq) was added portionwise to a stirred solution of the appropriate vinylheteroaryl (1 eq), 2,6-lutidine (2 eq), OsO_4 (4% w/w H_2O sol., 5 mol%), in dioxane/H_2O (1/1) (C = 0.2 M) maintained at 0 °C. The reaction mixture was vigorously stirred at 0 °C for 1h, brought back to room temperature and stirred another 4h. Upon completion (TLC), the mixture was partitioned between AcOEt and H_2O. The aqueous layer was extracted with AcOEt (x3). The combined organic layers were washed with sat. $NH_4Cl_{(aq)}$, sat. $NaHCO_{3(aq)}$, dried over $MgSO_4$, filtered, and concentrated *in vacuo* (trace amounts of 2,6-lutidine were removed by co-evaporation with toluene). The solid residue was adsorbed on silica and purified by FC on silica gel using the appropriate gradient of solvents (see details below for each compound).

Synthesis of benzo[*d*][1,2,3]thiadiazole-6-carbaldehyde (7.1)



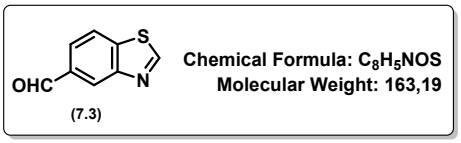
Compound (**7.1**) was synthesized according to **GP6** : reaction carried out on a 9.04 mmol scale of intermediate (**6.1**). Purification by FC : elution : cyclohexane/AcOEt : 95/5 to 8/2. Colorless solid, 41% (609 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 10.26 (s, 1H), 9.01 (s, 1H), 8.87 (d, J = 8.3 Hz, 1H), 8.18 (d, J = 8.5 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 192.9, 159.4, 141.1, 135.5, 126.5, 124.2, 124.2. MS (ESI$^+$): $[M+H]^+$ 165.0.

Synthesis of 2-methylbenzo[*d*]thiazole-6-carbaldehyde (7.2)



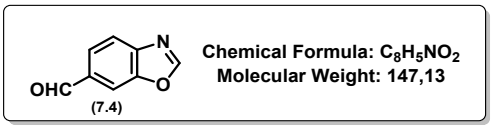
Compound (**7.2**) was synthesized according to **GP6** : reaction carried out on a 3.99 mmol scale of intermediate (**6.2**). Purification by FC : elution : cyclohexane/AcOEt : 9/1 to 7/3. Light beige solid. 84% (594 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 10.08 (s, 1H), 8.64 (d, J = 1.2 Hz, 1H), 8.06 (d, J = 8.4 Hz, 1H), 7.97 (dd, J = 8.4, 1.7 Hz, 1H), 2.85 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 192.2, 172.4, 156.7, 135.9, 132.7, 126.4, 125.2, 122.4, 20.2. MS (ESI$^+$): $[M+H]^+$ 177.9.

Synthesis of benzo[*d*]thiazole-5-carbaldehyde (7.3)



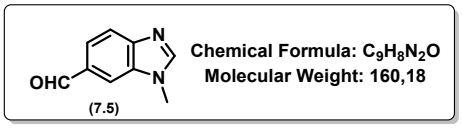
Compound (**7.3**) was synthesized according to **GP6** : reaction carried out on a 8.68 mmol scale of intermediate (**6.3**). Purification by FC : elution : cyclohexane/AcOEt : 9/1 to 7/3. Colorless solid, 63% (887 mg) ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 10.17 (s, 1H), 9.56 (s, 1H), 8.64 (d, J = 1.2 Hz, 1H), 8.40 (d, J = 8.3 Hz, 1H), 7.98 (dd, J = 8.3, 1.4 Hz, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 192.8, 158.6, 153.1, 140.0, 134.8, 125.7, 124.1, 123.5. MS (ESI$^+$): $[M+H]^+$ 164.8.

Synthesis of benzo[*d*]oxazole-6-carbaldehyde (7.4)



Compound (**7.4**) was synthesized according to **GP6** : reaction carried out on a 20.66 mmol scale of intermediate (**6.4**). Purification by FC : elution : cyclohexane/AcOEt : 99/1 to 7/3. Light beige solid, 87% (2.654 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 10.12 (s, 1H), 9.01 (s, 1H), 8.34 (s, 1H), 8.16 – 7.91 (m, 2H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 192.1, 157.5, 149.5, 144.6, 134.0, 126.0, 120.7, 112.6. MS (ESI$^+$): $[M+H]^+$ 147.9.

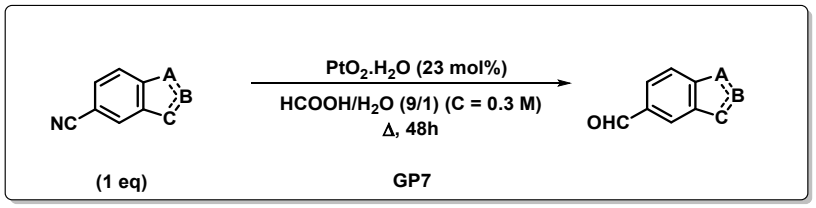
Synthesis of 1-methyl-1*H*-benzo[*d*]imidazole-6-carbaldehyde (7.5)



Compound (**7.5**) was synthesized according to **GP6** : reaction carried out on a 3.48 mmol scale of intermediate (**6.5**). Purification by FC : elution : DCM/MeOH : 99/1 to 94/6. Colorless solid, 54% (300 mg). ^{1}H NMR (400 MHz, $CDCl_3$, 300K) δ_H 10.12 (s, 1H), 8.39 – 8.22 (m, 1H), 8.02 (s, 1H), 7.95

(d, J = 8.4 Hz, 1H), 7.87 (d, J = 8.3 Hz, 1H), 3.98 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, 300K) δ_C 192.1, 148.5, 147.0, 134.9, 132.1, 124.7, 120.9, 111.4, 31.5. MS (ESI^+): $[M+H]^+$ 161.1.

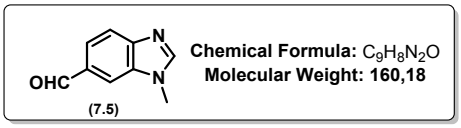
General protocol 7 - Alternative synthesis of heteroarylcarbaldehydes from heteroarylcarbonitriles – Adam's catalyst-mediated oxidation (GP7)



GP7: Adam's catalyst (23 mol%) was carefully added portionwise to a stirred solution of the appropriate carbonitrile (1 eq) in a $HCOOH/H_2O$ solution (9/1) (C = 0.3 M). The resulting mixture was refluxed for 48h. Upon completion (TLC), the mixture was brought back to room temperature and filtered off on pad of celite. The celite was rinsed with HCOOH. The filtrate was concentrated *in vacuo* and partitioned between DCM and sat. $NaHCO_{3(aq)}$. The aqueous layer was extracted three times with DCM. The combined organic layers were washed with sat. $NaHCO_{3(aq)}$, water, dried over $MgSO_4$, filtered, concentrated *in vacuo*, adsorbed on silica, and purified by FC on silica gel (see details below).

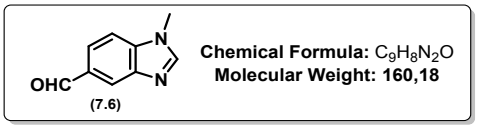
Note: further developments indicated that the reaction proceeds better with sequential additions of PtO_2: one portion added at t_0 (15 mol%), then another at t_0+24h (8 mol%) for a total amount of 23 mol% of Adam's catalyst over 48h.

Synthesis of 1-methyl-1*H*-benzo[*d*]imidazole-6-carbaldehyde (7.5)



Compound (**7.5**) was synthesized according to **GP7** : reaction carried out on a 30.32 mmol scale of intermediate (**5.3**). Purification by FC : elution : DCM/MeOH : 99/1 to 94/6. Colorless solid, 61% (2.986 g). The final product required a reprecipitation from DCM/pentane at 0 °C. Spectroscopic and analytical data were identical to those described above. **Note**: the initial purity of the nitrile precursor strongly influences the outcome of the reaction and ease of purification.

Synthesis of 1-methyl-1*H*-benzo[*d*]imidazole-5-carbaldehyde (7.6)

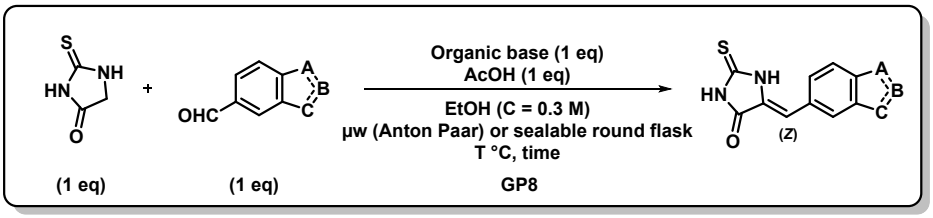


Compound (**7.6**) was synthesized according to **GP7** : reaction carried out on a 25.44 mmol scale of (**5.4**). Purification by FC : elution : DCM/MeOH : 99/1 to 94/6. The final product required a

reprecipitation from DCM/pentane at 0 °C. Colorless solid, 51% (2.079 g). ^{1}H NMR (400 MHz, $CDCl_3$, 300K) δ_H 10.10 (s, 1H), 8.33 (s, 1H), 8.26 – 8.19 (m, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.53 (d, *J* = 8.4 Hz, 1H), 3.95 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$, 300K) δ_C 192.1, 145.7, 143.2, 138.8, 132.0, 124.6, 123.6, 110.3, 31.6. MS (ESI$^+$): $[M+H]^+$ 161.1. **Note**: the initial purity of the nitrile precursor strongly influences the outcome of the reaction and ease of purification.

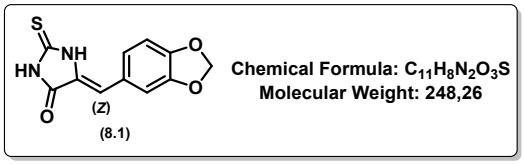
4. NMR descriptions and synthetic protocols for Knoevenagel adducts

General protocol 8 – Knoevenagel condensation between thiohydantoin and heteroarylcarbalhydes (GP8)



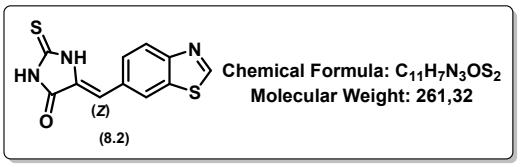
GP8: a stirred solution of thiohydantoin (1 eq), the appropriate heteroarylcarbaldehyde (1 eq), organic base (1 eq) and AcOH (1 eq) in EtOH (C = 0.3 M) was heated in a sealed tube in a microwave oven (Anton Paar), or in a sealable round flask, for the indicated time at the adequate temperature (see details below for each compound). Upon completion (followed by consumption of the heteroarylcarbaldehyde on TLC), the reaction medium was cooled down and added onto stirred water. The precipitated solid was stirred for 30 min and filtered off on a fritted glass funnel, thoroughly dried, and could be used in the next step without further purification. Higher purity may be achieved by means of trituration.

Synthesis of (*Z*)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-thioxoimidazolidin-4-one (8.1)



Compound (**8.1**) was synthesized according to **GP8** : reaction carried out on a 33.61 mmol scale of 2-thiohydantoin, piperonal, AcOH and piperidine as the organic base, in a sealable round flask. Reaction temperature: 115 °C, time: 24h. The final product required a trituration in EtOH. Yellow solid, 95% (7.893 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.31 (br s, 1H, NH, D_2O exchanged), 12.08 (br s, 1H, NH, D_2O exchanged), 7.45 (d, *J* = 1.8 Hz, 1H), 7.27 (dd, *J* = 8.2, 1.8 Hz, 1H), 6.98 (d, *J* = 8.1 Hz, 1H), 6.44 (s, 1H), 6.09 (s, 2H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.7, 165.8, 148.4, 147.9, 126.5, 126.3, 126.1, 112.2, 109.3, 108.7, 101.7. MS (ESI$^+$): $[M+H]^+$ 249.1.

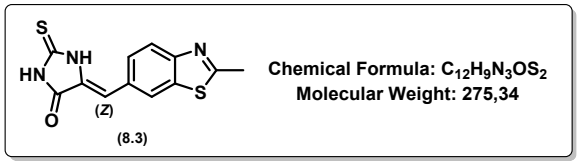
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-thioxoimidazolidin-4-one (8.2)



(8.2)

Compound (**8.2**) was synthesized according to **GP8** : reaction carried out on a 67.21 mmol scale of 2-thiohydantoin, benzo[*d*]thiazole-6-carbaldehyde, AcOH and piperidine as the organic base, in a sealable round flask. Reaction temperature: 125 °C, time: 24h. The final product required a trituration in EtOH. Yellow solid, 88% (30.964 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 12.44 (br s, 1H, NH, D_2O exchanged), 12.25 (br s, 1H, NH, D_2O exchanged), 9.47 (s, 1H), 8.61 (d, J = 1.8 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.84 (dd, J = 8.6, 1.8 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C 179.3, 165.7, 158.0, 153.1, 134.4, 129.8, 128.9, 128.1, 123.7, 123.1, 110.9. MS (ESI$^+$): $[M+H]^+$ 262.1.

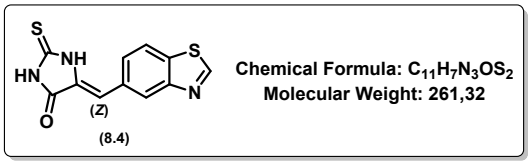
Synthesis of (*Z*)-5-((2-methylbenzo[*d*]thiazol-6-yl)methylene)-2-thioxoimidazolidin-4-one (8.3)



(8.3)

Compound (**8.3**) was synthesized according to **GP8:** reaction was carried out on a 7.34 mmol scale of 2-thiohydantoin, 2-methylbenzo[*d*]thiazole-6-carbaldehyde (**7.2**), AcOH and piperidine as the organic base, in a sealed tube (µw Anton Paar). Reaction temperature: 110 °C, time: 90 min. The final product required a trituration in EtOH. Yellow solid, 94% (1.898 g). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H 12.42 (br s, 1H, NH, D_2O exchanged), 12.21 (br s, 1H, NH, D_2O exchanged), 8.48 (s, 1H), 7.91 (d, J = 8.4 Hz, 1H), 7.77 (d, J = 8.5 Hz, 1H), 6.60 (s, 1H), 2.82 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C 179.2, 169.1, 165.7, 153.1, 136.0, 129.0, 128.8, 127.7, 123.0, 122.0, 111.1, 20.0. MS (ESI$^+$): $[M+H]^+$ 275.9.

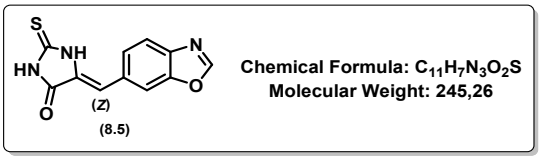
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-5-ylmethylene)-2-thioxoimidazolidin-4-one (8.4)



(8.4)

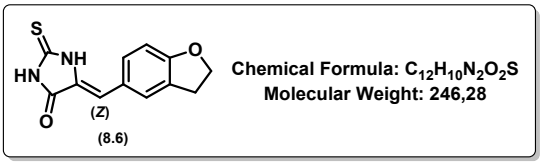
Compound (**8.4**) was synthesized according to **GP8:** reaction was carried out on a 49.11 mmol scale of 2-thiohydantoin, benzo[*d*]thiazole-5-carbaldehyde (**7.3**), AcOH and piperidine as the organic base, in a sealable round flask. Reaction temperature: 125 °C, time: 24h. The final product required a trituration in EtOH. Yellow solid, 72% (9.283 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.41 (br s, 1H, NH, D_2O exchanged), 12.36 (br s, 1H, NH, D_2O exchanged), 9.46 (s, 1H), 8.52 (s, 1H), 8.21 (d, J = 8.4 Hz, 1H), 7.83 (dd, J = 8.4, 1.7 Hz, 1H), 6.68 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 179.4, 165.8, 157.3, 153.5, 134.5, 130.6, 128.0, 127.3, 124.4, 122.8, 111.3. MS (ESI$^+$): $[M+H]^+$ 262.1.

Synthesis of (*Z*)-5-(benzo[*d*]oxazol-6-ylmethylene)-2-thioxoimidazolidin-4-one (8.5)



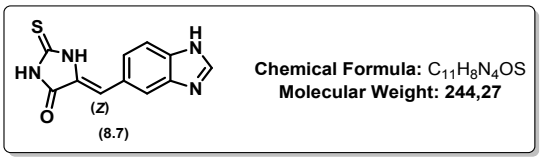
Compound (**8.5**) was synthesized according to **GP8** : reaction carried out on a 2.72 mmol scale of 2-thiohydantoin, benzo[*d*]oxazole-6-carbaldehyde (**7.4**), AcOH, and ethanolamine as the organic base, in a sealed tube (µw Anton Paar). Reaction temperature: 80 °C, time: 15 min (µw Anton Paar). The final product required a trituration in EtOH. Yellow solid, 72% (483 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.33 (br s, 2H, NH, D_2O exchanged), 8.84 (s, 1H), 8.25 (s, 1H), 7.82 (d, J = 8.3 Hz, 1H), 7.75 (d, J = 8.4 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 179.4, 165.8, 155.7, 149.8, 140.3, 130.2, 128.0, 127.7, 120.2, 112.2, 111.1. MS (ESI$^+$): $[M+H]^+$ 245.8.

Synthesis of (*Z*)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.6)



Compound (**8.6**) was synthesized according to **GP8** : reaction carried out on a 13.49 mmol scale of 2-thiohydantoin, 2,3-dihydrobenzofuran-5-carbaldehyde, AcOH, and piperidine as the organic base, in a sealable round flask. Reaction temperature: 125 °C, time: 24h. The final product required a trituration in EtOH. Yellow solid, 81% (2.683 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.27 (br s, 1H, NH, D_2O exchanged), 12.02 (br s, 1H, NH, D_2O exchanged), 7.75 (s, 1H), 7.49 (d, J = 8.4 Hz, 1H), 6.81 (d, J = 8.3 Hz, 1H), 6.46 (s, 1H), 4.60 (t, J = 8.7 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.3, 165.8, 161.1, 131.9, 128.5, 126.8, 125.4, 124.9, 112.9, 109.4, 71.8, 28.6. MS (ESI$^+$): $[M+H]^+$ 246.9.

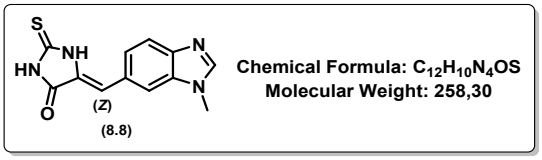
Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.7)



Compound (**8.7**) was synthesized according to **GP8** : reaction carried out on a 4.20 mmol scale of 2-thiohydantoin, 1*H*-benzimidazole-5-carbaldehyde, AcOH and piperidine as the organic base, in a sealed tube (µw Anton Paar). Reaction temperature: 110 °C, time: 60 min. The final product required a trituration in EtOH. Yellow solid, 95% (958 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major

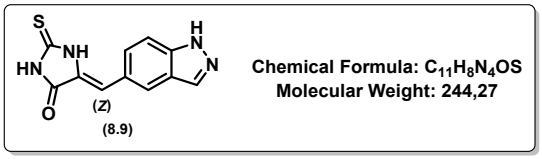
tautomer δ_H 12.42 (bs, 1H, NH, D_2O exchanged), 12.03 (bs, 2H, NH, D_2O exchanged), 8.25 (s, 1H), 8.03 (br s, 1H), 7.69 – 7.51 (m, 2H), 6.64 (s, 1H). MS (ESI^+): $[M+H]^+$ 245.8.

Synthesis of (*Z*)-5-((1-methyl-1*H*-benzo[*d*]imidazol-6-yl)methylene)-2-thioxoimidazolidin-4-one (8.8)



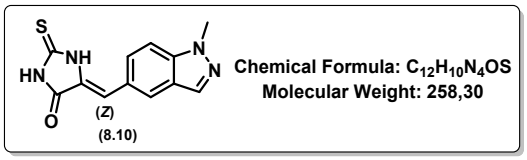
Compound (**8.8**) was synthesized according to **GP8** : reaction carried out on a 4.37 mmol scale of 2-thiohydantoin, 1-methyl-1*H*-benzo[*d*]imidazole-6-carbaldehyde (**7.5**), AcOH and piperidine as the organic base, in a sealed tube (µw Anton Paar). Reaction temperature : 110 °C, time : 60 min. The final product required a trituration in EtOH. Yellow solid, 76% (858 mg). ^1H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.38 (bs, 1H, NH, D_2O exchanged), 12.24 (bs, 1H, NH, D_2O exchanged), 8.29 (s, 1H), 8.02 (s, 1H), 7.66 (d, J = 8.4 Hz, 1H), 7.52 (d, J = 8.2 Hz, 1H), 6.65 (s, 1H), 3.92 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.8, 165.8, 146.6, 144.3, 135.1, 126.5, 126.4, 125.4, 119.6, 113.2, 111.6, 31.2. MS (ESI^+): $[M+H]^+$ 259.1.

Synthesis of (*Z*)-5-((1*H*-indazol-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.9)



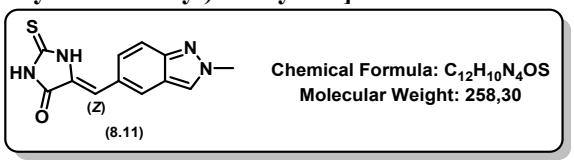
Compound (**8.9**) was synthesized according to **GP8**: reaction carried out on a 4.42 mmol scale of 2-thiohydantoin, indazole-5-carbaldehyde, AcOH, and piperidine as the organic base, in a sealed tube (µw Anton Paar). Reaction temperature: 110 °C, time: 60 min. The final product required a trituration in EtOH. Yellow solid, 89% (742 mg). ^1H NMR (400 MHz, DMSO-d_6, 300K) δ_H 13.24 (bs, 1H, NH, D_2O exchanged), 12.33 (bs, 1H, NH, D_2O exchanged), 12.19 (bs, 1H, NH, D_2O exchanged), 8.27 (s, 1H), 8.14 (s, 1H), 7.70 (d, J = 8.7 Hz, 1H), 7.55 (d, J = 8.7 Hz, 1H), 6.64 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 179.2, 166.3, 140.1, 135.0, 129.0, 126.8, 125.2, 123.8, 113.6, 111.0. MS (ESI^+): $[M+H]^+$ 244.9.

Synthesis of (*Z*)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.10)



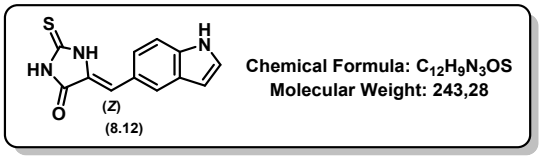
Compound (**8.10**) was synthesized according to **GP8** : reaction carried out on a 1.72 mmol scale of 2-thiohydantoin, 1-methylindazole-5-carbaldehyde, AcOH, and piperidine as the organic base, in a sealed tube (μw Anton Paar). Reaction temperature: 110 °C, time: 60 min. The final product required a trituration in EtOH. Yellow solid, 92% (408 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.33 (bs, 1H, NH, D_2O exchanged), 12.20 (bs, 1H, NH, D_2O exchanged), 8.24 (s, 1H), 8.11 (d, J = 0.9 Hz, 1H), 7.75 (dd, J = 8.9, 1.4 Hz, 1H), 7.67 (d, J = 8.8 Hz, 1H), 6.64 (s, 1H), 4.06 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.8, 165.8, 139.4, 133.5, 128.4, 126.4, 124.8, 123.9, 123.6, 112.9, 110.1, 35.5. MS (ESI$^+$): $[M+H]^+$ 258.9.

Synthesis of (5*Z*)-5-[(2-methylindazol-5-yl)methylene]-2-thioxo-imidazolidin-4-one (8.11)



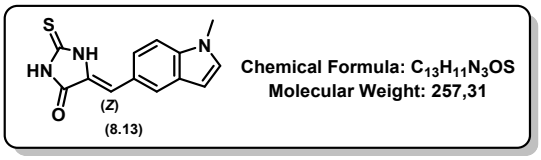
Compound (**8.11**) was synthesized according to **GP8** : reaction carried out on a 10.69 mmol scale of 2-thiohydantoin, 2-methylindazole-5-carbaldehyde, AcOH and piperidine as the organic base, in a sealable round flask. Reaction temperature : 110 °C, time : 60 min. The final product required a trituration in EtOH. Yellow solid, 89% (485 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.31 (bs, 1H, NH, D_2O exchanged), 12.16 (bs, 1H, NH, D_2O exchanged), 8.44 (s, 1H), 8.22 (s, 1H), 7.62 – 7.54 (m, 2H), 6.58 (s, 1H), 4.19 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.6, 165.8, 147.7, 127.5, 126.3, 126.1, 125.2, 123.9, 121.9, 117.0, 113.3, 39.9. MS (ESI$^+$): $[M+H]^+$ 259.1.

Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.12)



Compound (**8.12**) was synthesized according to **GP8** : reaction carried out on a 8.66 mmol scale of 2-thiohydantoin, 1*H*-indole-5-carbaldehyde, AcOH and piperidine as the organic base, in a sealable round flask. The final product required a trituration in EtOH. Yellow solid, 74% (1.56 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.14 (br s, 2H, NH, D_2O exchanged), 11.32 (s, 1H, NH, D_2O exchanged), 8.08 (s, 1H), 7.51 – 7.46 (m, 1H), 7.46 – 7.39 (m, 2H), 6.63 (s, 1H), 6.52 – 6.47 (m, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.2, 165.9, 136.5, 128.1, 126.8, 125.2, 124.2, 123.3, 123.2, 115.0, 111.9, 102.0. MS (ESI$^+$): $[M+H]^+$ 243.8.

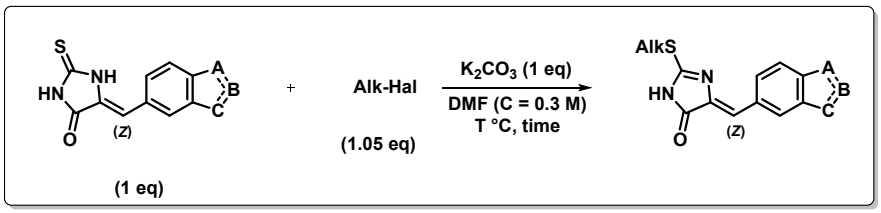
Synthesis of (*Z*)-5-((1-methyl-1*H*-indol-5-yl)methylene)-2-thioxoimidazolidin-4-one (8.13)



Compound (**8.13**) was synthesized according to **GP8** : reaction carried out on a 8.66 mmol scale of 2-thiohydantoin, 1-methyl-1*H*-indole-5-carbaldehyde, AcOH and piperidine as the organic base, in a sealable round flask. The final product required a trituration in EtOH. Yellow solid, 98% (1.59 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.26 (br s, 1H, NH, D_2O exchanged), 12.11 (br s, 1H, NH, D_2O exchanged), 8.07 (s, 1H), 7.55 (d, J = 8.6 Hz, 1H), 7.48 (d, J = 8.6 Hz, 1H), 7.39 (d, J = 3.1 Hz, 1H), 6.63 (s, 1H), 6.49 (d, J = 3.1 Hz, 1H), 3.81 (s, 1H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 178.3, 165.9, 136.9, 131.1, 128.4, 125.2, 124.1, 123.5, 123.3, 114.7, 110.2, 101.4, 32.6. MS (ESI$^+$): $[M+H]^+$ 258.9.

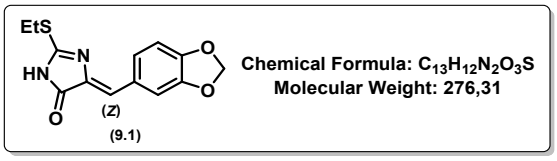
5. NMR descriptions and synthetic protocols for the regioselective *S*-alkylation of Knoevenagel adducts

General protocol 9 - *S*-Alkylation of (5*Z*)-5-heteroarylmethylene-2-thioxo-imidazolidin-4-ones (ROUTE 2)



GP9 : The appropriate alkyliodide (1.05 eq) was added dropwise to a stirred solution of the adequate 5-heteroaryl-2-thioxo-imidazolidin-4-one (1 eq) and K_2CO_3 (1 eq) in DMF (C = 0.3 M) at the appropriate temperature (see details below). The resulting mixture was stirred at the appropriate temperature, for the indicated time. Upon completion (TLC), the mixture was poured into water. The precipitated solid was stirred for 30 min and filtered off on a fritted glass funnel, thoroughly dried, and could be used in the next step without further purification. Trace impurities resulting from double-alkylation may be removed by trituration or FC.

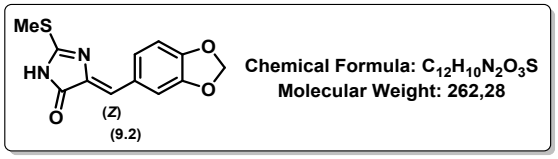
Synthesis of (*Z*)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.1)



Compound (**9.1**) was synthesized according to **GP9:** reaction was carried out on a 4.03 mmol scale of intermediate (**8.1**) and EtI, at room temperature, for 12h. Yellow solid, 86% (953 mg). ^{1}H NMR (400

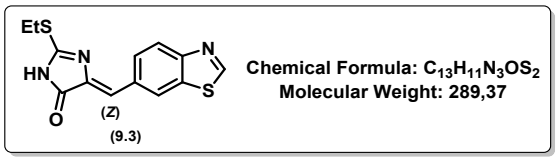
MHz, DMSO-d_6) δ_H 11.71 (br s, 1H, NH, D_2O exchanged), 8.00 (s, 1H), 7.53 (d, J = 8.2 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.69 (s, 1H), 6.08 (s, 2H), 3.26 (q, J = 7.3 Hz, 2H), 1.41 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.5, 163.1, 148.6, 147.6, 137.7, 128.8, 127.5, 121.0, 110.0, 108.6, 101.5, 24.2, 14.5. MS (ESI$^+$): $[M+H]^+$ 277.9.

Synthesis of (*Z*)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.2)



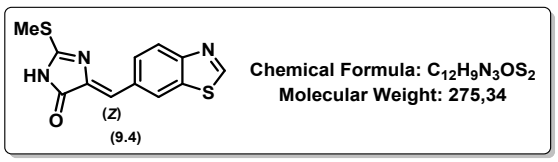
Compound (**9.2**) was synthesized according to **GP9:** reaction was carried out on a 31.67 mmol scale of intermediate (**8.1**) and MeI, at 0 °C for 6h, then r.t. for 12h. After filtration and drying, the final product required a trituration in min. DCM. Yellow solid, 96% (7.995 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.75 (br s, 1H, NH, D_2O exchanged), 8.00 (s, 1H), 7.56 (d, J = 8.0 Hz, 1H), 6.99 (d, J = 8.1 Hz, 1H), 6.70 (s, 1H), 6.08 (s, 2H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6) δ_C 170.6, 163.76, 148.6, 147.6, 137.8, 128.7, 127.6, 121.0, 110.1, 108.5, 101.5, 12.2. MS (ESI$^+$): $[M+H]^+$ 263.1.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.3)



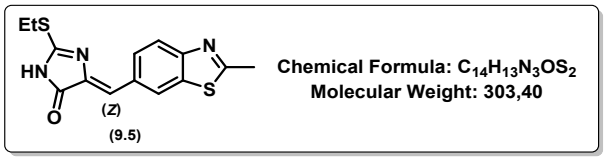
Compound (**9.3**) was synthesized according to **GP9:** reaction was carried out on a 7.69 mmol scale of intermediate (**8.2**) and EtI, at room temperature, for 12h. Yellow solid, 89% (978 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.85 (br s, 1H, NH, D_2O exchanged), 9.46 (s, 1H), 8.90 (s, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 6.88 (s, 1H), 3.70 – 3.17 (m, 2H), 1.44 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.5, 165.0, 157.8, 153.2, 139.5, 134.1, 132.0, 129.2, 125.4, 123.0, 119.9, 24.4, 14.5. MS (ESI$^+$): $[M+H]^+$ 289.9.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.4)



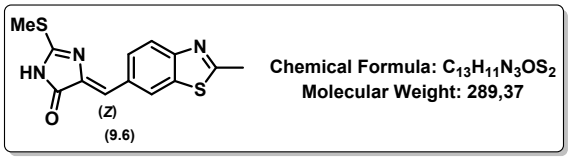
Compound (**9.4**) was synthesized according to **GP9:** reaction was carried out on a 246.24 mmol scale of intermediate (**8.2**) and MeI, at 0 °C for 6h, then r.t. for 12h. After filtration and drying, the final product required a trituration in min. DCM. Yellow solid, 95% (64.598 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.89 (br s, 1H, NH, D_2O exchanged), 9.46 (s, 1H), 8.92 (d, J = 1.6 Hz, 1H), 8.45 (d, J = 8.6 Hz, 1H), 8.12 (d, J = 8.6 Hz, 1H), 6.88 (s, 1H), 2.72 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ 171.1, 166.1, 158.3, 153.7, 140.0, 134.6, 132.4, 129.8, 125.9, 123.5, 120.4, 12.8. MS (ESI$^+$): $[M+H]^+$ 275.9.

Synthesis of (*Z*)-2-(ethylthio)-5-((2-methylbenzo[d]thiazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (9.5)



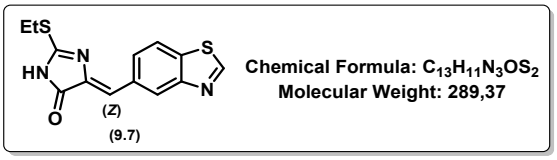
Compound (**9.5**) was synthesized according to **GP9:** reaction was carried out on a 1.45 mmol scale of (**8.3**) and EtI, at room temperature, for 12h. Yellow solid, 84% (368 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.82 (br s, 1H, NH, D_2O exchanged), 8.75 (s, 1H), 8.39 (d, J = 8.5 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 6.85 (s, 1H), 3.43 – 3.21 (m, 2H), 2.82 (s, 3H), 1.44 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.5, 169.0, 164.6, 153.3, 139.2, 135.7, 131.2, 129.1, 124.8, 122.0, 120.1, 24.3, 19.9, 14.5. MS (ESI$^+$): $[M+H]^+$ 303.9.

Synthesis of (*Z*)-5-((2-methylbenzo[*d*]thiazol-6-yl)methylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.6)



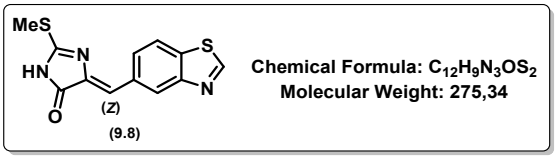
Compound (**9.6**) was synthesized according to **GP9:** reaction was carried out on a 3.63 mmol scale of (**8.3**) and MeI, at 0 °C for 6h, then r.t. for 12h. After filtration and drying, the final product required a trituration in min. DCM. Yellow solid, 92% (962 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.86 (br s, 1H, NH, D_2O exchanged), 8.77 (s, 1H), 8.39 (d, J = 8.6 Hz, 1H), 7.94 (d, J = 8.6 Hz, 1H), 6.85 (s, 1H), 2.82 (s, 3H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.6, 169.0, 165.3, 153.3, 139.2, 135.7, 131.2, 129.3, 124.9, 121.9, 120.2, 19.9, 12.3. MS (ESI$^+$): $[M+H]^+$ 290.1.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-5-ylmethylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.7)



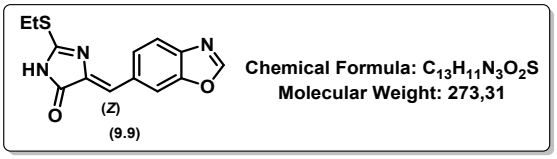
Compound (**9.7**) was synthesized according to **GP2:** reaction was carried out on a 1.91 mmol scale of (**8.4**) and EtI, at room temperature, for 12h. Yellow solid, 93% (516 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.84 (br s, 1H, NH, D_2O exchanged), 9.43 (s, 1H), 8.93 (s, 1H), 8.31 (d, J = 8.5 Hz, 1H), 8.20 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 3.41 – 3.27 (m, 2H), 1.45 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.5, 164.8, 157.1, 153.5, 139.5, 134.7, 132.7, 128.2, 125.7, 122.5, 120.3, 24.3, 14.6. MS (ESI$^+$): $[M+H]^+$ 290.9.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-5-ylmethylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.8)



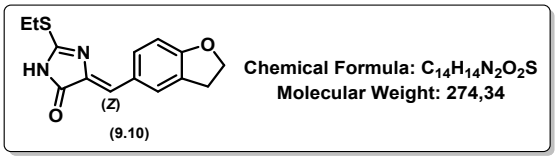
Compound (**9.8**) was synthesized according to **GP2:** reaction was carried out on a 3.41 mmol scale of (**8.4**) and MeI, at 0 °C for 6h, then r.t. for 12h. After filtration and drying, the final product required a trituration in min. DCM. Yellow solid, 85% (800 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.88 (br s, 1H, NH, D_2O exchanged), 9.43 (s, 1H), 8.92 (s, 1H), 8.34 (d, J = 8.5 Hz, 1H), 8.21 (d, J = 8.4 Hz, 1H), 6.94 (s, 1H), 2.71 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.7, 165.5, 157.1, 153.4, 139.5, 134.7, 132.7, 128.3, 125.8, 122.5, 120.4, 12.3. MS (ESI$^+$): $[M+H]^+$ 276.1.

Synthesis of (*Z*)-5-(benzo[*d*]oxazol-6-ylmethylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.9)



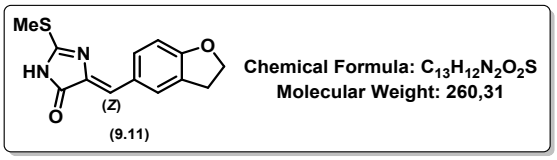
Compound (**9.9**) was synthesized according to **GP2:** reaction was carried out on a 1.97 mmol scale of (**8.5**) and EtI, at room temperature, for 12h. Yellow solid, 76% (411 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.85 (br s, 1H, NH, D_2O exchanged), 8.82 (s, 1H), 8.69 (s, 1H), 8.16 (d, J = 8.4 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 6.90 (s, 1H), 3.33 – 3.27 (m, 2H), 1.45 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.4, 165.0, 155.7, 149.6, 140.6, 139.4, 132.3, 128.6, 120.1, 120.0, 113.1, 24.4, 14.5. MS (ESI$^+$): $[M+H]^+$ 273.9.

Synthesis of (*Z*)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.10)



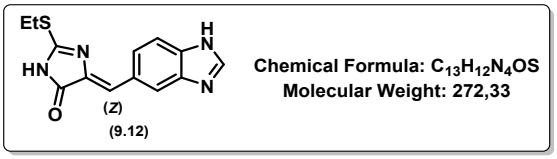
Compound (**9.10**) was synthesized according to **GP2:** reaction was carried out on a 877 µmol scale of (**8.6**) and EtI, at room temperature, for 12h. The final product required a trituration in warm EtOH. Yellow solid, 73% (176 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.65 (br s, 1H, NH, D_2O exchanged), 8.11 (s, 1H), 7.95 (d, J = 8.3 Hz, 1H), 6.83 (d, J = 8.4 Hz, 1H), 6.70 (s, 1H), 4.59 (t, J = 8.7 Hz, 2H), 3.30 – 3.17 (m, 4H), 1.40 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.6, 162.1, 161.2, 137.0, 132.7, 128.4, 128.1, 127.2, 121.7, 109.3, 71.6, 28.7, 24.2, 14.6. MS (ESI$^+$): $[M+H]^+$ 275.9.

Synthesis of (*Z*)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.11)



Compound (**9.11**) was synthesized according to **GP2:** reaction was carried out on a 10.23 mmol scale of (**8.6**) and MeI, at 0 °C for 6h, then at r.t for 12h. The final product required a trituration in DCM. Yellow solid, 96% (2.57 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.68 (br s, 1H, NH, D_2O exchanged), 8.13 (s, 1H), 7.96 (d, J = 8.2 Hz, 1H), 6.84 (d, J = 8.4 Hz, 1H), 6.70 (s, 1H), 4.59 (t, J = 8.7 Hz, 2H), 3.22 (t, J = 8.7 Hz, 2H), 2.65 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.7, 162.8, 161.2, 137.0, 132.8, 128.4, 128.1, 127.1, 121.7, 109.3, 71.6, 28.6, 12.2. MS (ESI$^+$): $[M+H]^+$ 261.1.

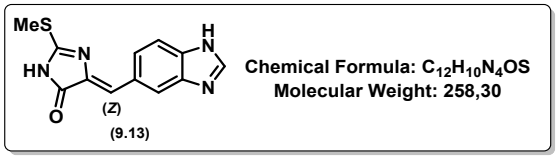
Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.12)



Compound (**9.12**) was synthesized according to **GP2** : reaction carried out on a 1.64 mmol scale of (**8.7**) and EtI, at r.t. for 12h. Yellow solid, 61% (274 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.85 – 12.51 (br m, 1H, NH, D_2O exchanged), 11.71 (br s, 1H, NH, D_2O exchanged), 8.52 (s, 1H),

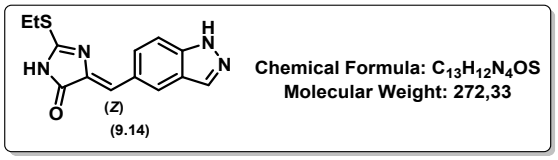
8.29 (s, 1H), 8.17 – 7.90 (m, 1H), 7.74 – 7.48 (m, 1H), 6.89 (s, 1H), 3.38 – 3.29 (m, 2H), 1.45 (t, *J* = 7.3 Hz, 3H). MS (ESI$^+$): $[M+H]^+$ 272.9.

Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.13)



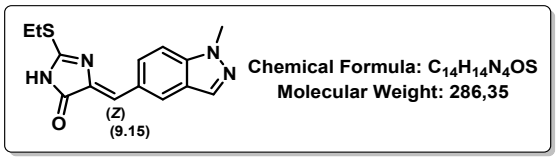
Compound (**9.13**) was synthesized according to **GP9** : reaction carried out with intermediate (**8.7**) (16.04 mmol) and MeI, at 0 °C for 6h, then at r.t for 12h. The final product required a trituration in DCM. Yellow solid, 92% (3.827 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 12.64 (br s, 1H, NH, D_2O exchanged), 11.75 (br s, 1H, NH, D_2O exchanged), 8.53 (s, 1H), 8.29 (s, 1H), 8.05 (br s, 1H), 7.72 – 7.53 (m, 1H), 6.89 (s, 1H), 2.71 (s, 3H). MS (ESI$^+$): $[M+H]^+$ 259.1.

Synthesis of (*Z*)-5-((1*H*-indazol-5-yl)methylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.14)



Compound (**9.14**) was synthesized according to **GP9** : reaction carried out on a 2.05 mmol scale of (**8.9**) and EtI, at r.t. for 12h. Yellow solid, 86% (481 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 13.24 (bs, 1H, NH, D_2O exchanged), 11.71 (bs, 1H, NH, D_2O exchanged), 8.52 (s, 1H), 8.36 (d, *J* = 8.9 Hz, 1H), 8.16 (s, 1H), 7.58 (d, *J* = 8.8 Hz, 1H), 6.88 (s, 1H), 3.58 – 3.03 (m, 2H), 1.44 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.6, 162.8, 139.9, 137.8, 134.8, 129.0, 127.1, 125.2, 123.3, 122.2, 110.4, 24.2, 14.6. MS (ESI$^+$): $[M+H]^+$ 272.9.

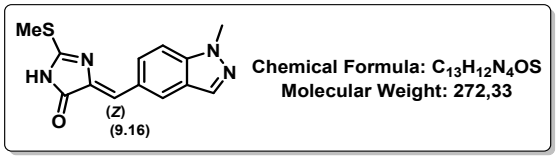
Synthesis of (*Z*)-2-(ethylthio)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (9.15)



Compound (**9.15**) was synthesized according to **GP9** : reaction carried out on a 1.58 mmol scale of (**8.10**) and EtI, at r.t. for 12h. Yellow solid, 76% (344 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.73 (bs, 1H, NH, D_2O exchanged), 8.50 (s, 1H), 8.41 (d, *J* = 8.9 Hz, 1H), 8.14 (s, 1H), 7.69 (d, *J* = 9.0 Hz, 1H), 6.89 (s, 1H), 4.05 (s, 3H), 3.31 (q, *J* = 7.3 Hz, 2H), 1.45 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR

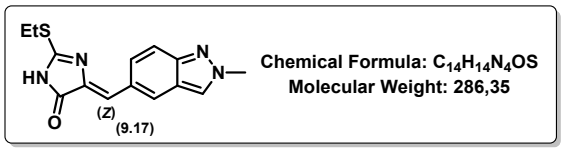
(101 MHz, DMSO-d_6, 300K) δ_C 170.6, 163.0, 139.5, 137.9, 133.7, 128.9, 127.1, 125.3, 123.8, 122.0, 110.0, 35.5, 24.3, 14.6. MS (ESI^+): $[M+H]^+$ 287.9.

Synthesis of (*Z*)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.16)



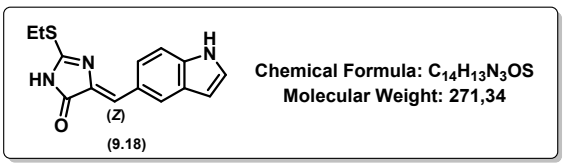
Compound (**9.16**) was synthesized according to **GP9** : reaction carried out on a 12.00 mmol scale of (**8.10**) and MeI, at 0 °C for 6h, then at r.t for 12h. The final product required a trituration in DCM. Yellow solid, 94% (3.060 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.75 (bs, 1H, NH, D_2O exchanged), 8.53 (s, 1H), 8.39 (d, J = 8.9 Hz, 1H), 8.14 (s, 1H), 7.69 (d, J = 8.9 Hz, 1H), 6.89 (s, 1H), 4.06 (s, 3H), 2.70 (s, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.7, 163.7, 139.5, 137.9, 133.7, 129.1, 127.1, 125.3, 123.8, 122.0, 109.9, 35.4, 12.2. MS (ESI^+): $[M+H]^+$ 273.2.

Synthesis of (*Z*)-2-(ethylthio)-5-((2-methyl-2*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (9.17)



Compound (**9.17**) was synthesized according to **GP9:** reaction carried out on a 1.87 mmol scale of (**8.11**) and EtI, at r.t. for 12h. Yellow solid, 88% (471 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.70 (br s, 1H, NH, D_2O exchanged), 8.46 (s, 1H), 8.40 (s, 1H), 8.31 (d, J = 9.1 Hz, 1H), 7.60 (d, J = 9.1 Hz, 1H), 6.83 (s, 1H), 4.17 (s, 3H), 3.32 – 3.26 (m, 2H), 1.44 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.6, 162.6, 148.0, 137.7, 127.8, 127.7, 126.4, 126.0, 122.4, 121.9, 116.9, 39.9, 24.2, 14.6. MS (ESI^+): $[M+H]^+$ 287.9.

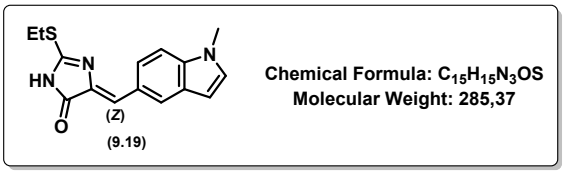
Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.18)



Compound (**9.18**) was synthesized according to **GP9**: reaction carried out on a 2.47 mmol scale of (**8.12**) and EtI, at r.t. for 12h. The final product required purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Yellow solid, 57% (380 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.61 (br s, 1H, NH, D_2O exchanged), 11.32 (br s, 1H, NH, D_2O exchanged), 8.34 (s, 1H), 8.09 (d, J = 8.6 Hz, 1H),

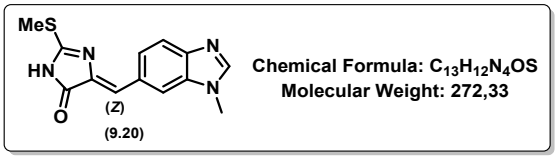
7.43 (d, *J* = 8.6 Hz, 1H), 7.39 (s, 1H), 6.85 (s, 1H), 6.53 – 6.46 (m, 1H), 3.34 – 3.27 (m, 2H), 1.45 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.8, 161.4, 136.8, 136.7, 127.9, 126.5, 125.6, 125.2, 124.8, 124.0, 111.8, 102.2, 24.2, 14.7. MS (ESI$^+$): $[M+H]^+$ 272.9.

Synthesis of (*Z*)-2-(ethylthio)-5-((1-methyl-1*H*-indol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (9.19)



Compound (**9.19**) was synthesized according to **GP9**: reaction carried out on a 3.89 mmol scale of (**8.13**) and EtI, at r.t. for 12h. The final product required purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Yellow solid, 73% (805 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.62 (br s, 1H, NH, D_2O exchanged), 8.33 (s, 1H), 8.17 (d, *J* = 8.7 Hz, 1H), 7.50 (d, *J* = 8.7 Hz, 1H), 7.37 (s, 1H), 6.86 (s, 1H), 6.49 (s, 1H), 3.81 (s, 3H), 3.35 – 3.27 (m, 2H), 1.45 (t, *J* = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, DMSO-d_6, 300K) δ_C 170.7, 161.6, 137.0, 136.9, 130.8, 128.2, 125.6, 125.3, 124.8, 123.7, 110.1, 101.6, 32.6, 24.2, 14.7. MS (ESI$^+$): $[M+H]^+$ 286.9.

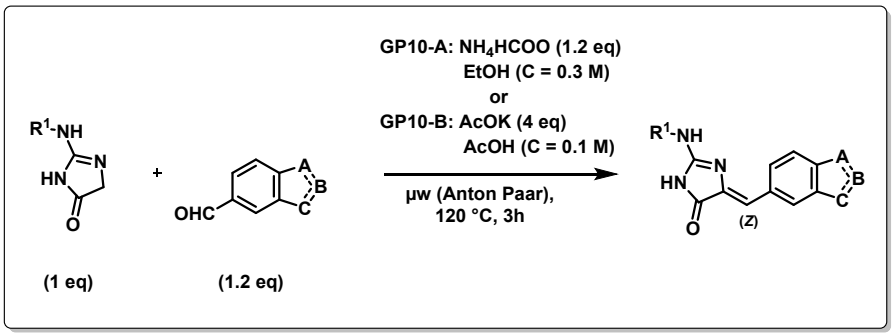
Synthesis of (*Z*)-5-((1-methyl-1*H*-benzo[*d*]imidazol-6-yl)methylene)-2-(methylthio)-3,5-dihydro-4*H*-imidazol-4-one (9.20)



Compound (**9.20**) was synthesized according to **GP9**: reaction carried out on a 12.99 mmol scale of (**8.8**) and MeI, at 0 °C for 6h, then at r.t for 12h. The final product required a trituration in DCM. Yellow solid, 96% (3.395 g). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 11.79 (br s, 1H, NH, D_2O exchanged), 8.52 (s, 1H), 8.28 (s, 1H), 8.07 (d, *J* = 8.5 Hz, 1H), 7.67 (d, *J* = 8.5 Hz, 1H), 6.90 (s, 1H), 3.86 (s, 3H), 2.71 (s, 3H). MS (ESI$^+$): $[M+H]^+$ 273.1.

6. NMR descriptions and synthetic protocols for Leucettinibs using pathway 2 (late-stage Knoevenagel)

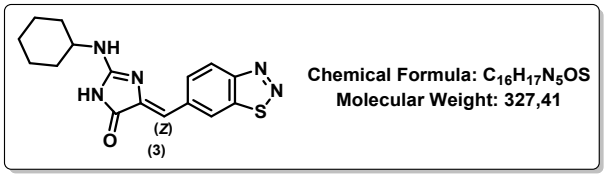
General protocol 10 - Knoevenagel condensation between *N*2-functionalized 2-amino-1,4-dihydroimidazol-5-ones and heteroarylcarbalhydes (GP10)



GP10-A: a stirred solution of the appropriate *N*2-functionalized 2-amino-1,4-dihydroimidazol-5-one (1 eq), heteroarylcarboxaldehyde (1.2 eq) and NH_4HCOO (1.2 eq) in EtOH (C = 0.3 M) was heated in a sealed tube in a microwave oven (Anton Paar) at 120 °C for 3h. Upon completion (followed by consumption of the heteroarylcarboxaldehyde on TLC), the mixture was brought back to room temperature, adsorbed on silica and purified by FC (see details below). After FC, higher purity may be achieved by reprecipitation, trituration, or recrystallization (see details below).

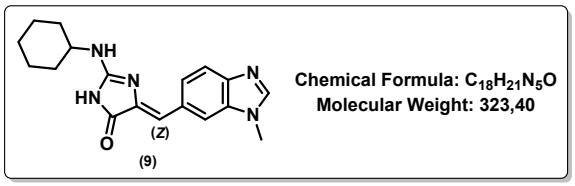
GP10-B: a stirred solution of the appropriate *N*2-functionalized 2-amino-1,4-dihydroimidazol-5-one (1 eq), heteroarylcarboxaldehyde (1.2 eq) and AcOK (4 eq) in AcOH (C = 0.1 M) was heated in a sealed tube in a microwave oven (Anton Paar) at 120 °C for 3h. Upon completion (followed by consumption of the heteroarylcarboxaldehyde on TLC), the mixture was brought back to room temperature, slowly added on sat. $Na_2CO_{3(aq)}$. The precipitated solid was filtered off on a fritted-glass funnel, adsorbed on silica and purified by FC (see details below). After FC, higher purity may be achieved by reprecipitation, trituration, or recrystallization (see details below).

Synthesis of (*Z*)-5-(benzo[*d*][1,2,3]thiadiazol-6-ylmethylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (3)



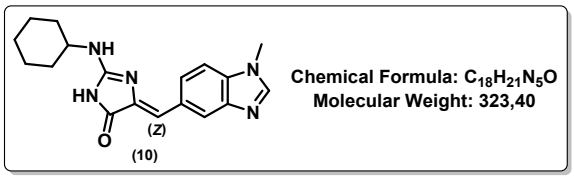
Compound (**3**) was synthesized according to **GP10-B** on a 276 µmol scale of intermediate (**2.1**), with 1.2 eq of aldehyde (**7.1**). Purification by FC (elution: DCM/MeOH: 99/1 to 95/5). The final product required a trituration in min. ACN at 0 °C. Yellow solid. Isolated yield: 49% (44 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.59 (br s, 1H, NH, D_2O exchanged), 8.91 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H), 7.63 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 3.76 (br s, 1H), 1.94 (s, 2H), 1.81 – 1.72 (m, 2H), 1.67 – 1.56 (m, 1H), 1.48 – 1.31 (m, 4H), 1.30 – 1.16 (m, 1H). MS (ESI$^+$): $[M+H]^+$ 328.3. HPLC: 96% (*Z*) + 2% (*E*).

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (9)



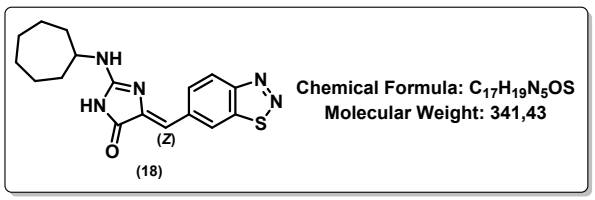
Compound (**9**) was synthesized according to **GP10-A** on a 400 µmol scale of intermediate (**2.1**), with 1.2 eq of aldehyde (**7.5**). Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a reprecipitation from DCM/pentane at 0 °C. Pale yellow solid. Isolated yield: 47% (60 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.23 (br s, 1H, NH, D_2O exchanged), 8.43 (br s, 1H), 8.14 (s, 1H), 7.79 (br s, 1H), 7.59 (d, J = 8.2 Hz, 1H), 7.13 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 3.84 (s, 3H), 3.74 (br s, 1H), 1.99 (br s, 2H), 1.83 – 1.68 (m, 2H), 1.67 – 1.56 (m, 1H), 1.47 – 1.13 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 324.2. HPLC: 97%.

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (10)



Compound (**10**) was synthesized according to **GP10-A** on a 352 µmol scale of intermediate (**2.1**), with 1.2 eq of aldehyde (**7.6**). Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a trituration in min. ACN at 0 °C. Colorless solid. Isolated yield: 40% (55 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.20 (br s, 1H, NH, D_2O exchanged), 8.44 (br s, 1H), 8.12 (s, 1H), 7.93 (br s, 1H), 7.51 (s, 1H), 7.06 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.83 (s, 3H), 3.73 (s, 1H), 1.95 (s, 2H), 1.74 (s, 2H), 1.65 – 1.55 (m, 1H), 1.47 – 1.30 (m, 4H), 1.30 – 1.16 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 324.3. HPLC: >98%.

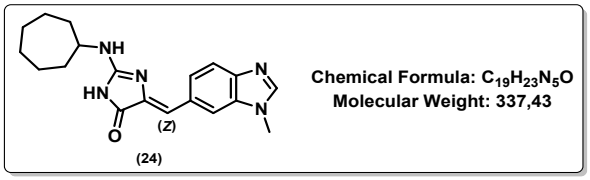
Synthesis of (*Z*)-5-(benzo[*d*][1,2,3]thiadiazol-6-ylmethylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (18)



Compound (**18**) was synthesized according to **GP10-B** on a 276 µmol scale of intermediate (**2.2**), with 1.2 eq of aldehyde (**7.1**). Purification by FC (elution: DCM/MeOH: 99/1 to 95/5). The final product required a trituration in min. ACN at 0 °C. Yellow solid. Isolated yield: 26% (24 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.49 (br s, 1H, NH, D_2O exchanged), 8.94 (s, 1H), 8.58 (d, J = 8.8 Hz, 1H), 8.45 (d, J = 8.8 Hz, 1H), 7.62 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 3.98

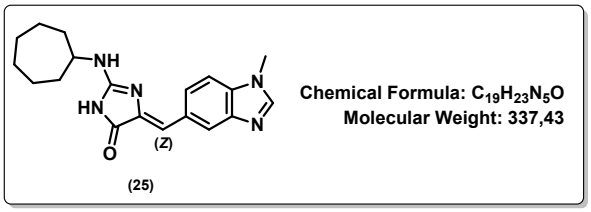
(br s, 1H), 2.07 – 1.88 (m, 2H), 1.77 – 1.42 (m, 10H). MS (ESI$^+$): $[M+H]^+$ 342.3. HPLC: 96% (*Z*) + 3% (*E*)

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (24)



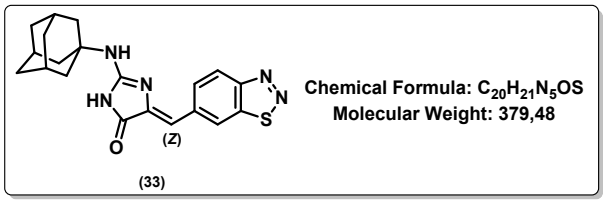
Compound (**24**) was synthesized according to **GP10-A** on a 276 µmol scale of intermediate (**2.2**), with 1.2 eq of aldehyde (**7.5**). Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a reprecipitation from DCM/pentane at 0 °C. Pale yellow solid. Isolated yield: 31% (59 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.15 (br s, 1H, NH, D_2O exchanged), 8.45 (s, 1H), 8.12 (s, 1H), 7.80 (d, *J* = 8.5 Hz, 1H), 7.57 (d, *J* = 8.4 Hz, 1H), 7.10 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.97 (br s, 1H), 3.83 (s, 3H), 2.11 – 1.85 (m, 2H), 1.82 – 1.40 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 338.3. HPLC: >98%.

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (25)



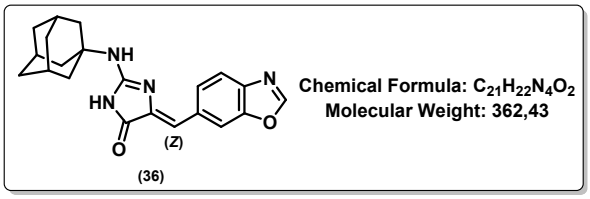
Compound (**25**) was synthesized according to **GP10-A** on a 352 µmol scale of intermediate (**2.2**), with 1.2 eq of aldehyde (**7.6**). Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a trituration in min. ACN at 0 °C. Colorless solid. Isolated yield: 54% (74 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.11 (br s, 1H, NH, D_2O exchanged), 8.46 (s, 1H), 8.10 (s, 1H), 7.95 (d, *J* = 8.5 Hz, 1H), 7.49 (d, *J* = 8.5 Hz, 1H), 7.04 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.96 (br s, 1H), 3.83 (s, 3H), 1.97 (br s, 2H), 1.79 – 1.41 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 338.3. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-(benzo[*d*][1,2,3]thiadiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (33)



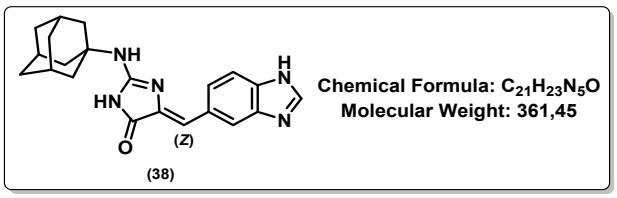
Compound (**33**) was synthesized according to **GP10-B** on a 276 µmol scale of intermediate (**2.3**), with 1.2 eq of aldehyde (**7.1**). Instead of a purification by FC, the solid isolated after precipitation directly underwent two successive triturations in refluxing EtOH. Beige solid. Isolated yield: 70% (70 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.89 (br s, 1H, NH, D_2O exchanged), 8.98 (s, 1H), 8.60 (d, J = 8.8 Hz, 1H), 8.52 – 8.39 (m, 1H), 7.02 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 2.31 – 2.02 (m, 9H), 1.75 (s, 6H). MS (ESI$^+$): $[M+H]^+$ 380.3. HPLC: 96%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-(benzo[*d*]oxazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (36)



Compound (**36**) was synthesized according to **GP10-B** on a 429 µmol scale of intermediate (**2.3**), with 1.2 eq of aldehyde (**7.4**). Purification by FC (elution: DCM/MeOH: 99/1 to 94/6). Beige solid. Isolated yield: 19% (19 mg). The final product required a trituration in ACN at 0 °C. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.80 (br s, 1H, NH, D_2O exchanged), 8.75 (s, 1H), 8.66 (s, 1H), 7.86 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 6.87 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 2.30 – 1.95 (m, 9H), 1.73 (s, 6H). MS (ESI$^+$) : $[M+H]^+$ 363.3. HPLC: 97%.

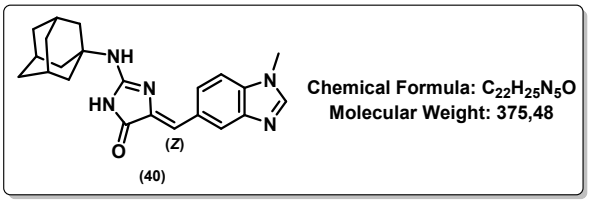
Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-((adamantan-1-yl)amino)-3,5-dihydro-4H-imidazol-4-one (38)



Compound (**38**) was synthesized according to **GP10-A**, on a 343 µmol scale of intermediate (**2.3**), with 1.2 eq of 1*H*-benzimidazole-5-carbaldehyde. Purification by FC (elution: DCM/MeOH: 99/1 to 9/1 (7N NH_3). The final product required a trituration in EtOH at 0 °C. Isolated yield: 19% (23 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 12.40 (br s, 1H, NH, D_2O exchanged), 9.69 (br s, 1H, NH, D_2O exchanged), 8.40 (br s, 1H), 8.17 (s, 1H), 7.91 – 7.81 (m,

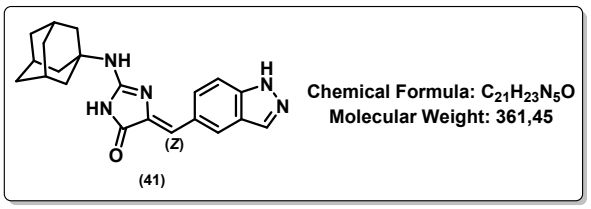
1H), 7.65 – 7.46 (m, 1H), 6.60 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 2.37 – 1.94 (m, 9H), 1.92 – 1.52 (m, 6H). MS (ESI^+) : $[M+H]^+$ 362.3. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (40)



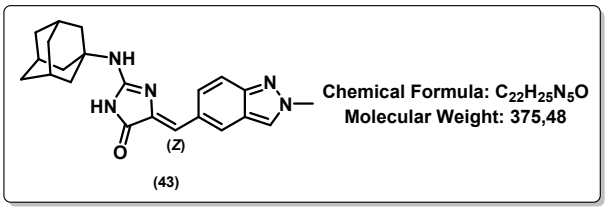
Compound (**40**) was synthesized according to **GP10-A** on a 321 µmol scale of intermediate (**2.3**), with 1.2 eq of aldehyde (**7.6**). Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a trituration in min. EtOH at 0 °C. Pale yellow solid. Isolated yield: 57% (69 mg). ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.80 (br s, 1H, NH, D_2O exchanged), 8.47 (s, 1H), 8.15 (s, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.52 (d, J = 8.6 Hz, 1H), 6.77 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 3.83 (s, 3H), 2.25 – 2.01 (m, 9H), 1.81 – 1.60 (m, 6H). MS (ESI^+) : $[M+H]^+$ 376.3. HPLC: >98%.

Synthesis of (*Z*)-5-((1*H*-indazol-5-yl)methylene)-2-((adamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (41)



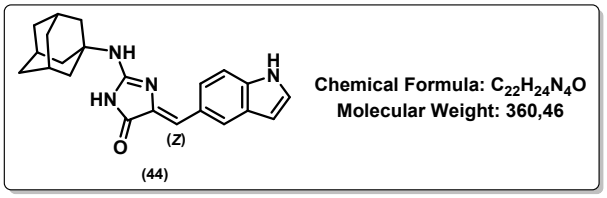
Compound (**41**) was synthesized according to **GP10-A** on a 427 µmol scale of intermediate (**2.3**), with 1.2 eq of 1*H*-indazole-5-carbaldehyde. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a trituration in min. EtOH at 0 °C. Pale yellow solid. Isolated yield: 36% (55 mg). ^1H NMR (400 MHz, DMSO-d_6, 300K) δ_H 13.10 (s, 1H, NH, D_2O exchanged), 8.54 (s, 1H), 8.20 (d, J = 8.8 Hz, 1H), 8.00 (s, 1H), 7.49 (d, J = 8.8 Hz, 1H), 6.71 (s, 1H, NH, D_2O exchanged), 6.55 (s, 1H), 3.07 (s, 3H), 2.32 – 2.24 (m, 6H), 2.16 (s, 3H), 1.75 (s, 6H). MS (ESI^+) : $[M+H]^+$ 376.2. HPLC: 97%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((2-methyl-2*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (43)



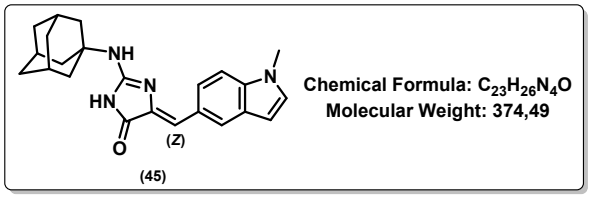
Compound (**43**) was synthesized according to **GP10-A**, on a 321 µmol scale of intermediate (**2.3**), with 1.2 eq of 2-methyl-2*H*-indazole-5-carbaldehyde. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 94/6). The final product required a trituration in EtOH at 0 °C. Isolated yield: 27% (33 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.70 (br s, 1H, NH, D_2O exchanged), 8.38 (s, 1H), 8.28 (s, 1H), 8.04 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 6.63 (br s, 1H, NH, D_2O exchanged), 6.37 (s, 1H), 4.15 (s, 3H), 2.33 – 1.96 (m, 9H), 1.71 (d, J = 23.1 Hz, 6H). MS (ESI$^+$) : $[M+H]^+$ 376.4. HPLC: >98%

Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-((adamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (44)



Compound (**44**) was synthesized according to **GP10-A**, on a 364 µmol scale of intermediate (**2.3**), with 1.2 eq of 1*H*-indole-5-carbaldehyde. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in min. EtOH. Isolated yield: 59% (69 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.12 (s, 1H, NH, D_2O exchanged), 9.74 (s, 1H, NH, D_2O exchanged), 8.40 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.51 – 7.28 (m, 2H), 6.65 (br s, 1H, NH, D_2O exchanged), 6.48 – 6.30 (m, 2H), 2.24 – 2.00 (m, 9H), 1.81 – 1.63 (m, 6H). HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((1-methyl-1*H*-indol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (45)

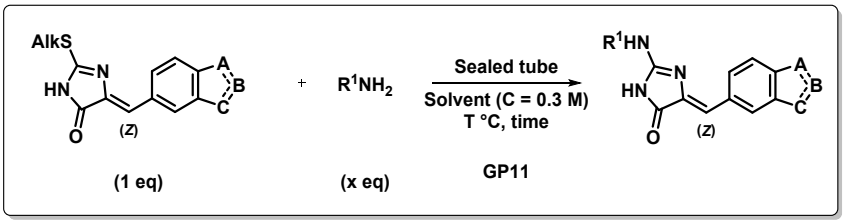


Compound (**45**) was synthesized according to **GP10-A**, on a 364 µmol scale of intermediate (**2.3**), with 1.2 eq of 1-methyl-1*H*-indole-5-carbaldehyde. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in min. EtOH. Isolated yield: 45% (61 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.74 (br s, 1H, NH, D_2O exchanged), 8.30 (s, 1H),

7.99 (d, *J* = 8.6 Hz, 1H), 7.52 – 7.24 (m, 2H), 6.66 (br s, 1H, NH, D_2O exchanged), 6.51 – 6.31 (m, 2H), 3.78 (s, 3H), 2.28 – 2.00 (m, 9H), 1.84 – 1.63 (m, 6H). HPLC: >98%.

7. NMR descriptions and synthetic protocols for Leucettinibs using pathway 1 (late-stage S_NAr)

General protocol 11 - Addition of amines on (*Z*)-heteroarylmethylene-2-alkylsulfanyl-1*H*-imidazol-5-ones (GP11)

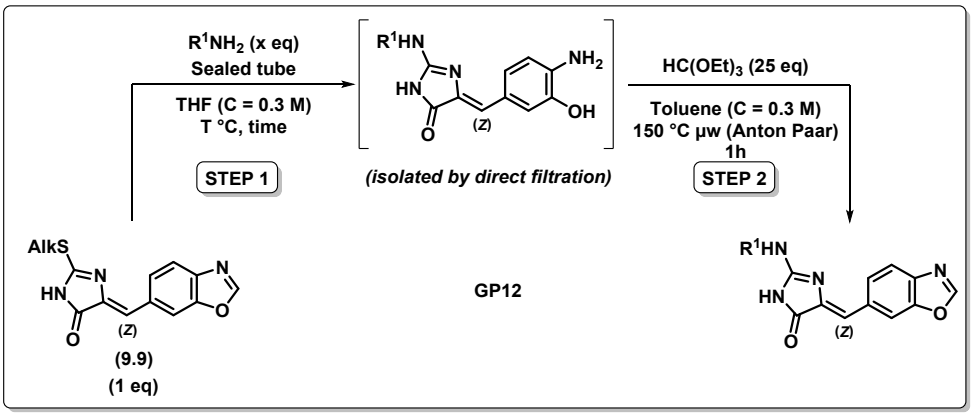


GP11-A: A stirred solution of the appropriate amine (x eq), (4*Z*)-4-heteroaryl-2-alkylsulfanyl-1*H*-imidazol-5-one[(a)] (1 eq) in the appropriate solvent (C = 0.3 M) was heated in a sealed tube (heating block or μw) or sealable round flask. Upon completion (followed by consumption of the isothiourea on TLC), the mixture was brought back to room temperature.

- **GP11-A : direct precipitation of the desired product** : The reaction medium was stirred 1h at 0 °C. The precipitated solid was filtered off on a fritted-glass funnel. High purity may be achieved after filtration by washing, reprecipitation, trituration, or recrystallization.
- **GP11-B : the product failed to precipitate** : the reaction mixture was concentrated *in vacuo*, adsorbed on silica, and purified by FC. High purity may be achieved after filtration by reprecipitation, trituration, or recrystallization.
- **GP11-C : the product failed to precipitate** : the reaction mixture was concentrated *in vacuo*. The resulting crude was triturated in EtOH (at r.t. or reflux), filtered off on a fritted-glass funnel.

- (a) May require activation with AcOH depending on the amine (see details below).

General protocol 12 – Addition of amines on (*Z*)-5-(benzo[*d*]oxazol-6-ylmethylene)-2-(ethylthio)-3,5-dihydro-4*H*-imidazol-4-one (GP12)



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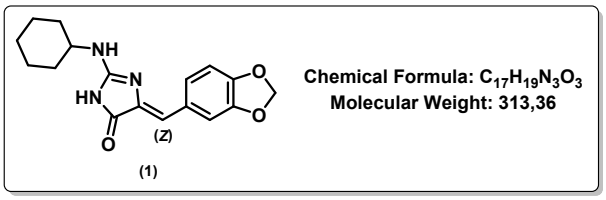
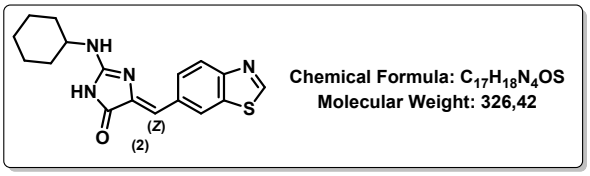
- **GP12 - Step 1**: a stirred solution of the appropriate amine (x eq), (4*Z*)-4-(1,3-benzoxazol-6-ylmethylene)-2-alkylsulfanyl-1*H*-imidazol-5-one (1 eq) in THF (C = 0.3 M) was heated in a sealed tube (heating block). Upon completion (followed by consumption of the isothiourea on TLC), the mixture was brought back to room temperature. The precipitated red/brown solid was isolated by filtration, washed with ice-cold THF or dioxane and dried.
- **GP12 - Step 2**: a stirred solution of the previously isolated solid (1 eq) and $HC(OEt)_3$ (25 eq) in toluene (C = 0.3 M) was heated in a sealed tube in a microwave oven (Anton Paar) at 150 °C for 1h. Upon completion, the mixture was directly adsorbed on silica and purified by FC (see details below). Higher purity may be achieved by reprecipitation, trituration, or recrystallization (see details below).

Synthesis of (*Z*)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (1)



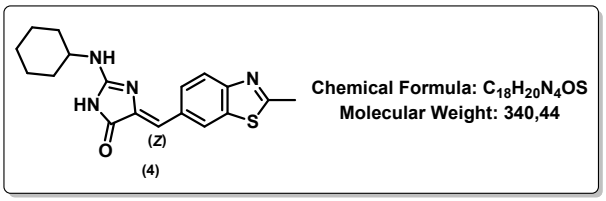
Compound (**1**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.81 mmol scale of (**9.1**), with 5 eq of cyclohexylamine at 115 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Colorless solid. Isolated yield: 56% (315 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ 10.47 (br s, 1H, NH, D_2O exchanged), 7.93 (s, 1H), 7.44 (br s, 1H, NH, D_2O exchanged), 7.33 (d, J = 8.1 Hz, 1H), 6.89 (d, J = 8.1 Hz, 1H), 6.21 (s, 1H), 6.01 (s, 2H), 3.65 (br s, 1H), 1.89 (br s, 2H), 1.71 (br s, 2H), 1.64 – 1.51 (m, 1H), 1.46 – 1.05 (m, 5H). MS (ESI$^+$): $[M+H]^+$ 314.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (2)



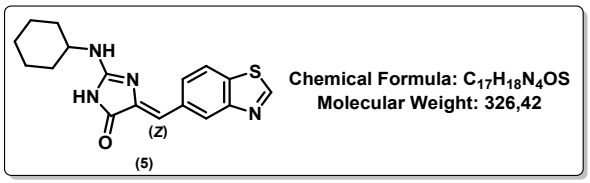
Compound (**2**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 2.73 mmol scale of (**9.4**), with 4 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Pale yellow solid. Isolated yield: 34% (303 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.62 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.90 – 8.65 (m, 1H), 8.37 – 8.13 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.49 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 3.97 – 3.46 (m, 1H), 2.07 – 1.80 (m, 2H), 1.80 – 1.65 (m, 2H), 1.65 – 1.53 (m, 1H), 1.49 – 1.05 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 327.2. HPLC: >98%

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((2-methylbenzo[*d*]thiazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (4)



Compound (**4**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 593 µmol scale of (**9.5**), with 4 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 69% (140 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.14 (br s, 1H, NH, D_2O exchanged), 8.78 – 8.51 (m, 1H), 8.20 – 7.95 (m, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.33 (br s, 1H, NH, D_2O exchanged), 6.37 (s, 1H), 3.79 – 3.66 (m, 1H), 2.79 (s, 3H), 2.01 – 1.87 (m, 2H), 1.80 – 1.69 (m, 2H), 1.65 – 1.56 (m, 1H), 1.43 – 1.15 (m, 5H). MS (ESI$^+$): $[M+H]^+$ 341.2. HPLC: >98%.

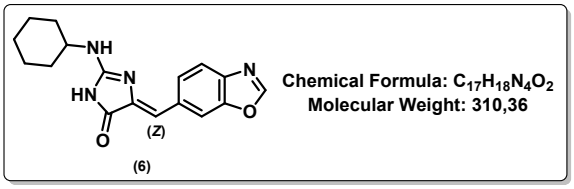
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-5-ylmethylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (5)



Compound (**5**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 518 µmol scale of (**9.7**) with 4 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from

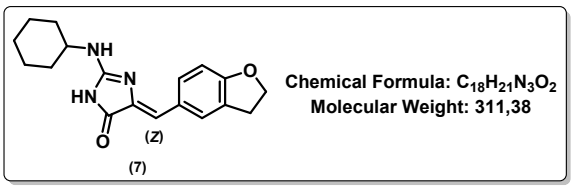
DCM/pentane at 0 °C. Isolated yield: 49% (83 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.36 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.85 (s, 1H), 8.08 (s, 2H), 7.30 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.74 (br s, 1H), 1.95 (br s, 2H), 1.75 (br s, 2H), 1.65 – 1.54 (m, 1H), 1.47 – 1.15 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 327.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]oxazol-6-ylmethylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (6)



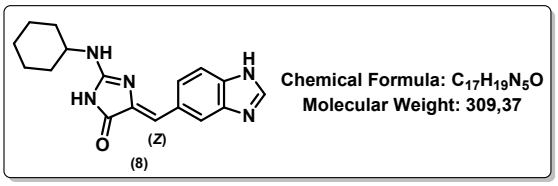
Compound (**6**) was synthesized according to **GP12 – step 1**, in THF (0.3M/isothiourea), on a 915 µmol scale of intermediate (**9.9**), with 12 eq of cyclohexylamine, at 110 °C (sealed tube, heating block), for 12h. The isolated aminophenol intermediate was cyclized according to **GP12 – step 2**. Purification by FC (elution: DCM/MeOH: 99/1 to 9/1). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 34% (96 mg, 2 steps). Beige solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.39 (br s, 1H, NH, D_2O exchanged), 8.79 – 8.45 (m, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.34 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 3.73 (s, 1H), 1.94 (s, 2H), 1.83 – 1.66 (m, 2H), 1.68 – 1.55 (m, 1H), 1.48 – 1.28 (m, 4H), 1.28 – 1.11 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 311.2. HPLC: 97%.

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (7)



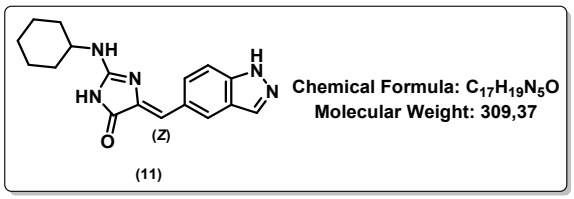
Compound (**7**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 365 µmol scale of (**9.10**), with 5 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Pale yellow solid. Isolated yield: 50% (56 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.10 (br s, 1H, NH, D_2O exchanged), 8.00 (s, 1H), 7.75 (d, J = 8.3 Hz, 1H), 6.98 (br s, 1H, NH, D_2O exchanged), 6.73 (d, J = 8.4 Hz, 1H), 6.25 (s, 1H), 4.55 (t, J = 8.5 Hz, 2H), 3.66 (br s, 1H), 3.18 (t, J = 8.6 Hz, 2H), 1.92 (br s, 2H), 1.73 (br s, 2H), 1.66 – 1.53 (m, 1H), 1.43 – 1.13 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 312.2. HPLC: >98%

Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (8)



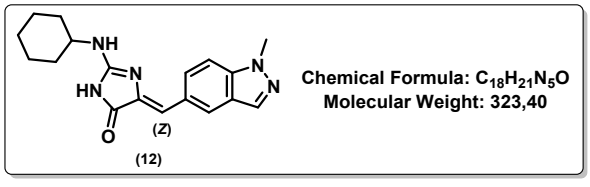
Compound (**8**) was synthesized according to **GP11-B**, in a THF/dioxane mixture (1/1, 0.3M/isothiourea), on a 387 µmol scale of (**9.12**), with 3 eq of cyclohexylamine and 15 eq of AcOH at 130 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 88/12). The final product required a trituration in EtOH at 0 °C. Isolated yield: 24% (29 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 12.28 (br s, 1H, NH, D_2O exchanged), 10.21 (br s, 1H, NH, D_2O exchanged), 8.32 (br s, 1H), 8.16 (s, 1H), 7.77 (br s, 1H), 7.54 (d, J = 8.3 Hz, 1H), 7.08 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 3.73 (br s, 1H), 2.09 – 1.83 (m, 2H), 1.80 – 1.49 (m, 3H), 1.47 – 1.12 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 310.2. HPLC: >98%.

Synthesis of (*Z*)-5-((1*H*-indazol-5-yl)methylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (11)



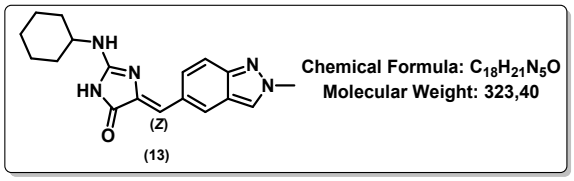
Compound (**11**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 734 µmol scale of (**9.14**), with 6 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Pale yellow solid. Isolated yield: 54% (123 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 13.08 (br s, 1H, NH, D_2O exchanged), 10.51 (br s, 1H, NH, D_2O exchanged), 8.41 (br s, 1H), 8.13 (br s, 1H), 8.06 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.31 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 3.81 – 3.54 (m, 1H), 2.00 – 1.83 (m, 2H), 1.80 – 1.66 (m, 2H), 1.66 – 1.53 (m, 1H), 1.47 – 1.06 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 310.2. HPLC: >98%

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (12)



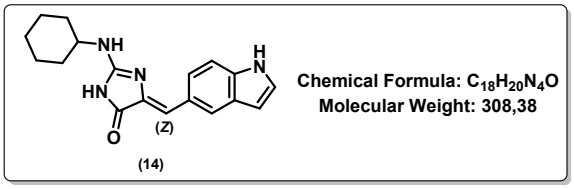
Compound (**12**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 698 µmol scale of (**9.15**), with 5 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 39% (88 mg). Colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.19 (br s, 1H, NH, D_2O exchanged), 8.37 (br s, 1H), 8.18 (br s, 1H), 8.01 (s, 1H), 7.58 (d, J = 8.7 Hz, 1H), 7.13 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.04 (s, 3H), 3.72 (br s, 1H), 2.03 – 1.85 (m, 2H), 1.82 – 1.68 (m, 2H), 1.66 – 1.56 (m, 1H), 1.48 – 1.29 (m, 4H), 1.29 – 1.15 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 324.3. HPLC: >98%

Synthesis of (*Z*)-2-(cyclohexylamino)-5-((2-methyl-2*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (13)



Compound (**13**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 873 µmol scale of (**9.17**), with 4 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 50% (142 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.24 (br s, 1H, NH, D_2O exchanged), 8.43 – 8.19 (m, 2H), 8.04 (d, J = 9.1 Hz, 1H), 7.51 (d, J = 9.0 Hz, 1H), 7.10 (br s, 1H, NH, D_2O exchanged), 6.37 (s, 1H), 4.15 (s, 3H), 3.71 (br s, 1H), 1.94 (br s, 2H), 1.84 – 1.68 (m, 2H), 1.66 – 1.52 (m, 1H), 1.47 – 1.13 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 324.3. HPLC: >98%.

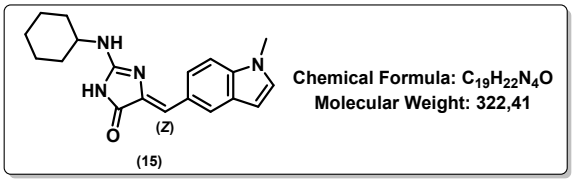
Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (14)



Compound (**14**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.11 mmol scale of (**9.18**), with 5 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 58% (200 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.92 (br s, 1H, NH, D_2O exchanged), 10.12 (br s, 1H, NH, D_2O exchanged), 8.25 (s, 1H), 7.86 (d, J = 8.5 Hz, 1H), 7.46 – 7.23 (m, 2H), 6.90 (br s, 1H, NH, D_2O exchanged), 6.54 – 6.34 (m,

2H), 3.71 (br s, 1H), 1.95 (br s, 2H), 1.74 (br s, 2H), 1.65 – 1.54 (m, 1H), 1.45 – 1.17 (m, 5H). MS (ESI^+) : $[M+H]^+$ 309.3. HPLC: >98%.

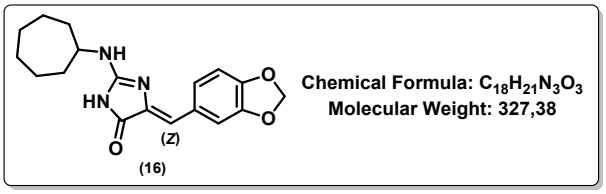
Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-(cyclohexylamino)-3,5-dihydro-4*H*-imidazol-4-one (15)



(15)

Compound (**15**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.05 mmol scale of (**9.19**), with 4 eq of cyclohexylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 46% (156 mg). ^1H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.01 (br s, 1H, NH, D_2O exchanged), 8.24 (br s, 1H), 7.94 (br s, 1H), 7.53 – 7.16 (m, 2H), 6.94 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 2H), 3.79 (s, 3H), 3.72 (br s, 1H), 1.95 (br s, 2H), 1.74 (br s, 2H), 1.66 – 1.55 (m, 1H), 1.47 – 1.14 (m, 5H). MS (ESI^+) : $[M+H]^+$ 323.2. HPLC: >98%.

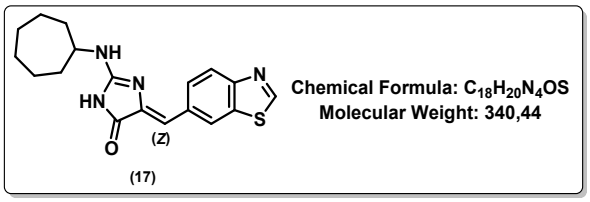
Synthesis of (*Z*)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (16)



(16)

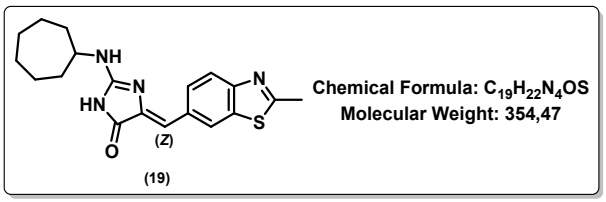
Compound (**16**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.085 mmol scale of (**9.1**), with 6 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 30% (108 mg). Colorless solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.99 (br s, 1H), 7.91 (br s, 1H), 7.30 (br s, 1H), 7.06 (br s, 1H), 6.88 (d, J = 8.1 Hz, 1H), 6.23 (s, 1H), 6.01 (s, 2H), 3.91 (br s, 1H), 2.03 – 1.87 (m, 2H), 1.76 – 1.32 (m, 10H). MS (ESI^+) : $[M+H]^+$ 328.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (17)



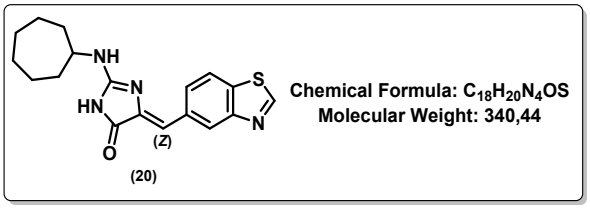
Compound (**17**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 12.20 mmol mmol scale of (**9.4**), with 4 eq of cycloheptylamine at 110 °C (sealed round flask, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 72% (2.988 g). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.40 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 9.05 – 8.69 (m, 1H), 8.42 – 8.13 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.54 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 3.98 (s, 1H), 1.93 (s, 2H), 1.78 – 1.35 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 341.2. HPLC: >98%

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((2-methylbenzo[*d*]thiazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (19)



Compound (**19**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 369 µmol scale of (**9.6**), with 4 eq of cycloheptylamine at 115 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 50% (66 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.29 (br s, 1H, NH, D_2O exchanged), 8.93 – 8.59 (m, 1H), 8.26 – 7.98 (m, 1H), 7.84 (d, J = 8.4 Hz, 1H), 7.31 (br s, 1H, NH, D_2O exchanged), 6.38 (s, 1H), 4.03 – 3.83 (m, 1H), 2.79 (s, 3H), 2.06 – 1.88 (m, 2H), 1.81 – 1.40 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 355.2. HPLC: >98%.

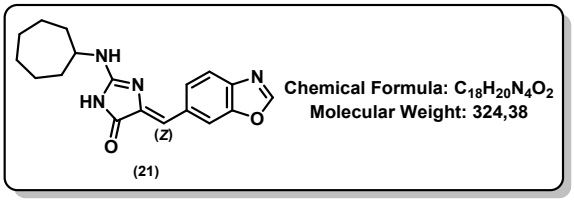
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-5-ylmethylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (20)



Compound (**20**) was synthesized according to GP11-A, in THF (0.3M/isothiourea), on a 518 µmol scale of (9.7), with 4 eq of cycloheptylamine at 115 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold

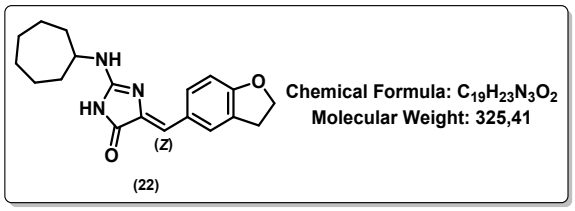
THF, then pentane. Isolated yield: 32% (56 mg). Colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.25 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.85 (br s, 1H), 8.08 (s, 2H), 7.31 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.96 (br s, 1H), 2.05 – 1.89 (m, 2H), 1.78 – 1.37 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 341.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]oxazol-6-ylmethylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (21)



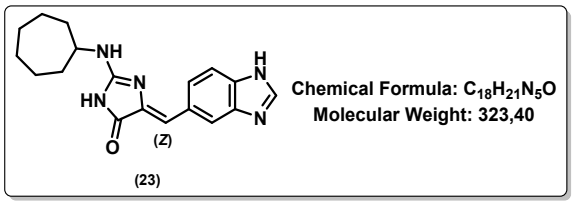
Compound (**21**) was synthesized according to **GP12 – step 1**, in THF (0.3M/isothiourea), on a 695 µmol scale of intermediate (**9.9**), with 6 eq of cycloheptylamine, at 110 °C (sealed tube, heating block), for 12h. The isolated aminophenol intermediate was cyclized according to **GP12 – step 2**. Purification by FC (elution: DCM/MeOH: 99/1 to 9/1). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 38% (72 mg, 2 steps). Beige solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H ^{1}H NMR 10.29 (br s, 1H, NH, D_2O exchanged), 8.63 (s, 2H), 7.92 (d, J = 8.3 Hz, 1H), 7.71 (d, J = 8.3 Hz, 1H), 7.33 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 3.96 (s, 1H), 2.09 – 1.86 (m, 2H), 1.85 – 1.35 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 325.2. HPLC: 95%.

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (22)



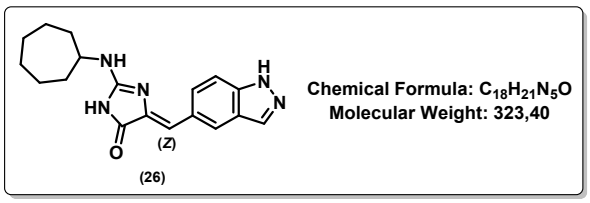
Compound (**22**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 288 µmol scale of (**9.11**), with 3 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 62% (58 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 8.05 (s, 1H), 7.86 – 7.62 (m, 1H), 7.16 (br s, 1H, NH, D_2O exchanged), 6.74 (d, J = 8.4 Hz, 1H), 6.24 (s, 1H), 4.55 (t, J = 8.6 Hz, 2H), 3.87 (br s, 1H), 3.21 – 3.10 (m, 2H), 2.00 – 1.86 (m, 2H), 1.75 – 1.36 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 326.3. HPLC: >98%

Synthesis of (*Z*)-5-((1*H*-benzo[*d*]imidazol-5-yl)methylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (23)



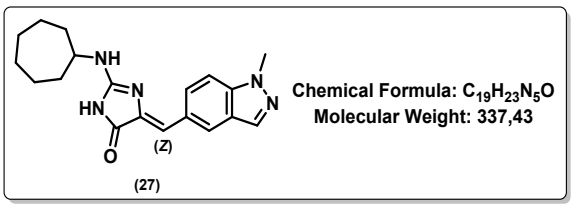
Compound (**23**) was synthesized according to **GP11-B**, in THF/dioxane mixture (1/1, 0.3M/isothiourea), on a 387 µmol scale of (**9.12**), with 3 eq of cycloheptylamine and 15 eq of AcOH at 130 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH(7N NH_3): 99/1 to 88/12). The final product required a trituration in EtOH at 0 °C. Isolated yield: 34% (43 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 12.28 (br s, 1H, NH, D_2O exchanged), 10.13 (br s, 1H, NH, D_2O exchanged), 8.35 (br s, 1H), 8.16 (s, 1H), 7.81 (br s, 1H), 7.54 (d, J = 8.2 Hz, 1H), 7.07 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 3.96 (br s, 1H), 2.15 – 1.81 (m, 2H), 1.77 – 1.33 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 324.3. HPLC: >98%.

Synthesis of (*Z*)-5-((1*H*-indazol-5-yl)methylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (26)



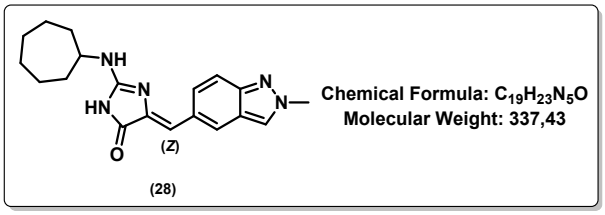
Compound (**26**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 368 µmol scale of (**9.14**), with 4 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 57% (68 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 12.91 (br s, 1H, NH, D_2O exchanged), 10.03 (br s, 1H, NH, D_2O exchanged), 8.42 (br s, 1H), 8.13 (br s, 1H), 8.03 (s, 1H), 7.49 (d, J = 8.6 Hz, 1H), 7.11 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.03 – 3.84 (m, 1H), 2.12 – 1.91 (m, 2H), 1.82 – 1.34 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 324.4. HPLC: >98%.

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (27)



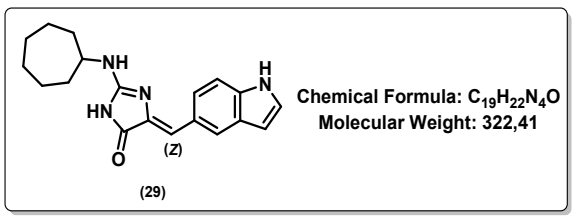
Compound (**27**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 288 µmol scale of (**9.16**), with 3 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 46% (43 mg). Colorless solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.30 (br s, 1H, NH, D_2O exchanged), 8.40 (br s, 1H), 8.23 (d, J = 8.9 Hz, 1H), 8.01 (br s, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.26 (br s, 1H, NH, D_2O exchanged), 6.42 (br s, 1H), 4.04 (s, 3H), 3.93 (br s, 1H), 2.05 – 1.95 (m, 2H), 1.75 – 1.40 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 338.3. HPLC: >98%.

Synthesis of (*Z*)-2-(cycloheptylamino)-5-((2-methyl-2*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (28)



Compound (**28**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 368 µmol scale of (**9.17**), with 4 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 49% (61 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.15 (br s, 1H, NH, D_2O exchanged), 8.32 (s, 1H), 8.28 (s, 1H), 8.16 – 7.96 (m, 1H), 7.67 – 7.45 (m, 1H), 7.09 (br s, 1H, NH, D_2O exchanged), 6.37 (s, 1H), 4.16 (s, 3H), 3.94 (s, 1H), 1.96 (q, J = 6.9, 5.0 Hz, 2H), 1.82 – 1.39 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 338.4. HPLC: >98%.

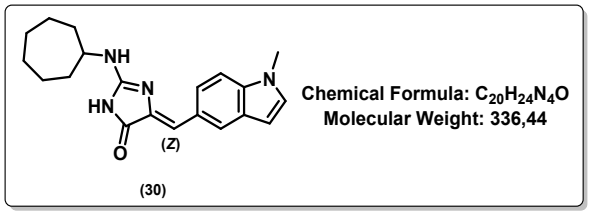
Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (29)



Compound (**29**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 369 µmol scale of (**9.18**), with 4 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 18% (21 mg). Pale yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.94 (br s, 1H, D_2O exchanged), 10.06 (br s, 1H, D_2O exchanged), 8.28

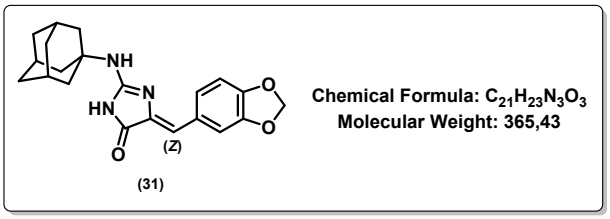
(br s, 1H), 7.99 – 7.80 (m, 1H), 7.44 – 7.23 (m, 2H), 6.92 (br s, 1H, D_2O exchanged), 6.41 (s, 2H), 3.93 (br s, 1H), 1.97 (br s, 2H), 1.85 – 1.36 (m, 10H). MS (ESI^+) : $[M+H]^+$ 323.4. HPLC: >98%.

Synthesis of (*Z*)-5-((1*H*-indol-5-yl)methylene)-2-(cycloheptylamino)-3,5-dihydro-4*H*-imidazol-4-one (30)



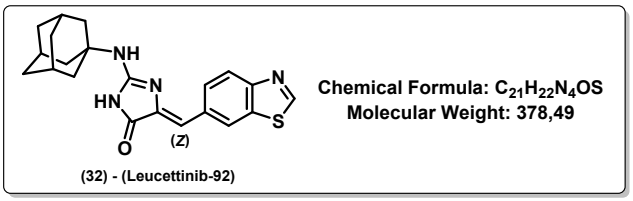
Compound (**30**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 369 µmol scale of (**9.19**), with 4 eq of cycloheptylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 65% (80 mg). Pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) δ_H 10.06 (br s, 1H, D_2O exchanged), 8.26 (s, 1H), 7.95 (d, J = 8.6 Hz, 1H), 7.51 – 7.18 (m, 2H), 6.95 (br s, 1H, D_2O exchanged), 6.56 – 6.29 (m, 2H), 3.94 (s, 1H), 3.79 (s, 3H), 1.97 (s, 2H), 1.77 – 1.42 (m, 10H). MS (ESI^+) : $[M+H]^+$ 337.4. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-(benzo[*d*][1,3]dioxol-5-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (31)



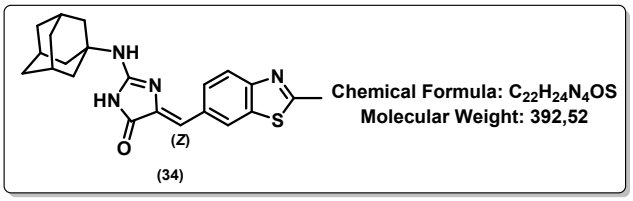
Compound (**31**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 1.53 mmol scale of intermediate (**9.2**), with 3 eq of adamantan-1-amine and 9 eq. of AcOH at 165 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was diluted with EtOH, isolated after filtration, washing with EtOH, then pentane. The final product required two successive triturations in EtOH at 0 °C. Pale yellow solid. Isolated yield: 21% (118 mg). ^1H NMR (400 MHz, DMSO-d_6, 343K) δ 9.65 (br s, 1H, NH, D_2O exchanged), 8.03 (br s, 1H), 7.27 (br s, 1H), 6.88 (d, J = 8.0 Hz, 1H), 6.60 (br s, 1H, NH, D_2O exchanged), 6.24 (s, 1H), 6.01 (s, 2H), 2.28 – 2.00 (m, 9H), 1.79 – 1.64 (m, 6H). MS (ESI^+) : $[M+H]^+$ 366.3. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (32) (Leucettinib-92)



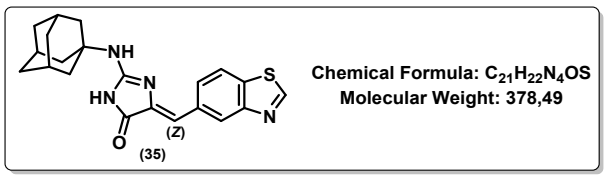
Compound (**32**) was synthesized according to **GP11-A**, in a dioxane/EtOH mixture (9/1, 0.3M/isothiourea), on a 54.48 mmol scale of intermediate (**9.4**), with 3.4 eq of adamantan-1-amine and 9 eq of AcOH at 155 °C (sealed round flask, heating block), for 36h. The product directly precipitated in the reaction medium: it was diluted with EtOH, isolated after filtration, washing with EtOH, then pentane. The final product required two successive triturations in refluxing EtOH. Isolated yield: 41% (8.392 g). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.99 (br s, 1H, D_2O exchanged), 9.35 (s, 1H), 9.02 (s, 1H), 8.17 – 8.13 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.09 (br s, 1H, D_2O exchanged), 6.42 (s, 1H), 2.26 – 2.02 (m, 9H), 1.80 – 1.64 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((2-methylbenzo[*d*]thiazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (34)



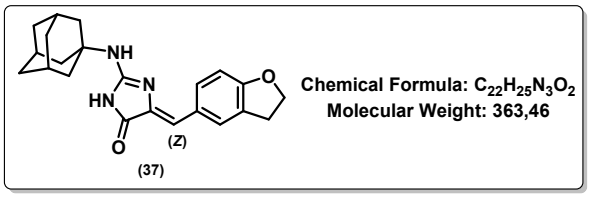
Compound (**34**) was synthesized according to **GP11-A**, in a dioxane/EtOH mixture (9/1, 0.3M/isothiourea), on a 545 µmol scale of intermediate (**9.6**), with 4 eq of adamantan-1-amine and 6 eq of AcOH at 165 °C (sealed tube, heating block), for 30h. The product directly precipitated in the reaction medium: it was diluted with EtOH, isolated after filtration, washing with EtOH, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 59% (127 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.95 (br s, 1H, NH, D_2O exchanged), 8.94 (s, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.84 (d, J = 8.6 Hz, 1H), 7.05 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 2.80 (s, 3H), 2.36 – 1.98 (m, 9H), 1.90 – 1.56 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 393.3. HPLC: 98%

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-(benzo[*d*]thiazol-5-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (35) (iso-Leucettinib-92)



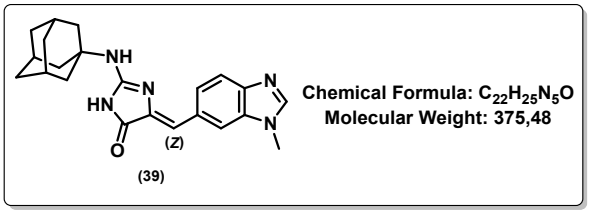
Compound (**35**) was synthesized according to **GP11-A**, in a dioxane/EtOH mixture (1/1, C = 0.2 M/isothiourea), on a 545 µmol scale of intermediate (**9.8**), with 4 eq of adamantan-1-amine and 6 eq of AcOH, at 155 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold EtOH, then pentane. The final product required two successive triturations in refluxing EtOH. Isolated yield: 39% (81 mg). Beige solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.59 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.94 (br s, 1H), 8.08 (s, 2H), 6.75 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 2.31 – 2.01 (m, 9H), 1.86 – 1.60 (m, 6H) MS (ESI$^+$) : $[M+H]^+$ 379.3. HPLC: >98%

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((2,3-dihydrobenzofuran-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (37)



Compound (**37**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 288 µmol scale of (**9.11**), with 3 eq of adamantan-1-amine at 150 °C (sealed tube, heating block), for 40h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 58% (60 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.65 (br s, 1H, NH, D_2O exchanged), 8.18 (s, 1H), 7.68 (d, J = 8.3 Hz, 1H), 6.73 (d, J = 8.3 Hz, 1H), 6.55 (br s, 1H, NH, D_2O exchanged), 6.25 (s, 1H), 4.54 (t, J = 8.7 Hz, 2H), 3.24 – 3.13 (m, 2H), 2.22 – 2.00 (m, 9H), 1.68 (dt, J = 12.6, 3.0 Hz, 6H). MS (ESI$^+$) : $[M+H]^+$ 364.2. HPLC: >98%.

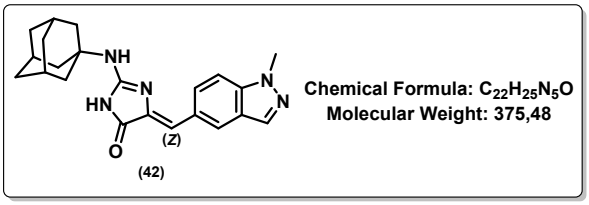
Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((1-methyl-1*H*-benzo[*d*]imidazol-6-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (39)



Compound (**39**) was synthesized according to **GP11-A**, in a THF/dioxane mixture (1/1, 0.3M/isothiourea), on a 551 µmol scale of (**9.20**), with 3 eq of adamantan-1-amine and 10 eq of AcOH, at 160 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it isolated after filtration, washing with cold THF, then pentane. Pale yellow solid. Isolated yield: 33% (69 mg). ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.71 (br s, 1H, NH, D_2O exchanged), 8.57 (s, 1H), 8.15 (s, 1H), 7.67 (d, J = 8.4 Hz, 1H), 7.57 (d, J = 8.4 Hz, 1H), 6.66 (br

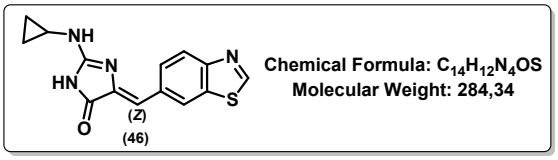
s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 3.82 (s, 3H), 2.29 – 2.02 (m, 9H), 1.81 – 1.61 (m, 6H). MS (ESI^+) : $[M+H]^+$ 376.3. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-1-yl)amino)-5-((1-methyl-1*H*-indazol-5-yl)methylene)-3,5-dihydro-4*H*-imidazol-4-one (42)



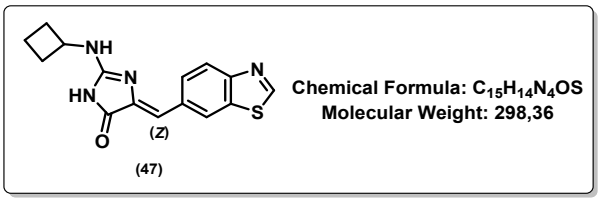
Compound (**42**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 273 µmol scale of (**9.16**), with 3 eq of adamantan-1-amine and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 72h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH. Isolated yield: 52% (53 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.72 (br s, 1H, NH, D_2O exchanged), 8.38 (s, 1H), 8.30 (d, J = 8.8 Hz, 1H), 7.97 (s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 6.65 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.04 (s, 3H), 2.26 – 2.00 (m, 9H), 1.81 – 1.61 (m, 6H). MS (ESI^+) : $[M+H]^+$ 376.3. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cyclopropylamino)-3,5-dihydro-4*H*-imidazol-4-one (46)



Compound (**46**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of cyclopropylamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 71% (151 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.13 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.83 (s, 1H), 8.26 (d, J = 8.6 Hz, 1H), 8.13 (br s, 1H, NH, D_2O exchanged), 8.03 (d, J = 8.6 Hz, 1H), 6.43 (s, 1H), 3.04 – 2.62 (m, 1H), 0.83 – 0.69 (m, 2H), 0.68 – 0.54 (m, 2H). MS (ESI^+) : $[M+H]^+$ 285.1. HPLC: >98%.

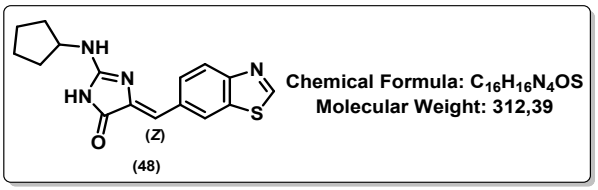
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cyclobutylamino)-3,5-dihydro-4*H*-imidazol-4-one (47)



(47)

Compound (**47)** was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 691 µmol scale of intermediate (**9.3**), with 6 eq of butylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 25% (52 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.72 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.79 (s, 1H), 8.34 – 8.22 (m, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.83 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.74 – 4.02 (m, 1H), 2.38 – 2.20 (m, 2H), 2.17 – 1.97 (m, 2H), 1.69 (s, 2H). MS (ESI$^+$) : $[M+H]^+$ 299.2. HPLC: >98%.

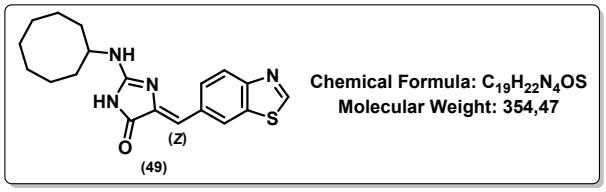
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cyclopentylamino)-3,5-dihydro-4*H*-imidazol-4-one (48)



(48)

Compound (**48**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 864 µmol scale of intermediate (**9.3**), with 6 eq of cyclopentylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 37%. Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.53 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.76 (s, 1H), 8.22 (s, 1H), 8.04 (d, J = 8.0 Hz, 1H), 7.84 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.43 – 4.05 (m, 1H), 2.04 – 1.92 (m, 2H), 1.76 – 1.67 (m, 2H), 1.56 (m, 2H), 1.40 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 313.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(cyclooctylamino)-3,5-dihydro-4*H*-imidazol-4-one (49)

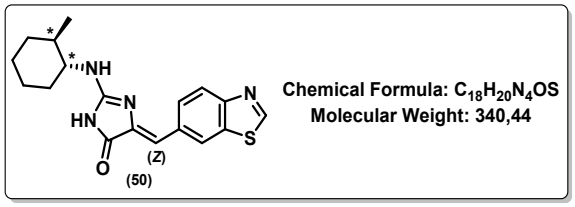


(49)

Compound (**49**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 2.07 mmol scale of intermediate (**9.3**), with 4 eq eq of cyclooctylamine at 110 °C (sealed tube, heating block), for

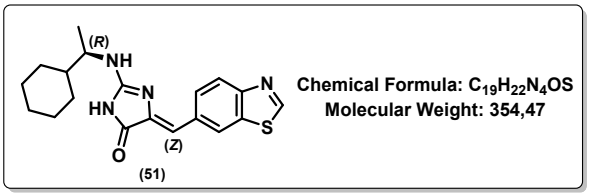
12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 59% (435 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.43 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.98 (m, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.56 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.25 – 3.91 (m, 1H), 1.94 – 1.35 (m, 14H). MS (ESI$^+$) : $[M+H]^+$ 355.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-2-methylcyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (50)



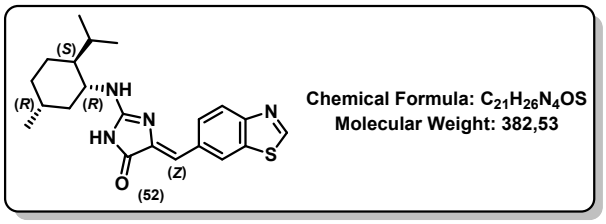
Compound (**50**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of (±)-*trans*-2-methylcyclohexan-1-amine at 130 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 14% (36 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.49 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.92 – 8.69 (m, 1H), 8.27 – 8.15 (m, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.42 (br s, 1H, NH, D_2O exchanged), 6.36 (s, 1H), 3.65 – 3.34 (m, 1H), 3.23 – 2.84 (m, 1H), 2.01 – 1.13 (m, 8H), 0.98 – 0.84 (m, 3H). MS (ESI$^+$) : $[M+H]^+$ 341.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclohexylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (51)



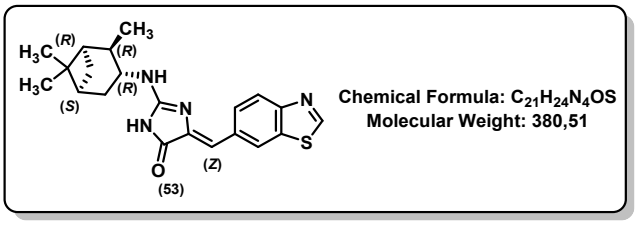
Compound (**51**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of (*R*)-1-cyclohexylethan-1-amine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 35% (93 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.34 (br s, 1H, NH, D_2O exchanged), 9.34 (d, J = 1.4 Hz, 1H), 8.92 – 8.73 (m, 1H), 8.26 – 8.18 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.37 (br s, 1H, NH, D_2O exchanged), 6.37 (s, 1H), 4.12 – 3.39 (m, 1H), 1.72 (d, J = 13.8 Hz, 4H), 1.65 – 1.57 (m, 1H), 1.46 (s, 1H), 1.26 – 0.96 (m, 8H). MS (ESI$^+$) : $[M+H]^+$ 355.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (52)



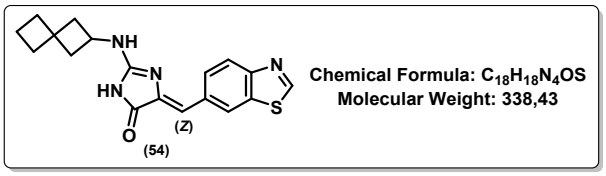
Compound (**52**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of (1*R*,2*S*,5*R*)-2-isopropyl-5-methylcyclohexan-1-amine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 32% (90 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.52 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.84 (s, 1H), 8.27 – 8.15 (m, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.37 (br s, 1H, NH, D_2O exchanged), 6.36 (s, 1H), 3.97 – 3.66 (m, 1H), 2.11 – 1.20 (m, 7H), 1.19 – 0.58 (m, 11H) MS (ESI$^+$) : $[M+H]^+$ 383.3. HPLC: 91%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*,3*R*,5*S*)-2,6,6-trimethylbicyclo[3.1.1]heptan-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (53)



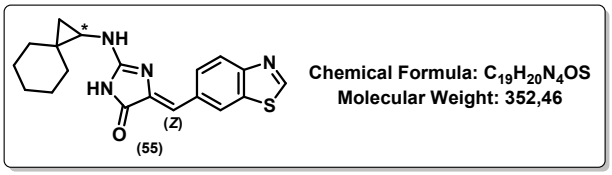
Compound (**53**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of (1*R*,2*R*,3*R*,5*S*)-(−)-isopinocampheylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 60% (169 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.64 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.12 – 8.81 (m, 1H), 8.17 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.5 Hz, 1H), 7.71 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 4.57 – 4.23 (m, 1H), 3.98 – 3.66 (m, 1H), 2.64 – 2.52 (m, 1H), 2.40 – 2.28 (m, 1H), 2.21 – 2.04 (m, 1H), 2.04 – 1.87 (m, 1H), 1.87 – 1.61 (m, 2H), 1.38 – 0.89 (m, 9H). MS (ESI$^+$) : $[M+H]^+$ 381.2. HPLC: 95%.

Synthesis of (Z)-5-(benzo[d]thiazol-6-ylmethylene)-2-(spiro[3.3]heptan-2-ylamino)-3,5-dihydro-4H-imidazol-4-one (54)



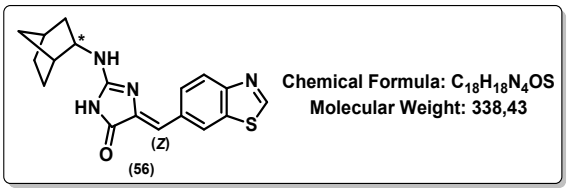
Compound (**54**) was synthesized according to **GP11-B,** in THF (0.3M/isothiourea), on a 847 µmol scale of (**9.3**), with 2 eq of spiro[3.3]heptan-2-amine hydrochloride and 2 eq of TEA at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 61% (175 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.71 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.80 (s, 1H), 8.32 – 8.17 (m, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.75 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 4.61 – 3.67 (m, 2H), 2.45 – 2.32 (m, 2H), 2.16 – 1.99 (m, 3H), 1.99 – 1.88 (m, 2H), 1.87 – 1.74 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 339.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(spiro[2.5]octan-1-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (55)



Compound (**55**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 773 µmol scale of intermediate (**9.3**), with 2 eq of spiro[2.5]octan-1-amine hydrochloride and 2 eq of TEA at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 61% (167 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.68 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 9.14 – 8.80 (m, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.72 – 2.58 (m, 1H), 1.92 – 1.20 (m, 10H), 0.71 (dd, J = 7.9, 5.1 Hz, 1H), 0.55 (t, J = 4.7 Hz, 1H). MS (ESI$^+$) : $[M+H]^+$ 353.2. HPLC: >98%.

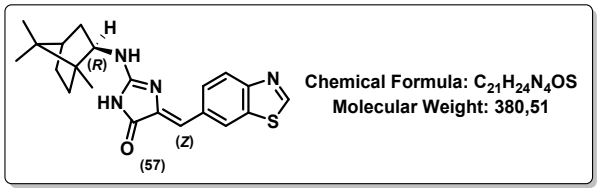
Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((-bicyclo[2.2.1]heptan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (56)



Compound (**56**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of (±)-2-aminonorbornane hydrochloride and 3 eq of TEA at 130°C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7).

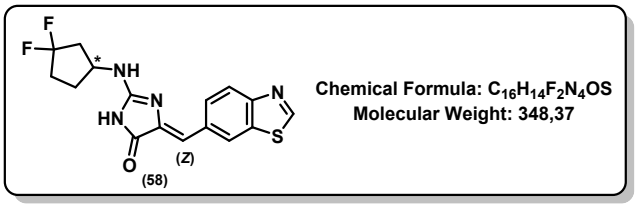
The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 67% (170 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.30 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.97 – 8.71 (m, 1H), 8.40 – 8.20 (m, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.65 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.30 – 3.71 (m, 1H), 2.47 – 2.34 (m, 1H), 2.27 – 2.12 (m, 1H), 2.08 – 1.86 (m, 1H), 1.74 – 1.25 (m, 6H), 1.18 – 1.02 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 339.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((2*R*)-1,7,7-trimethylbicyclo[2.2.1]heptan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (57)



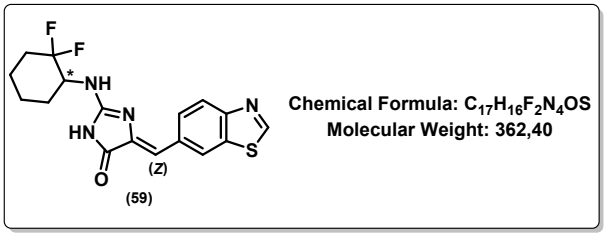
Compound (**57**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 2 eq of (+)-bornanamine at 135 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 34% (97 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.19 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.92 (s, 1H), 8.19 (dd, J = 8.7, 1.6 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.58 (br s, 1H, NH, D_2O exchanged), 6.38 (s, 1H), 4.50 – 3.70 (m, 1H), 2.39 – 2.17 (m, 1H), 1.67 (s, 3H), 1.42 – 1.20 (m, 2H), 1.14 – 0.61 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 381.2. HPLC: 96%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,3-difluorocyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (58)



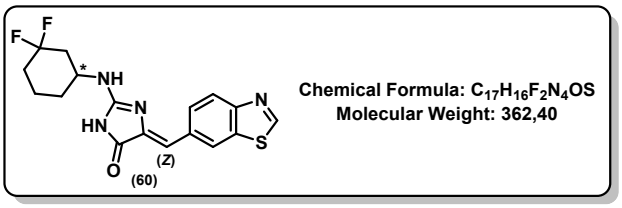
Compound (**58**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3,3-difluorocyclopentan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 4h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 93% (88 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.69 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.91 – 8.66 (m, 1H), 8.35 – 8.11 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.81 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.54 – 4.31 (m, 1H), 2.70 – 2.53 (m, 1H), 2.38 – 2.03 (m, 4H), 1.97 – 1.83 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 349.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2,2-difluorocyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (59)



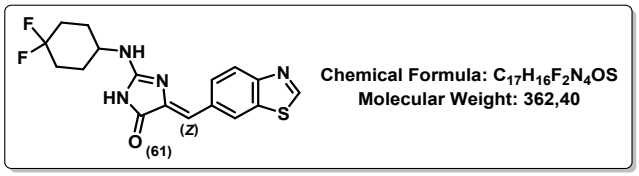
Compound (**59**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2,2-difluorocyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 4h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 43% (42 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.93 – 8.67 (m, 1H), 8.43 – 8.14 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.80 (br s, 1H, NH, D_2O exchanged), 6.48 (s, 1H), 4.43 – 4.12 (m, 1H), 2.21 – 2.08 (m, 1H), 2.05 – 1.38 (m, 7H). MS (ESI$^+$) : $[M+H]^+$ 363.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,3-difluorocyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (60)



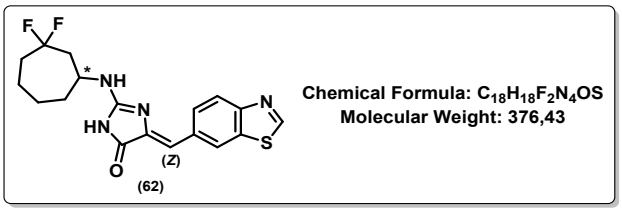
Compound (**60**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3,3-difluorocyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 4h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 76% (75 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.76 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.98 – 8.75 (m, 1H), 8.37 – 8.12 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.70 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 4.21 – 3.82 (m, 1H), 2.48 – 2.28 (m, 1H), 2.09 – 1.68 (m, 5H), 1.61 – 1.36 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 363.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4,4-difluorocyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (61)



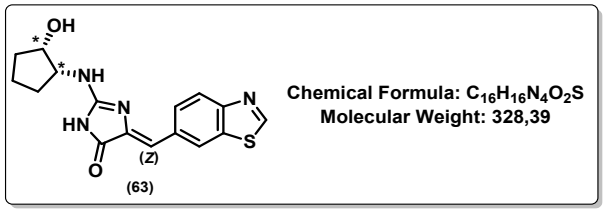
Compound (**61**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of 4,4-difluorocyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 54h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 41% (40 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.67 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.97 – 8.65 (m, 1H), 8.42 – 8.16 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.02 – 3.80 (m, 1H), 2.19 – 1.85 (m, 6H), 1.82 – 1.63 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 363.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,3-difluorocycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (62)



Compound (**62**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3,3-difluorocycloheptan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 8h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 64% (65 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.52 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 9.11 – 8.85 (m, 1H), 8.30 – 8.09 (m, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.54 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.19 – 3.99 (m, 1H), 2.70 – 2.52 (m, 1H), 2.45 – 2.26 (m, 1H), 2.25 – 1.96 (m, 3H), 1.85 – 1.50 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 377.2. HPLC: >98%.

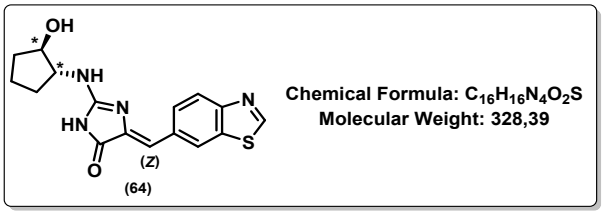
Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-hydroxycyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (63)



Compound (**63**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-2-aminocyclopentan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1

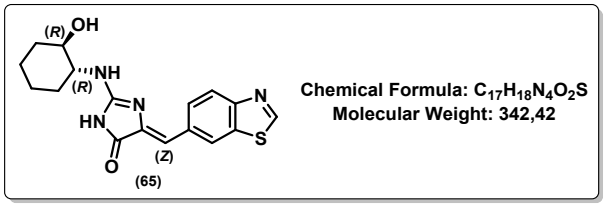
to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 52% (47 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.13 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.87 – 8.67 (m, 1H), 8.41 – 8.13 (m, 1H), 8.09 – 7.94 (m, 1H), 6.73 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.73 (br s, 1H, OH, D_2O exchanged), 4.22 – 3.96 (m, 2H), 2.11 – 1.51 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 329.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-2-hydroxycyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (64)



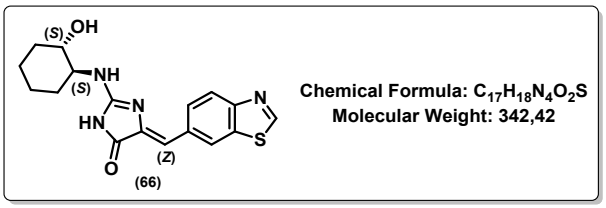
Compound (**64**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-2-aminocyclopentan-1-ol at 120 °C (sealed tube, heating block), for 3h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 30% (27 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.53 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.93 – 8.63 (m, 1H), 8.35 – 8.12 (m, 1H), 8.03 (d, J = 8.3 Hz, 1H), 7.61 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.94 (br s, 1H, OH, D_2O exchanged), 4.10 – 3.75 (m, 2H), 2.18 – 2.03 (m, 1H), 1.98 – 1.82 (m, 1H), 1.79 – 1.42 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 329.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (65)



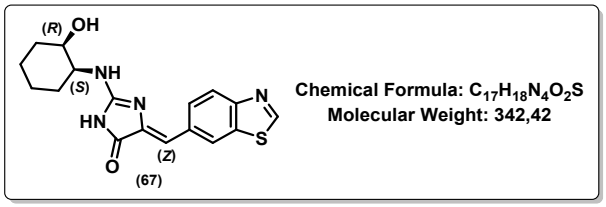
Compound (**65**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of (1*R*,2*R*)-2-aminocyclohexan-1-ol at 100 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 11% (23 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.45 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.83 (s, 1H), 8.31 – 8.09 (m, 1H), 8.09 – 7.96 (m, 1H), 7.35 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 4.64 (br s, 1H, OH, D_2O exchanged), 3.59 – 3.31 (m, 2H), 2.13 – 1.84 (m, 2H), 1.78 – 1.58 (m, 2H), 1.48 – 1.11 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*S*,2*S*)-2-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (66)



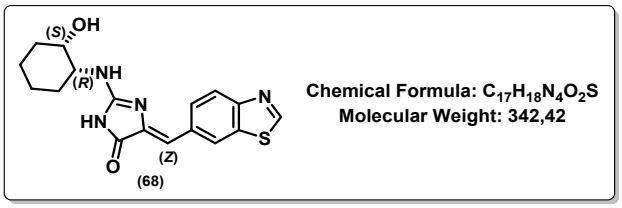
Compound (**66**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (1*S*,2*S*)-2-aminocyclohexan-1-ol at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 94/6). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 20% (51 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.45 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.83 (s, 1H), 8.31 – 8.09 (m, 1H), 8.09 – 7.96 (m, 1H), 7.35 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 4.64 (br s, 1H, OH, D_2O exchanged), 3.59 – 3.31 (m, 2H), 2.13 – 1.84 (m, 2H), 1.78 – 1.58 (m, 2H), 1.48 – 1.11 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*S*,2*R*)-2-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (67)



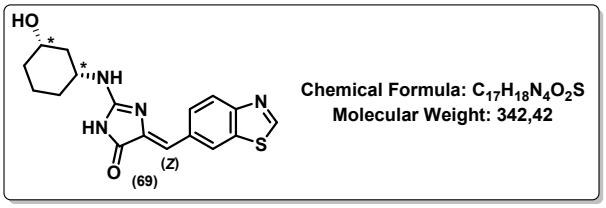
Compound (**67**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of (**9.4**), with 3 eq of (1*R*,2*S*)-2-aminocyclohexan-1-ol hydrochloride and 4 eq of DIPEA at 140 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 22% (56 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.18 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.80 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 6.86 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.77 – 4.63 (m, 1H, OH, D_2O exchanged), 4.02 – 3.74 (m, 2H), 1.88 – 1.47 (m, 6H), 1.46 – 1.25 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*S*)-2-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (68)



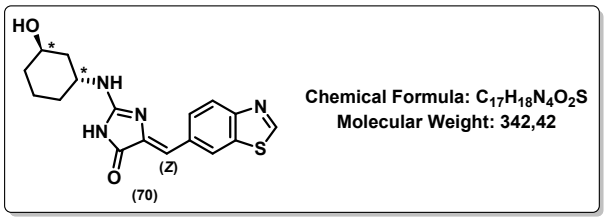
Compound (**68**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of (**9.4**), with 3 eq of (1*S*,2*R*)-2-aminocyclohexan-1-ol hydrochloride and 4 eq of DIPEA at 140 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 9/1). The final product required a trituration in EtOH at 0 °C. Isolated yield: 27% (70 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.18 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.80 (s, 1H), 8.22 (d, J = 8.3 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 6.86 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.77 – 4.63 (m, 1H, OH, D_2O exchanged), 4.02 – 3.74 (m, 2H), 1.88 – 1.47 (m, 6H), 1.46 – 1.25 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-3-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (69)



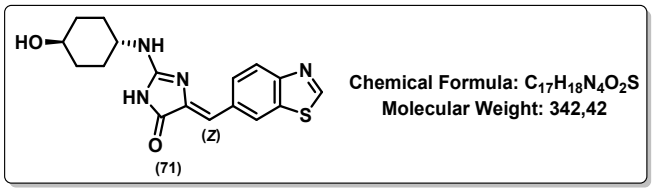
Compound (**69**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-3-aminocyclohexan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 64% (60 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.24 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.91 – 8.53 (m, 1H), 8.31 – 8.05 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.24 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.39 (br s, 1H, OH, D_2O exchanged), 3.88 – 3.75 (m, 1H), 3.66 – 3.53 (m, 1H), 2.21 – 2.05 (m, 1H), 1.94 – 1.69 (m, 3H), 1.41 – 1.14 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-3-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (70)



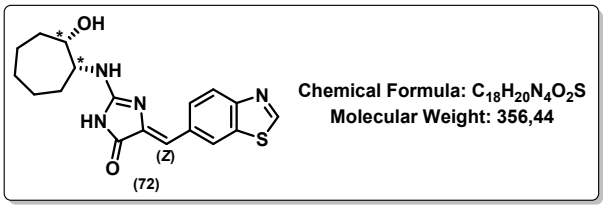
Compound (**70**) was synthesized according to **GP11-B**, in THF/EtOH mixture (1/1, 0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-3-aminocyclohexan-1-ol and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 74% (69 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.34 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.97 – 8.55 (m, 1H), 8.37 – 8.09 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.40 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.53 – 4.32 (br s, 1H, OH, D_2O exchanged), 4.24 – 4.02 (m, 1H), 4.01 – 3.91 (m, 1H), 1.90 – 1.60 (m, 4H), 1.59 – 1.34 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-4-hydroxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (71)



Compound (**71**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of *trans*-4-aminocyclohexan-1-ol at 120 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 63% (161 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.34 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 9.05 – 8.54 (m, 1H), 8.41 – 8.08 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.36 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.36 (d, J = 4.4 Hz, 1H, OH, D_2O exchanged), 3.79 – 3.55 (m, 1H), 3.52 – 3.34 (m, 1H), 2.12 – 1.76 (m, 4H), 1.55 – 1.20 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

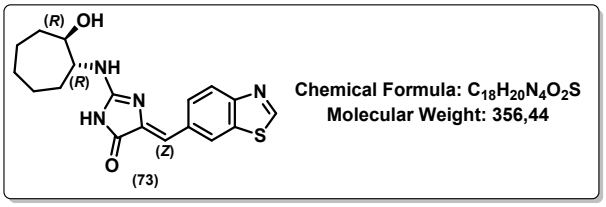
Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (72)



Compound (**72**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-2-aminocycloheptan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 10h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 56% (54 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.15 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.90 (s, 1H), 8.22 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.07 (br s,

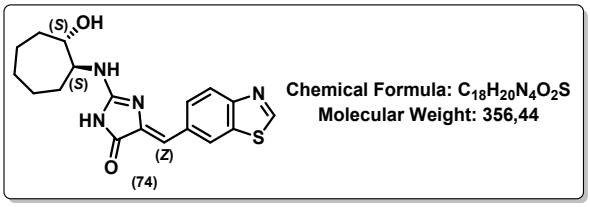
1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.96 (br s, 1H, OH, D_2O exchanged), 4.08 – 3.77 (m, 2H), 1.98 – 1.29 (m, 10H). MS (ESI^+) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (73)



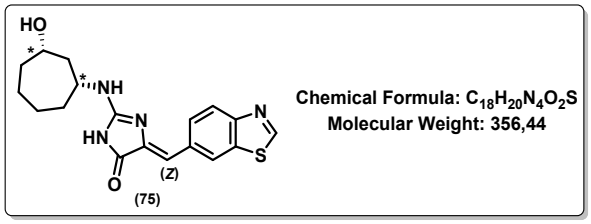
Compound (**73**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of (**9.3**), with 3 eq of (1*R*,2*R*)-2-aminocycloheptan-1-ol at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 49% (130 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 9.08 – 8.72 (m, 1H), 8.39 – 8.09 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.45 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.76 (br s, 1H, OH, D_2O exchanged), 3.89 – 3.53 (m, 2H), 2.03 – 1.37 (m, 10H). MS (ESI^+) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*S*,2*S*)-2-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (74)



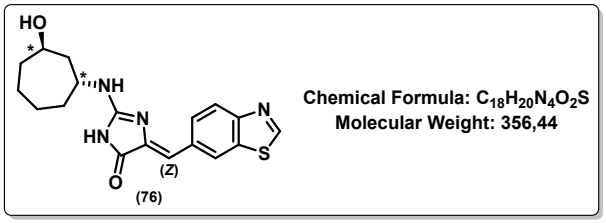
Compound (**74**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of (**9.4**), with 3 eq of (1*S*,2*S*)-2-aminocycloheptan-1-ol at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 45% (121 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 9.08 – 8.72 (m, 1H), 8.39 – 8.09 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.45 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.76 (br s, 1H, OH, D_2O exchanged), 3.89 – 3.53 (m, 2H), 2.03 – 1.37 (m, 10H). MS (ESI^+) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-3-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (75)



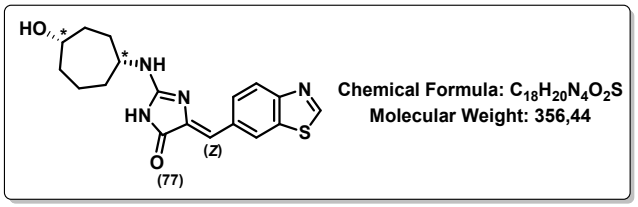
Compound (**75**) was synthesized according to **GP11-B**, in a THF/EtOH mixture (2/1, 0.3M/isothiourea), on a 218 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-3-aminocycloheptan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 46% (36 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.15 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.99 – 8.54 (m, 1H), 8.28 – 8.06 (m, 1H), 8.02 (d, J = 7.8 Hz, 1H), 7.17 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.23 (br s, 1H, OH, D_2O exchanged), 4.05 – 3.91 (m, 1H), 3.90 – 3.77 (m, 1H), 2.21 – 2.05 (m, 1H), 2.05 – 1.39 (m, 9H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-3-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (76)



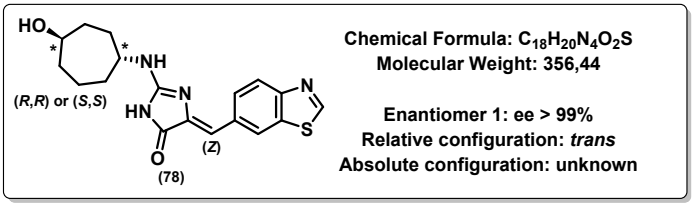
Compound (**76**) was synthesized according to **GP11-B**, in a THF/EtOH mixture (2/1, 0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-3-aminocycloheptan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 31h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 67% (65 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.33 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.99 – 8.65 (m, 1H), 8.34 – 8.07 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.51 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.47 (br s, 1H, OH, D_2O exchanged), 4.19 – 4.01 (m, 1H), 3.96 – 3.83 (m, 1H), 2.08 – 1.89 (m, 3H), 1.86 – 1.30 (m, 7H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-4-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (77)



Compound (**77**) was synthesized according to **GP11-B**, in a THF/EtOH mixture (2/1, 0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-4-aminocycloheptan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 22h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 64% (62 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.37 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.97 – 8.59 (m, 1H), 8.36 – 8.08 (m, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.56 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.46 – 4.23 (m, 1H, OH, D_2O exchanged), 4.09 – 3.83 (m, 1H), 3.83 – 3.69 (m, 1H), 2.01 – 1.53 (m, 8H), 1.53 – 1.39 (m, 1H), 1.38 – 1.21 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (1*S*,4*S*)- or (1*R*,4*R*)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (78) (ENANTIOMER 1*)



Compound (**78**) and (**79**) required the initial synthesis of the racemic compound. Synthesis of racemic compound: reaction was carried out according to **GP11-B**, in a THF/EtOH mixture (2/1, 0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-4-aminocycloheptan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 43% (42 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.36 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.85 (s, 1H), 8.20 (d, *J* = 8.6 Hz, 1H), 8.01 (d, *J* = 8.6 Hz, 1H), 7.35 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.23 (d, *J* = 4.2 Hz, 1H, OH, D_2O exchanged), 4.04 – 3.82 (m, 1H), 3.79 – 3.64 (m, 1H), 2.05 – 1.72 (m, 4H), 1.69 – 1.39 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 357.2. MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Preparative chiral SFC from racemic compound (200 mg): Chiralpak IG (20 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 218 nm, $V_{injection}$: 500 µL (8 mg)/injection; isocratic conditions: 4/6 ($MeOH/CO_2$). Isolated quantity of enantiomer (**78**): 70 mg. ^{1}H NMR of (**78**) was identical to racemate.

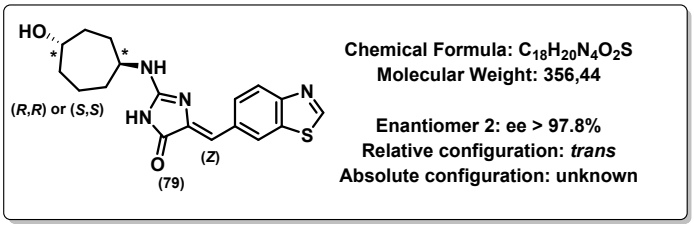
Analytical chiral SFC of racemic mixture: Chiralpak IG (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, $V_{injection}$: 1 µL; isocratic conditions: 1/1 (MeOH/CO_2 (0.2% v/v NH_3)), t_R(**78**): 1.79 min, t_R(**79**): 2.34 min.

Analytical chiral SFC of (78) (conditions as described above): t_R(**78**) after chiral purification: 1.80 min, ee = >99% (first eluting enantiomer).

HPLC: >98%.

*The relative configuration of (**78**) is *trans*, but the absolute configuration of the chiral centers could not be assigned. The absolute stereochemistry of (**78**) is therefore either (1*R*,4*R*) or (1*S*, 4*S*).

Synthesis of (1*S*,4*S*)- or (1*R*,4*R*)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-hydroxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (79) (ENANTIOMER 2*)



Preparative chiral SFC from racemic compound (200 mg): Chiralpak IG (20 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 218 nm, $V_{injection}$: 500 µL (8 mg)/injection; isocratic conditions: 4/6 (MeOH/CO_2). Isolated quantity: 70 mg. ^{1}H NMR of (**79**) was identical to racemate and (**78**).

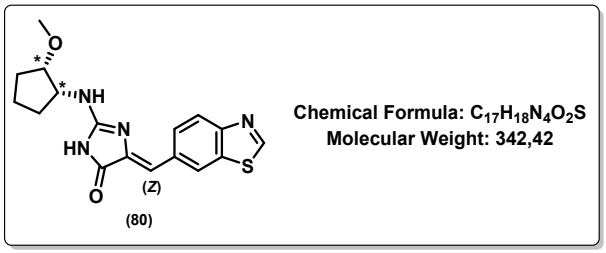
Analytical chiral SFC of racemic mixture: Chiralpak IG (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, inj. vol.: 1 µL; isocratic conditions: 1/1 (MeOH/CO_2 (0.2% v/v NH_3)), t_R(**78**): 1.79 min, t_R(**79**): 2.34 min.

Analytical chiral SFC of (79) (conditions as described above): t_R(**79**) after chiral purification: 2.36 min, ee = >97.8% (second eluting enantiomer).

HPLC: >98%.

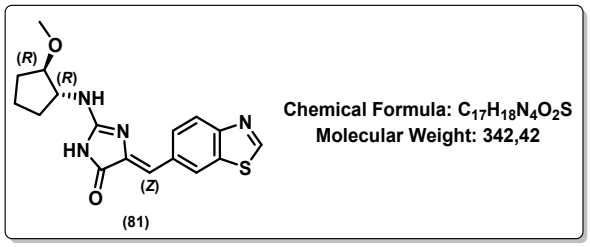
*The relative configuration of (**79**) is *trans*, but the absolute configuration of the chiral centers could not be assigned. The absolute stereochemistry of (**79**) is therefore either (1*S*,4*S*) or (1*R*, 4*R*).

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-methoxycyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (80)



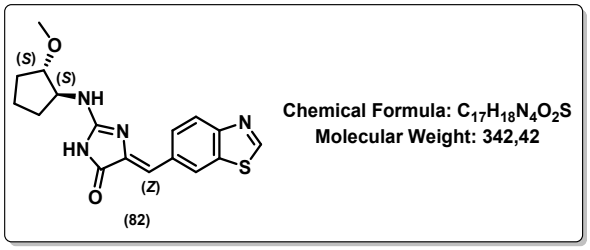
Compound (**80**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate intermediate (**9.4**), with 3 eq of (±)-*cis*-2-methoxycyclopentan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 8h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 84% (80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.18 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.79 (s, 1H), 8.44 – 8.15 (m, 1H), 8.15 – 7.97 (m, 1H), 6.96 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.24 (s, 1H), 3.81 (s, 1H), 3.30 (s, 3H), 2.13 – 1.90 (m, 1H), 1.89 – 1.50 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-methoxycyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (81)



Compound (**81**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*R*,2*R*)-2-methoxycyclopentan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 75% (70 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.12 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.97 – 8.76 (m, 1H), 8.25 – 8.09 (m, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.28 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.21 – 4.12 (m, 1H), 3.86 – 3.79 (m, 1H), 3.38 (s, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.88 (m, 1H), 1.80 – 1.58 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

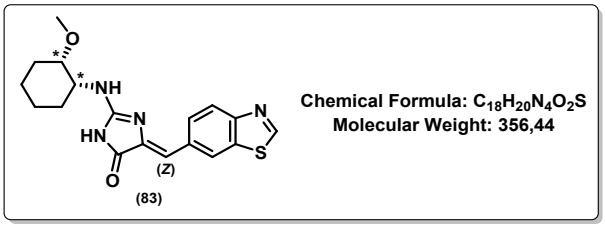
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*S*,2*S*)-2-methoxycyclopentyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (82)



Compound (**82**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*S*,2*S*)-2-methoxycyclopentan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 16h. Purification by FC (elution:

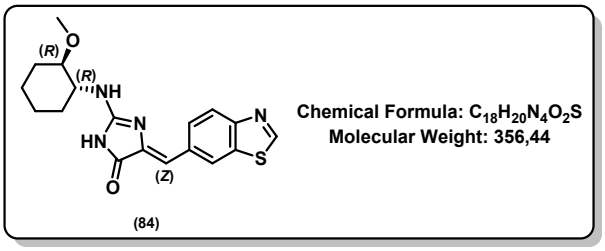
DCM/MeOH: 99/1 to 93/7). Isolated yield: 83% (80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.12 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.97 – 8.76 (m, 1H), 8.25 – 8.09 (m, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.28 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.21 – 4.12 (m, 1H), 3.86 – 3.79 (m, 1H), 3.38 (s, 3H), 2.17 – 2.04 (m, 1H), 2.00 – 1.88 (m, 1H), 1.80 – 1.58 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (83)



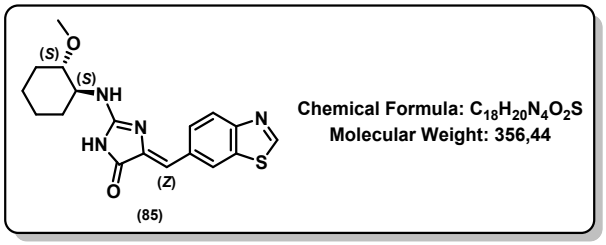
Compound (**83**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-2-methoxycyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 78% (78 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.06 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.81 (s, 1H), 8.23 (d, J = 8.1 Hz, 1H), 8.02 (d, J = 8.9 Hz, 1H), 6.96 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.15 – 3.83 (m, 1H), 3.59 – 3.44 (m, 1H), 3.32 (s, 3H), 2.00 – 1.88 (m, 1H), 1.81 – 1.57 (m, 3H), 1.57 – 1.30 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (84)



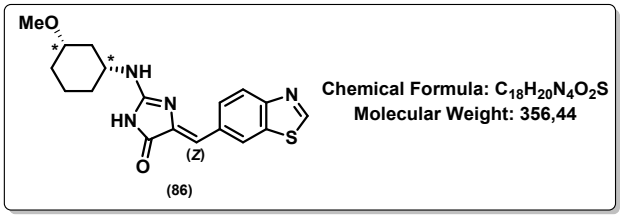
Compound (**84**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*R*,2*R*)-2-methoxycyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 63% (61 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.62 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.84 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.65 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 3.82 – 3.53 (m, 1H), 3.31 (s, 3H), 3.25 – 3.12 (m, 1H), 2.15 – 1.90 (m, 2H), 1.76 – 1.59 (m, 2H), 1.47 – 1.15 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*S*,2*S*)-2-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (85)



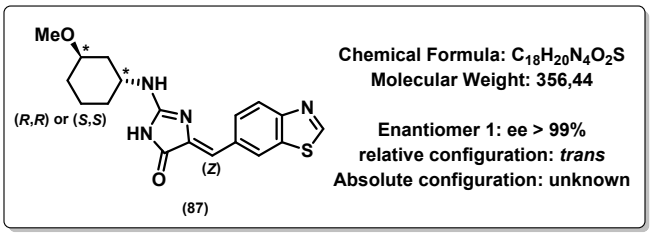
Compound (**85**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*S*,2*S*)-2-methoxycyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 60% (58 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.62 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.84 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.65 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 3.82 – 3.53 (m, 1H), 3.31 (s, 3H), 3.25 – 3.12 (m, 1H), 2.15 – 1.90 (m, 2H), 1.76 – 1.59 (m, 2H), 1.47 – 1.15 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-3-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (86)



Compound (**86**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-3-methoxycyclohexan-1-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 79% (77 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.29 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 9.00 – 8.58 (m, 1H), 8.34 – 8.07 (m, 1H), 8.02 (d, J = 8.2 Hz, 1H), 7.19 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 3.87 – 3.74 (m, 1H), 3.36 – 3.22 (m, 4H), 2.39 – 2.24 (m, 1H), 1.99 – 1.72 (m, 3H), 1.41 – 1.15 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (87) (ENANTIOMER 1*)

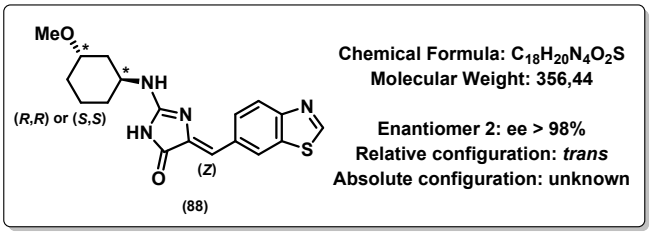


Compound (**87**) and (**88**) required the initial synthesis of the racemic compound. Synthesis of racemic compound: reaction was carried out according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-3-methoxycyclohexan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 22h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 69% (67 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.40 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.99 – 8.76 (m, 1H), 8.31 – 8.11 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.39 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.14 – 3.91 (m, 1H), 3.65 – 3.53 (m, 1H), 3.35 (s, 3H), 2.34 – 2.04 (m, 1H), 1.93 – 1.81 (m, 1H), 1.76 – 1.35 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Preparative chiral SFC from racemic compound (189 mg): Lux A2 (21.2 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 218 nm, $V_{injection}$: 500 µL (10 mg)/injection; isocratic conditions: 25/75 ($MeOH/CO_2$). Isolated quantity of enantiomer (**87**): 75 mg. ^{1}H NMR of (**87**) was identical to racemate.
Analytical chiral SFC of racemic mixture: Lux A2 (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, $V_{injection}$: 1 µL; isocratic conditions: 25/75 ($MeOH/CO_2$ (0.2% v/v NH_3)), t_R(**87**): 5.06 min, t_R(**88**): 6.27 min.
Analytical chiral SFC of (87) (conditions as described above): t_R(**87**) after chiral chiral purification: 5.04 min, ee = >99% (first eluting enantiomer).
HPLC: >98%

*The relative configuration of (**87**) is *trans*, but the absolute configuration of the chiral centers could not be assigned. The absolute stereochemistry of (**79**) is therefore either (1*S*,3*S*) or (1*R*, 3*R*).

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (88) (ENANTIOMER 2*)



Preparative chiral SFC from racemic compound (189 mg): Lux A2 (21.2 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 218 nm, $V_{injection}$: 500 µL (10 mg)/injection; isocratic conditions: 25/75

(MeOH/CO_2). Isolated quantity of enantiomer (**88**): 75 mg. ^{1}H NMR of (**88**) was identical to racemate and (**87**).

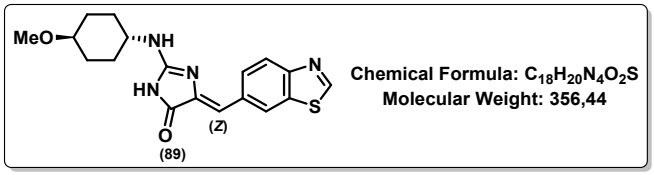
Analytical chiral SFC of racemic mixture: Lux A2 (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, $V_{injection}$: 1 µL; isocratic conditions: 25/75 (MeOH/CO_2 (0.2% v/v NH_3)), t_R(**87**): 5.06 min, t_R(**88**): 6.27 min.

Analytical chiral SFC of (88) (conditions as described above): t_R(**88**) after chiral chiral purification: 6.25 min, ee = >98%. (second eluting enantiomer).

HPLC: >98%

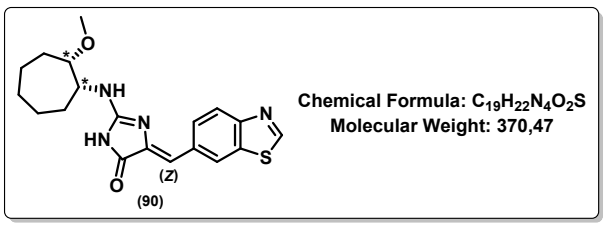
*The relative configuration of (**88**) is *trans*, but the absolute configuration of the chiral centers could not be assigned. The absolute stereochemistry of (**88**) is therefore either (1*R*,3*R*) or (1*S*, 3*S*).

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-4-methoxycyclohexyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (89)



Compound (**89**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3eq of *trans*-4-methoxycyclohexan-1-amine at 130 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 27% (73 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.51 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.83 (s, 1H), 8.20 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.41 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 3.82 – 3.62 (m, 1H), 3.27 (s, 3H), 3.22 – 3.12 (m, 1H), 2.10 – 1.93 (m, 4H), 1.50 – 1.36 (m, 2H), 1.36 – 1.22 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

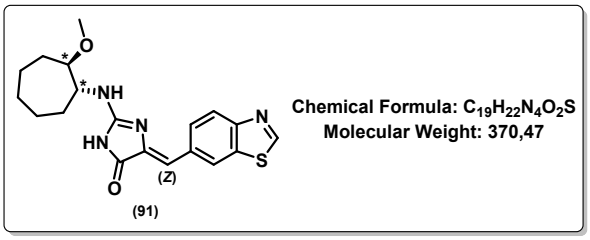
Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (90)



Compound (**90**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-2-methoxycycloheptan-1-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 79%

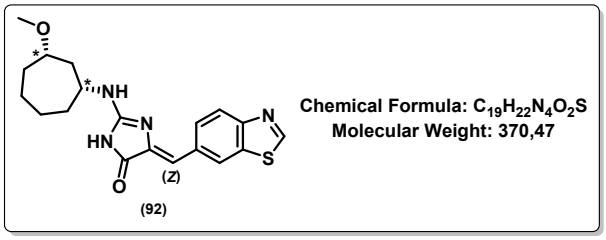
(80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.04 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.89 (s, 1H), 8.23 (d, J = 9.0 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.21 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.25 – 3.85 (m, 1H), 3.74 – 3.49 (m, 1H), 3.31 (s, 3H), 2.03 – 1.28 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-2-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (91)



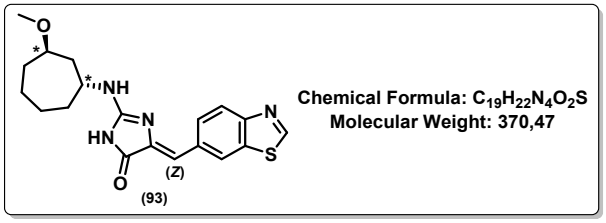
Compound (**91**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-2-methoxycycloheptan-1-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 79% (80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.39 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.90 (s, 1H), 8.18 (d, J = 8.6 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.47 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.00 – 3.83 (m, 1H), 3.51 – 3.38 (m, 1H), 3.31 (s, 3H), 1.93 – 1.40 (m, 10H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-3-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (92)



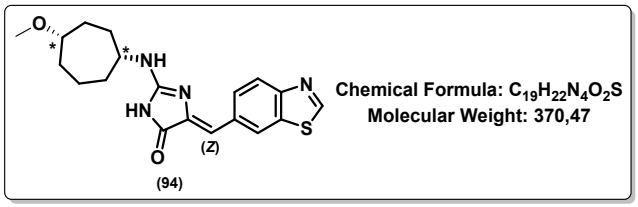
Compound (**92**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-3-methoxycycloheptan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 22h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 77% (78 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.50 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.90 (s, 1H), 8.27 – 8.13 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.45 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.14 – 3.78 (m, 1H), 3.55 – 3.36 (m, 1H), 3.26 (s, 3H), 2.39 – 2.14 (m, 1H), 2.04 – 1.80 (m, 2H), 1.81 – 1.38 (m, 7H). MS (ESI$^+$): $[M+H]^+$ 371.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-3-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (93)



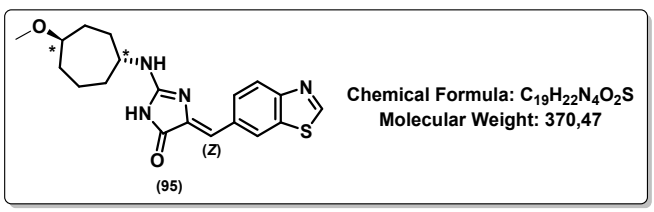
Compound (**93**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-3-methoxycycloheptan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 74% (75 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.44 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.90 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.48 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.21 – 3.96 (m, 1H), 3.57 – 3.45 (m, 1H), 3.28 (s, 3H), 2.23 – 2.06 (m, 1H), 2.05 – 1.78 (m, 3H), 1.78 – 1.33 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-3-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (94)



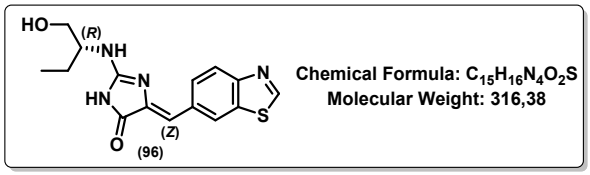
Compound (**94**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-4-methoxycycloheptan-1-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 68% (69 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.92 – 8.75 (m, 1H), 8.28 – 8.16 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.51 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.08 – 3.79 (m, 1H), 3.45 – 3.34 (m, 1H), 3.23 (s, 3H), 2.01 – 1.48 (m, 9H), 1.42 – 1.29 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-3-methoxycycloheptyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (95)



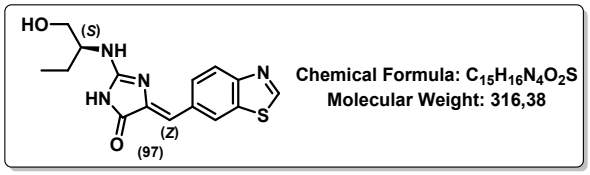
Compound (**95**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-4-methoxycycloheptan-1-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 73% (74 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 9.03 – 8.63 (m, 1H), 8.31 – 8.09 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.51 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.09 – 3.81 (m, 1H), 3.43 – 3.31 (m, 1H), 3.24 (s, 3H), 2.08 – 1.88 (m, 3H), 1.86 – 1.74 (m, 1H), 1.73 – 1.44 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-hydroxybutan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (96)



Compound (**96**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of (**9.3**), with 4 eq of (*R*)-(-)-2-amino-propan-1-ol at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 6% (13 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.42 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.92 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.26 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.87 (br s, 1H, OH, D_2O exchanged), 4.34 – 4.04 (m, 1H), 3.62 – 3.42 (m, 2H), 1.86 – 1.57 (m, 1H), 1.60 – 1.34 (m, 2H), 1.15 – 0.77 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 345.2. HPLC: >98%.

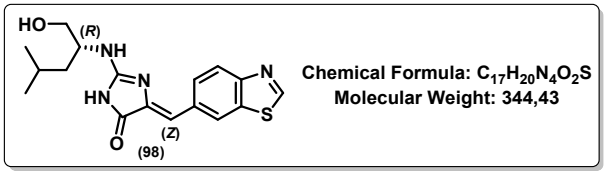
Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-hydroxybutan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (97)



Compound (**97**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of (*R*)-(-)-2-amino-propan-1-ol at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 8% (20 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.42 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.92 (s, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.26 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.87 (br s, 1H, OH, D_2O exchanged), 4.34 – 4.04 (m, 1H),

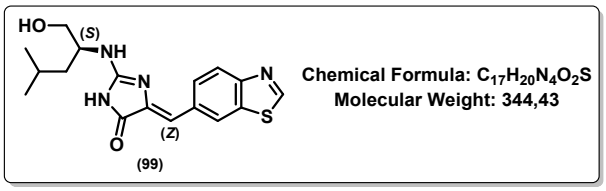
3.62 – 3.42 (m, 2H), 1.86 – 1.57 (m, 1H), 1.60 – 1.34 (m, 2H), 1.15 – 0.77 (m, 6H). MS (ESI^+) : $[M+H]^+$ 345.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-hydroxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (98)



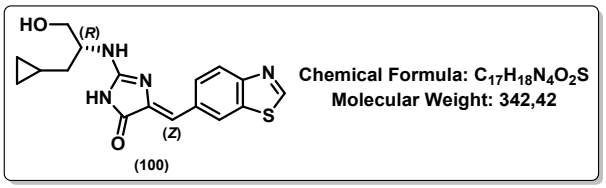
Compound (**98**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 21.79 mmol scale of intermediate (**9.4**), with 4 eq of (*R*)-leucinol at 120 °C (sealable round flask, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required two triturations in ACN at 0 °C. Isolated yield: 45% (3.383 g). Bright yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.87 (br s, 1H), 8.13 (br s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.08 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.68 (br s, 1H, OH, D_2O exchanged), 4.01 (br s, 1H), 3.60 – 3.44 (m, 2H), 1.79 – 1.65 (m, 1H), 1.61 – 1.36 (m, 2H), 1.05 – 0.86 (m, 6H). MS (ESI^+) : $[M+H]^+$ 345.2. HPLC: 97%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-hydroxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (99)



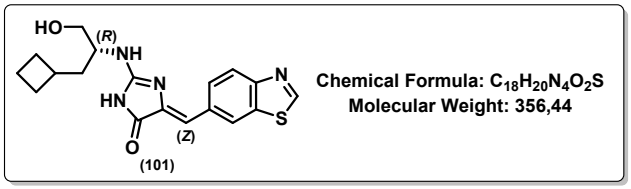
Compound (**99**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of (*S*)-leucinol at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 39% (99 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.87 (br s, 1H), 8.13 (br s, 1H), 8.01 (d, J = 8.3 Hz, 1H), 7.08 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.68 (br s, 1H, OH, D_2O exchanged), 4.01 (br s, 1H), 3.60 – 3.44 (m, 2H), 1.79 – 1.65 (m, 1H), 1.61 – 1.36 (m, 2H), 1.05 – 0.86 (m, 6H). MS (ESI^+) : $[M+H]^+$ 345.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclopropyl-3-hydroxypropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (100)



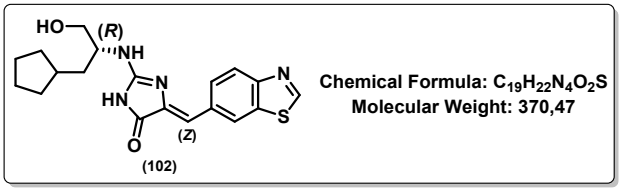
Compound (**100**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-3-cyclopropylpropan-1-ol at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 48% (45 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.37 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.98 – 8.72 (m, 1H), 8.34 – 8.12 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.23 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.77 (br s, 1H, OH, D_2O exchanged), 4.11 – 3.87 (m, 1H), 3.70 – 3.44 (m, 2H), 1.69 – 1.51 (m, 1H), 1.51 – 1.40 (m, 1H), 0.87 – 0.71 (m, 1H), 0.52 – 0.37 (m, 2H), 0.25 – 0.03 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 343.1. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclobutyl-3-hydroxypropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (101)



Compound (**101**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-3-cyclobutylpropan-1-ol at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 46% (45 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.38 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 9.03 – 8.72 (m, 1H), 8.19 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.22 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.86 (br s, 1H, OH, D_2O exchanged), 4.14 – 3.75 (m, 1H), 3.71 – 3.39 (m, 2H), 2.44 – 2.30 (m, 1H), 2.18 – 1.92 (m, 2H), 1.88 – 1.45 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

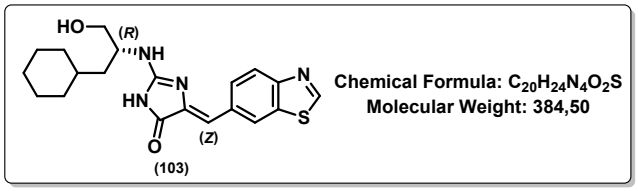
Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclopentyl-3-hydroxypropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (102)



Compound (**102**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-3-cyclopentylpropan-1-ol at 120 °C (sealed tube,

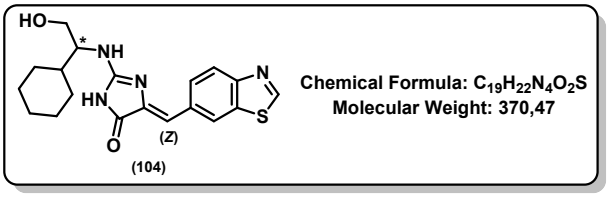
heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 52% (52 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.11 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 9.03 – 8.85 (m, 1H), 8.28 – 8.09 (m, 1H), 8.07 – 7.95 (m, 1H), 6.91 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.55 (br s, 1H, OH, D_2O exchanged), 4.08 – 3.86 (m, 1H), 3.66 – 3.44 (m, 2H), 1.99 – 1.08 (m, 11H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclohexyl-3-hydroxypropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (103)



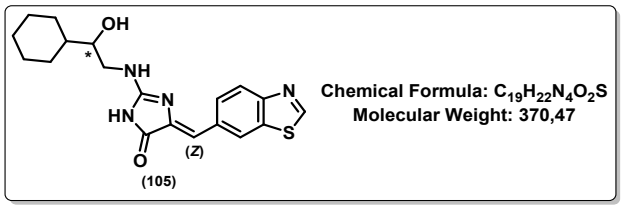
Compound (**103**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-3-cyclohexylpropan-1-ol at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 53% (56 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.07 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 9.03 – 8.63 (m, 1H), 8.35 – 8.04 (m, 1H), 8.04 – 7.90 (m, 1H), 6.90 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.54 (br s, 1H, OH, D_2O exchanged), 4.14 – 3.93 (m, 1H), 3.66 – 3.44 (m, 2H), 1.95 – 0.90 (m, 13H). MS (ESI$^+$) : $[M+H]^+$ 385.2. HPLC: 96%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclohexyl-2-hydroxyethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (104)



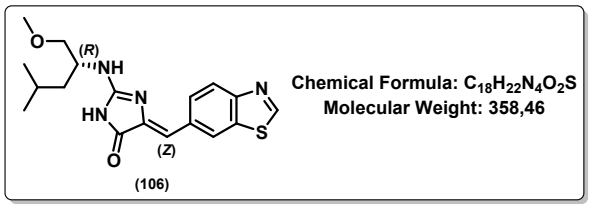
Compound (**104**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2-amino-2-cyclohexylethan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 44h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 43% (43 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.26 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.84 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.11 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.81 – 4.55 (m, 1H, OH, D_2O exchanged), 3.91 – 3.69 (m, 1H), 3.67 – 3.50 (m, 2H), 1.90 – 1.53 (m, 6H), 1.34 – 0.98 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 371.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-cyclohexyl-2-hydroxyethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (105)



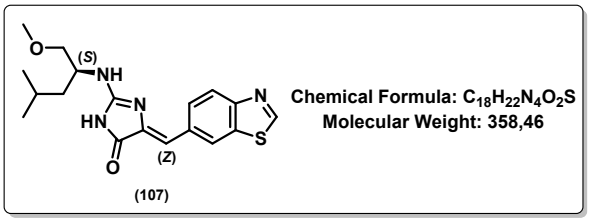
Compound (**105**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2-amino-1-cyclohexylethan-1-ol hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 2.5h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 72% (73 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 298K) of major tautomer δ_H 10.54 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.94 (s, 1H), 8.29 – 8.09 (m, 1H), 8.01 (d, J = 8.6 Hz, 1H), 7.42 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.95 – 4.72 (br s, 1H, OH, D_2O exchanged), 3.82 – 3.36 (m, 2H), 3.25 – 3.08 (m, 1H), 2.02 – 1.50 (m, 5H), 1.45 – 0.91 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 371.3. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methoxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (106)



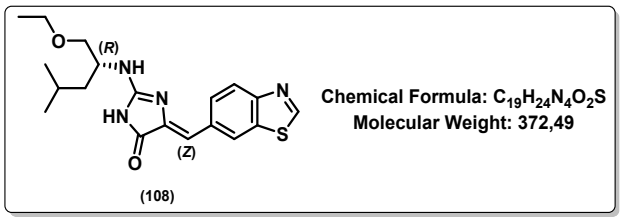
Compound (**106**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 2.91 mmol scale of intermediate (**9.4**), with 2.5 eq of (*R*)-1-methoxy-4-methylpentan-2-amine at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 74% (772 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.16 (br s, 1H, NH, D_2O exchanged), 9.27 (s, 1H), 8.89 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.01 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.19 (s, 1H), 3.53 – 3.41 (m, 2H), 3.34 (s, 3H), 1.83 – 1.66 (m, 1H), 1.62 – 1.39 (m, 2H), 1.14 – 0.81 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 359.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methoxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (107)



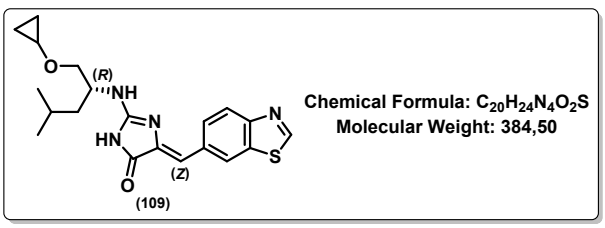
Compound (**107**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 2.91 mmol scale of intermediate (**9.4**), with 2.5 eq of (*S*)-1-methoxy-4-methylpentan-2-amine hydrochloride and 4 eq DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 84% (82 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.16 (br s, 1H, NH, D_2O exchanged), 9.27 (s, 1H), 8.89 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 7.99 (d, J = 8.4 Hz, 1H), 7.01 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.19 (s, 1H), 3.53 – 3.41 (m, 2H), 3.34 (s, 3H), 1.83 – 1.66 (m, 1H), 1.62 – 1.39 (m, 2H), 1.14 – 0.81 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 359.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-ethoxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (108)



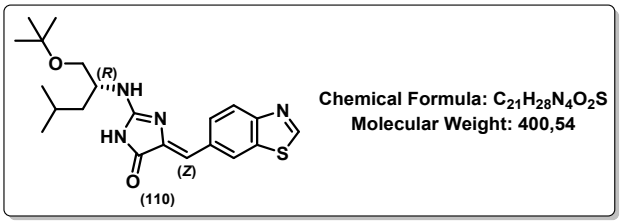
Compound (**108**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 291 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-1-ethoxy-4-methylpentan-2-amine at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in ACN at 0 °C. Isolated yield: 34% (37 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.35 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.91 (s, 1H), 8.16 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.18 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.24 – 4.06 (m, 1H), 3.62 – 3.39 (m, 4H), 1.80 – 1.63 (m, 1H), 1.59 – 1.38 (m, 2H), 1.14 (t, J = 7.0 Hz, 3H), 1.05 – 0.82 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 373.1. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclopropoxy-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (109)



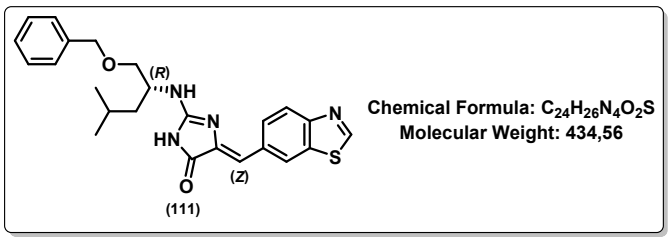
Compound (**109**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 291 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-1-cyclopropoxy-4-methylpentan-2-amine at 135 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in ACN at 0 °C. Isolated yield: 40% (59 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.34 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.91 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.18 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.28 – 4.05 (m, 1H), 3.63 – 3.47 (m, 2H), 3.42 – 3.31 (m, 1H), 1.79 – 1.60 (m, 1H), 1.57 – 1.34 (m, 2H), 1.04 – 0.83 (m, 6H), 0.57 – 0.37 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 385.3. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-(tert-butoxy)-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (110)



Compound (**110**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-1-(*tert*-butoxy)-4-methylpentan-2-amine at 140 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 70% (102 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.31 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.92 (s, 1H), 8.16 (d, J = 8.5 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.02 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.21 – 3.92 (m, 1H), 3.60 – 3.32 (m, 2H), 1.81 – 1.62 (m, 1H), 1.61 – 1.40 (m, 2H), 1.18 (s, 9H), 0.97 (t, J = 7.4 Hz, 6H). MS (ESI$^+$) : $[M+H]^+$ 401.3. HPLC: >98%.

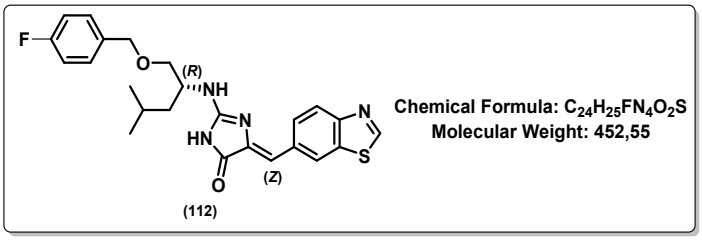
Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-(benzyloxy)-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (111)



Compound (**111**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-1-(benzyloxy)-4-methylpentan-2-amine at 135 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 30% (47 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.40 (br s,

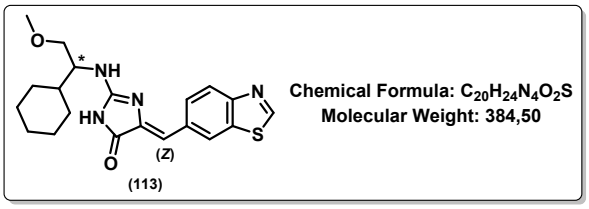
1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.91 (s, 1H), 8.18 (d, *J* = 8.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.55 – 7.06 (m, 5H + NH, D_2O exchanged), 6.43 (s, 1H), 4.66 – 4.49 (m, 2H), 4.36 – 4.14 (m, 1H), 3.66 – 3.49 (m, 2H), 1.81 – 1.63 (m, 1H), 1.62 – 1.42 (m, 2H), 1.08 – 0.87 (m, 6H). MS (ESI^+) : $[M+H]^+$ 435.2. HPLC: 97%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-((4-fluorobenzyl)oxy)-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (112)



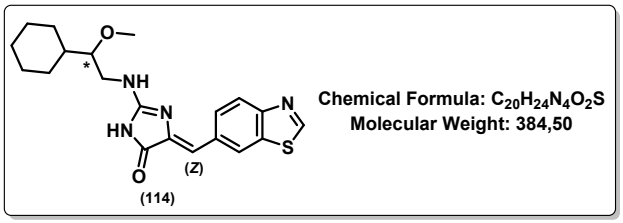
Compound (**112**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-1-((4-fluorobenzyl)oxy)-4-methylpentan-2-amine at 135 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 35% (58 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.39 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.89 (s, 1H), 8.17 (dd, *J* = 8.6, 1.6 Hz, 1H), 8.00 (d, *J* = 8.6 Hz, 1H), 7.37 (dd, *J* = 8.5, 5.7 Hz, 2H), 7.24 (br s, 1H, NH, D_2O exchanged), 7.10 (t, *J* = 8.9 Hz, 2H), 6.42 (s, 1H), 4.61 – 4.47 (m, 2H), 4.31 – 4.12 (m, 1H), 3.56 (d, *J* = 5.4 Hz, 2H), 1.78 – 1.64 (m, 1H), 1.61 – 1.40 (m, 2H), 1.05 – 0.84 (m, 6H). MS (ESI^+) : $[M+H]^+$ 453.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-cyclohexyl-2-methoxyethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (113)



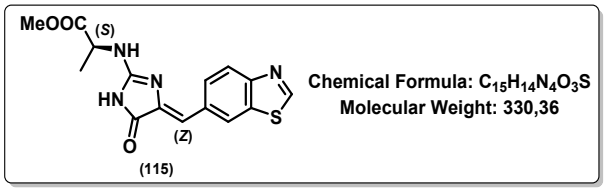
Compound (**113**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-1-cyclohexyl-2-methoxyethan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 74% (77 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.27 (br s, 1H, NH, D_2O exchanged), 9.38 – 9.24 (m, 1H), 8.94 – 8.72 (m, 1H), 8.39 – 8.12 (m, 1H), 8.12 – 7.96 (m, 1H), 7.24 (br s, 1H, NH, D_2O exchanged), 6.50 – 6.25 (m, 1H), 4.03 – 3.83 (m, 1H), 3.60 – 3.44 (m, 2H), 3.31 (s, 3H), 1.86 – 1.53 (m, 6H), 1.30 – 1.03 (m, 5H). MS (ESI^+) : $[M+H]^+$ 385.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-cyclohexyl-2-methoxyethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (114)



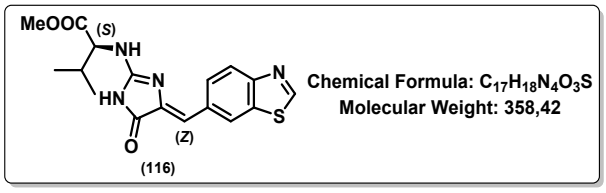
Compound (**114**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of 2-cyclohexyl-2-methoxyethan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 2.5h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 80% (87 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.46 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.96 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.42 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 3.71 – 3.55 (m, 1H), 3.45 – 3.33 (m, 4H), 3.32 – 3.23 (m, 1H), 1.90 – 1.50 (m, 6H), 1.28 – 1.07 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 385.2. HPLC: 97%.

Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-L-alaninate (115)



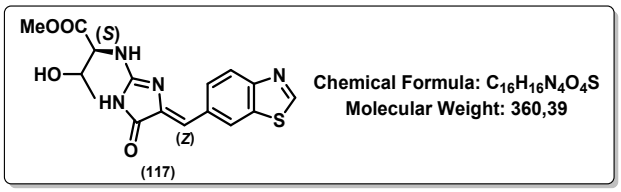
Compound (**115**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of methyl L-alaninate hydrochloride and 6 eq of TEA at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 17% (43 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.85 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.83 (s, 1H), 8.19 (d, J = 8.5 Hz, 1H), 8.14 (br s, 1H, NH, D_2O exchanged ed), 8.03 (d, J = 8.6 Hz, 1H), 6.47 (s, 1H), 4.68 – 4.45 (m, 1H), 3.71 (s, 3H), 1.45 (d, J = 7.2 Hz, 3H). MS (ESI$^+$) : $[M+H]^+$ 331.1. HPLC: 97%.

Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-L-valinate (116)



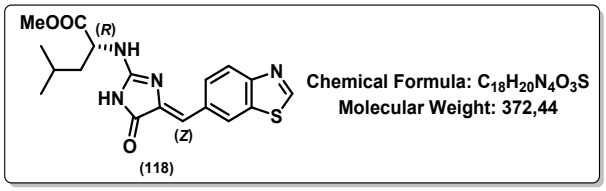
Compound (**116**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of methyl L-valinate hydrochloride and 6 eq of TEA at 140 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 13% (35 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.41 (br s, 1H, NH, D_2O exchanged), 9.38 (s, 1H), 8.83 (s, 1H), 8.39 – 7.86 (m, 2H + NH, D_2O exchanged), 6.48 (s, 1H), 4.50 – 4.26 (m, 1H), 3.73 (s, 3H), 2.29 – 2.16 (m, 1H), 1.16 – 0.80 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 359.2. HPLC: 97%.

Synthesis of methyl (2*S*)-2-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)-3-hydroxybutanoate (117)



Compound (**117**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of methyl (2*S*)-2-amino-3-hydroxybutanoate hydrochloride and 6 eq of TEA at 140 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 26% (71 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.28 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.78 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.58 – 7.34 (br s, 1H, NH, D_2O exchanged), 6.49 (s, 1H), 5.31 (br s, 1H, OH, D_2O exchanged), 4.66 – 4.49 (m, 1H), 4.35 – 4.16 (m, 1H), 3.72 (s, 3H), 1.20 (d, J = 6.3 Hz, 3H). MS (ESI$^+$) : $[M+H]^+$ 361.2. HPLC: >98%.

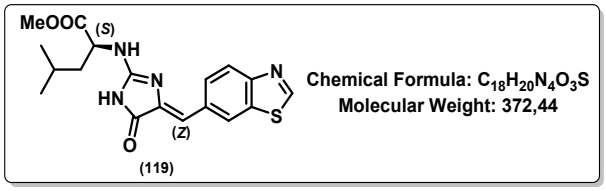
Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-D-leucinate (118)



Compound (**118**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of methyl D-leucinate hydrochloride and 4 eq DIPEA at 120 °C (sealed tube, heating block), for 8h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 69% (70 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.75 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.85 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H),

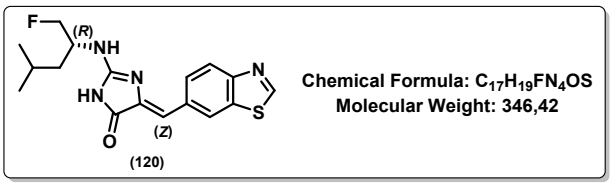
8.09 (br s, 1H, NH, D_2O exchanged), 8.03 (d, *J* = 8.6 Hz, 1H), 6.47 (s, 1H), 4.70 – 4.41 (m, 1H), 3.71 (s, 3H), 1.84 – 1.57 (m, 3H), 1.07 – 0.77 (m, 6H). MS (ESI^+) : $[M+H]^+$ 373.2. HPLC: >98%.

Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-L-leucinate (119)



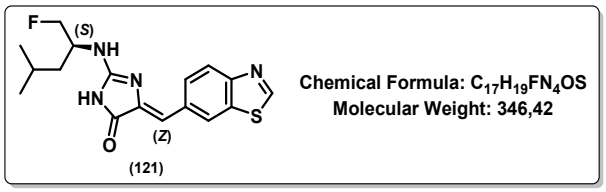
Compound (**119**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of methyl L-leucinate hydrochloride and 6 eq TEA at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 27% (75 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.75 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.85 (s, 1H), 8.19 (d, *J* = 8.6 Hz, 1H), 8.09 (br s, 1H, NH, D_2O exchanged), 8.03 (d, *J* = 8.6 Hz, 1H), 6.47 (s, 1H), 4.70 – 4.41 (m, 1H), 3.71 (s, 3H), 1.84 – 1.57 (m, 3H), 1.07 – 0.77 (m, 6H). MS (ESI^+) : $[M+H]^+$ 373.2. HPLC: 91%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-fluoro-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (120)



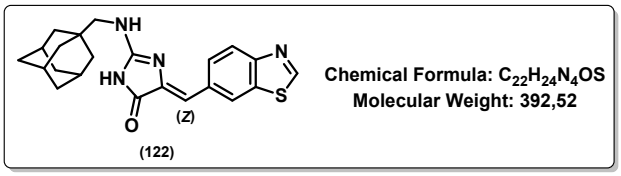
Compound (**120**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-1-fluoro-4-methylpentan-2-amine at 120 °C (sealed tube, heating block), for 72h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 41% (25 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.28 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.85 (s, 1H), 8.17 (d, *J* = 8.2 Hz, 1H), 8.00 (d, *J* = 8.5 Hz, 1H), 7.25 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.64 – 4.52 (m, 1H), 4.50 – 4.40 (m, 1H), 4.37 – 4.22 (m, 1H), 1.84 – 1.71 (m, 1H), 1.65 – 1.55 (m, 1H), 1.52 – 1.41 (m, 1H), 1.04 – 0.81 (m, 6H). MS (ESI^+) : $[M+H]^+$ 347.2. HPLC: 95%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-fluoro-4-methylpentan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (121)



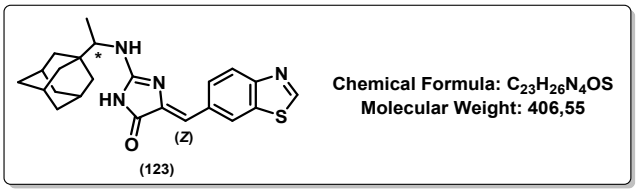
Compound (**121**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-1-fluoro-4-methylpentan-2-amine at 120 °C (sealed tube, heating block), for 72h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 41% (31 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.28 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.85 (s, 1H), 8.17 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.25 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.64 – 4.52 (m, 1H), 4.50 – 4.40 (m, 1H), 4.37 – 4.22 (m, 1H), 1.84 – 1.71 (m, 1H), 1.65 – 1.55 (m, 1H), 1.52 – 1.41 (m, 1H), 1.04 – 0.81 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 347.2. HPLC: >98%.

Synthesis of (*Z*)-2-(((adamantan-1-yl)methyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (122)



Compound (**122**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 2 eq of (adamantan-1-yl)methanamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 68% (198 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.33 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.85 (s, 1H), 8.35 – 8.14 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.41 (br s, 1H, NH, D_2O exchanged), 6.38 (s, 1H), 3.25 – 2.80 (m, 2H), 1.96 (s, 3H), 1.72 – 1.43 (m, 12H). MS (ESI$^+$) : $[M+H]^+$ 393.3. HPLC: >98%.

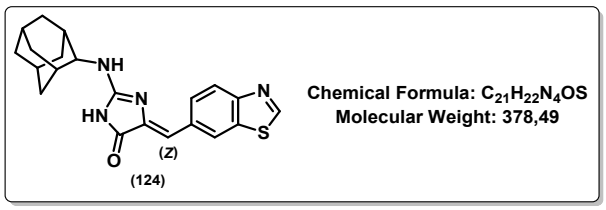
Synthesis of (±)-(*Z*)-2-((1-(adamantan-1-yl)ethyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (123)



Compound (**123**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 2 eq of (±)-1-(adamantan-1-yl)ethan-1-amine hydrochloride and 3 eq of DIPEA at 150 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH:

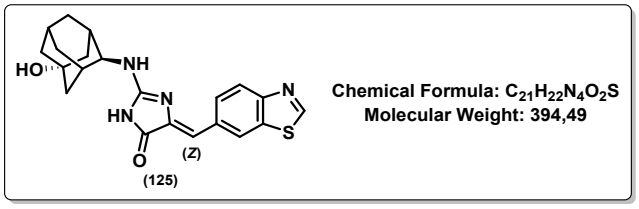
99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 32% (97 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.82 (s, 1H), 8.22 (d, J = 8.8 Hz, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.14 (br s, 1H, NH, D_2O exchanged), 6.39 (s, 1H), 3.76 – 3.59 (m, 1H), 1.99 (s, 3H), 1.77 – 1.49 (m, 12H), 1.17 – 1.05 (m, 3H). MS (ESI$^+$) : $[M+H]^+$ 407.3. HPLC: >98%.

Synthesis of (*Z*)-2-((adamantan-2-yl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (124)



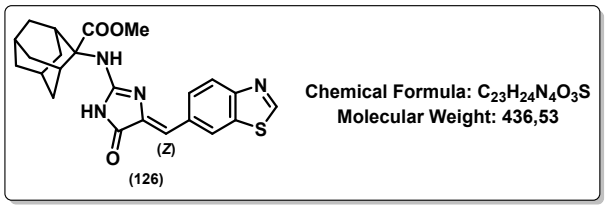
Compound (**124**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 4 eq of adamantan-2-amine and 15 eq of AcOH at 170 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 44% (125 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.06 (br s, 1H, D_2O e xchanged), 9.31 (s, 1H), 8.87 (s, 1H), 8.20 (d, J = 8.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.35 (br s, 1H, D_2O exchanged), 6.44 (s, 1H), 4.15 – 3.95 (m, 1H), 2.13 – 1.56 (m, 14H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: 93%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((5-hydroxyadamantan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (125)



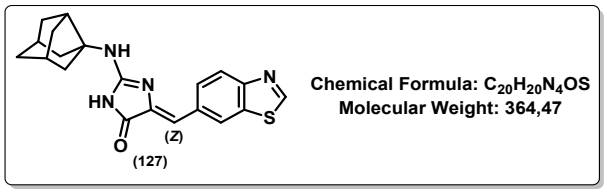
Compound (**125**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 4 eq of *trans*-4-aminoadamantan-1-ol and 15 eq of AcOH at 160 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 27% (80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.93 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.98 – 8.76 (m, 1H), 8.37 – 8.11 (m, 1H), 8.11 – 7.97 (m, 1H), 7.48 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.57 – 4.36 (br s, 1H, OH, D_2O exchanged), 4.20 – 3.78 (m, 1H), 2.25 – 2.00 (m, 3H), 1.97 – 1.74 (m, 4H), 1.72 – 1.60 (m, 4H), 1.49 – 1.32 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 395.2. HPLC: >98%.

Synthesis of methyl 2-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantane-2-carboxylate (126)



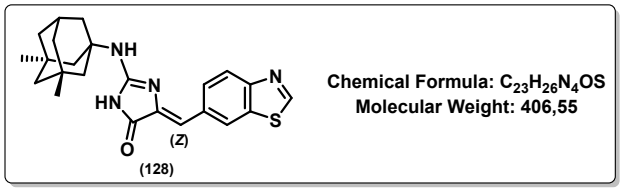
Compound (**126**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of methyl 2-aminoadamantane-2-carboxylate and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 96h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: <10% (9 mg).Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.91 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.95 (s, 1H), 8.05 (d, J = 8.8 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.46 (**br** s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 3.63 (s, 3H), 2.70 – 2.58 (m, 2H), 2.19 – 2.00 (m, 4H), 1.91 – 1.58 (m, 8H). MS (ESI$^+$) : $[M+H]^+$ 437.0. Purity : 85% (^{1}H NMR)

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(noradamantylamino)-3,5-dihydro-4*H*-imidazol-4-one (127)



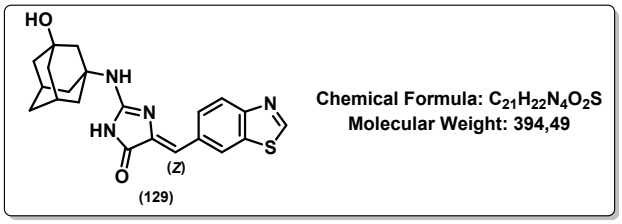
Compound (**127**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 545 µmol scale of intermediate (**9.4**), with 4 eq of 3-noradamantanamine hydrochloride and 8 eq of DIPEA at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 46% (92 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.95 (br s, 1H, NH, D_2O exchanged), 9.30 (s, 1H), 8.99 (s, 1H), 8.12 (dd, J = 8.6, 1.6 Hz, 1H), 7.99 (d, J = 8.5 Hz, 1H), 7.29 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.72 (t, J = 6.7 Hz, 1H), 2.37 – 2.26 (m, 4H), 2.22 – 2.12 (m, 2H), 2.03 – 1.94 (m, 2H), 1.74 – 1.53 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 365.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,5-dimethyladamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (128)



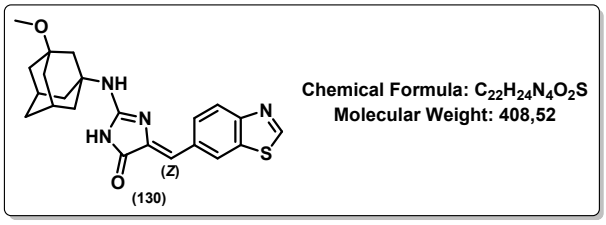
Compound (**128**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 4 eq of memantine and 15 eq of AcOH at 160 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 44% (132 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.04 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 9.17 (s, 1H), 8.02 (s, 2H), 7.16 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 2.23 – 2.13 (m, 1H), 2.02 – 1.70 (m, 6H), 1.49 – 1.28 (m, 4H), 1.25 – 1.14 (m, 2H), 0.98 – 0.85 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 407.2. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-hydroxyadamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (129)



Compound (**129**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 4 eq of 3-amino-1-adamantanol and 15 eq of AcOH at 160 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 59% (173 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.01 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 9.00 (s, 1H), 8.15 (dd, J = 8.6, 1.6 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.17 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.62 (br s, 1H, OH, D_2O exchanged), 2.28 – 2.17 (m, 2H), 2.12 – 2.01 (m, 5H), 1.99 – 1.91 (m, 1H), 1.69 – 1.45 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 395.2. HPLC: 97%.

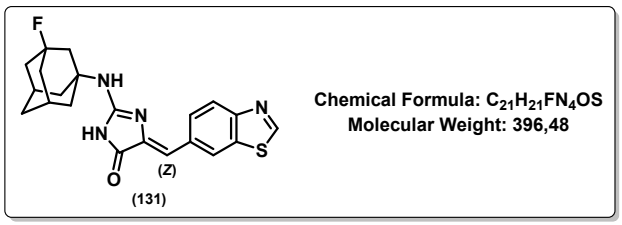
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-methoxyadamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (130)



Compound (**130**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 331 µmol scale of intermediate (**9.4**), with 2.5 eq of 3-methoxyadamantan-1-amine and 10 eq of AcOH at 140 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH at 0 °C. Isolated yield: 25% (34 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.08 (br s, 1H, NH, D_2O exchanged), 9.35

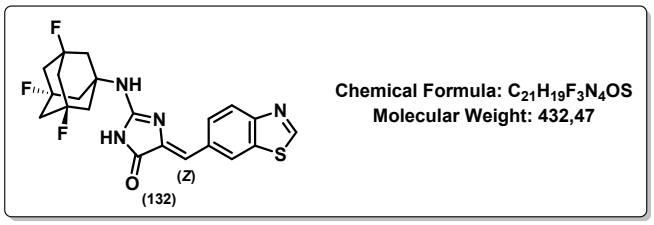
(s, 1H), 9.04 (s, 1H), 8.12 (d, *J* = 8.6 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.27 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 3.18 (s, 3H), 2.38 – 1.91 (m, 8H), 1.83 – 1.47 (m, 6H). MS (ESI^+) : $[M+H]^+$ 409.3. HPLC: 96%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-fluoroadamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (131)



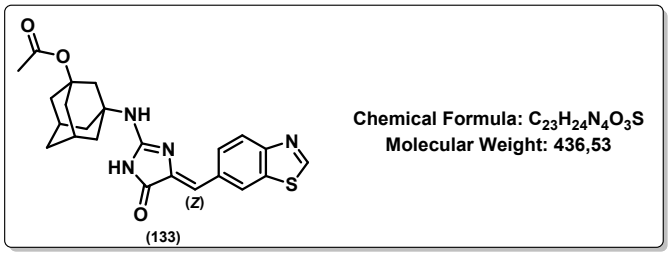
Compound (**131**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 494 µmol scale of intermediate (**9.4**), with 3 eq of 3-fluoroadamantan-1-amine and 6 eq of AcOH at 150 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 54% (106 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.89 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.97 (s, 1H), 8.13 (d, *J* = 8.6 Hz, 1H), 8.02 (d, *J* = 8.5 Hz, 1H), 7.04 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 2.44 – 2.25 (m, 4H), 2.23 – 1.98 (m, 4H), 1.96 – 1.83 (m, 4H), 1.67 – 1.53 (m, 2H). MS (ESI^+) : $[M+H]^+$ 397.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,5,7-trifluoroadamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (132)



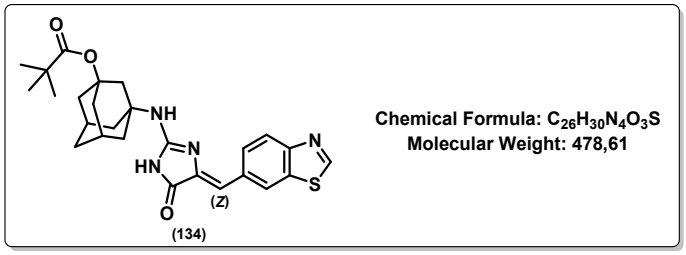
Compound (**132**) was synthesized according to **GP11-B**, in a dioxane/EtOH mixture (3/1, 0.3M/isothiourea), on a 158 µmol scale of intermediate (**9.4**), with 4 eq of 3,5,7-trifluoroadamantan-1-amine and 6 eq of AcOH at 155 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in ACN at 0 °C. Isolated yield: 29% (20 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.12 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.15 – 8.77 (m, 1H), 8.31 – 7.93 (m, 2H), 7.50 (br s, 1H, NH, D_2O exchanged), 6.52 (s, 1H), 2.48 – 2.05 (m, 12H). MS (ESI^+) : $[M+H]^+$ 433.2. HPLC: >98%.

Synthesis of 3-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl acetate (133)



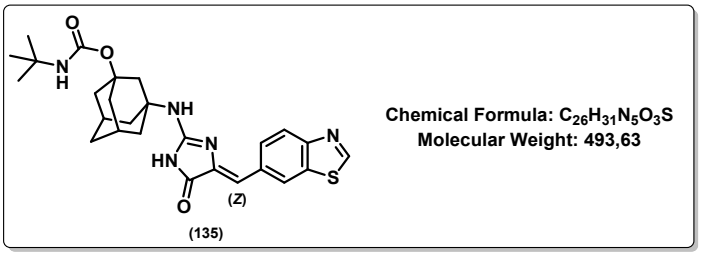
Compound (**133**) was synthesized according to **GP11-B**, in a dioxane/EtOH mixture (3/1, 0.3M/isothiourea), on a 373 µmol scale of intermediate (**9.4**), with 2.5 eq of 3-aminoadamantan-1-yl acetate hydrochloride and 4 eq DIPEA at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 37% (60 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.09 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.03 (s, 1H), 8.13 (d, J = 8.5 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.29 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.67 (s, 2H), 2.35 – 2.00 (m, 8H), 1.99 – 1.88 (m, 5H), 1.66 – 1.54 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 437.3. HPLC: 97%.

Synthesis of 3-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl pivalate (134)



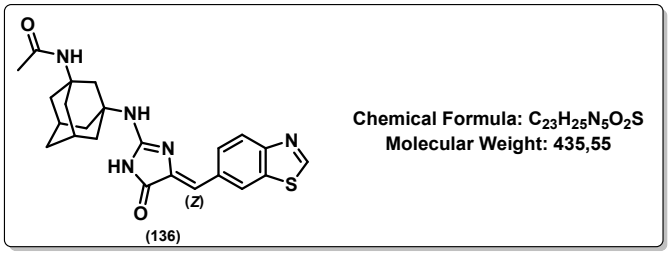
Compound (**134**) was synthesized according to **GP11-B**, in a dioxane/EtOH mixture (8/2, 0.3M/isothiourea), on a 217 µmol scale of intermediate (**9.4**), with 2.5 eq of 3-aminoadamantan-1-yl pivalate hydrochloride and 4 eq DIPEA at 160 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 31% (32 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 9.84 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 9.01 (s, 1H), 8.12 (dd, J = 8.7, 1.7 Hz, 1H), 8.01 (d, J = 8.5 Hz, 1H), 7.00 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 2.68 (s, 2H), 2.39 – 1.90 (m, 10H), 1.69 – 1.58 (m, 2H), 1.12 (s, 9H). MS (ESI$^+$) : $[M+H]^+$ 479.4. HPLC: 98%.

Synthesis of 3-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl *tert*-butylcarbamate (135)



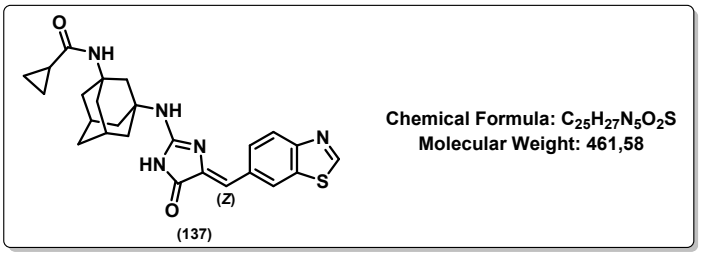
Compound (**135**) was synthesized according to **GP11-B**, in a dioxane/EtOH mixture (3/1, 0.3M/isothiourea), on a 472 µmol scale of intermediate (**9.4**), with 2.5 eq of 3-aminoadamantan-1-yl *tert*-butylcarbamate hydrochloride and 4 eq DIPEA at 160 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 17% (40 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 9.81 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.95 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 6.98 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 6.20 (br s, 1H, NH, D_2O exchanged), 2.60 (s, 1H), 2.40 – 1.93 (m, 9H), 1.68 – 1.39 (m, 4H), 1.31 – 1.09 (m, 9H). MS (ESI$^+$) : $[M+H]^+$ 494.3. Purity : 92% (^{1}H NMR).

Synthesis of *N*-(3-(((Z)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl)acetamide (136)



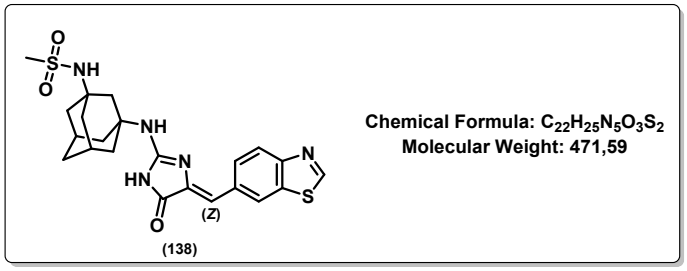
Compound (**136**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *N*-(3-aminoadamantan-1-yl)acetamide and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. The final product required a trituration in EtOH. Isolated yield: 13% (15 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.87 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 9.00 (s, 1H), 8.15 (d, J = 8.7 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.36 (br s, 1H, NH, D_2O exchanged), 6.99 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.49 – 2.43 (m, 2H), 2.35 – 2.11 (m, 4H), 2.10 – 1.85 (m, 6H), 1.76 (s, 3H), 1.68 – 1.55 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 436.2. HPLC: >98%.

Synthesis of *N*-(3-(((Z)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl)cyclopropanecarboxamide (137)



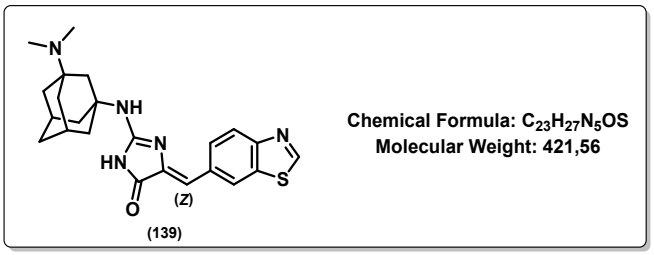
Compound (**137**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *N*-(3-aminoadamantan-1-yl)cyclopropanecarboxamide and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH. Isolated yield: 33% (42 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.87 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.99 (s, 1H), 8.15 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.58 (br s, 1H, NH, D_2O exchanged), 7.01 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.49 – 2.44 (m, 2H), 2.38 – 2.11 (m, 4H), 2.11 – 1.84 (m, 6H), 1.70 – 1.51 (m, 3H), 0.75 – 0.44 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 462.2. HPLC: >98%.

Synthesis of *N*-(3-(((*Z*)-4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)adamantan-1-yl)methanesulfonamide (138)



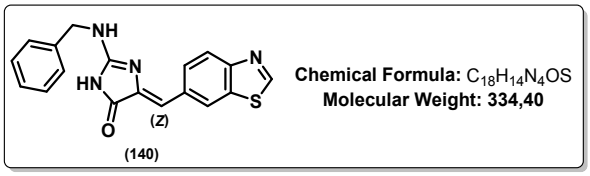
Compound (**138**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *N*-(3-aminoadamantan-1-yl)methanesulfonamide and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 102h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH. Isolated yield: 47% (61 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.90 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.94 (s, 1H), 8.17 (d, J = 8.6 Hz, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.04 (br s, 1H, NH, D_2O exchanged), 6.93 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 2.97 (s, 3H), 2.43 (s, 2H), 2.29 – 1.84 (m, 10H), 1.68 – 1.54 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 472.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-(dimethylamino)adamantan-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (139)



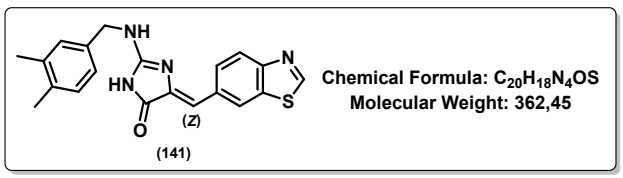
Compound (**139**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of N^1,N^1-dimethyladamantane-1,3-diamine and 9 eq of AcOH at 150 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 56% (64 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 9.61 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 9.10 – 8.85 (m, 1H), 8.26 – 8.06 (m, 1H), 8.00 (d, J = 7.9 Hz, 1H), 6.71 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 2.27 (s, 6H), 2.26 – 1.93 (m, 8H), 1.79 – 1.53 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 422.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(benzylamino)-3,5-dihydro-4*H*-imidazol-4-one (140)



Compound (**140**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.38 mmol scale of intermediate (**9.3**), with 4 eq of benzylamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 80% (367 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.86 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.84 (s, 1H), 8.26 – 8.20 (m, 1H), 8.19 – 8.06 (br s, 1H, NH, D_2O exchanged), 8.03 (d, J = 8.6 Hz, 1H), 7.55 – 7.20 (m, 5H), 6.43 (s, 1H), 4.67 – 4.48 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 335.2. HPLC: 97%.

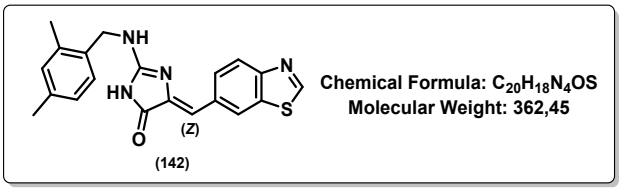
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3,4-dimethylbenzyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (141)



Compound (**141**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (3,4-dimethylphenyl)methanamine at 120 °C (sealed tube, heating block), for 3.5h. The product directly precipitated in the reaction medium: it was isolated after

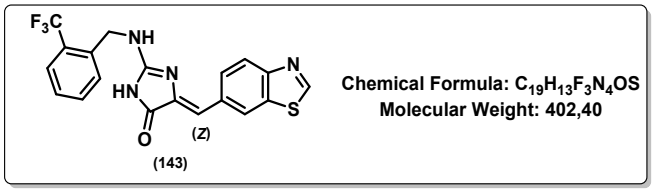
filtration, washing with cold THF, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 59% (58 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.79 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.86 (s, 1H), 8.24 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.99 (br s, 1H, NH, D_2O exchanged), 7.28 – 7.06 (m, 3H), 6.42 (s, 1H), 4.50 (s, 2H), 2.21 (s, 3H), 2.18 (s, 3H) MS (ESI$^+$) : $[M+H]^+$ 363.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2,4-dimethylbenzyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (142)



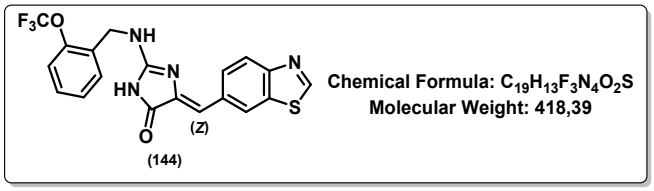
Compound (**142**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (2,4-dimethylphenyl)methanamine at 120 °C (sealed tube, heating block), for 3.5h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 67% (66 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.69 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.88 (s, 1H), 8.22 (d, J = 7.9 Hz, 1H), 8.15 (br s, 1H, NH, D_2O exchanged), 8.03 (d, J = 8.0 Hz, 1H), 7.29 – 7.17 (m, 1H), 7.14 – 7.03 (m, 1H), 7.03 – 6.89 (m, 1H), 6.43 (s, 1H), 4.54 (s, 2H), 2.36 (s, 3H), 2.25 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 363.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(trifluoromethyl)benzyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (143)



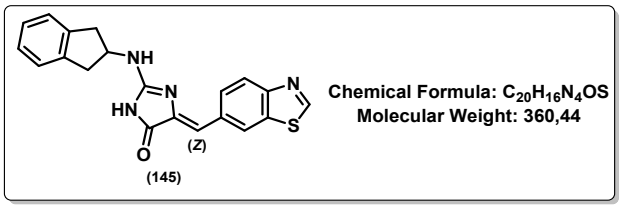
Compound (**143**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (2-(trifluoromethyl)phenyl)methanamine at 120 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 72% (79 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.96 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.87 (s, 1H), 8.23 (br s, 1H, NH, D_2O exchanged), 8.10 – 7.93 (m, 2H), 7.77 (d, J = 7.8 Hz, 1H), 7.74 – 7.62 (m, 2H), 7.55 – 7.43 (m, 1H), 6.44 (s, 1H), 4.80 (s, 2H) MS (ESI$^+$) : $[M+H]^+$ 403.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(trifluoromethoxy)benzyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (144)



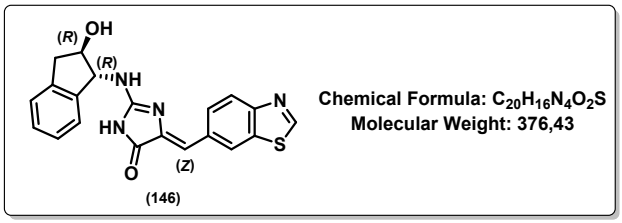
Compound (**144**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (2-(trifluoromethoxy)phenyl)methanamine at 120 °C (sealed tube, heating block), for 5.5h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 59% (67 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.93 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.83 (s, 1H), 8.23 (d, J = 8.5 Hz, 1H), 8.14 (br s, 1H, NH, D_2O exchanged), 8.02 (d, J = 8.5 Hz, 1H), 7.57 – 7.36 (m, 3H), 7.27 (d, J = 7.6 Hz, 1H), 6.45 (s, 1H), 4.63 (s, 2H). MS (ESI$^+$) : $[M+H]^+$ 419.2. HPLC: 98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2,3-dihydro-1*H*-inden-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (145)



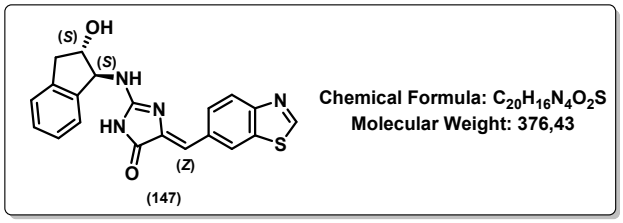
Compound (**145**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of 2,3-dihydro-1*H*-inden-2-amine hydrochloride and 3 eq of DIPEA at 150 °C (sealed tube, heating block), for 3h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 72% (47 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.55 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.81 (s, 1H), 8.44 – 8.17 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.92 (br s, 1H, NH, D_2O exchanged), 7.32 – 7.22 (m, 2H), 7.20 – 7.17 (m, 2H), 6.44 (s, 1H), 4.96 – 4.44 (m, 1H), 3.38 – 3.31 (m, 2H), 3.09 – 2.88 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 361.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (146)



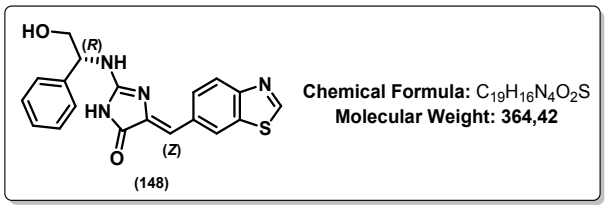
Compound (**146**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*R*,2*R*)-1-amino-2,3-dihydro-1*H*-inden-2-ol at 120 °C (sealed tube, heating block), for 40h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 66% (68 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.18 (br s, 1H, NH, D_2O exchanged), 9.27 (s, 1H), 8.87 – 8.56 (m, 1H), 8.27 – 8.06 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 7.39 – 7.11 (m, 4H), 6.49 (s, 1H), 5.55 – 4.90 (m, 1H + OH, D_2O exchanged), 4.49 (q, *J* = 6.7 Hz, 1H), 3.26 (dd, *J* = 15.7, 7.1 Hz, 1H), 2.82 (dd, *J* = 15.7, 6.9 Hz, 1H). MS (ESI$^+$) : $[M+H]^+$ 377.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1*R*,2*R*)-2-hydroxy-2,3-dihydro-1*H*-inden-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (147)



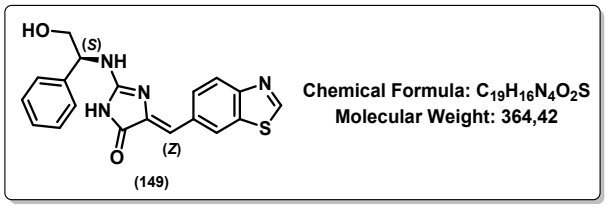
Compound (**147**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (1*S*,2*S*)-1-amino-2,3-dihydro-1*H*-inden-2-ol at 120 °C (sealed tube, heating block), for 40h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 62% (64 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.18 (br s, 1H, NH, D_2O exchanged), 9.27 (s, 1H), 8.87 – 8.56 (m, 1H), 8.27 – 8.06 (m, 1H), 8.01 (d, *J* = 8.4 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 7.39 – 7.11 (m, 4H), 6.49 (s, 1H), 5.55 – 4.90 (m, 1H + OH, D_2O exchanged), 4.49 (q, *J* = 6.7 Hz, 1H), 3.26 (dd, *J* = 15.7, 7.1 Hz, 1H), 2.82 (dd, *J* = 15.7, 6.9 Hz, 1H). MS (ESI$^+$) : $[M+H]^+$ 377.1. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-hydroxy-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (148)



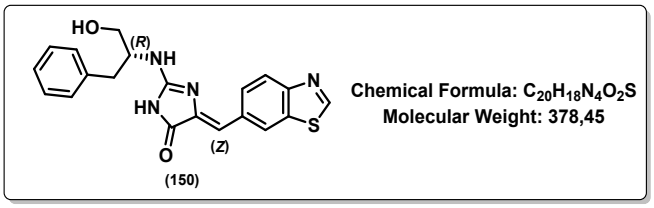
Compound (**148**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-2-phenylethan-1-ol at 120 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 23% (63 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.50 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.00 – 8.63 (m, 1H), 8.25 – 8.07 (m, 1H), 8.07 – 7.97 (m, 1H), 7.92 (br s, 1H, NH, D_2O exchanged), 7.51 – 7.43 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.40 (s, 1H), 5.25 – 4.77 (m, 1H + OH, D_2O exchanged), 3.75 (d, *J* = 6.1 Hz, 2H). MS (ESI$^+$) : $[M+H]^+$ 365.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-hydroxy-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (149)



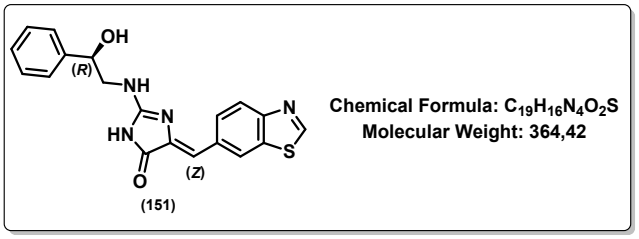
Compound (**149**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-2-amino-2-phenylethan-1-ol at 120 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 43% (117 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.50 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.00 – 8.63 (m, 1H), 8.25 – 8.07 (m, 1H), 8.07 – 7.97 (m, 1H), 7.92 (br s, 1H, NH, D_2O exchanged), 7.51 – 7.43 (m, 2H), 7.37 (t, *J* = 7.6 Hz, 2H), 7.26 (t, *J* = 7.3 Hz, 1H), 6.40 (s, 1H), 5.25 – 4.77 (m, 1H + OH, D_2O exchanged), 3.75 (d, *J* = 6.1 Hz, 2H). MS (ESI$^+$) : $[M+H]^+$ 365.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-hydroxy-3-phenylpropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (150)



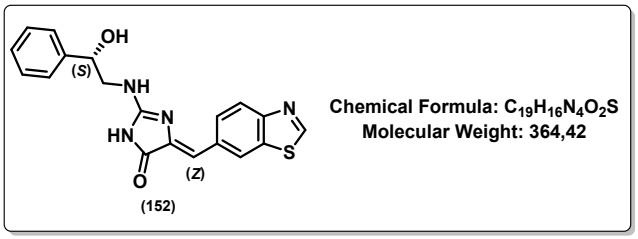
Compound (**150**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-3-phenylpropan-1-ol at 120 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 36% (37 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.45 (br s, 1H, NH, D_2O exchanged), 9.38 (s, 1H), 9.04 – 8.83 (m, 1H), 8.31 – 8.10 (m, 1H), 8.05 (d, J = 8.4 Hz, 1H), 7.46 (br s, 1H, NH, D_2O exchanged), 7.42 – 7.26 (m, 4H), 7.26 – 7.10 (m, 1H), 6.41 (s, 1H), 5.33 – 4.75 (m, 1H, OH, D_2O exchanged), 4.30 – 3.84 (m, 1H), 3.68 – 3.39 (m, 2H), 3.11 – 2.70 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-hydroxy-2-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (151)



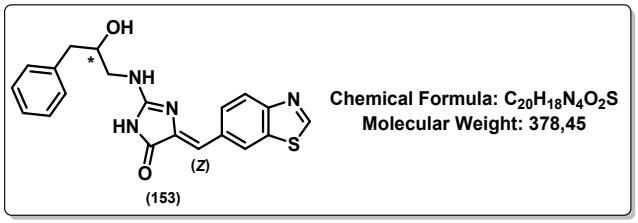
Compound (**151**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-amino-1-phenylethan-1-ol at 120 °C (sealed tube, heating block), for 3h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 83% (83 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.57 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 9.05 – 8.80 (m, 1H), 8.30 – 8.13 (m, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.57 (br s, 1H, NH, D_2O exchanged), 7.53 – 7.23 (m, 5H), 6.44 (s, 1H), 5.69 (br s, 1H, OH, D_2O exchanged), 5.19 – 4.67 (m, 1H), 3.85 – 3.50 (m, 1H), 3.48 – 3.33 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 365.1. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-hydroxy-2-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (152)



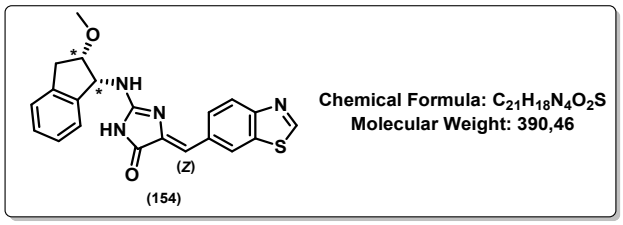
Compound (**152**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-2-amino-1-phenylethan-1-ol at 120 °C (sealed tube, heating block), for 3h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 78% (77 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.57 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 9.05 – 8.80 (m, 1H), 8.30 – 8.13 (m, 1H), 8.05 (d, J = 8.5 Hz, 1H), 7.57 (br s, 1H, NH, D_2O exchanged), 7.53 – 7.23 (m, 5H), 6.44 (s, 1H), 5.69 (br s, 1H, OH, D_2O exchanged), 5.19 – 4.67 (m, 1H), 3.85 – 3.50 (m, 1H), 3.48 – 3.33 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 365.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-hydroxy-3-phenylpropyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (153)



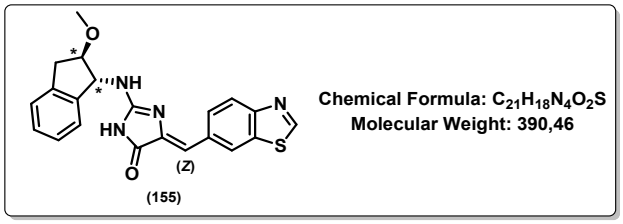
Compound (**153**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-1-amino-3-phenylpropan-2-ol at 120 °C (sealed tube, heating block), for 2h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 58% (60 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.13 (br s, 1H, NH, D_2O exchanged), 9.29 (s, 1H), 8.75 – 8.59 (m, 1H), 8.21 – 8.05 (m, 1H), 8.01 (d, J = 8.1 Hz, 1H), 7.35 – 7.15 (m, 5H), 7.14 – 6.92 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 5.12 – 4.60 (m, 1H, OH, D_2O exchanged), 4.12 – 3.86 (m, 1H), 3.54 (dd, J = 13.4, 3.8 Hz, 1H), 3.34 (dd, J = 13.3, 7.0 Hz, 1H), 2.89 – 2.72 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: 98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*cis*-2-methoxy-2,3-dihydro-1*H*-inden-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (154)



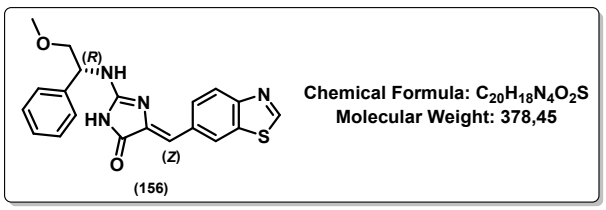
Compound (**154**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*cis*-2-methoxy-2,3-dihydro-1*H*-inden-1-amine at 120 °C (sealed tube, heating block), for 26h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 55% (59 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.82 (s, 1H), 8.44 – 8.23 (m, 1H), 8.02 (d, J = 8.6 Hz, 1H), 7.51 (br s, 1H, NH, D_2O exchanged), 7.44 – 7.15 (m, 4H), 6.51 (s, 1H), 5.77 – 5.54 (m, 1H), 4.39 – 4.19 (m, 1H), 3.35 (s, 3H), 3.19 – 3.01 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 391.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((*trans*-2-methoxy-2,3-dihydro-1*H*-inden-1-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (155)



Compound (**155**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*trans*-2-methoxy-2,3-dihydro-1*H*-inden-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 26h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 69% (74 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.73 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.82 (s, 1H), 8.23 (dd, J = 8.6, 1.6 Hz, 1H), 8.12 (br s, 1H, NH, D_2O exchanged), 8.01 (d, J = 8.6 Hz, 1H), 7.44 – 7.10 (m, 4H), 6.48 (s, 1H), 5.60 – 5.22 (m, 1H), 4.30 – 4.13 (m, 1H), 3.46 (s, 3H), 3.41 – 3.33 (m, 1H), 2.93 – 2.74 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 391.2. HPLC: >98%.

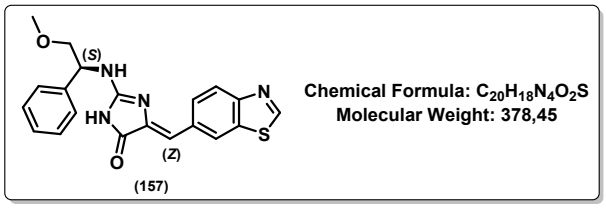
Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-methoxy-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (156)



Compound (**155**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 12.71 mmol scale of intermediate (**9.4**), with 3 eq of (*R*)-2-methoxy-1-phenylethan-1-amine at 140 °C (sealable

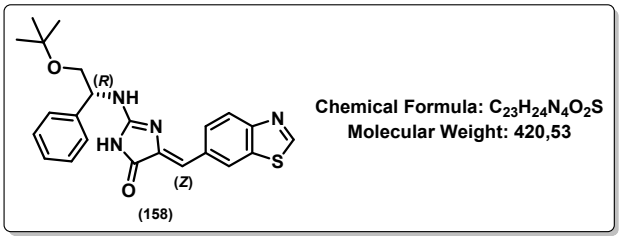
round flask, heating block), for 26h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required two successive triturations in refluxing EtOH. Isolated yield: 51% (2.455 g). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.55 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.82 (s, 1H), 8.29 – 7.92 (m, 2H + NH, D_2O exchanged), 7.48 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 6.42 (s, 1H), 5.35 – 5.11 (m, 1H), 3.88 – 3.58 (m, 2H), 3.34 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-methoxy-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (157)



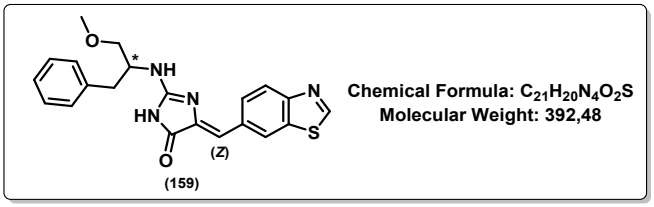
Compound (**157**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-2-methoxy-1-phenylethan-1-amine at 140 °C (sealed tube, heating block), for 26h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. Isolated yield: 28% (78 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.55 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.82 (s, 1H), 8.29 – 7.92 (m, 2H + NH, D_2O exchanged), 7.48 (d, J = 7.6 Hz, 2H), 7.38 (t, J = 7.5 Hz, 2H), 7.28 (t, J = 7.3 Hz, 1H), 6.42 (s, 1H), 5.35 – 5.11 (m, 1H), 3.88 – 3.58 (m, 2H), 3.34 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: >98%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(*tert*-butoxy)-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (158)



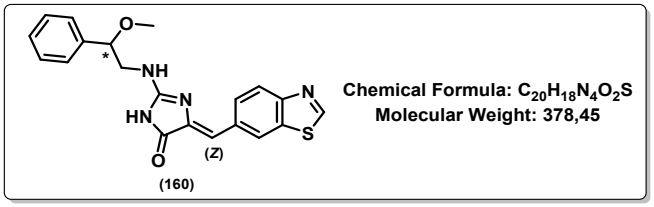
Compound (**158**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 545 µmol scale of intermediate (**9.4**), with 4 eq of (*R*)-2-(*tert*-butoxy)-1-phenylethan-1-amine and 2 eq of AcOH at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 22% (50 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.39 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.82 (s, 1H), 8.13 (d, J = 8.6 Hz, 1H), 8.00 (d, J = 8.5 Hz, 1H), 7.66 (br s, 1H, NH, D_2O exchanged), 7.55 – 7.19 (m, 5H), 6.42 (s, 1H), 5.16 – 4.96 (m, 1H), 3.81 – 3.58 (m, 2H), 1.16 (s, 9H). MS (ESI$^+$) : $[M+H]^+$ 421.3. HPLC: 95%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methoxy-3-phenylpropan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (159)



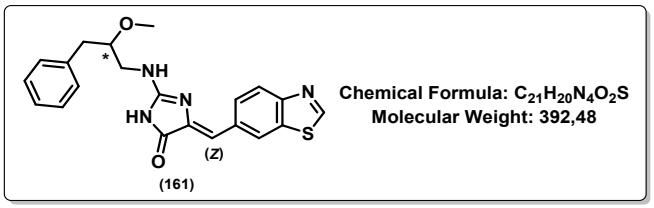
Compound (**159**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-1-methoxy-3-phenylpropan-2-amine at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 55% (59 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.09 (br s, 1H, NH, D_2O exchanged), 9.29 (s, 1H), 8.96 – 8.72 (m, 1H), 8.33 – 8.07 (m, 1H), 8.03 (d, J = 8.0 Hz, 1H), 7.39 – 7.26 (m, 4H), 7.25 – 7.18 (m, 1H), 7.12 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.38 – 4.26 (m, 1H), 3.57 – 3.44 (m, 2H), 3.35 (s, 3H), 3.05 – 2.90 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 393.2. HPLC: 96%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-methoxy-2-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (160)



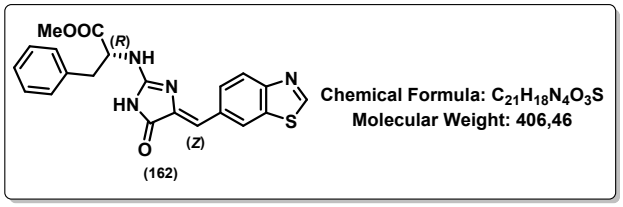
Compound (**160**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2-methoxy-2-phenylethan-1-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 78% (80 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.57 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.94 (s, 1H), 8.20 (dd, J = 8.6, 1.6 Hz, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 7.53 – 7.26 (m, 5H), 6.45 (s, 1H), 4.73 – 4.41 (m, 1H), 3.80 – 3.42 (m, 2H), 3.21 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 379.2. HPLC: 98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-methoxy-3-phenylpropyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (161)



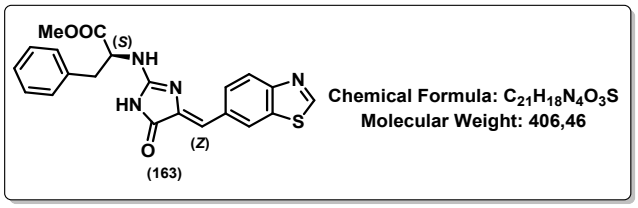
Compound (**161**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2-methoxy-3-phenylpropan-1-amine at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 61% (65 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.44 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.94 – 8.73 (m, 1H), 8.36 – 8.10 (m, 1H), 8.00 (d, J = 8.6 Hz, 1H), 7.41 (br s, 1H, NH, D_2O exchanged), 7.36 – 7.17 (m, 5H), 6.43 (s, 1H), 3.77 – 3.66 (m, 1H), 3.60 – 3.41 (m, 2H), 3.35 (s, 3H), 2.91 – 2.78 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 393.2. HPLC: 96%.

Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-D-phenylalaninate (162)



Compound (**162**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 4 eq of methyl D-phenylalaninate hydrochloride and 6 eq of TEA at 140 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 19% (57 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.68 (br s, 1H, D_2O exchanged), 9.38 (s, 1H), 8.82 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.00 (br s, 1H, NH, D_2O exchanged), 7.39 – 7.18 (m, 5H), 6.47 (s, 1H), 4.82 – 4.66 (m, 1H), 3.68 (s, 3H), 3.26 – 3.09 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 407.1. HPLC: >98%.

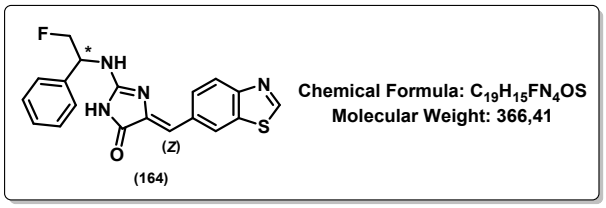
Synthesis of methyl (*Z*)-(4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)-L-phenylalaninate (163)



Compound (**163**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of methyl L-phenylalaninate hydrochloride and 4 eq of DIPEA at

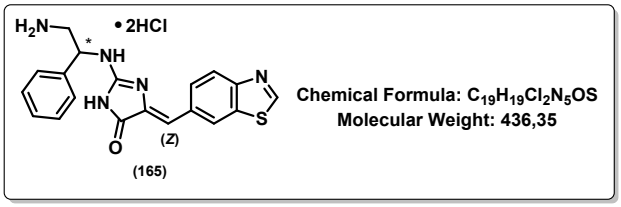
120 °C (sealed tube, heating block), for 8h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 65% (72 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.68 (br s, 1H, D_2O exchanged), 9.38 (s, 1H), 8.82 (s, 1H), 8.19 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.5 Hz, 1H), 8.00 (br s, 1H, NH, D_2O exchanged), 7.39 – 7.18 (m, 5H), 6.47 (s, 1H), 4.82 – 4.66 (m, 1H), 3.68 (s, 3H), 3.26 – 3.09 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 407.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-fluoro-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (164)



Compound (**164**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-2-fluoro-1-phenylethan-1-amine at 120 °C (sealed tube, heating block), for 96h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 50% (53 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.76 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.83 (s, 1H), 8.45 (br s, 1H, NH, D_2O exchanged), 8.19 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.58 – 7.16 (m, 5H), 6.44 (s, 1H), 5.58 – 5.22 (m, 1H), 4.96 – 4.52 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 367.1. HPLC: 94%.

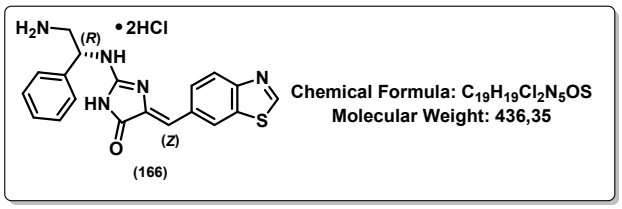
Synthesis of (*Z*)-2-((2-amino-1-phenylethyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one dihydrochloride (165)



Compound (**165**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*tert*-butyl (2-amino-2-phenylethyl)carbamate at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final compound was isolated after deprotection of Boc with HCl dioxane (4M) in THF at 70 °C and lyophilization. Isolated yield: 63% (107 mg, 2 steps). Hygroscopic pale yellow foamy solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.38 (s, 1H), 8.88 – 8.73 (m, 1H), 8.28 (br s, 3H, NH, D_2O exchanged), 8.14 – 8.02 (m, 2H), 7.53 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 6.55 (s, 1H), 5.53 – 5.35 (m, 1H), 4.45 (br s, 3H, NH, D_2O exchanged), 3.50 – 3.37 (m, 1H), 3.34 – 3.22 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 364.1 (+2HCl). HPLC: >98%.

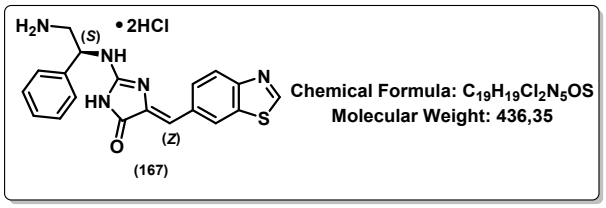
Note: attempt to run the final deprotection of Boc at r.t. will result in a mixture of mono- and bis-hydrochlorides.

Synthesis of (*R*,*Z*)-2-((2-amino-1-phenylethyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one dihydrochloride (166)



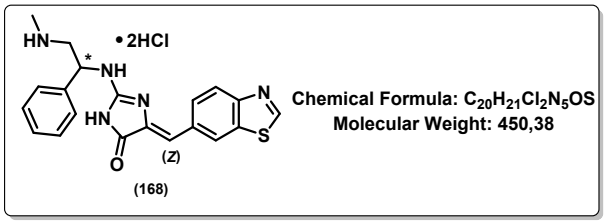
Compound (**166**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *tert*-butyl (*R*)-(2-amino-2-phenylethyl)carbamate at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final compound was isolated after deprotection of Boc with HCl dioxane (4M) in THF at 70 °C and lyophilization. Isolated yield: 72% (121 mg, 2 steps). Hygroscopic pale yellow foamy solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.38 (s, 1H), 8.88 – 8.73 (m, 1H), 8.28 (br s, 3H, NH, D_2O exchanged), 8.14 – 8.02 (m, 2H), 7.53 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 6.55 (s, 1H), 5.53 – 5.35 (m, 1H), 4.45 (br s, 3H, NH, D_2O exchanged), 3.50 – 3.37 (m, 1H), 3.34 – 3.22 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 364.1 (+2HCl). HPLC: 98%.

Synthesis of (*R*,*Z*)-2-((2-amino-1-phenylethyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one dihydrochloride (167)



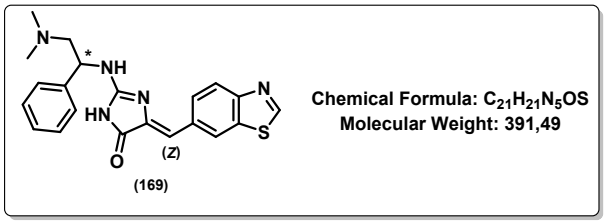
Compound (**167**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *tert*-butyl (*S*)-(2-amino-2-phenylethyl)carbamate at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final compound was isolated after deprotection of Boc with HCl dioxane (4M) in THF at 70 °C and lyophilization. Isolated yield: 59% (100 mg, 2 steps). Hygroscopic pale yellow foamy solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 9.38 (s, 1H), 8.88 – 8.73 (m, 1H), 8.28 (br s, 3H, NH, D_2O exchanged), 8.14 – 8.02 (m, 2H), 7.53 (d, J = 7.3 Hz, 2H), 7.44 (t, J = 7.6 Hz, 2H), 7.35 (t, J = 7.3 Hz, 1H), 6.55 (s, 1H), 5.53 – 5.35 (m, 1H), 4.45 (br s, 3H, NH, D_2O exchanged), 3.50 – 3.37 (m, 1H), 3.34 – 3.22 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 364.1 (+2HCl). HPLC: 98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(methylamino)-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one dihydrochloride (168)



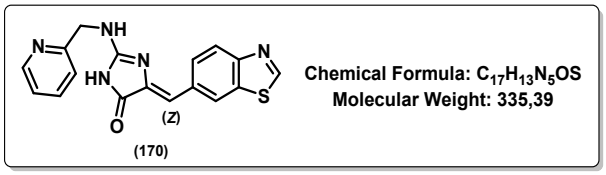
Compound (**168**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 3 eq of (±)-*tert*-butyl (2-amino-2-phenylethyl)(methyl)carbamate at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final compound was isolated after deprotection of Boc with HCl dioxane (4M) in THF at 70 °C and lyophilization. Isolated yield: 54% (93 mg, 2 steps). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6 + D_2O, 300K) of major tautomer δ_H 9.39 (s, 1H), 8.82 (s, 1H), 8.18 (s, 1H), 8.06 (d, J = 8.3 Hz, 1H), 7.73 – 7.28 (m, 5H), 6.52 (s, 1H), 5.61 – 5.43 (m, 1H), 3.43 – 3.33 (m, 1H), 3.14 – 3.04 (m, 1H), 2.66 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 378.2 (+2HCl). HPLC: 84% (mono-HCl) + 14% (di-HCl).

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(dimethylamino)-1-phenylethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (169)



Compound (**169**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-N^1,N^1-dimethyl-2-phenylethane-1,2-diamine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in EtOH. Isolated yield: 68% (72 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.56 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.86 – 8.66 (m, 1H), 8.15 – 7.96 (m, 2H), 7.83 (br s, 1H, NH, D_2O exchanged), 7.51 – 7.21 (m, 5H), 6.40 (s, 1H), 5.17 – 4.80 (m, 1H), 2.81 (dd, J = 12.5, 9.4 Hz, 1H), 2.49 – 2.42 (m, 1H), 2.26 (s, 6H). MS (ESI$^+$) : $[M+H]^+$ 392.1. HPLC: >98%.

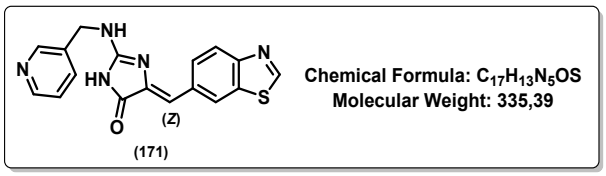
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((pyridin-2-ylmethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (170)



(170)

Compound (**170**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of pyridin-2-ylmethanamine at 120 °C (sealed tube, heating block), for 3h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 76% (46 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.84 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.79 (s, 1H), 8.57 (d, J = 4.9 Hz, 1H), 8.21 (d, J = 8.6 Hz, 1H), 8.12 (br s, 1H, NH, D_2O exchanged), 8.01 (d, J = 8.5 Hz, 1H), 7.81 (td, J = 7.7, 1.9 Hz, 1H), 7.51 – 7.43 (m, 1H), 7.34 – 7.26 (m, 1H), 6.44 (s, 1H), 4.72 – 4.48 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 336.2. HPLC: >98%.

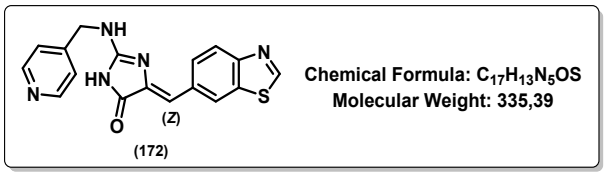
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((pyridin-3-ylmethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (171)



(171)

Compound (**171**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of pyridin-3-ylmethanamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH at 0 °C. Isolated yield: 72% (181 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.95 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.91 – 8.75 (m, 1H), 8.73 – 8.57 (m, 1H), 8.47 (dd, J = 4.8, 1.7 Hz, 1H), 8.30 – 8.20 (m, 1H), 8.15 (br s, 1H, NH, D_2O exchanged), 8.03 (d, J = 8.5 Hz, 1H), 7.89 – 7.78 (m, 1H), 7.39 (dd, J = 7.8, 4.8 Hz, 1H), 6.45 (s, 1H), 4.72 – 4.48 (m, 2H). MS (ESI$^+$) : $[M+H]^+$: 336.2. HPLC: >98%.

Synthesis of (Z)-5-(benzo[d]thiazol-6-ylmethylene)-2-((pyridin-4-ylmethyl)amino)-3,5-dihydro-4H-imidazol-4-one (172)

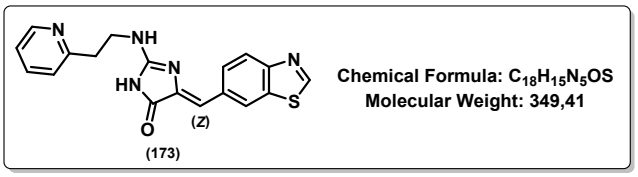


(172)

Compound (**172**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.3**), with 3 eq of pyridin-4-ylmethanamine at 110 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was isolated after

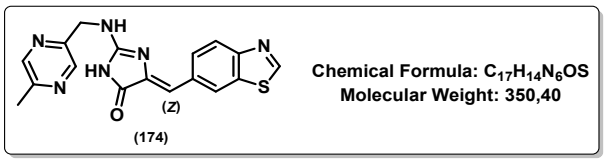
filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH at 0 °C. Isolated yield: 55% (137 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.04 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.79 (s, 1H), 8.55 (d, J = 5.9 Hz, 2H), 8.20 (d, J = 8.4 Hz, 1H), 8.15 (br s, 1H, NH, D_2O exchanged), 8.02 (d, J = 8.6 Hz, 1H), 7.41 (d, J = 4.6 Hz, 2H), 6.45 (s, 1H), 4.72 – 4.54 (m, 2H). MS (ESI$^+$) : $[M+H]^+$: 336.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(pyridin-2-yl)ethyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (173)



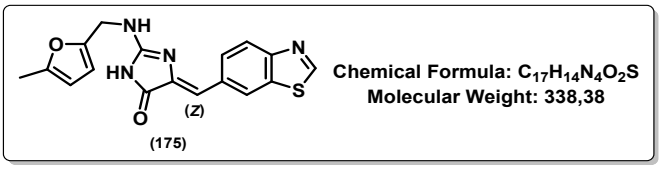
Compound (**173**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of 2-(pyridin-2-yl)ethan-1-amine at 120 °C (sealed tube, heating block), for 3.5h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 77% (73 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.67 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.87 (s, 1H), 8.54 (d, J = 4.9 Hz, 1H), 8.30 – 8.18 (m, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.75 (td, J = 7.6, 1.9 Hz, 1H), 7.53 (br s, 1H, NH, D_2O exchanged verifier), 7.35 (d, J = 7.8 Hz, 1H), 7.27 – 7.22 (m, 1H), 6.41 (s, 1H), 3.85 – 3.68 (m, 2H), 3.16 – 3.03 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 350.1. HPLC: 95%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((5-methylpyrazin-2-yl)methyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (174)



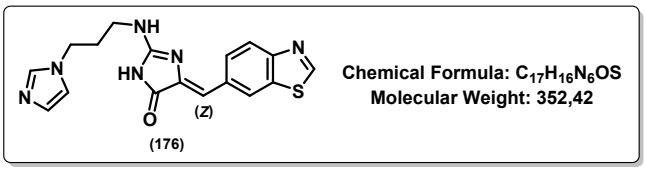
Compound (**174**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 145 µmol scale of intermediate (**9.4**), with 3 eq of (5-methylpyrazin-2-yl)methanamine at 80 °C (sealed tube, heating block), for 16h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 47% (24 mg). Yellow solid. ^{1}H NMR (500 MHz, Methanol-d_4, 300K) of major tautomer δ_H 9.24 (s, 1H), 8.89 – 8.56 (m, 2H), 8.52 (s, 1H), 8.22 – 7.78 (m, 2H), 6.65 (s, 1H), 4.81 (s, 2H), 2.54 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 351.2. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((5-methylfuran-2-yl)methyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (175)



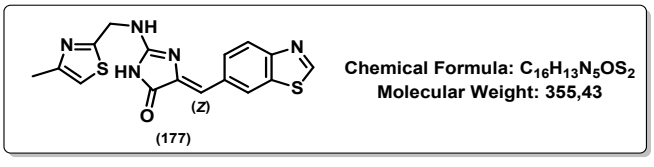
Compound (**175**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of (5-methylfuran-2-yl)methanamine at 120 °C (sealed tube, heating block), for 5h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 59% (36 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.77 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.86 (s, 1H), 8.27 (d, J = 8.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.99 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 6.26 (d, J = 3.1 Hz, 1H), 6.02 (dd, J = 3.0, 1.3 Hz, 1H), 4.53 (s, 2H), 2.25 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 339.2. HPLC: >98%.

Synthesis of (*Z*)-2-((3-(1*H*-imidazol-1-yl)propyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (176)



Compound (**176**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of 3-(1*H*-imidazol-1-yl)propan-1-amine at 120 °C (sealed tube, heating block), for 2h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 77% (75 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.86 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.86 – 8.71 (m, 1H), 8.39 – 8.20 (m, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.74 (s, 1H), 7.65 (br s, 1H, NH, D_2O exchanged), 7.26 (s, 1H), 6.95 (s, 1H), 6.42 (s, 1H), 4.08 (t, J = 7.0 Hz, 2H), 3.45 – 3.28 (m, 2H), 2.12 – 1.97 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 353.2. HPLC: >98%.

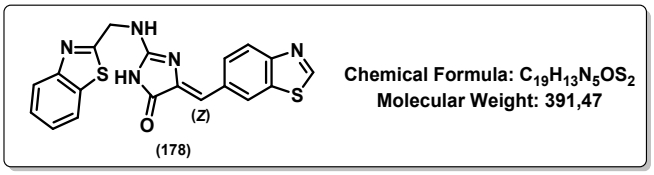
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((4-methylthiazol-2-yl)methyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (177)



Compound (**177**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of (4-methylthiazol-2-yl)methanamine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a trituration in refluxing EtOH. Isolated yield: 40% (26 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.01 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.88

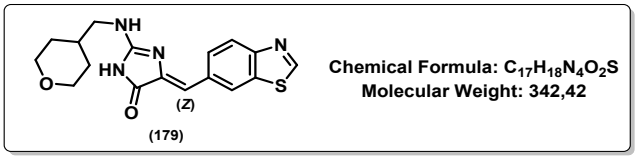
(s, 1H), 8.33 (br s, 1H, NH, D_2O exchanged), 8.22 (d, *J* = 8.5 Hz, 1H), 8.02 (d, *J* = 8.6 Hz, 1H), 7.18 (s, 1H), 6.49 (s, 1H), 4.84 (s, 2H), 2.36 (s, 3H). MS (ESI^+) : $[M+H]^+$ 356.2. HPLC: >98%.

Synthesis of (*Z*)-2-((benzo[*d*]thiazol-2-ylmethyl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (178)



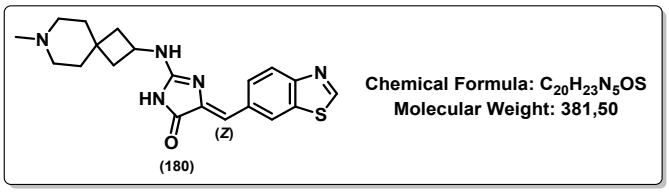
Compound (**178**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of benzo[*d*]thiazol-2-ylmethanamine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required two successive triturations: one in refluxing EtOH and the other in refluxing MeOH. Isolated yield: 94% (100 mg). Yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.13 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.86 (s, 1H), 8.47 (br s, 1H, NH, D_2O exchanged), 8.19 (d, *J* = 8.5 Hz, 1H), 8.06 (d, *J* = 8.1 Hz, 1H), 8.00 (t, *J* = 9.0 Hz, 2H), 7.51 (t, *J* = 7.6 Hz, 1H), 7.41 (t, *J* = 7.6 Hz, 1H), 6.50 (s, 1H), 5.12 – 4.91 (m, 2H). MS (ESI^+) : $[M+H]^+$ 392.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((tetrahydro-2*H*-pyran-4-yl)methyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (179)



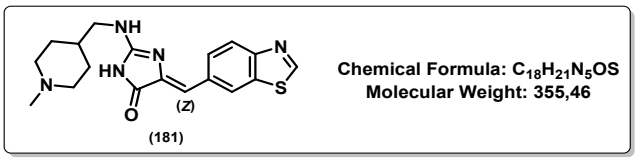
Compound (**179**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of (tetrahydro-2*H*-pyran-4-yl)methanamine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 51% (32 mg). Yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.64 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.83 (s, 1H), 8.36 – 8.18 (m, 1H), 8.03 (d, *J* = 8.5 Hz, 1H), 7.56 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 3.97 – 3.78 (m, 2H), 3.31 – 3.11 (m, 3H), 2.03 – 1.74 (m, 1H), 1.63 (d, *J* = 13.1 Hz, 2H), 1.43 – 1.10 (m, 3H). MS (ESI^+) : $[M+H]^+$ 343.3. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((7-methyl-7-azaspiro[3.5]nonan-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (180)



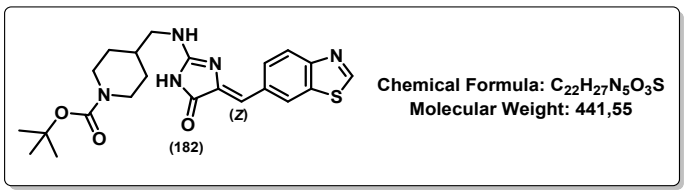
Compound (**180**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 540 µmol scale of intermediate (**9.3**), with 3 eq of 7-methyl-7-azaspiro[3.5]nonan-2-amine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 17% (35 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.22 (br s, 1H, NH, D_2O exchanged), 9.33 (s, 1H), 8.93 – 8.64 (m, 1H), 8.33 – 8.09 (m, 1H + NH, D_2O exchanged), 8.02 (d, J = 8.1 Hz, 1H), 6.39 (s, 1H), 4.45 – 4.14 (m, 1H), 2.33 – 2.16 (m, 4H), 2.11 (s, 3H), 1.95 – 1.74 (m, 3H), 1.65 – 1.45 (m, 5H). MS (ESI$^+$) : $[M+H]^+$ 382.3. HPLC : 90%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((1-methylpiperidin-4-yl)methyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (181)



Compound (**181**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 919 µmol scale of intermediate (**9.3**), with 4 eq of (1-methylpiperidin-4-yl)methanamine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 30% (99 mg). Yellow solid. ^{1}H NMR (500 MHz, Methanol-d_4, 300K) of major tautomer δ_H 9.24 (s, 1H), 8.81 – 7.74 (m, 3H), 6.65 (s, 1H), 3.59 – 3.36 (m, 2H), 3.28 – 3.14 (m, 2H), 2.73 – 2.42 (m, 5H), 2.09 – 1.76 (m, 3H), 1.63 – 1.38 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 356.2. HPLC : 92%.

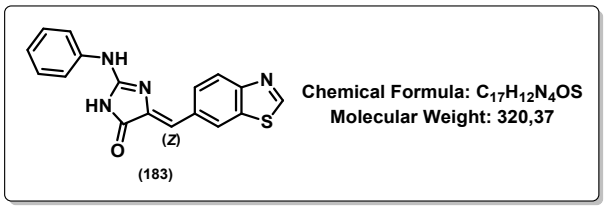
Synthesis of *tert*-butyl (*Z*)-4-(((4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)methyl)piperidine-1-carboxylate (182)



Compound (**182**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of *tert*-butyl 4-(aminomethyl)piperidine-1-carboxylate at 120 °C (sealed tube, heating block), for 3.5h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 50% (60 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.64 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.83 (s, 1H), 8.38 – 8.17 (m, 1H), 8.02 (d, J = 8.5 Hz, 1H), 7.56 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 4.15 – 3.81 (m, 2H), 3.31 – 3.01 (m,

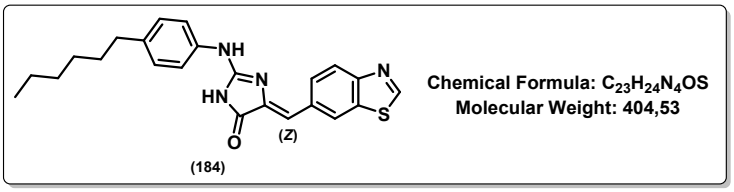
2H), 2.90 – 2.57 (m, 2H), 1.96 – 1.60 (m, 3H), 1.39 (s, 9H), 1.19 – 0.94 (m, 2H).. MS (ESI$^+$) : $[M+H]^+$ 442.3. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(phenylamino)-3,5-dihydro-4*H*-imidazol-4-one (183)



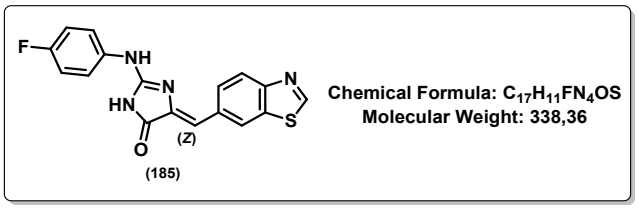
Compound (**183**) was synthesized according to **GP11-A**, in THF (1M/isothiourea), on a 873 µmol scale of intermediate (**9.3**), with 10 eq of aniline at 150 °C (sealed tube, µw Anton Paar), for 1.5h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 64% (178 mg). Beige solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) δ_H 10.79 (br s, 1H, NH, D_2O exchanged), 9.94 (br s, 1H, NH, D_2O exchanged), 9.41 (s, 1H), 8.86 (s, 1H), 8.35 (d, J = 8.6 Hz, 1H), 8.11 (d, J = 8.5 Hz, 1H), 7.82 (d, J = 7.9 Hz, 2H), 7.42 (t, J = 7.8 Hz, 2H), 7.12 (t, J = 7.4 Hz, 1H), 6.66 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 321.2. HPLC : >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-hexylphenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (184)



Compound (**184**) was synthesized according to **GP11-A**, in THF (1M/isothiourea), on a 1.05 mmol scale of intermediate (**9.3**), with 10 eq of 4-hexylaniline at 170 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 43% (183 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.76 (br s, 1H, NH, D_2O exchanged), 9.85 (br s, 1H, NH, D_2O exchanged), 9.41 (s, 1H), 8.85 (s, 1H), 8.49 – 8.24 (m, 1H), 8.22 – 8.02 (m, 1H), 7.90 – 7.54 (m, 2H), 7.37 – 7.11 (m, 2H), 6.63 (s, 1H), 2.67 – 2.53 (m, 2H), 1.72 – 1.47 (m, 2H), 1.29 (s, 6H), 0.87 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 405.3. HPLC: >98%.

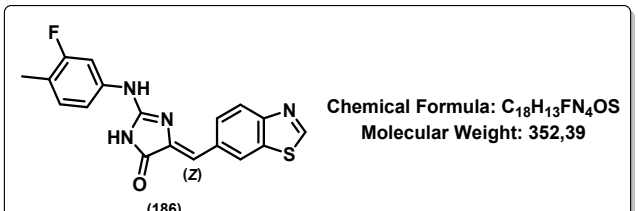
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-fluorophenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (185)



(185)

Compound (**185**) was synthesized according to **GP11-A**, in THF (0.2M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 4-fluoroaniline at 150 °C (sealed tube, heating block), for 4h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 57% (35 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.87 (br s, 1H, NH, D_2O exchanged), 9.97 (br s, 1H, NH, D_2O exchanged), 9.41 (s, 1H), 8.81 (s, 1H), 8.36 (d, J = 8.9 Hz, 1H), 8.10 (d, J = 8.6 Hz, 1H), 7.91 – 7.76 (m, 2H), 7.26 (t, J = 8.8 Hz, 2H), 6.65 (s, 1H).MS (ESI$^+$) : $[M+H]^+$ 339.1. HPLC: >98%.

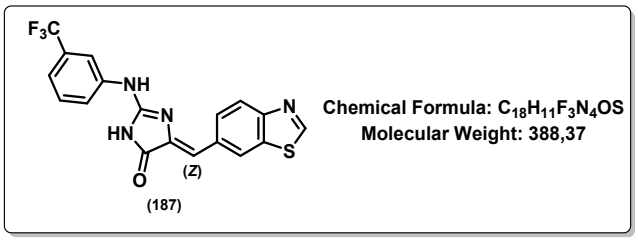
Synthesis of (Z)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-fluoro-4-methylphenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (186)



(186)

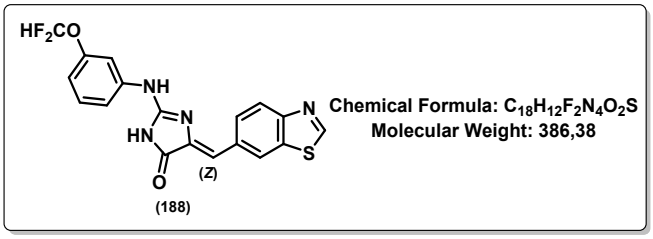
Compound (**186**) was synthesized according to **GP11-A**, in THF (0.2M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 3-fluoro-4-methylaniline at 150 °C (sealed tube, heating block), for 4h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 69% (44 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.89 (s, 1H, NH, D_2O exchanged), 10.08 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 8.95 (s, 1H), 8.25 (d, J = 7.0 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.92 (d, J = 12.9 Hz, 1H), 7.38 (d, J = 8.2 Hz, 1H), 7.29 (t, J = 8.5 Hz, 1H), 6.68 (s, 1H), 2.23 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 353.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-(trifluoromethyl)phenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (187)



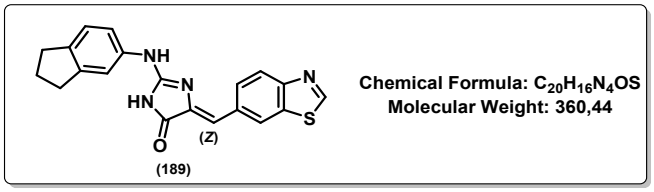
Compound (**187**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 3-(trifluoromethyl)aniline at 200 °C (sealed tube, µw Anton Paar), for 6h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 33% (23 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.02 (br s, 1H, NH, D_2O exchanged), 10.34 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 8.96 (s, 1H), 8.85 (s, 1H), 8.24 (d, *J* = 8.5 Hz, 1H), 8.05 (d, *J* = 8.5 Hz, 1H), 7.75 (d, *J* = 8.3 Hz, 1H), 7.62 (t, *J* = 7.8 Hz, 1H), 7.46 (d, *J* = 7.6 Hz, 1H), 6.74 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 389.1. HPLC: 95%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-(difluoromethoxy)phenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (188)



Compound (**188**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 254 µmol scale of intermediate (**9.4**), with 5 eq of 3-(difluoromethoxy)aniline at 200 °C (sealed tube, µw Anton Paar), for 4h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 36% (35 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.87 (br s, 1H, NH, D_2O exchanged), 10.19 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 8.88 (s, 1H), 8.37 – 8.27 (m, 1H), 8.17 (s, 1H), 8.06 (d, *J* = 8.5 Hz, 1H), 7.49 – 7.30 (m, 3H), 6.98 – 6.86 (m, 1H), 6.71 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 387.1. HPLC: 96%.

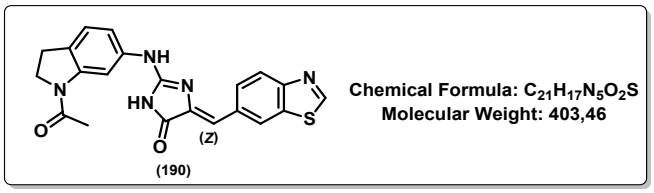
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2,3-dihydro-1*H*-inden-5-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (189)



Compound (**189**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 2,3-dihydro-1*H*-inden-5-amine at 150 °C (sealed tube, µw

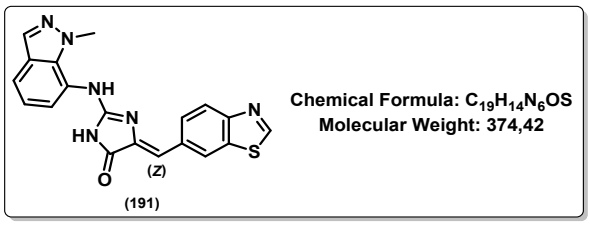
Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 76% (50 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.72 (br s, 1H, NH, D_2O exchanged), 9.83 (br s, 1H, NH, D_2O exchanged), 9.40 (s, 1H), 9.03 (s, 1H), 8.21 (d, J = 8.5 Hz, 1H), 8.08 (d, J = 8.5 Hz, 1H), 7.93 (s, 1H), 7.38 (d, J = 8.1 Hz, 1H), 7.23 (d, J = 8.1 Hz, 1H), 6.62 (s, 1H), 2.96 (t, J = 7.3 Hz, 2H), 2.86 (t, J = 7.3 Hz, 2H), 2.08 (p, J = 7.4 Hz, 2H). MS (ESI$^+$) : $[M+H]^+$ 361.1. HPLC: >98%.

Synthesis of (*Z*)-2-((1-acetylindolin-6-yl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (190)



Compound (**190**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 1-(6-aminoindolin-1-yl)ethan-1-one at 200 °C (sealed tube, µw Anton Paar), for 6h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 44% (32 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.57 (br s, 1H, NH, D_2O exchanged), 9.89 (br s, 1H, NH, D_2O exchanged), 9.39 (s, 1H), 9.27 – 9.00 (m, 2H), 8.32 – 8.00 (m, 2H), 7.36 – 7.06 (m, 2H), 6.64 (s, 1H), 4.31 – 4.04 (m, 2H), 3.20 – 3.06 (m, 2H), 2.31 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 404.2. HPLC: 98%.

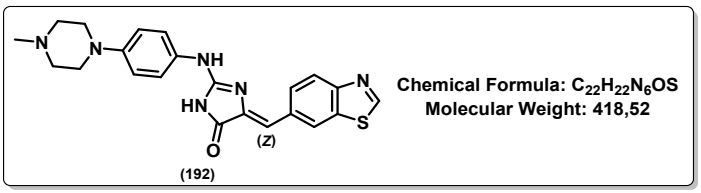
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methyl-1*H*-indazol-7-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (191)



Compound (**191**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 1-methyl-1*H*-indazol-7-amine and 15 eq of AcOH at 130 °C (sealed tube, µw Anton Paar), for 5h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 52% (36 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.21 (br s, 1H, NH, D_2O exchanged), 10.40 (br s, 1H, NH,

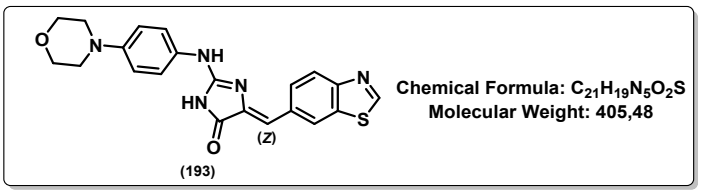
D_2O exchanged), 9.39 (s, 1H), 8.74 – 8.59 (m, 1H), 8.16 – 7.91 (m, 3H), 7.72 – 7.41 (m, 1H), 7.27 – 6.88 (m, 2H), 6.50 (s, 1H), 4.19 (s, 3H). MS (ESI^+) : $[M+H]^+$ 375.1. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-(4-methylpiperazin-1-yl)phenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (192)



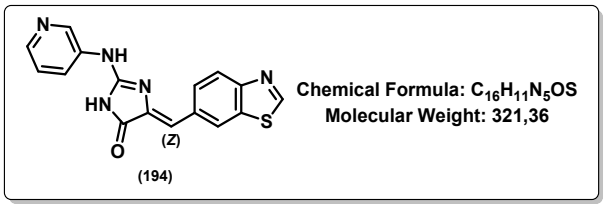
Compound (**192**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 831 µmol scale of intermediate (**9.3**), with 3 eq of 4-(4-methylpiperazin-1-yl)aniline at 150 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required two successive triturations in EtOH. Isolated yield: 65% (225 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.73 (br s, 1H, NH, D_2O exchanged), 9.73 (br s, 1H, NH, D_2O exchanged), 9.39 (s, 1H), 8.88 – 8.77 (m, 1H), 8.43 – 8.30 (m, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.73 – 7.53 (m, 2H), 6.99 (d, J = 8.5 Hz, 2H), 6.57 (s, 1H), 3.18 – 3.10 (m, 4H), 2.48 – 2.44 (m, 4H), 2.23 (s, 3H). MS (ESI^+) : $[M+H]^+$ 419.2. HPLC: 97%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4-morpholinophenyl)amino)-3,5-dihydro-4*H*-imidazol-4-one (193)



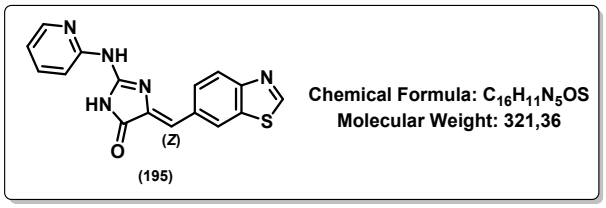
Compound (**193**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of 4-morpholinoaniline at 150 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 90% (66 mg). Yellow solid. ^1H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.72 (br s, 1H, NH, D_2O exchanged), 9.73 (br s, 1H, NH, D_2O exchanged), 9.39 (s, 1H), 8.83 (s, 1H), 8.35 (d, J = 8.7 Hz, 1H), 8.09 (d, J = 8.5 Hz, 1H), 7.66 (d, J = 8.2 Hz, 2H), 7.01 (d, J = 8.6 Hz, 2H), 6.58 (s, 1H), 3.81 – 3.72 (m, 4H), 3.15 – 3.06 (m, 4H). MS (ESI^+) : $[M+H]^+$ 406.2. HPLC: 98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(pyridin-3-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (194)



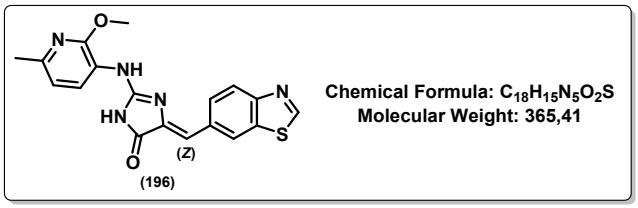
Compound (**193**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of pyridin-3-amine and 15 eq of AcOH at 150 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 87% (51 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.03 (br s, 1H, NH, D_2O exchanged), 10.16 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 9.06 – 8.90 (m, 1H), 8.87 – 8.78 (m, 1H), 8.44 – 8.21 (m, 3H), 8.11 (d, J = 8.5 Hz, 1H), 7.49 – 7.41 (m, 1H), 6.70 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 322.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(pyridin-2-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (195)



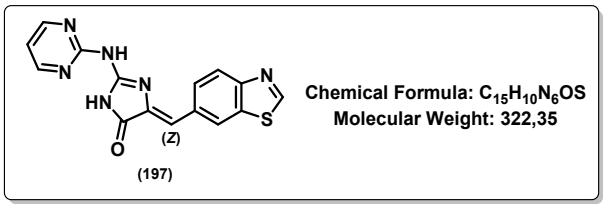
Compound (**195**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 1.04 mmol scale of intermediate (**9.3**), with 5 eq of pyridin-2-amine at 220 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 9% (31 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.20 (br s, 1H, NH, D_2O exchanged), 10.97 (br s, 1H, NH, D_2O exchanged), 9.43 (s, 1H), 8.88 (s, 1H), 8.49 – 8.26 (m, 2H), 8.12 (d, J = 8.6 Hz, 1H), 7.84 (t, J = 8.0 Hz, 1H), 7.66 – 7.33 (m, 1H), 7.23 – 6.98 (m, 1H), 6.76 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 322.2. HPLC: 96%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-methoxy-6-methylpyridin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (196)



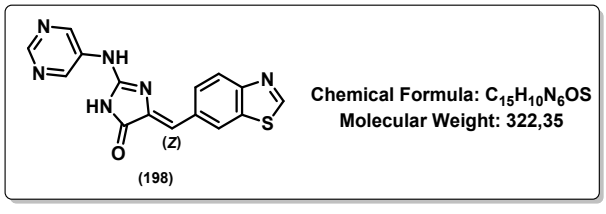
Compound (**196**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 2-methoxy-6-methylpyridin-3-amine and 15 eq of AcOH at 130 °C (sealed tube, µw Anton Paar), for 1.5h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 16% (11 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.30 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 9.06 (br s, 1H, NH, D_2O exchanged), 8.90 – 8.72 (m, 1H), 8.72 – 8.54 (m, 1H), 8.44 – 8.23 (m, 1H), 8.11 (d, J = 8.5 Hz, 1H), 6.99 (d, J = 7.7 Hz, 1H), 6.69 (s, 1H), 3.99 (s, 3H), 2.41 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 366.2. HPLC: 98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(pyrimidin-2-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (197)



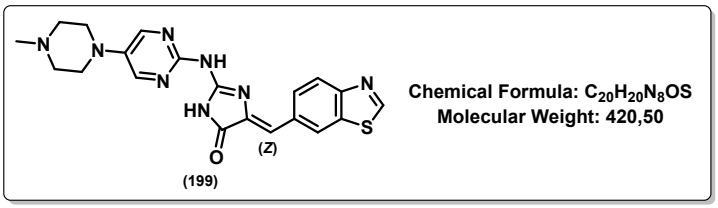
Compound (**197**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 873 µmol scale of intermediate (**9.3**), with 5 eq of pyrimidin-2-amine at 220 °C (sealed tube, µw Anton Paar), for 2h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in refluxing EtOH. Isolated yield: 8% (23 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.56 (br s, 1H, NH, D_2O exchanged), 11.37 (br s, 1H, NH, D_2O exchanged), 9.44 (s, 1H), 9.12 – 8.84 (m, 1H), 8.65 (d, J = 4.9 Hz, 2H), 8.42 – 8.25 (m, 1H), 8.12 (d, J = 8.5 Hz, 1H), 7.38 – 7.06 (m, 1H), 6.81 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 323.2. HPLC: 98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(pyrimidin-5-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (198)



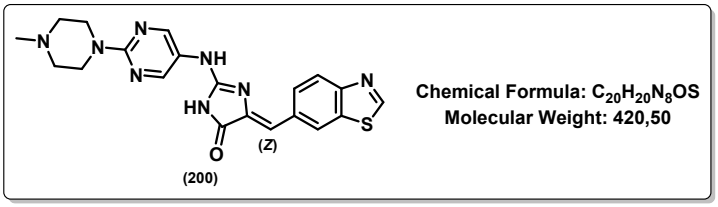
Compound (**198**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 363 µmol scale of intermediate (**9.4**), with 5 eq of pyrimidin-5-amine and 15 eq of AcOH at 120 °C (sealed tube, heating block), for 16h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 76% (89 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.30 (br s, 1H, NH, D_2O exchanged), 10.37 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 9.41 – 9.02 (m, 2H), 8.92 (s, 1H), 8.88 – 8.69 (m, 1H), 8.45 – 8.17 (m, 1H), 8.10 (d, J = 8.5 Hz, 1H), 6.93 – 6.49 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 323.1. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((5-(4-methylpiperazin-1-yl)pyrimidin-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (199)



Compound (**199**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 5 eq of 5-(4-methylpiperazin-1-yl)pyrimidin-2-amine and 15 eq of AcOH at 150 °C (sealed tube, heating block), for 96h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 49% (57 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 11.00 (br s, 2H, NH, D_2O exchanged), 9.35 (s, 1H), 8.79 (s, 1H), 8.38 (s, 2H), 8.25 – 7.98 (m, 2H), 6.72 (s, 1H), 3.26 – 3.17 (m, 4H), 2.54 – 2.51 (m, 4H), 2.27 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 421.2. HPLC: >98%.

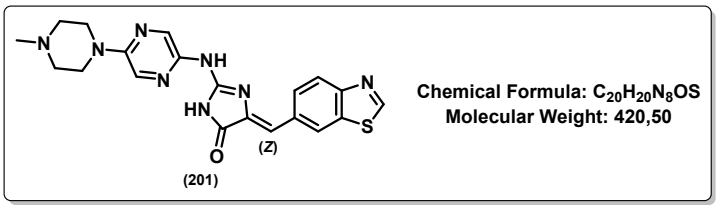
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((2-(4-methylpiperazin-1-yl)pyrimidin-5-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (200)



Compound (**200**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 5 eq of 2-(4-methylpiperazin-1-yl)pyrimidin-5-amine and 15 eq of AcOH at 150 °C (sealed tube, heating block), for 1.5h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 61% (70 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.12 (br s, 1H, NH, D_2O exchanged), 9.79 (br s, 1H, NH, D_2O exchanged), 9.39

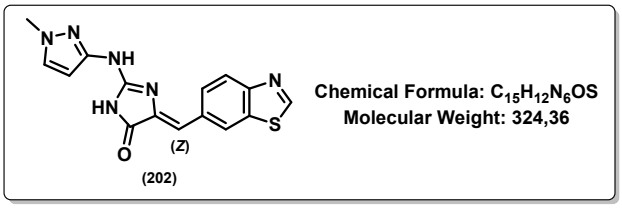
(s, 1H), 8.93 – 8.52 (m, 3H), 8.32 – 8.16 (m, 1H), 8.06 (d, *J* = 8.6 Hz, 1H), 6.58 (s, 1H), 3.86 – 3.65 (m, 4H), 2.48 – 2.36 (m, 4H), 2.26 (s, 3H). MS (ESI^+) : $[M+H]^+$ 421.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((5-(4-methylpiperazin-1-yl)pyrazin-2-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (201)



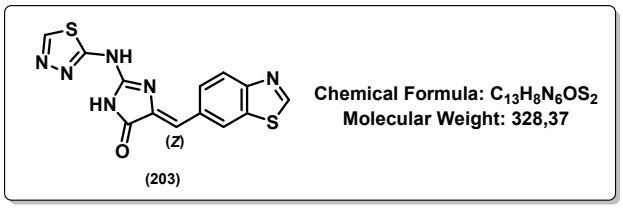
Compound (**201**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 5 eq of 5-(4-methylpiperazin-1-yl)pyrazin-2-amine and 15 eq of AcOH at 150 °C (sealed tube, heating block), for 4h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). The final product required a trituration in EtOH. Isolated yield: 43% (49 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 11.35 (br s, 1H, NH, D_2O exchanged), 10.82 (br s, 1H, NH, D_2O exchanged), 9.42 (s, 1H), 9.01 – 7.83 (m, 5H), 6.64 (s, 1H), 3.60 – 3.44 (m, 4H), 2.48 – 2.41 (m, 4H), 2.24 (s, 3H). MS (ESI^+) : $[M+H]^+$ 421.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methyl-1*H*-pyrazol-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (202)



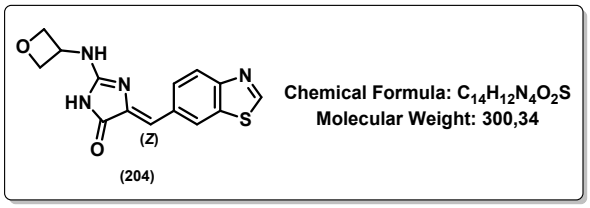
Compound (**202**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 1-methyl-1*H*-pyrazol-3-amine at 150 °C (sealed tube, heating block), for 3h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 71% (42 mg). Pale yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.58 (br s, 2H, NH, D_2O exchanged), 9.40 (s, 1H), 8.81 (s, 1H), 8.48 – 8.03 (m, 2H), 7.80 – 7.63 (m, 1H), 6.61 (s, 1H), 6.49 – 6.23 (m, 1H), 3.80 (s, 3H). MS (ESI^+) : $[M+H]^+$ 325.1. HPLC: >98%.

Synthesis of (*Z*)-2-((1,3,4-thiadiazol-2-yl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (203)



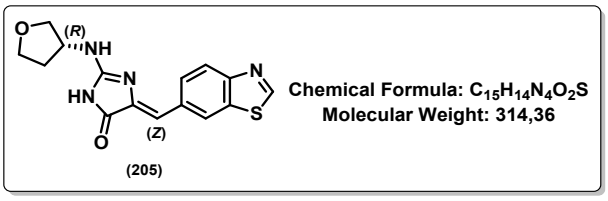
Compound (**203**) was synthesized according to **GP11-A**, in dioxane (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 5 eq of 1,3,4-thiadiazol-2-amine and 15 eq of AcOH at 150 °C (sealed tube, heating block), for 9h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required two successive triturations in refluxing EtOH. Isolated yield: 35% (21 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 12.52 (br s, 1H, NH, D_2O exchanged), 11.38 (br s, 1H, NH, D_2O exchanged), 9.44 (s, 1H), 9.18 – 9.03 (m, 1H), 8.87 – 8.71 (m, 1H), 8.53 – 8.24 (m, 1H), 8.15 (d, J = 8.4 Hz, 1H), 6.76 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 329.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(oxetan-3-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (204)



Compound (**204**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of oxetan-3-amine at 120 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 59% (48 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.92 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.92 – 8.73 (m, 1H), 8.44 (br s, 1H, NH, D_2O exchanged), 8.31 – 8.16 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H), 6.46 (s, 1H), 5.19 – 4.93 (m, 1H), 4.90 – 4.73 (m, 2H), 4.72 – 4.54 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 301.1. HPLC: >98%.

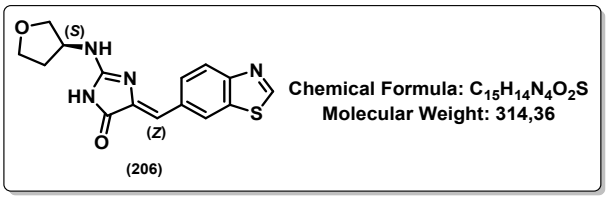
Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydrofuran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (205)



Compound (**205**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 1.04 mmol scale of intermediate (**9.3**), with 4 eq of (*R*)-tetrahydrofuran-3-amine at 110 °C (sealed tube, heating

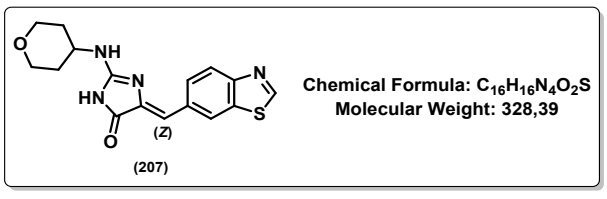
block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 34% (112 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.71 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.81 (s, 1H), 8.28 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.97 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.48 (s, 1H), 4.00 – 3.80 (m, 2H), 3.80 – 3.69 (m, 1H), 3.69 – 3.59 (m, 1H), 2.30 – 2.17 (m, 1H), 2.01 – 1.85 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 315.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydrofuran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (206)



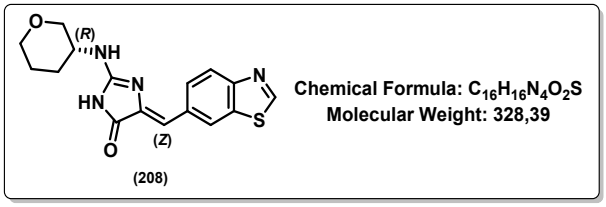
Compound (**206**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-tetrahydrofuran-3-amine at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 62% (153 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.71 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.81 (s, 1H), 8.28 (d, J = 8.7 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.97 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.48 (s, 1H), 4.00 – 3.80 (m, 2H), 3.80 – 3.69 (m, 1H), 3.69 – 3.59 (m, 1H), 2.30 – 2.17 (m, 1H), 2.01 – 1.85 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 315.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydro-2*H*-pyran-4-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (207)



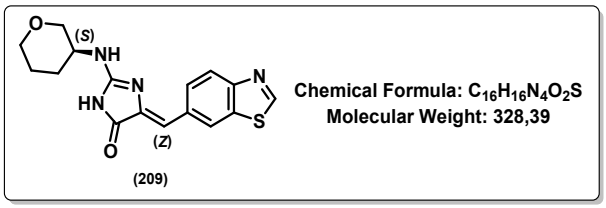
Compound (**207**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 182 µmol scale of intermediate (**9.4**), with 3 eq of tetrahydro-2*H*-pyran-4-amine at 100 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 70% (42 mg). Yellow solid. ^{1}H NMR (500 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.68 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.81 (s, 1H), 8.37 – 8.21 (m, 1H), 8.03 (d, J = 8.7 Hz, 1H), 7.66 (br s, 1H, NH, D_2O exchanged), 6.41 (s, 1H), 4.21 – 3.70 (m, 3H), 3.55 – 3.33 (m, 2H), 2.00 – 1.79 (m, 2H), 1.67 – 1.50 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 329.2. HPLC: 95%.

Synthesis of (*R*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydro-2*H*-pyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (208)



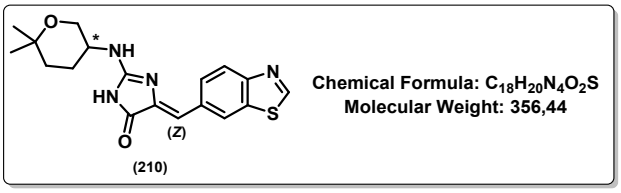
Compound (**208**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 1.04 mmol scale of intermediate (**9.3**), with 4 eq of (*R*)-tetrahydro-2*H*-pyran-3-amine hydrochloride and 6 eq of TEA at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required a reprecipitation from DCM/pentane at 0 °C. Isolated yield: 60% (203 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.45 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.77 (s, 1H), 8.28 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.62 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.18 – 3.36 (m, 5H), 2.09 – 1.88 (m, 1H), 1.81 – 1.46 (m, 3H). MS (ESI$^+$) : $[M+H]^+$ 329.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydro-2*H*-pyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (209)



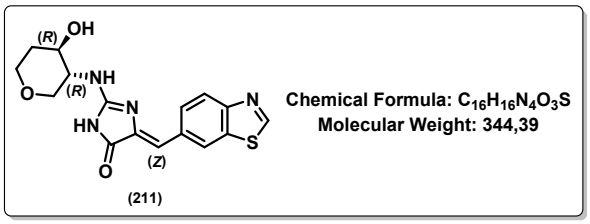
Compound (**209**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 7.53 mmol scale of intermediate (**9.4**), with 2.5 eq of (*S*)-tetrahydro-2*H*-pyran-3-amine hydrochloride and 6 eq of DIPEA at 130 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 92/8). The final product required a reprecipitation from DCM/Et_2O/pentane at 0 °C. Isolated yield: 68% (1.672 g). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.45 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.77 (s, 1H), 8.28 (s, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.62 (br s, 1H, NH, D_2O exchanged), 6.43 (s, 1H), 4.18 – 3.36 (m, 5H), 2.09 – 1.88 (m, 1H), 1.81 – 1.46 (m, 3H). MS (ESI$^+$) : $[M+H]^+$ 329.3 HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((6,6-dimethyltetrahydro-2*H*-pyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (210)



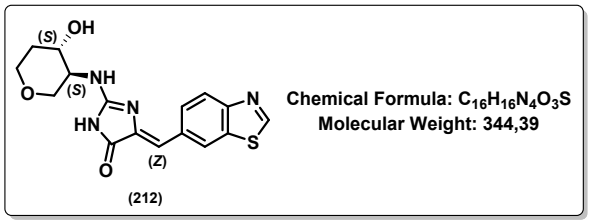
Compound (**210**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 261 µmol scale of intermediate (**9.4**), with 3 eq of (±)-6,6-dimethyltetrahydro-2*H*-pyran-3-amine at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 92/8). Isolated yield: 70% (65 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.20 (br s, 1H, NH, D_2O exchanged), 9.28 (s, 1H), 8.89 – 8.64 (m, 1H), 8.33 – 8.11 (m, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.14 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 3.95 – 3.72 (m, 2H), 3.62 – 3.49 (m, 1H), 2.01 – 1.76 (m, 2H), 1.73 – 1.60 (m, 1H), 1.58 – 1.46 (m, 1H), 1.29 – 1.15 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 357.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((3*R*,4*R*)-4-hydroxytetrahydro-2*H*-pyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (211)



Compound (**211**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 2.73 mmol scale of intermediate (**9.4**), with 2.5 eq of (3*R*,4*R*)-3-aminotetrahydro-2*H*-pyran-4-ol at 135 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was evaporated to dryness and triturated twice in MeOH at 0 °C. Isolated yield: 54% (512 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.12 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.89 – 8.54 (m, 1H), 8.34 – 8.08 (m, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.36 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 4.96 (br s, 1H, OH, D_2O exchanged), 4.01 (d, *J* = 11.2 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.78 – 3.58 (m, 2H), 3.41 (t, *J* = 10.7 Hz, 1H), 3.33 – 3.20 (m, 1H), 1.94 (d, *J* = 13.3 Hz, 1H), 1.63 – 1.47 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 345.2. HPLC: 97%.

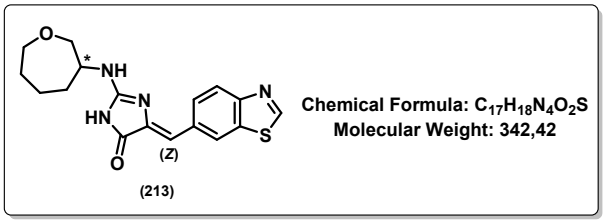
Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(((3*S*,4*S*)-4-hydroxytetrahydro-2*H*-pyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (212)



Compound (**212**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 508 µmol scale of intermediate (**9.4**), with 2.5 eq of (3*S*,4*S*)-3-aminotetrahydro-2*H*-pyran-4-ol at 135 °C (sealed tube, heating block), for 12h. The product directly precipitated in the reaction medium: it was evaporated to dryness and triturated twice in MeOH at 0 °C. Isolated yield: 58% (101 mg). Yellow

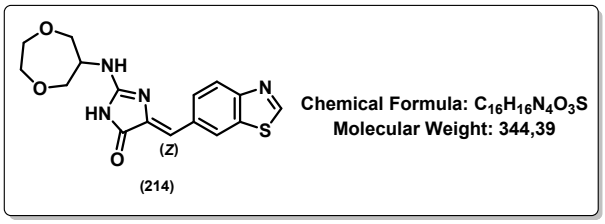
solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.12 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.89 – 8.54 (m, 1H), 8.34 – 8.08 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.36 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 4.96 (br s, 1H, OH, D_2O exchanged), 4.01 (d, J = 11.2 Hz, 1H), 3.93 – 3.79 (m, 1H), 3.78 – 3.58 (m, 2H), 3.41 (t, J = 10.7 Hz, 1H), 3.33 – 3.20 (m, 1H), 1.94 (d, J = 13.3 Hz, 1H), 1.63 – 1.47 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 345.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(oxepan-3-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (213)



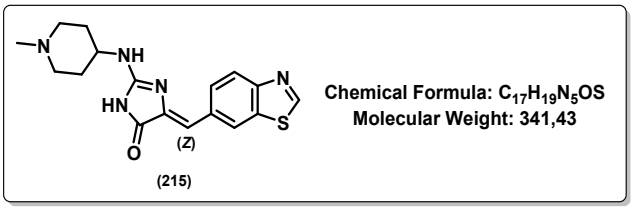
Compound (**213**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 1.2 eq of (±)-oxepan-3-amine at 120 °C (sealed tube, heating block), for 16h (35% conv.). Purification by FC (elution: DCM/MeOH: 99/1 to 92/8). Isolated yield: 33% (31 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.31 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.79 (s, 1H), 8.35 – 8.17 (m, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.51 (br s, 1H, NH, D_2O exchanged), 6.42 (s, 1H), 4.32 – 3.99 (m, 1H), 3.89 – 3.53 (m, 4H), 1.96 – 1.50 (m, 6H). MS (ESI$^+$) : $[M+H]^+$ 343.2. HPLC: >98%.

Synthesis of (*Z*)-2-((1,4-dioxepan-6-yl)amino)-5-(benzo[*d*]thiazol-6-ylmethylene)-3,5-dihydro-4*H*-imidazol-4-one (214)



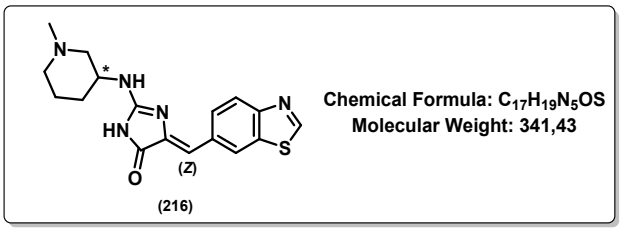
Compound (**214**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 520 µmol scale of intermediate (**9.4**), with 2.5 eq of 1,4-dioxepan-6-amine hydrochloride and 6 eq of DIPEA at 120 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). The final product required two successive triturations in MeOH. Isolated yield: 60% (107 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 343K) of major tautomer δ_H 10.41 (br s, 1H, NH, D_2O exchanged), 9.32 (s, 1H), 8.97 – 8.65 (m, 1H), 8.39 – 8.11 (m, 1H), 8.04 (d, J = 8.4 Hz, 1H), 7.36 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 3.92 – 3.71 (m, 3H), 3.71 – 3.57 (m, 2H), 3.56 – 3.29 (m, 4H). MS (ESI$^+$) : $[M+H]^+$ 345.2. HPLC: >98%.

Synthesis of (*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methylpiperidin-4-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (215)



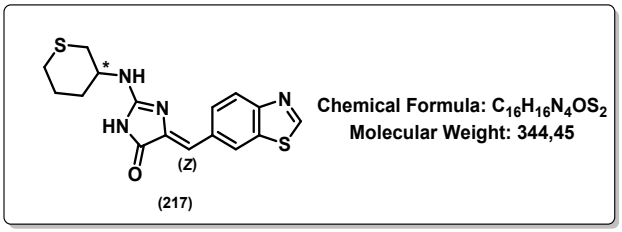
Compound (**215**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 864 µmol scale of intermediate (**9.3**), with 3 eq of 1-methylpiperidin-4-amine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 51% (150 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 9.74 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.82 – 8.66 (m, 1H), 8.36 – 8.09 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.78 (br s, 1H, NH, D_2O exchanged), 6.40 (s, 1H), 3.89 – 3.56 (m, 1H), 2.81 – 2.62 (m, 2H), 2.16 (s, 3H), 2.01 (s, 2H), 1.94 – 1.82 (m, 2H), 1.64 – 1.50 (m, 2H). MS (ESI$^+$) : $[M+H]^+$ 342.2. HPLC: 96%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methylpiperidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (216)



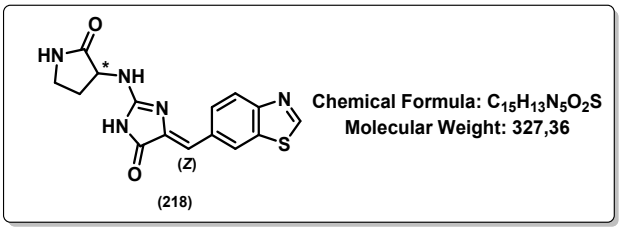
Compound (**216**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 1.48 mmol scale of intermediate (**9.3**), with 2 eq of (±)-1-methylpiperidin-3-amine at 110 °C (sealed tube, heating block), for 12h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 93/7). Isolated yield: 39% (197 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.59 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.80 (s, 1H), 8.43 – 8.18 (m, 1H), 8.04 (d, J = 8.5 Hz, 1H), 7.68 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.40 – 3.95 (m, 1H), 3.15 – 2.96 (m, 2H), 2.47 – 2.28 (m, 3H), 1.94 – 1.43 (m, 4H), 1.18 (t, J = 7.3 Hz, 2H). MS (ESI$^+$) : $[M+H]^+$ 342.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((tetrahydro-2*H*-thiopyran-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (217)



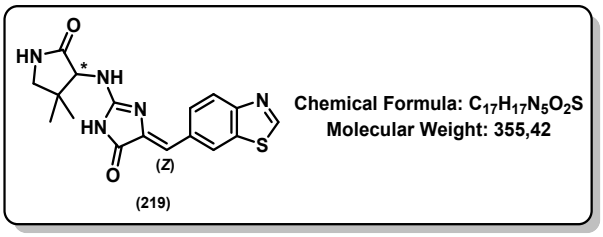
Compound (**217**) was synthesized according to **GP11-B**, in a THF/EtOH mixture (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-tetrahydro-2*H*-thiopyran-3-amine hydrochloride and 4 eq of DIPEA at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7). Isolated yield: 76% (91 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.20 (br s, 1H, NH, D_2O exchanged), 9.29 (s, 1H), 8.95 – 8.61 (m, 1H), 8.36 – 8.08 (m, 1H), 8.03 (d, J = 8.2 Hz, 1H), 7.24 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.16 – 3.99 (m, 1H), 2.95 – 2.88 (m, 1H), 2.66 (dd, J = 13.0, 8.9 Hz, 1H), 2.60 – 2.52 (m, 2H), 2.16 – 1.89 (m, 2H), 1.88 – 1.75 (m, 1H), 1.69 – 1.57 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 345.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[d]thiazol-6-ylmethylene)-2-((2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (218)



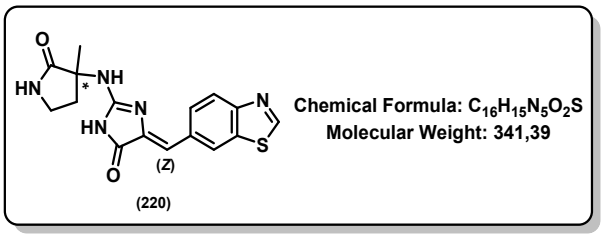
Compound (**218**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-aminopyrrolidin-2-one at 120 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 80% (71 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.65 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.90 – 8.70 (m, 1H), 8.34 – 8.16 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.90 (br s, 1H, NH, D_2O exchanged), 7.71 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.58 – 4.40 (m, 1H), 3.39 – 3.23 (m, 2H), 2.59 – 2.51 (m, 1H), 2.20 – 2.04 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 328.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((4,4-dimethyl-2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (219)



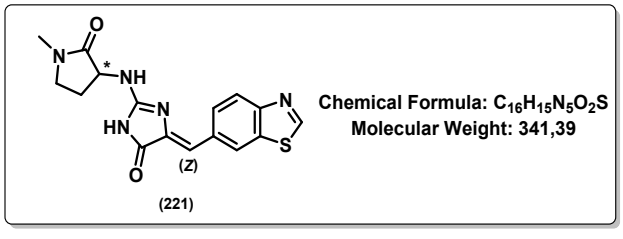
Compound (**219**) was synthesized according to **GP11-B**, in a THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-amino-4,4-dimethylpyrrolidin-2-one at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 63% (59 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.51 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 9.00 – 8.66 (m, 1H), 8.32 – 8.10 (m, 1H), 8.02 (d, J = 8.4 Hz, 1H), 7.87 (br s, 1H, NH, D_2O exchanged), 7.65 (br s, 1H, NH, D_2O exchanged), 6.47 (s, 1H), 4.62 – 4.37 (m, 1H), 3.19 – 3.13 (m, 1H), 3.00 (d, J = 9.7 Hz, 1H), 1.30 (s, 3H), 0.99 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 356.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((3-methyl-2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (220)



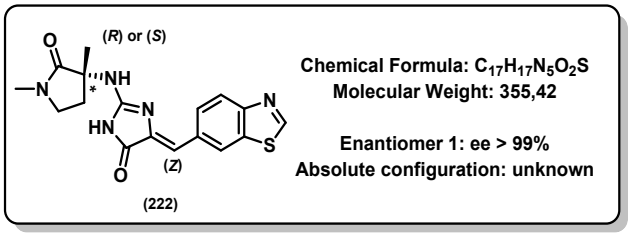
Compound (**220**) was synthesized according to **GP11-B**, in a dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-amino-3-methylpyrrolidin-2-one and 9 eq of AcOH at 120 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH: 99/1 to 93/7) then PTLC. Isolated yield: 51% (43 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.10 (br s, 1H, NH, D_2O exchanged), 9.35 (s, 1H), 8.80 (s, 1H), 8.26 (d, J = 8.7 Hz, 1H), 8.05 (d, J = 8.6 Hz, 1H), 7.94 (br s, 1H, NH, D_2O exchanged), 7.33 (br s, 1H, NH, D_2O exchanged), 6.48 (s, 1H), 3.46 – 3.25 (m, 2H), 2.85 – 2.70 (m, 1H), 2.30 (dd, J = 12.8 and 7.2 Hz, 1H), 1.46 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 342.1. HPLC: >98%.

Synthesis of (±)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1-methyl-2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (221)



Compound (**221**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-amino-1-methylpyrrolidin-2-one at 120 °C (sealed tube, heating block), for 20h. The product directly precipitated in the reaction medium: it was isolated after dilution with EtOH, filtration, washing with cold EtOH, then pentane. The final product required a trituration in EtOH. Isolated yield: 56% (52 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.72 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.79 (s, 1H), 8.22 (d, J = 8.6 Hz, 1H), 8.03 (d, J = 8.6 Hz, 1H), 7.77 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 4.66 – 4.43 (m, 1H), 3.48 – 3.32 (m, 2H), 3.20 (s, 3H), 2.49 – 2.42 (m, 1H), 2.19 – 2.01 (m, 1H). MS (ESI$^+$) : $[M+H]^+$ 342.2. HPLC: >98%.

Synthesis of (*R*)- or (*S*)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1,3-dimethyl-2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (222) (ENANTIOMER 1*)



Compound (**222**) and (**223**) required the initial synthesis of the racemic compound. Synthesis of racemic compound: reaction was carried out according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-amino-1,3-dimethylpyrrolidin-2-one and 9 eq of AcOH at 120 °C (sealed tube, heating block), for 46h (75% conv.). Purification by FC (elution: DCM/MeOH: 99/1 to 9/1). Isolated yield: 25% (24 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.33 (br s, 1H, NH, D_2O exchanged), 9.37 (s, 1H), 8.75 (s, 1H), 8.18 (dd, J = 8.6, 1.6 Hz, 1H), 8.04 (d, J = 8.6 Hz, 1H), 7.70 (br s, 1H, NH, D_2O exchanged), 6.46 (s, 1H), 3.56 – 3.41 (m, 2H), 2.89 (s, 3H), 2.83 – 2.71 (m, 1H), 2.18 – 2.06 (m, 1H), 1.40 (s, 3H). MS (ESI$^+$) : $[M+H]^+$ 356.2. HPLC: >98%.

Preparative chiral SFC from racemic compound (177 mg): Lux A1 (21.2 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 210 nm, $V_{injection}$: 1000 µL (19 mg in MeOH)/injection; isocratic conditions: 4/6 ($MeOH/CO_2$). Isolated quantity of enantiomer (**222**): 62 mg. ^{1}H NMR of (**222**) was identical to racemate.

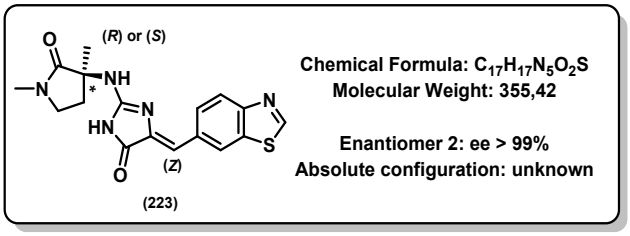
Analytical chiral SFC of racemic mixture: Amy-C (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, $V_{injection}$: 1 µL; isocratic conditions: 4/6 ($MeOH/CO_2$ (0.2% v/v NH_3)), t_R(**222**): 1.95 min, t_R(**223**): 2.53 min.

Analytical chiral SFC of (222) (conditions as described above): **)**: t_R(**222**) after chiral purification: 1.96 min, ee = >99% (first eluting enantiomer).

HPLC: >98%.

* The absolute configuration of the chiral center of (**222**) could not be assigned.

Synthesis of (*R*)- or (*S*)-(*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-((1,3-dimethyl-2-oxopyrrolidin-3-yl)amino)-3,5-dihydro-4*H*-imidazol-4-one (223) (ENANTIOMER 2*)



Preparative chiral SFC from racemic compound (177 mg): Lux A1 (21.2 mm x 250 mm, 5 um), (40 °C, 50 mL/min, 210 nm, $V_{injection}$: 1000 µL (19 mg in MeOH)/injection; isocratic conditions: 4/6 ($MeOH/CO_2$). Isolated quantity of enantiomer (**223**): 67 mg. ^1H NMR of (**223**) was identical to racemate and (**222**)

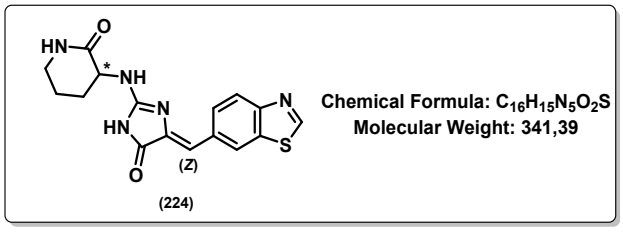
Analytical chiral SFC of racemic mixture: Amy-C (4.6 mm x 250 mm, 5 um), (40 °C, 4 mL/min, 210-400 nm, $V_{injection}$: 1 µL; isocratic conditions: 4/6 ($MeOH/CO_2$ (0.2% v/v NH_3)), t_R(**222**): 1.95 min, t_R(**223**): 2.53 min.

Analytical chiral SFC of (79) (conditions as described above): t_R(**223**) after chiral purification: 2.51 min, ee = >99% (second eluting enantiomer).

HPLC: >98%.

* The absolute configuration of the chiral center of (**223**) could not be assigned.

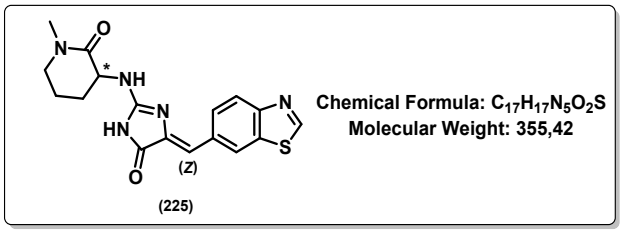
Synthesis of (±)-(*Z*)-3-((4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)piperidin-2-one (224)



Compound (**224**) was synthesized according to **GP11-A**, in THF (0.3M/isothiourea), on a 272 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-aminopiperidin-2-one at 120 °C (sealed tube, heating block), for 24h. The product directly precipitated in the reaction medium: it was isolated after filtration, washing with cold THF, then pentane. The final product required a trituration in EtOH. Isolated yield: 73% (68 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.75 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.84 (s, 1H), 8.23 (d, J = 8.6 Hz, 1H), 8.03 (d, J

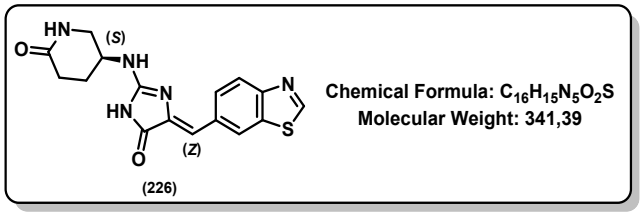
= 8.5 Hz, 1H), 7.78 (br s, 2H, NH, D_2O exchanged), 6.43 (s, 1H), 4.49 – 4.16 (m, 1H), 3.28 – 3.12 (m, 2H), 2.30 – 2.09 (m, 1H), 1.88 (s, 3H). MS (ESI^+) : $[M+H]^+$ 342.2. HPLC: >98%.

Synthesis of (±)-(*Z*)-3-((4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)-1-methylpiperidin-2-one (225)



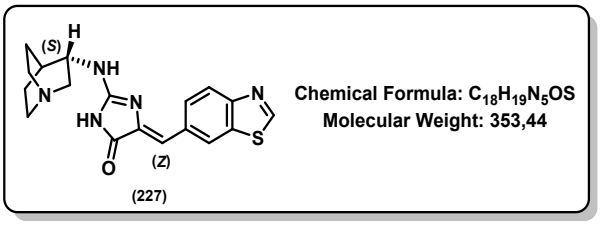
Compound (**225**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 520 µmol scale of intermediate (**9.4**), with 3 eq of (±)-3-amino-1-methylpiperidin-2-one at 120 °C (sealed tube, heating block), for 24h. Purification by FC (elution: DCM/MeOH: 99/1 to 9/1). Isolated yield: 80% (77 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 323K) of major tautomer δ_H 10.65 (br s, 1H, NH, D_2O exchanged), 9.34 (s, 1H), 8.91 – 8.70 (m, 1H), 8.34 – 8.12 (m, 1H), 8.03 (d, J = 8.5 Hz, 1H), 7.67 (br s, 1H, NH, D_2O exchanged), 6.45 (s, 1H), 4.41 – 4.22 (m, 1H), 3.46 – 3.27 (m, 2H), 2.89 (s, 3H), 2.35 – 2.17 (m, 1H), 2.10 – 1.86 (m, 3H). MS (ESI^+) : $[M+H]^+$ 356.1. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-((4-(benzo[*d*]thiazol-6-ylmethylene)-5-oxo-4,5-dihydro-1*H*-imidazol-2-yl)amino)piperidin-2-one (226)



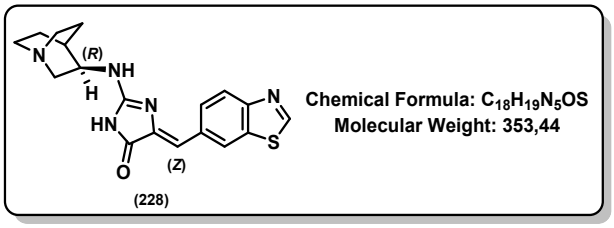
Compound (**226**) was synthesized according to **GP11-B**, in THF (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-5-aminopiperidin-2-one and 4eq of DIPEA at 170 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH (7N NH_3): 99/1 to 85/15). The final product required a trituration in EtOH at 0 °C. Isolated yield: 48% (122 mg). Yellow solid. ^1H NMR (400 MHz, DMSO-d_6, 300K) of major tautomer δ_H 10.76 (br s, 1H, NH, D_2O exchanged), 9.36 (s, 1H), 8.82 (s, 1H), 8.40 – 8.20 (m, 1H), 8.09 – 8.00 (m, 1H), 7.79 (br s, 1H, NH, D_2O exchanged), 7.52 (br s, 1H, NH, D_2O exchanged), 6.44 (s, 1H), 4.38 – 3.73 (m, 1H), 3.58 – 3.39 (m, 2H), 2.36 – 1.78 (m, 4H). MS (ESI^+) : $[M+H]^+$ 342.2. HPLC: >98%.

Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(quinuclidin-3-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (227)



Compound (**227**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-quinuclidin-3-amine dihydrochloride and 10 eq of DIPEA at 170 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH (7N NH_3): 9/1 to 7/3). The final product required a trituration in EtOH at 0 °C. Isolated yield: 11% (28 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.52 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.88 – 8.66 (m, 1H), 8.33 – 8.09 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.89 (br s, 1H, NH, D_2O exchanged), 6.47 (s, 1H), 4.21 – 4.05 (m, 1H), 3.61 – 3.43 (m, 1H), 3.18 – 2.81 (m, 5H), 2.23 – 2.08 (m, 1H), 2.01 – 1.72 (m, 3H), 1.67 – 1.53 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 354.2. HPLC: >98%.

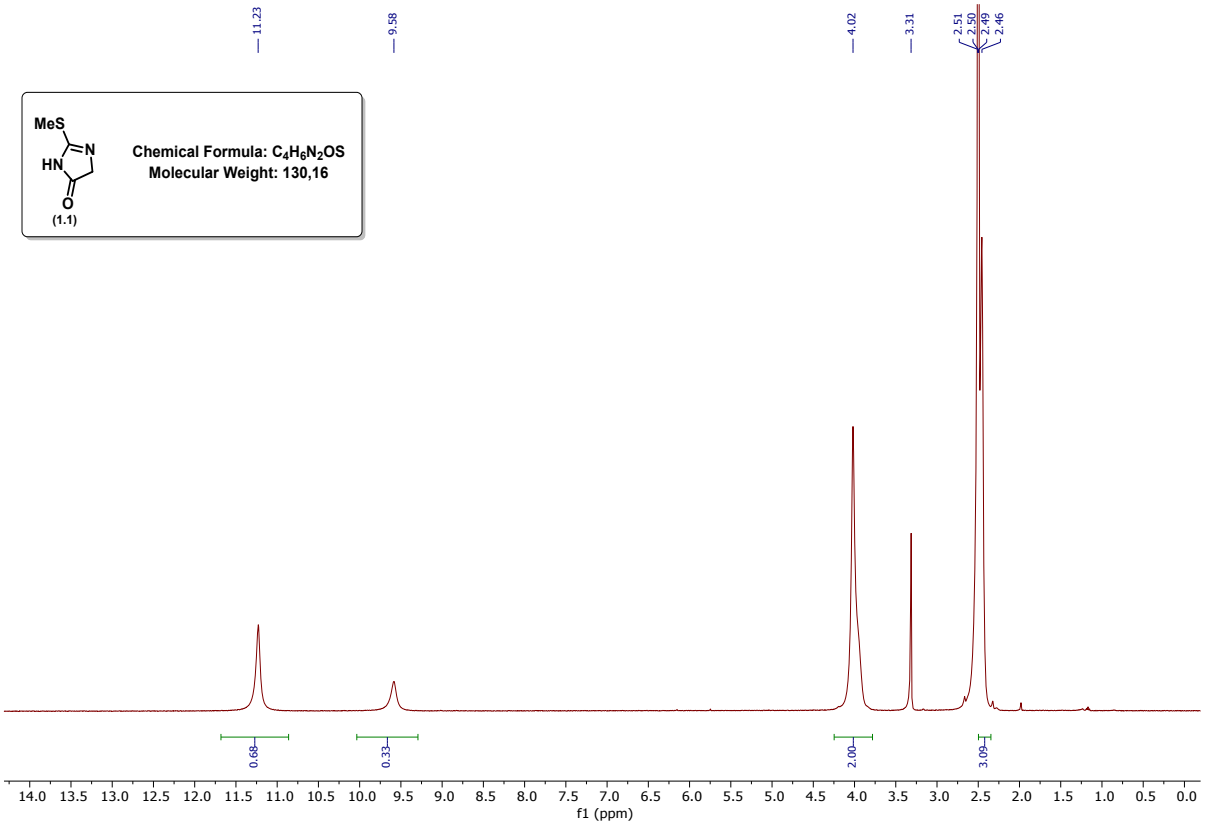
Synthesis of (*S*,*Z*)-5-(benzo[*d*]thiazol-6-ylmethylene)-2-(quinuclidin-3-ylamino)-3,5-dihydro-4*H*-imidazol-4-one (228)

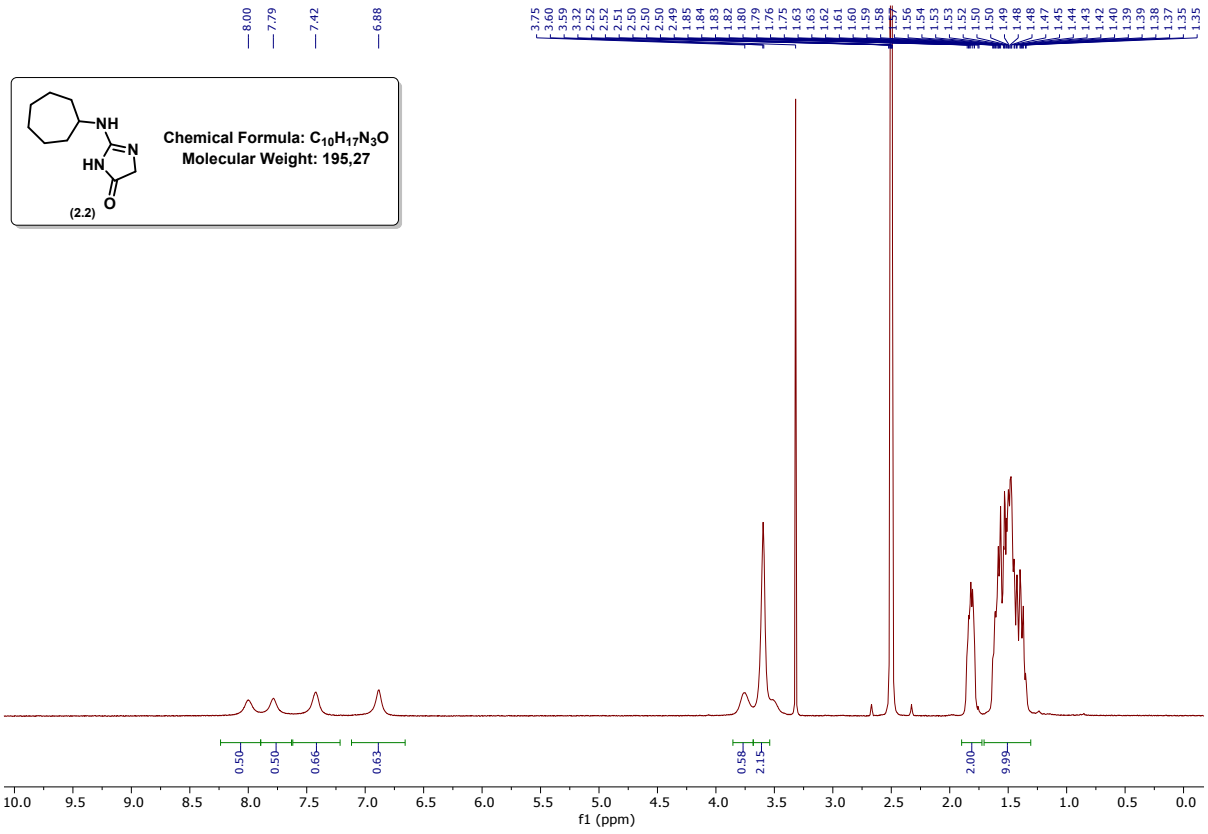


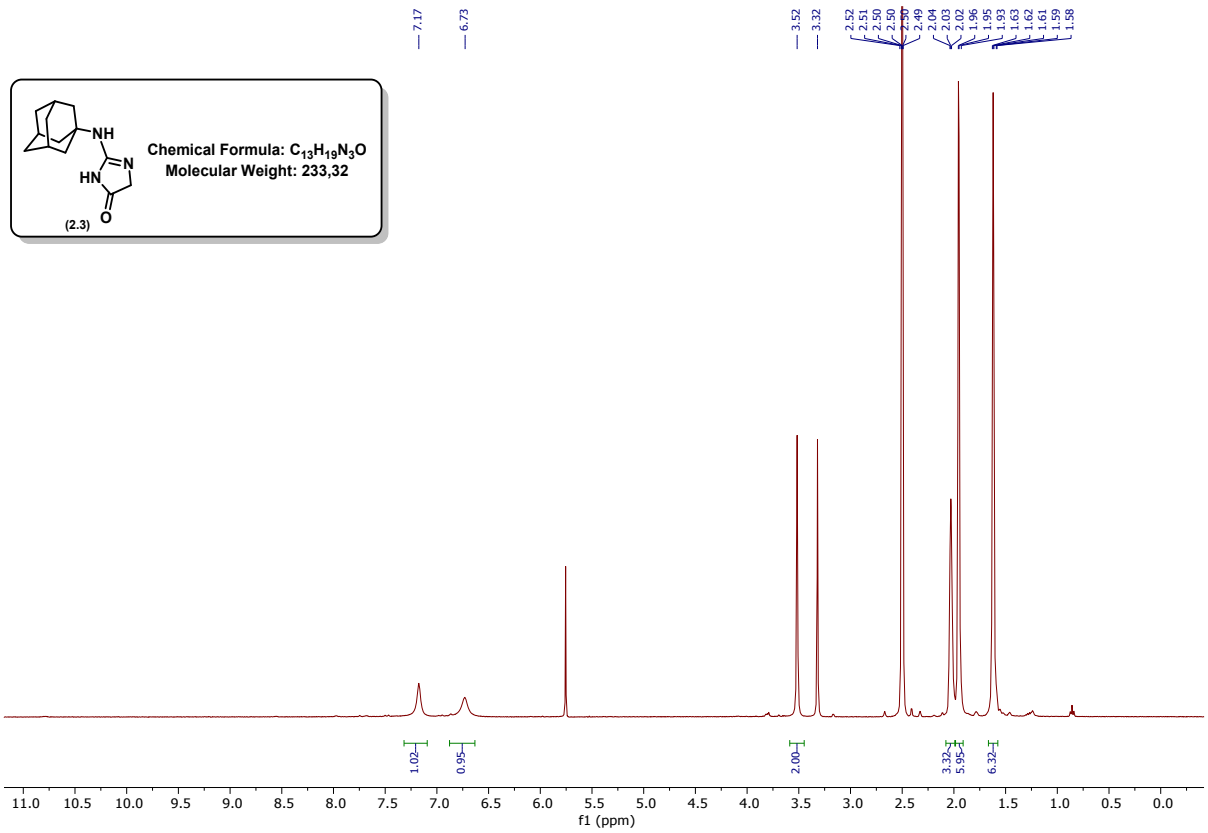
Compound (**228**) was synthesized according to **GP11-B**, in dioxane (0.3M/isothiourea), on a 746 µmol scale of intermediate (**9.4**), with 3 eq of (*S*)-quinuclidin-3-amine dihydrochloride and 10 eq of DIPEA at 170 °C (sealed tube, heating block), for 48h. Purification by FC (elution: DCM/MeOH (7N NH_3): 9/1 to 7/3). The final product required a trituration in EtOH at 0 °C. Isolated yield: 11% (28 mg). Yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6, 373K) of major tautomer δ_H 10.52 (br s, 1H, NH, D_2O exchanged), 9.31 (s, 1H), 8.88 – 8.66 (m, 1H), 8.33 – 8.09 (m, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.89 (br s, 1H, NH, D_2O exchanged), 6.47 (s, 1H), 4.21 – 4.05 (m, 1H), 3.61 – 3.43 (m, 1H), 3.18 – 2.81 (m, 5H), 2.23 – 2.08 (m, 1H), 2.01 – 1.72 (m, 3H), 1.67 – 1.53 (s, 1H). MS (ESI$^+$) : $[M+H]^+$ 354.2. HPLC: 97%.

8 Selected examples of NMR spectra and HPLC's of intermediate and final compounds

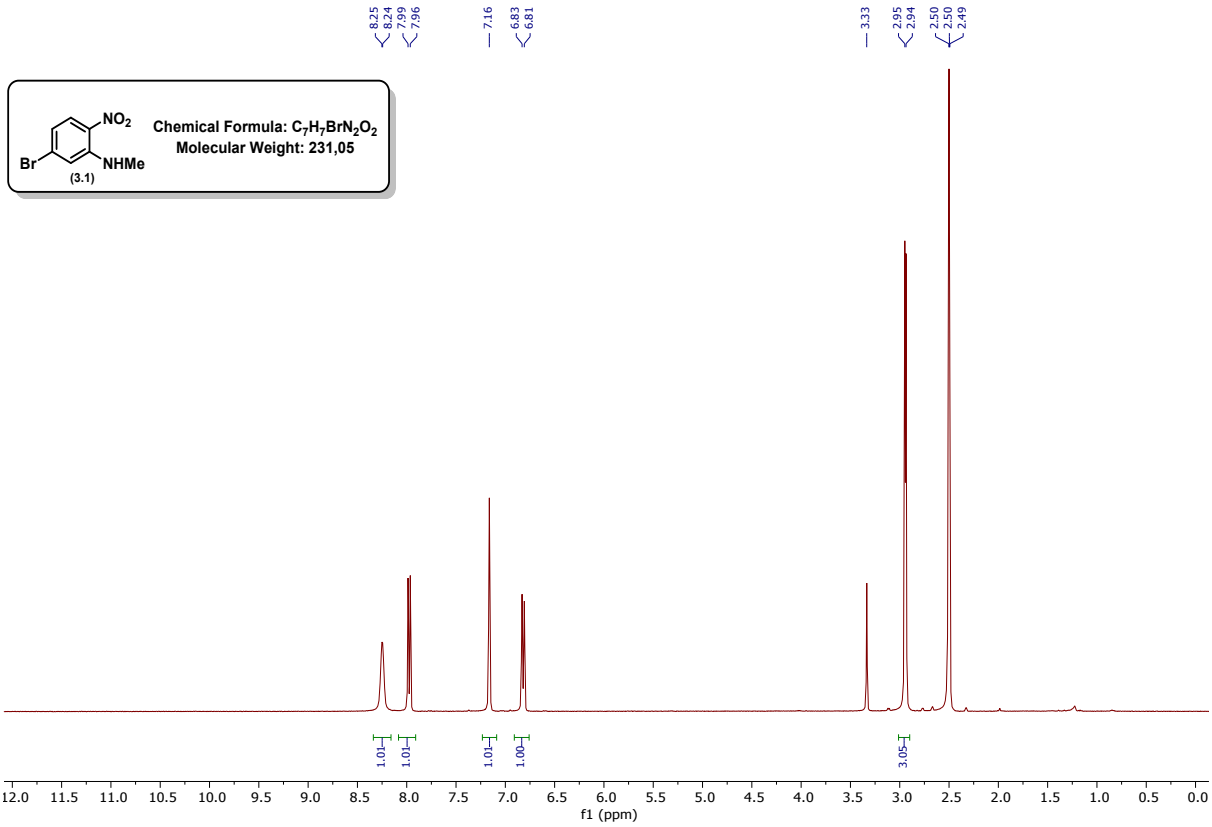
Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP1

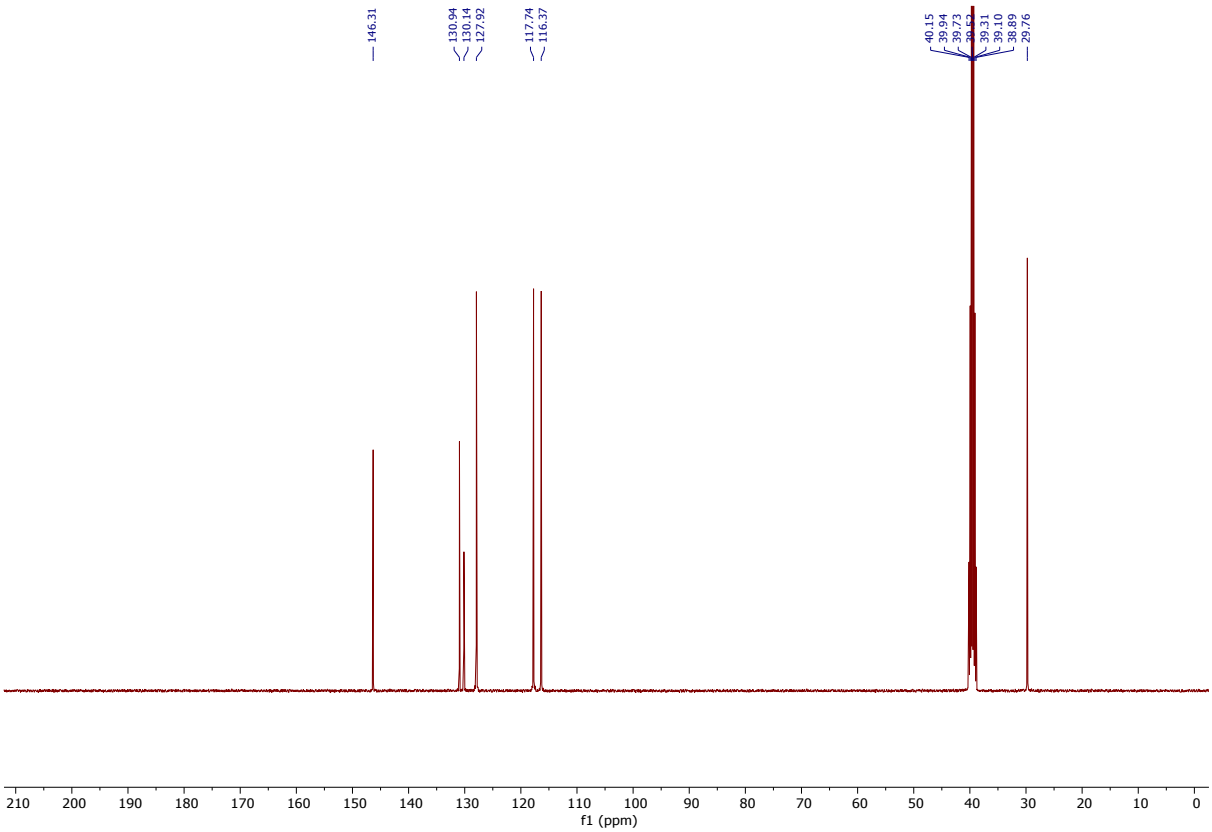


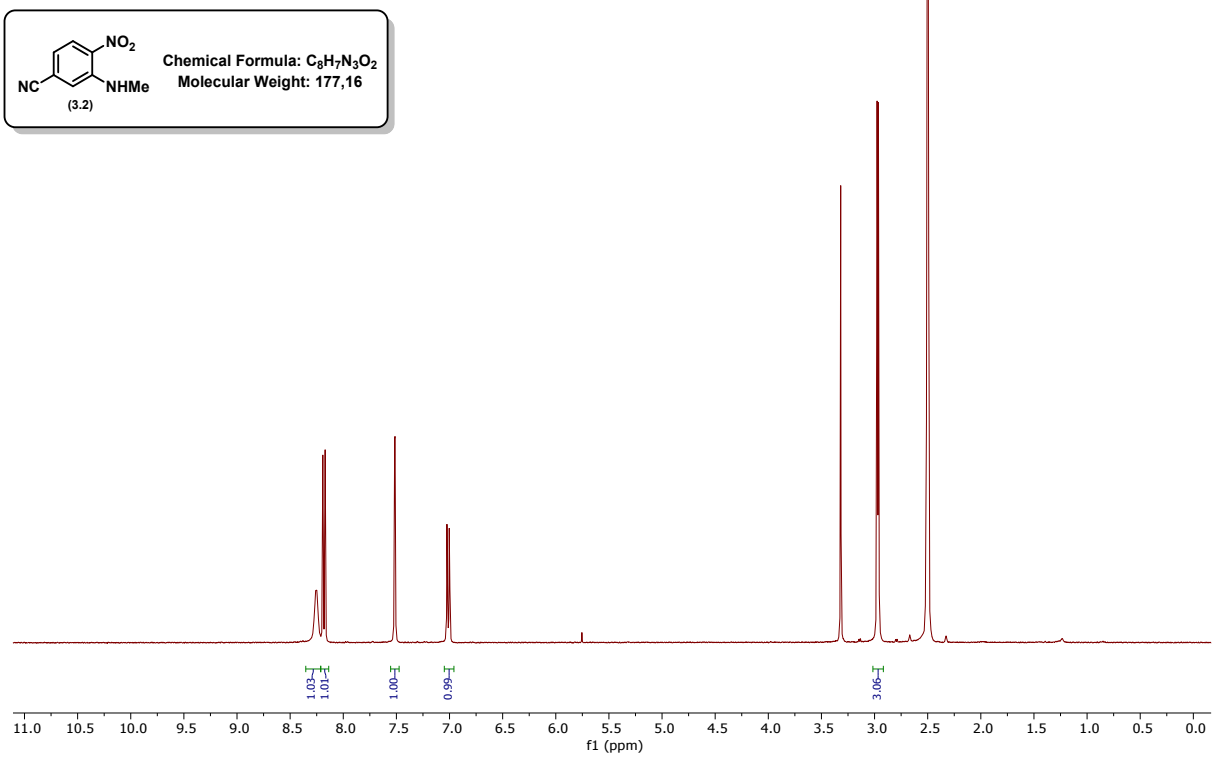


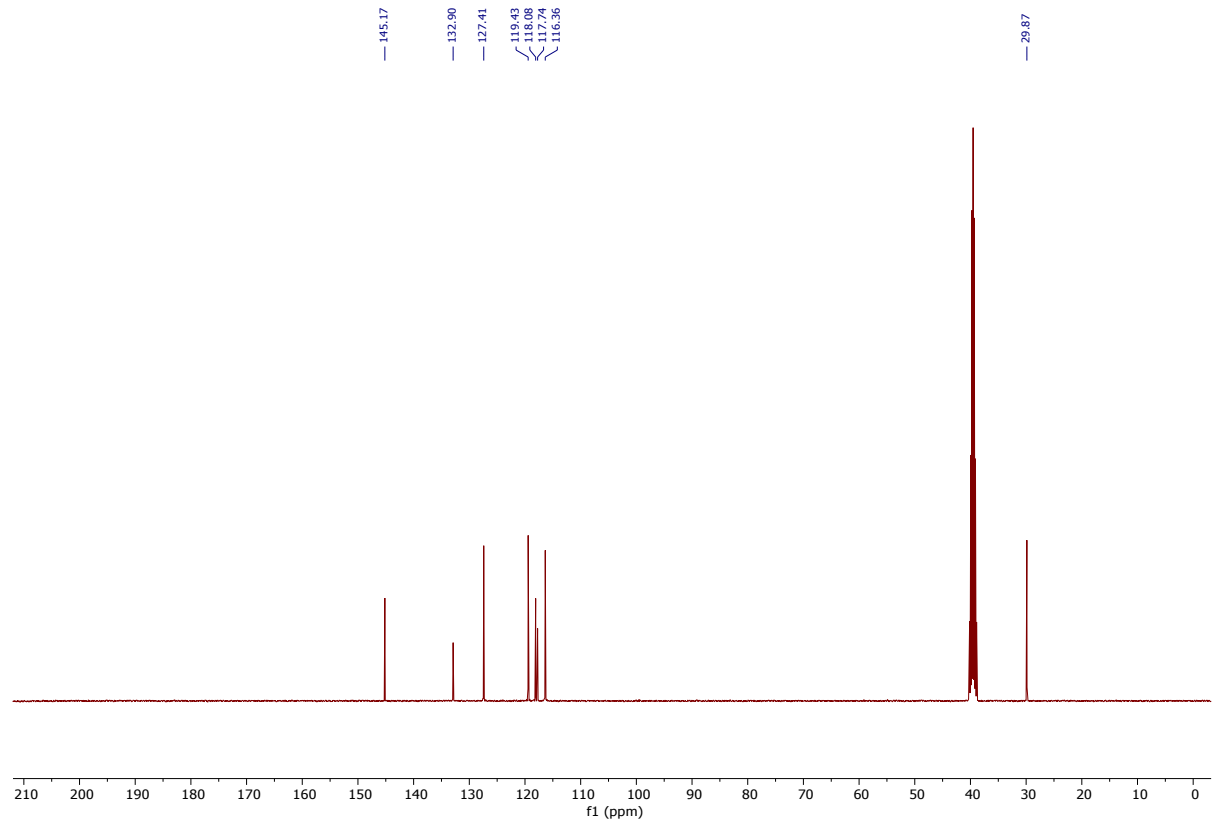

NH
HN
N
O
(2.3)
Chemical Formula: C13H19N3O
Molecular Weight: 233,32
7.17
6.73
3.52
3.32
2.52
2.51
2.50
2.50
2.49
2.04
2.03
2.02
1.96
1.95
1.93
1.63
1.62
1.61
1.59
1.58
1.02
0.95
2.00
3.32
5.95
6.32
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
f1 (ppm)

Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP2

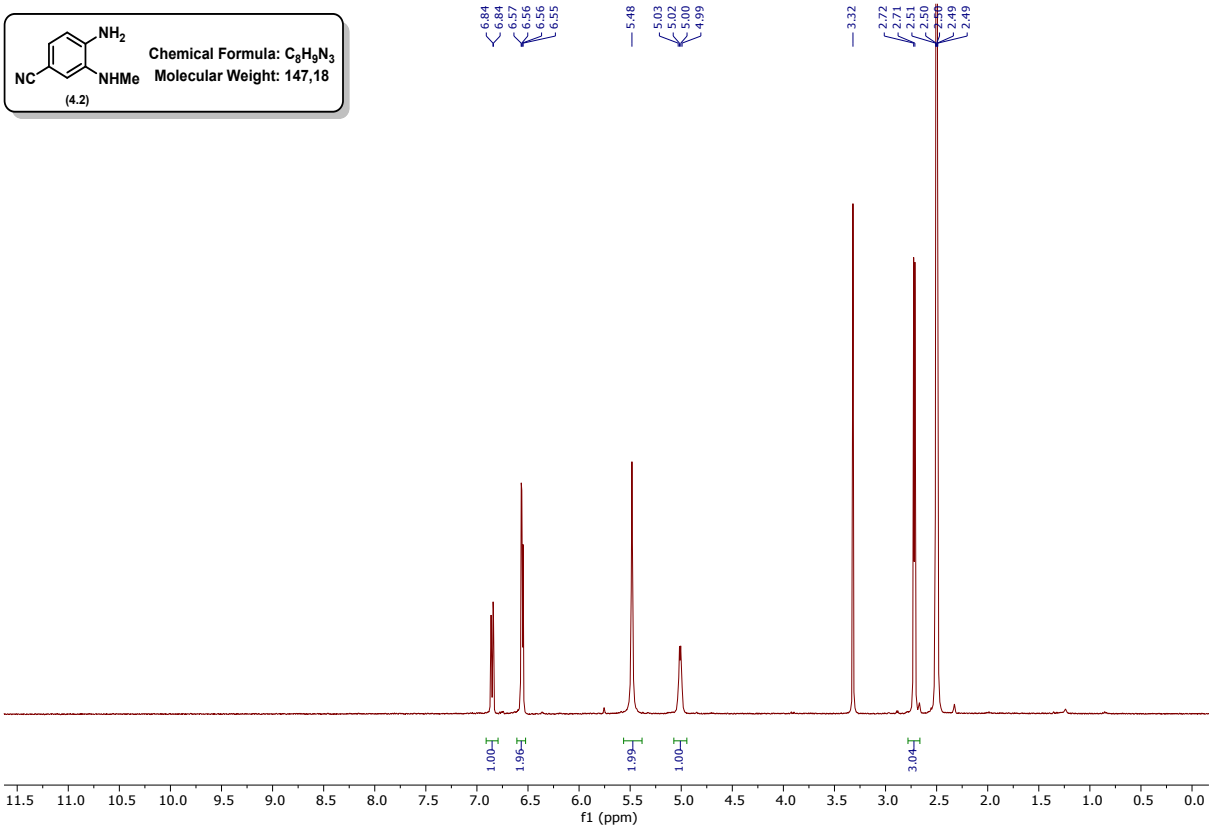


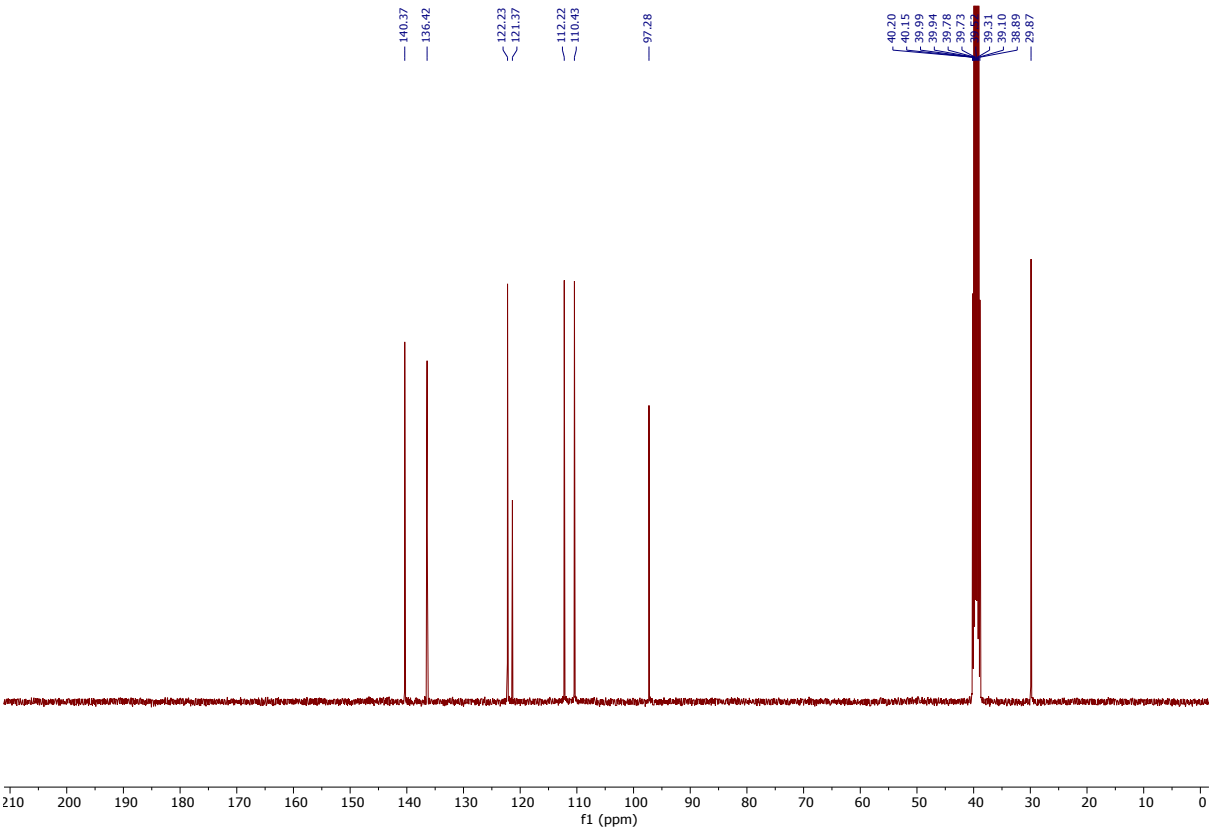



8.26
8.25
8.19
8.17
7.52
7.51
7.02
7.02
7.00
7.00
3.32
2.98
2.96
2.52
2.52
2.51
2.50
2.50
2.50
2.49
NO2
NC
NHMe
(3.2)
Chemical Formula: C8H7N3O2
Molecular Weight: 177,16
1.03
1.01
1.00
0.99
3.06
11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)

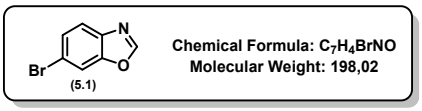

145.17
132.90
127.41
119.43
118.08
117.74
116.36
29.87
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0
f1 (ppm)

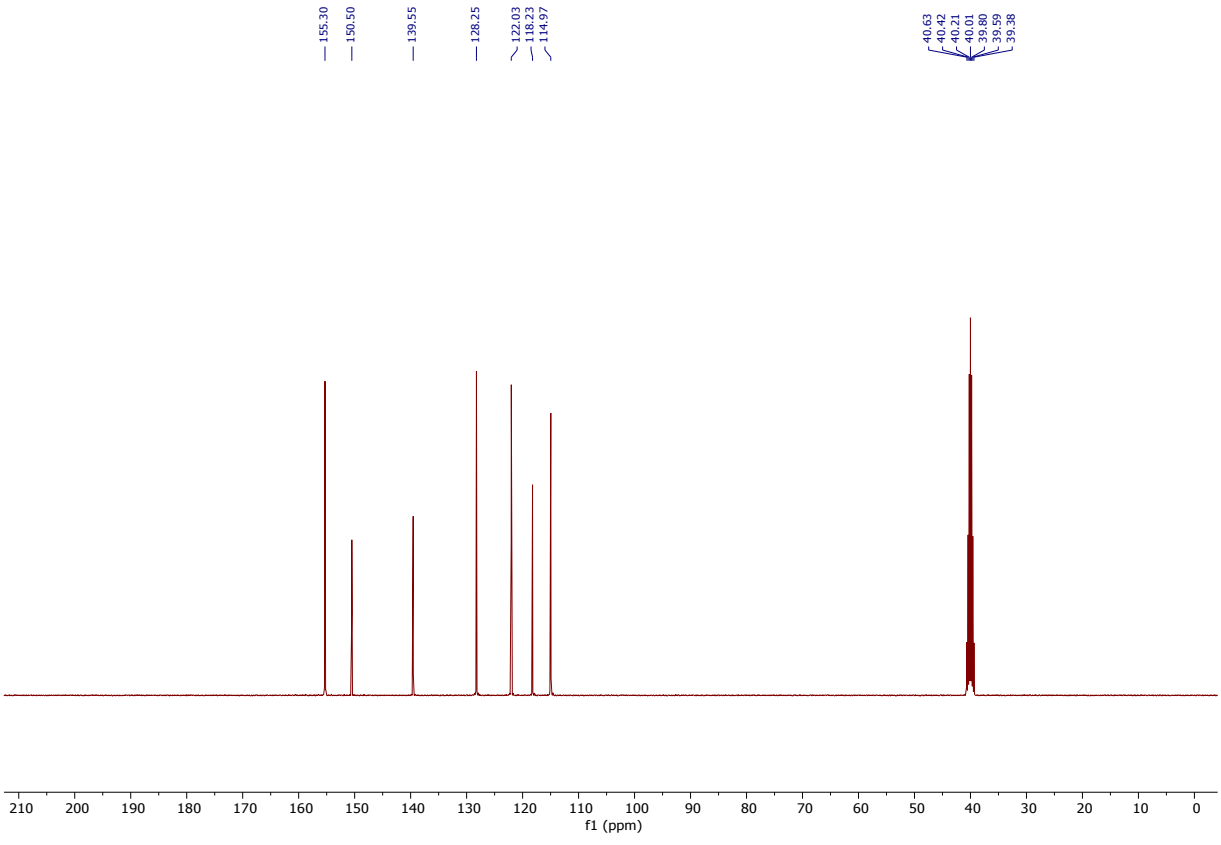
Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP3

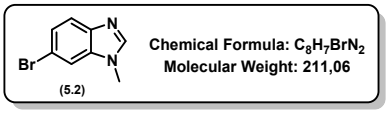




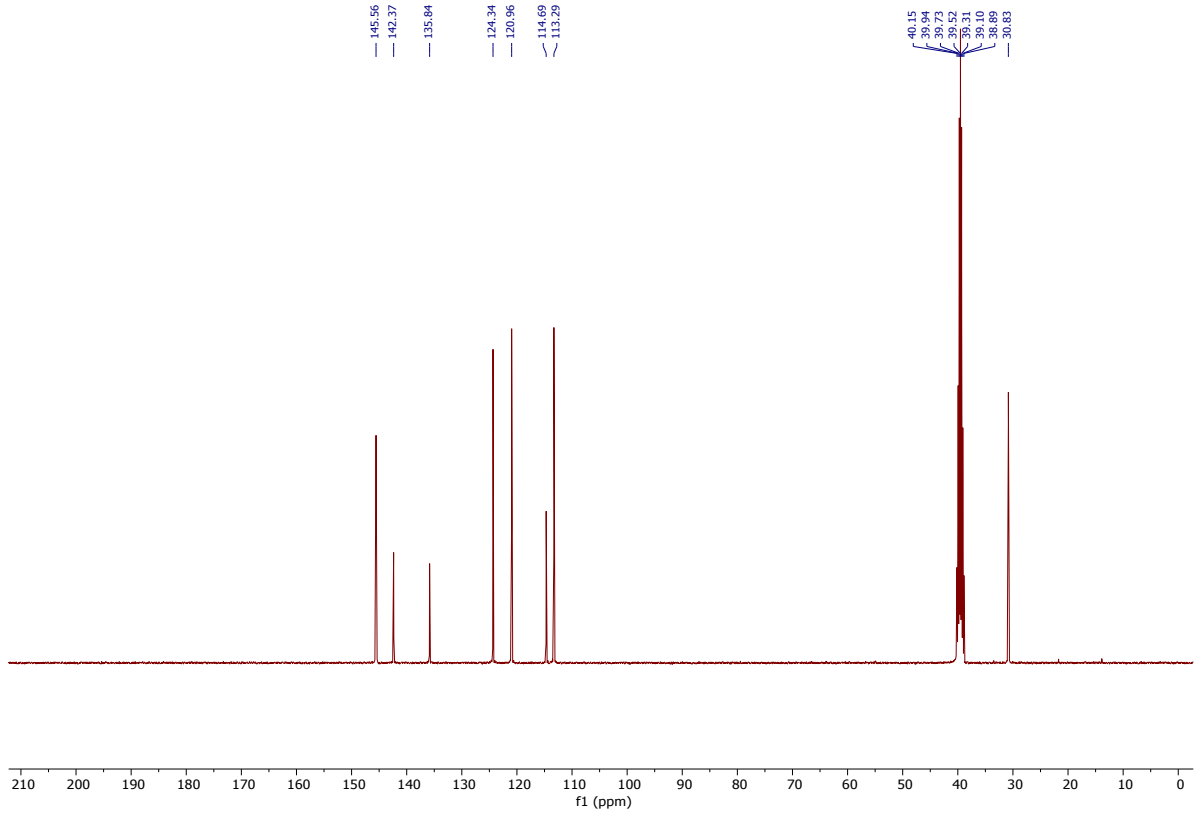
Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP4

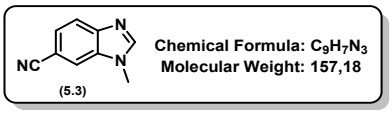






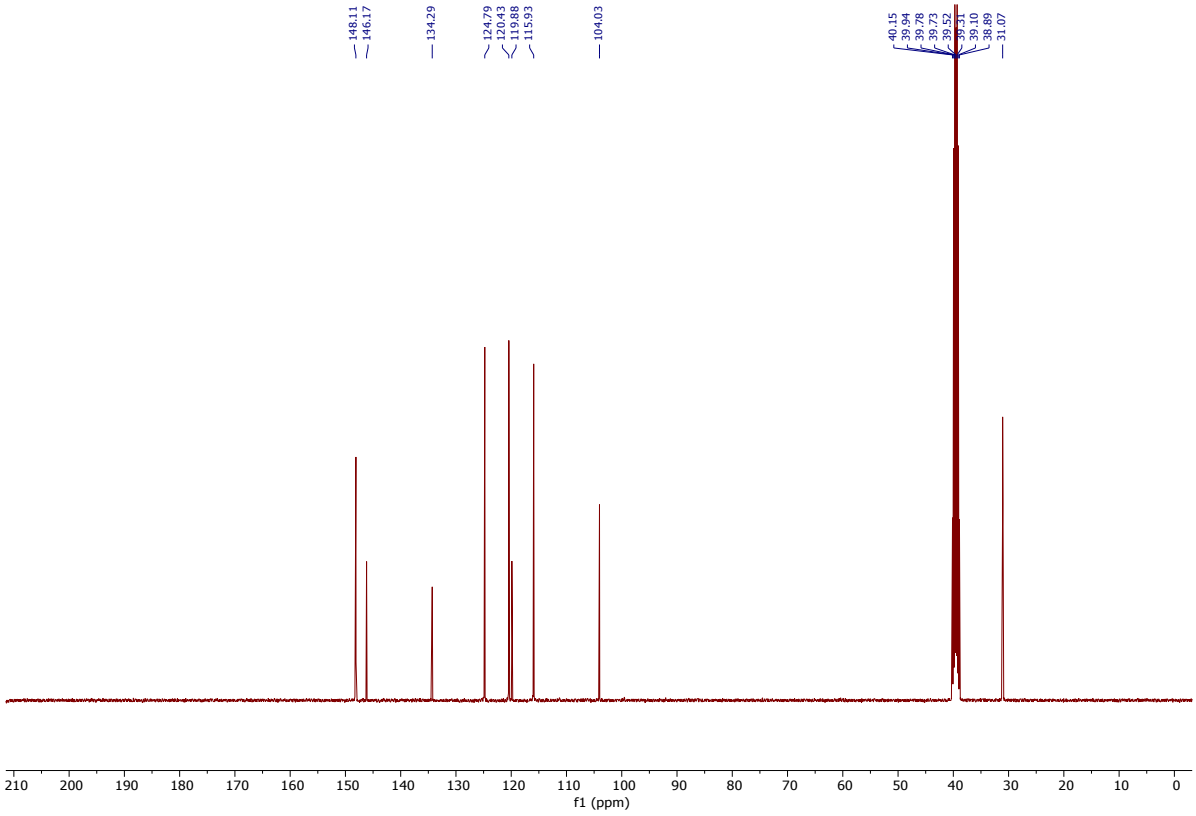
Chemical Formula: $C_8H_7BrN_2$
Molecular Weight: 211,06



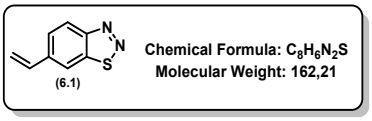


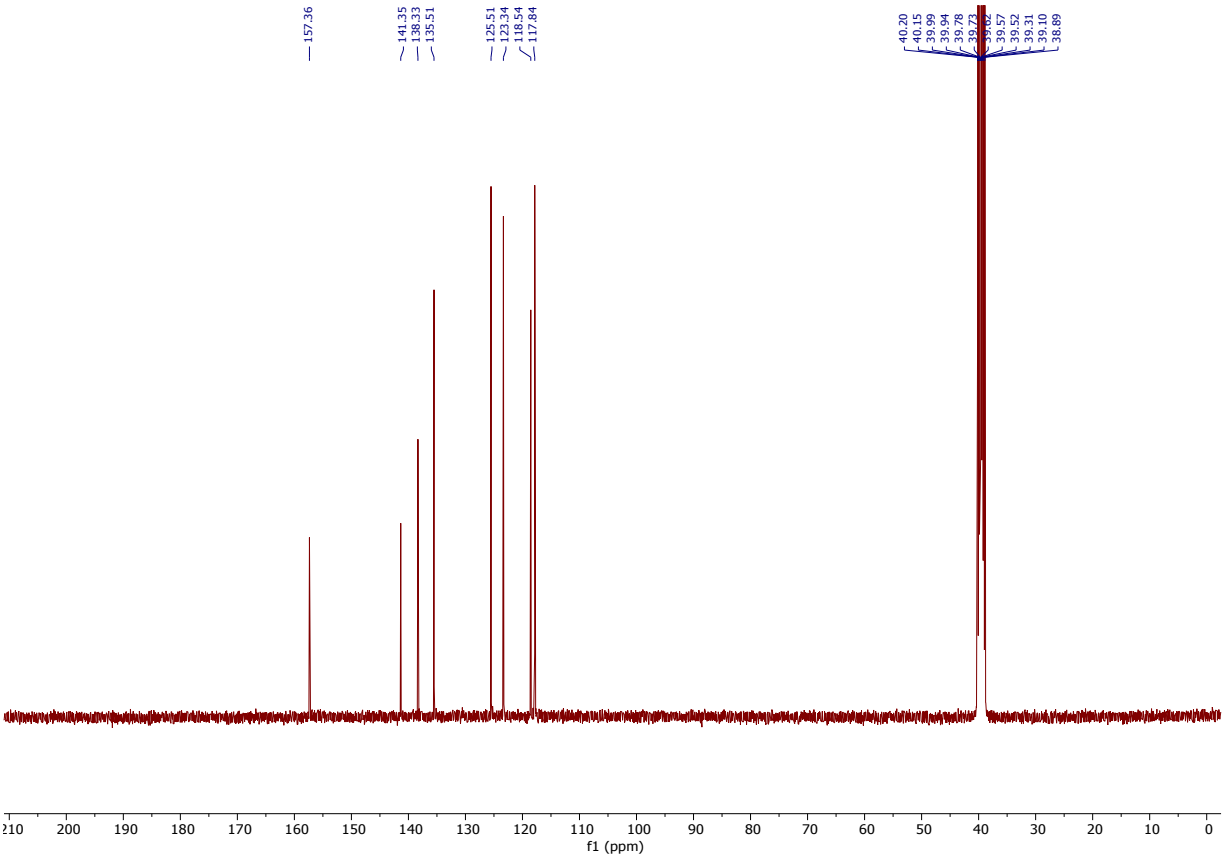
(5.3)

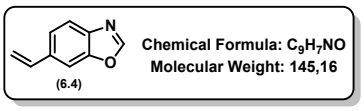
Chemical Formula: $C_9H_7N_3$
Molecular Weight: 157,18



Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP5

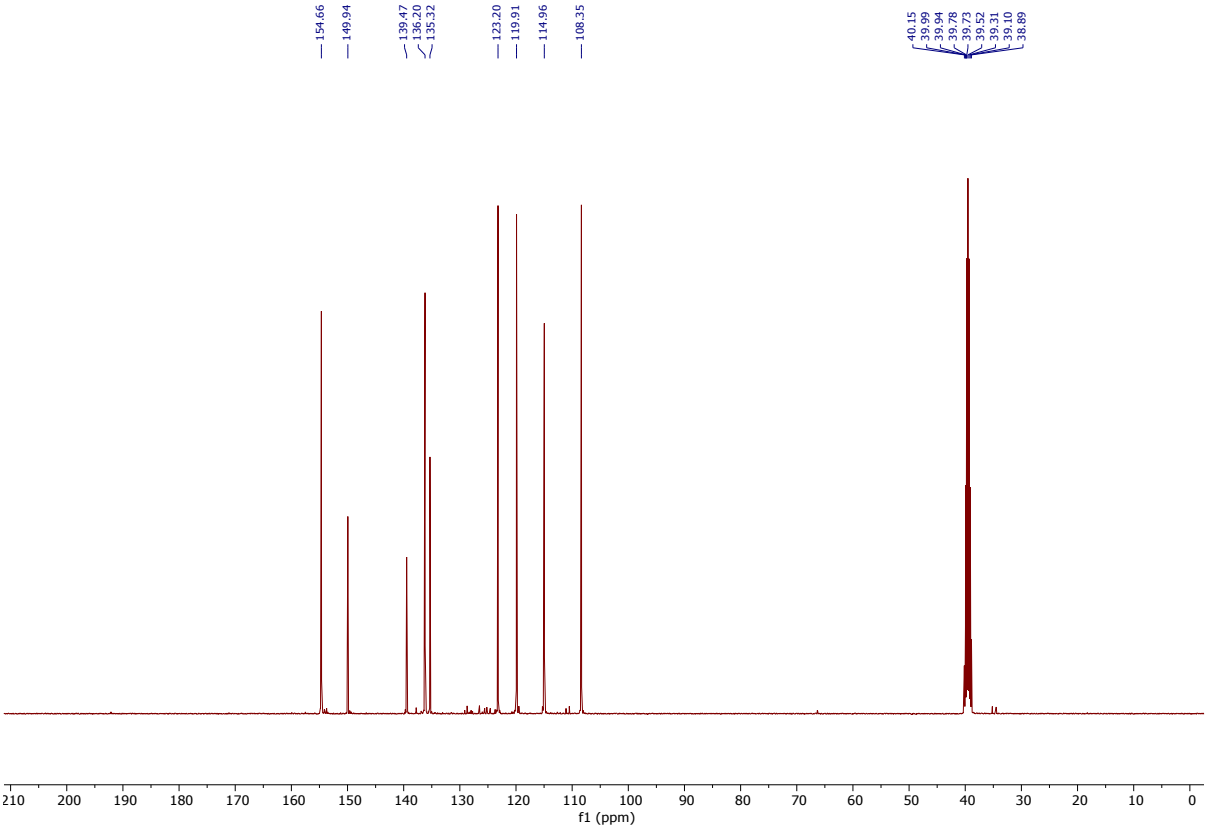


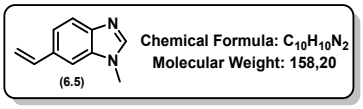




Chemical Formula: C_9H_7NO
Molecular Weight: 145,16

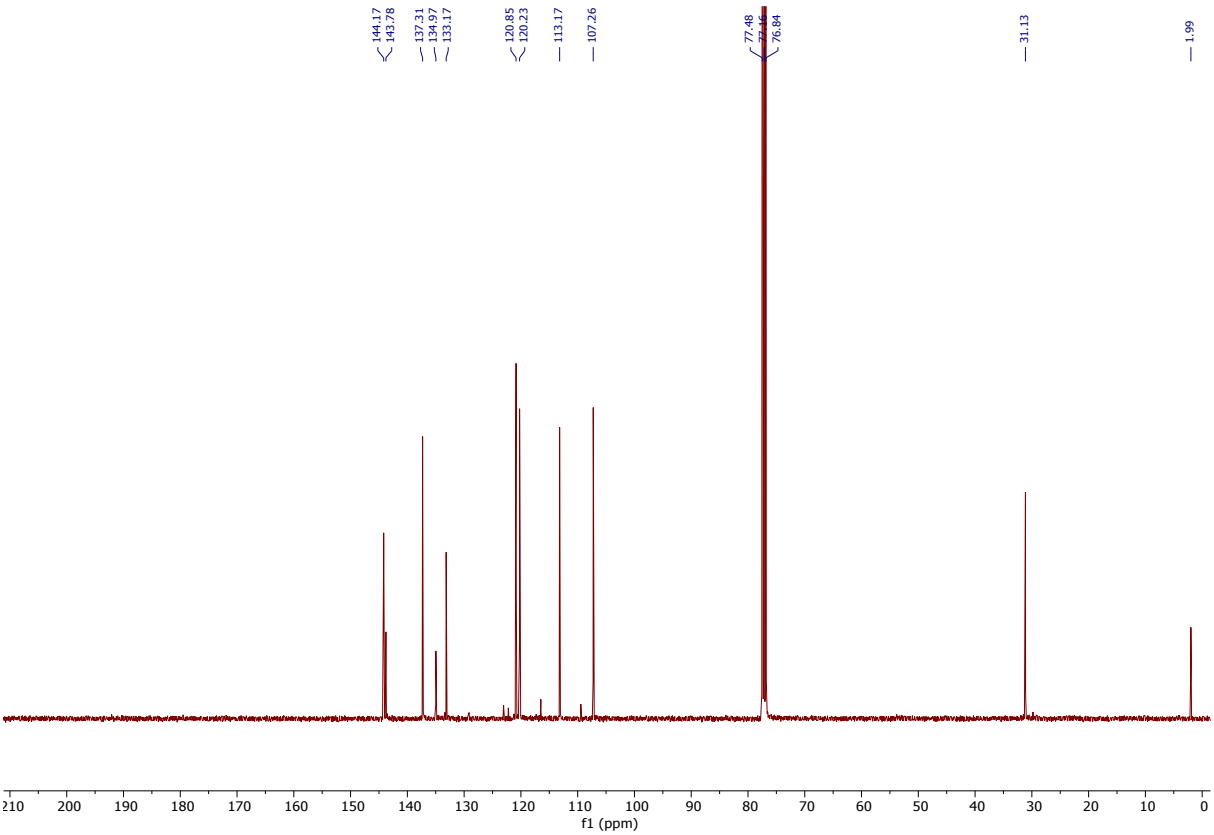
(6.4)



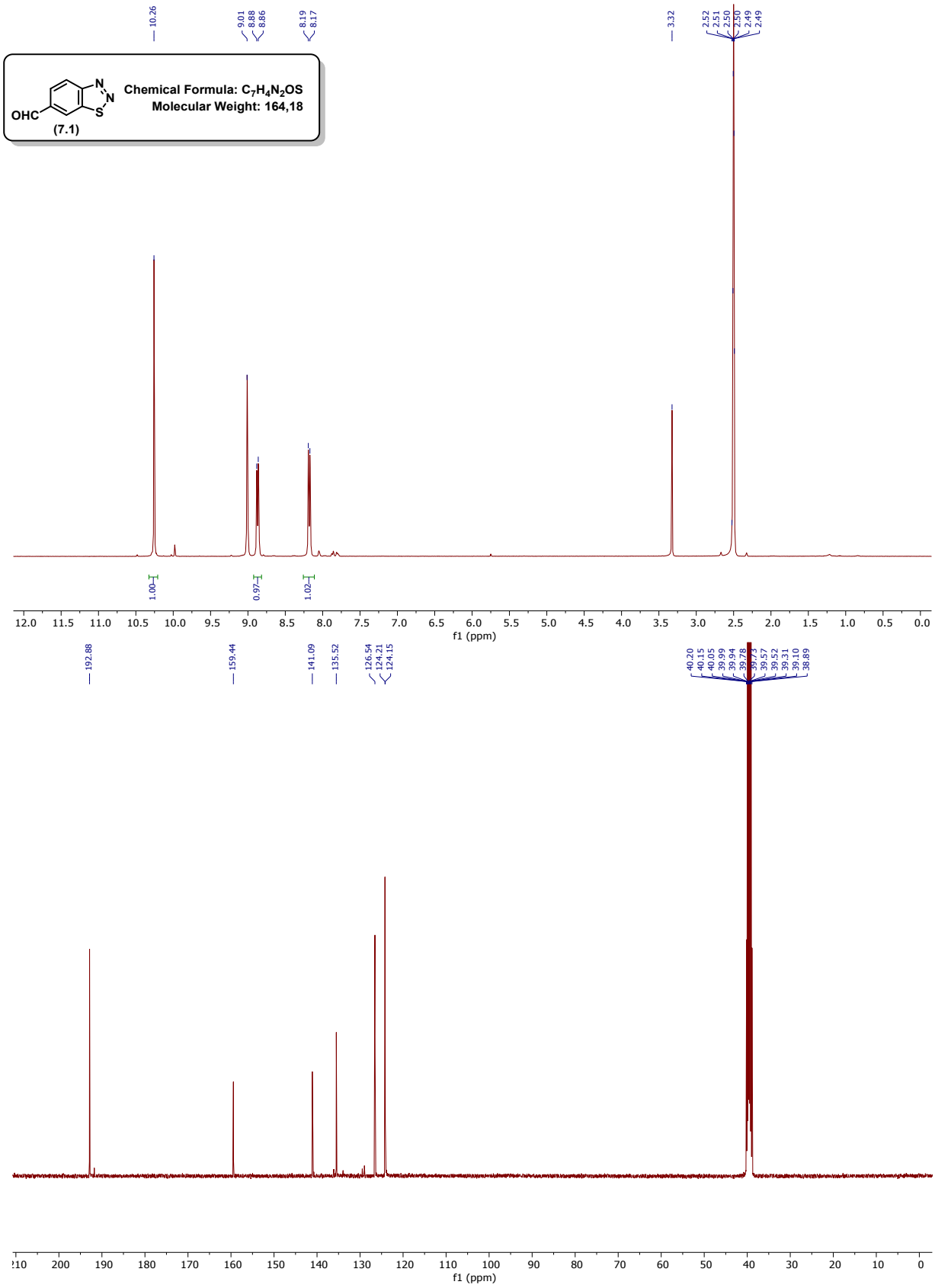


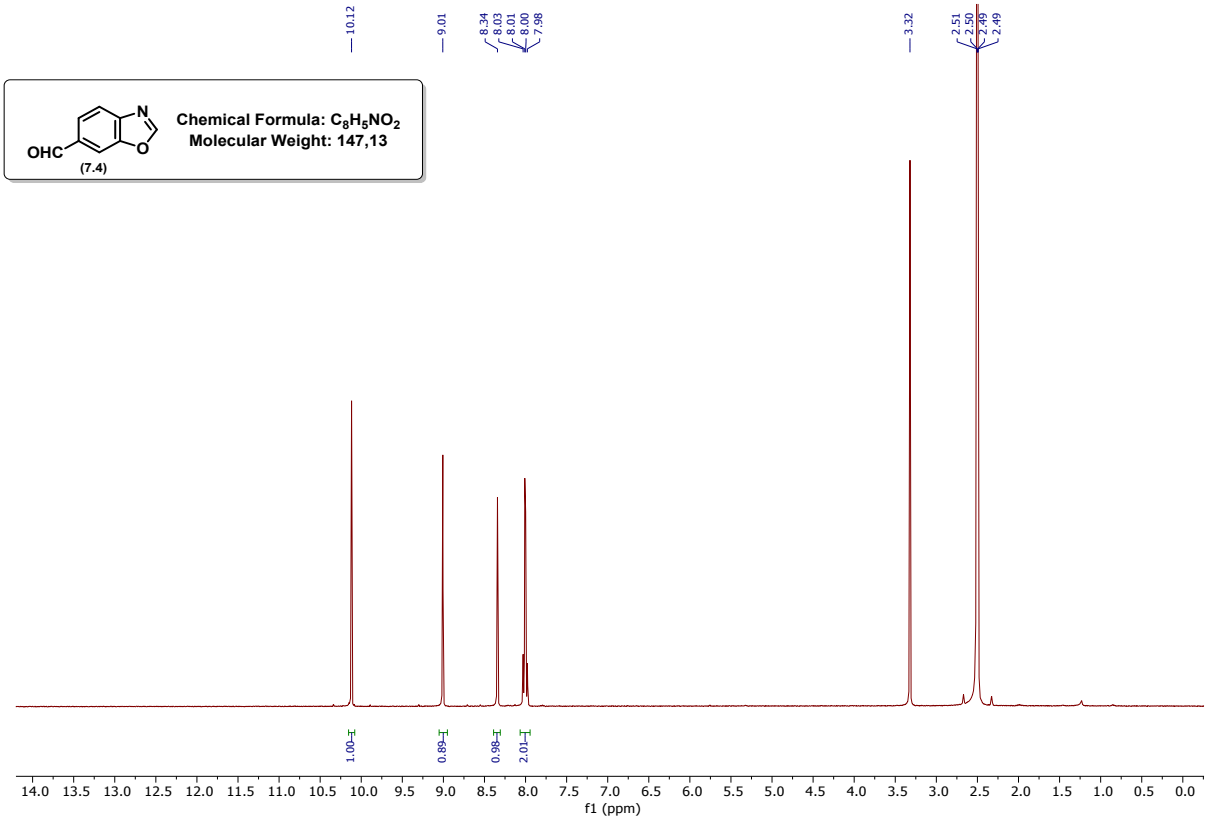
(6.5)

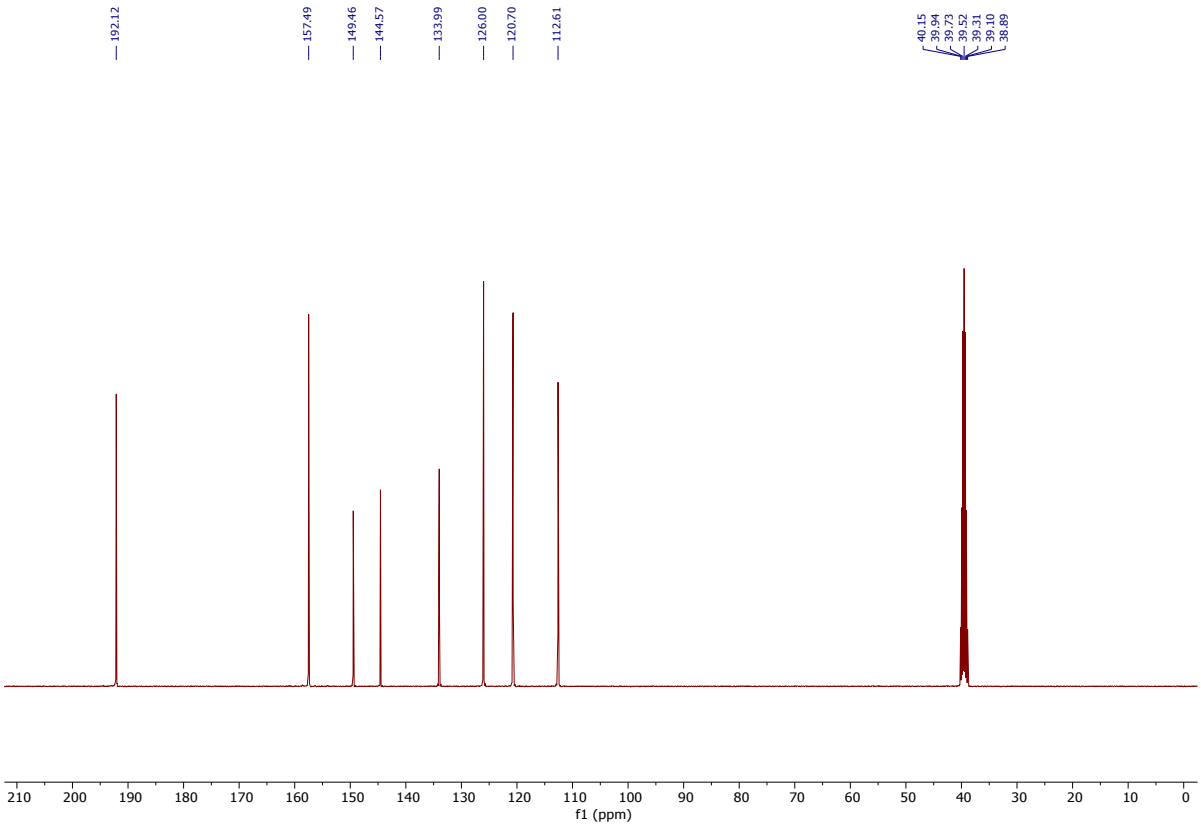
Chemical Formula: $C_{10}H_{10}N_2$
Molecular Weight: 158,20



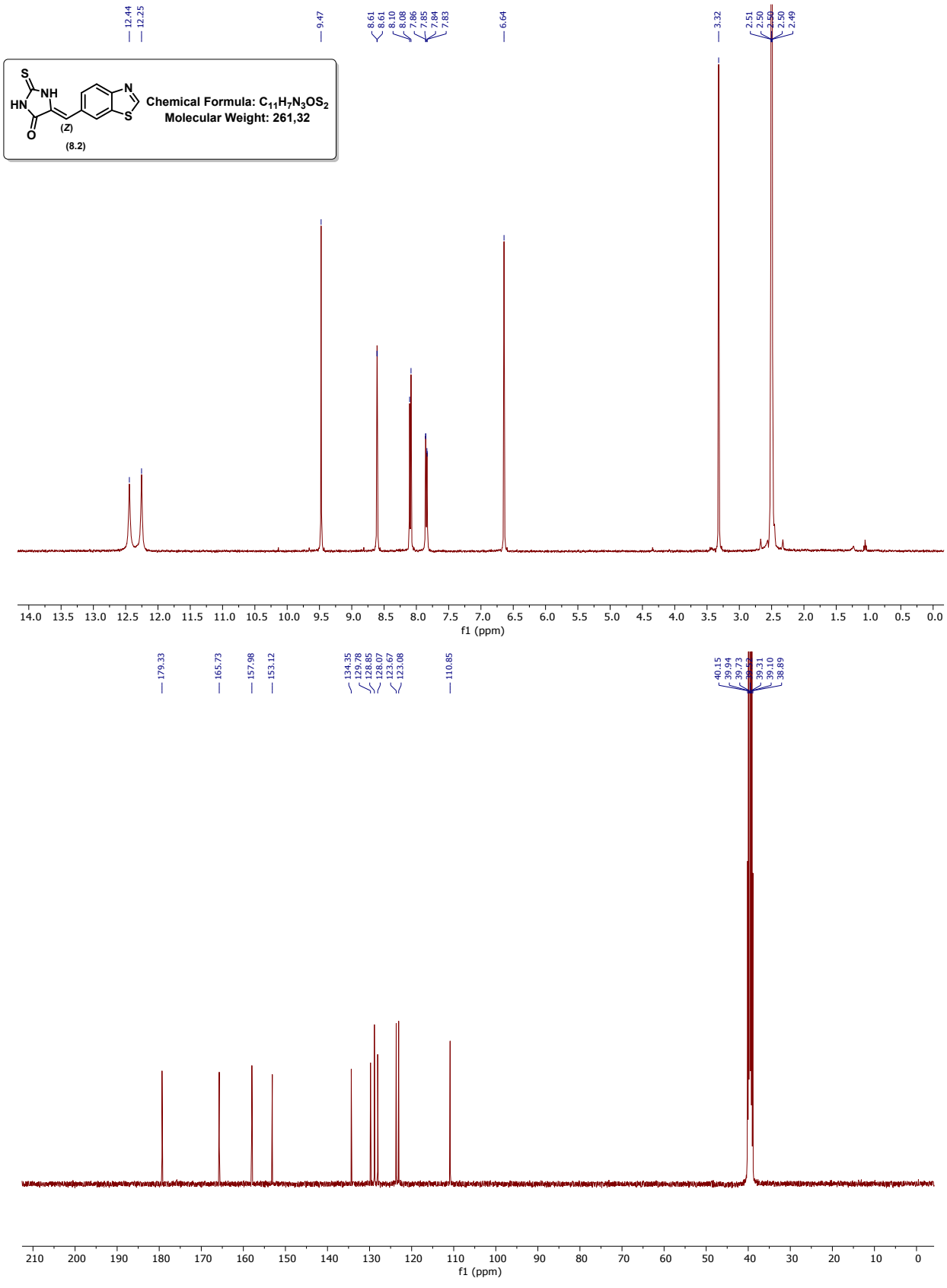
Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP6 and GP7

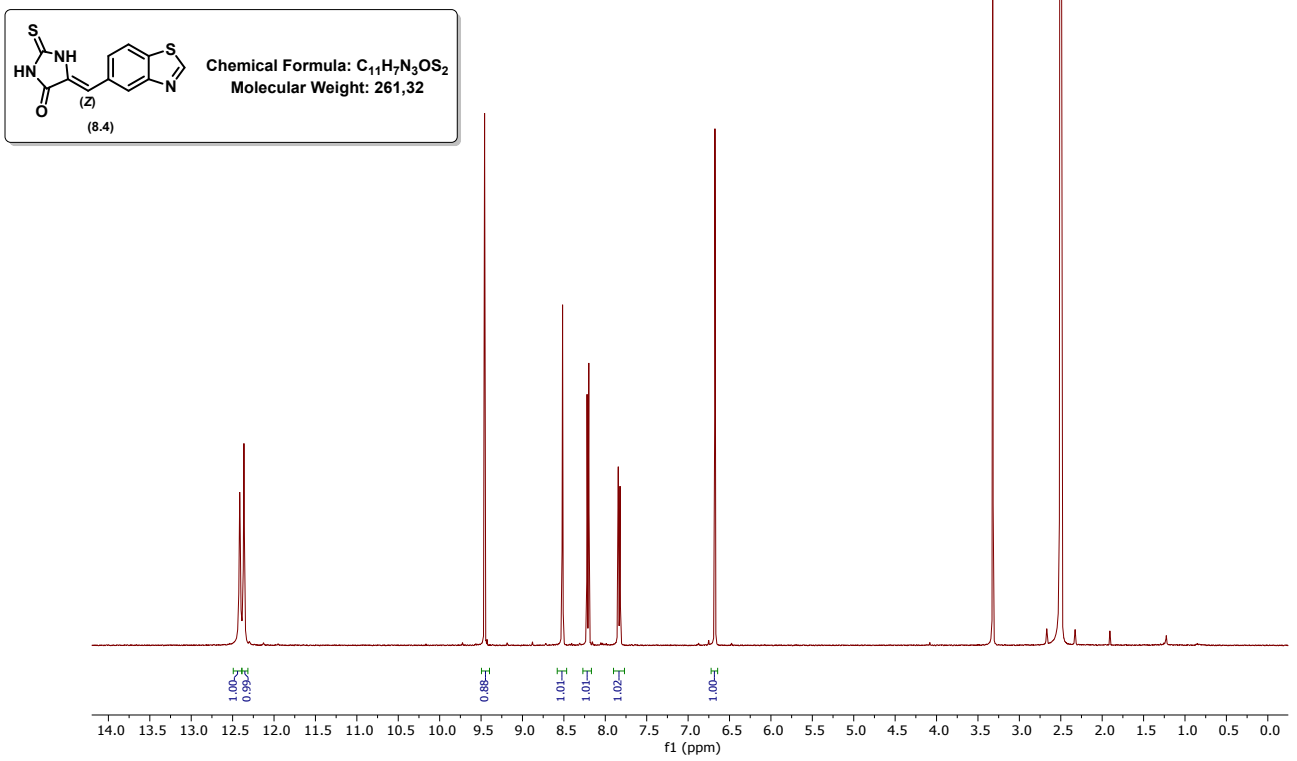


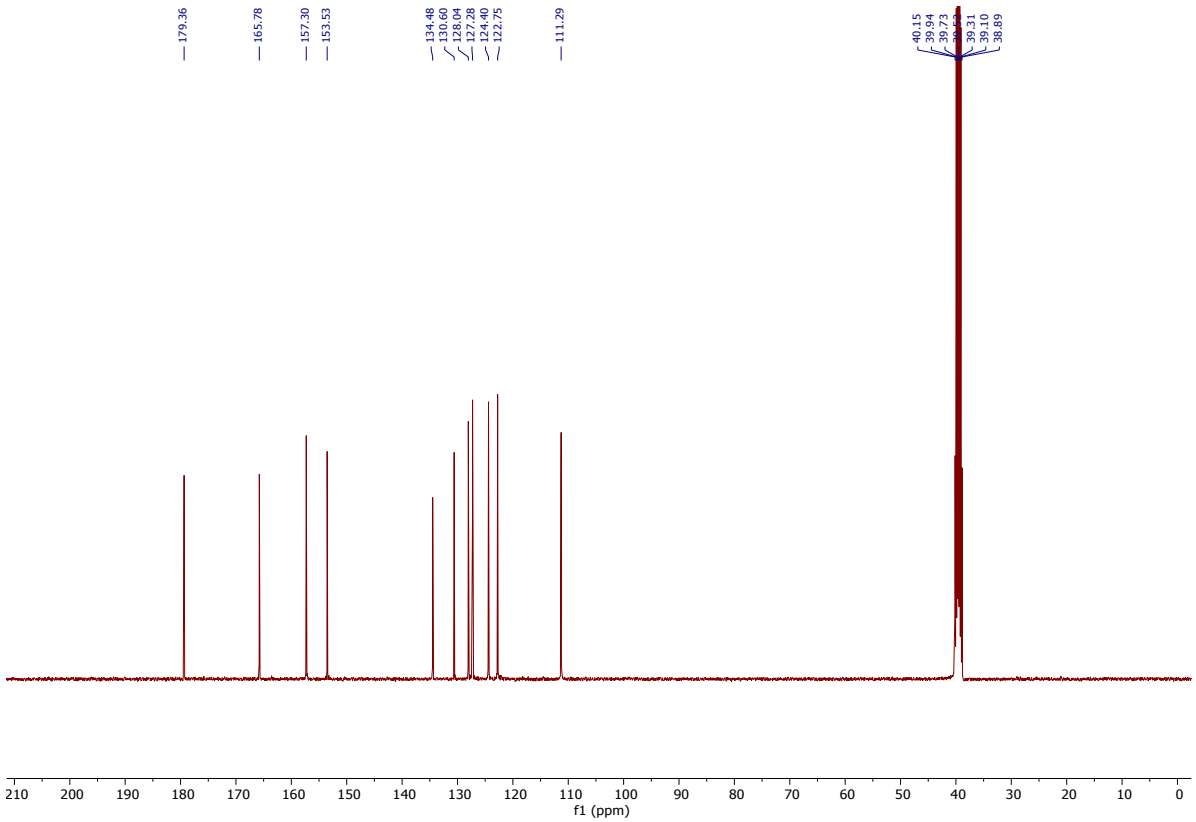

10.12
9.01
8.34
8.03
8.01
8.00
7.98
3.32
2.51
2.50
2.49
2.49
OHC
N
O
(7.4)
Chemical Formula: C8H5NO2
Molecular Weight: 147,13
1.00
0.89
0.98
2.01
f1 (ppm)

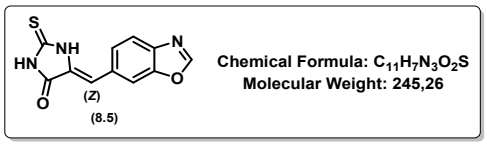

192.12
157.49
149.46
144.57
133.99
126.00
120.70
112.61
40.15
39.94
39.73
39.52
39.31
39.10
38.89
f1 (ppm)

Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP8

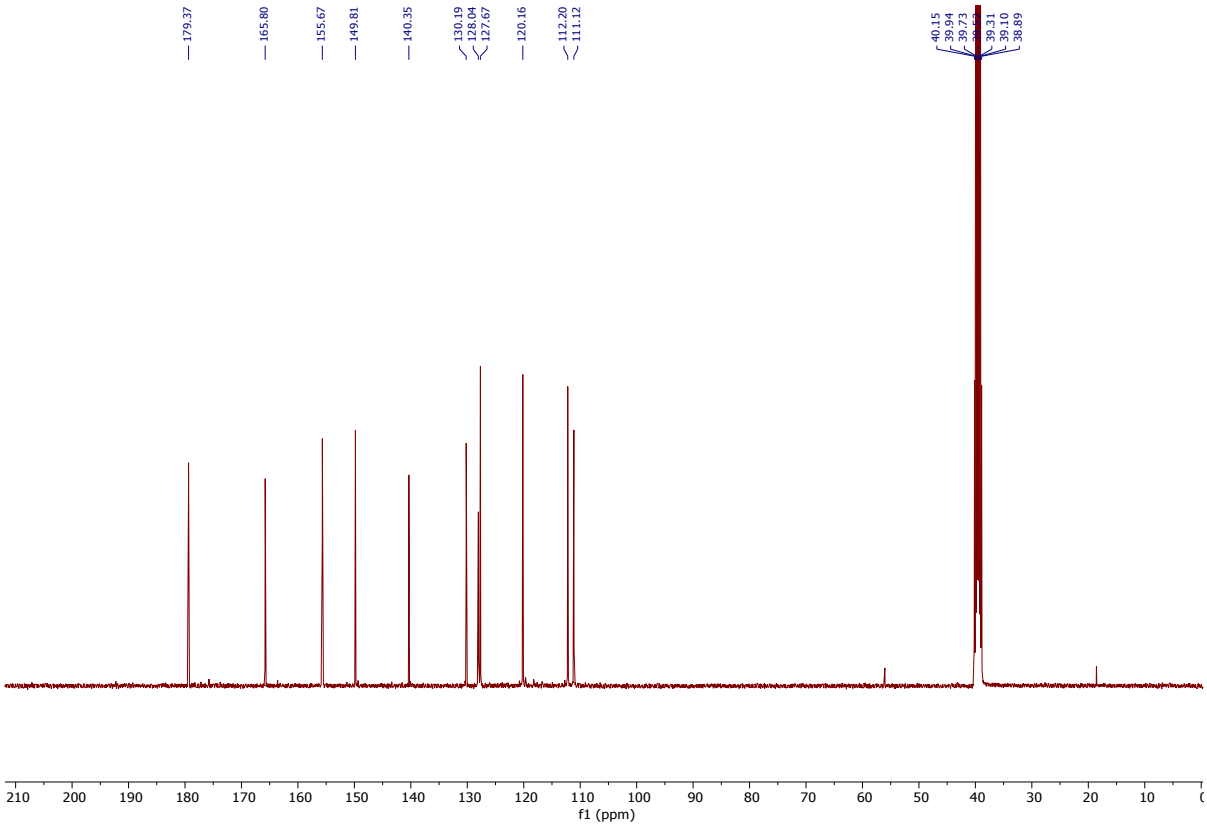


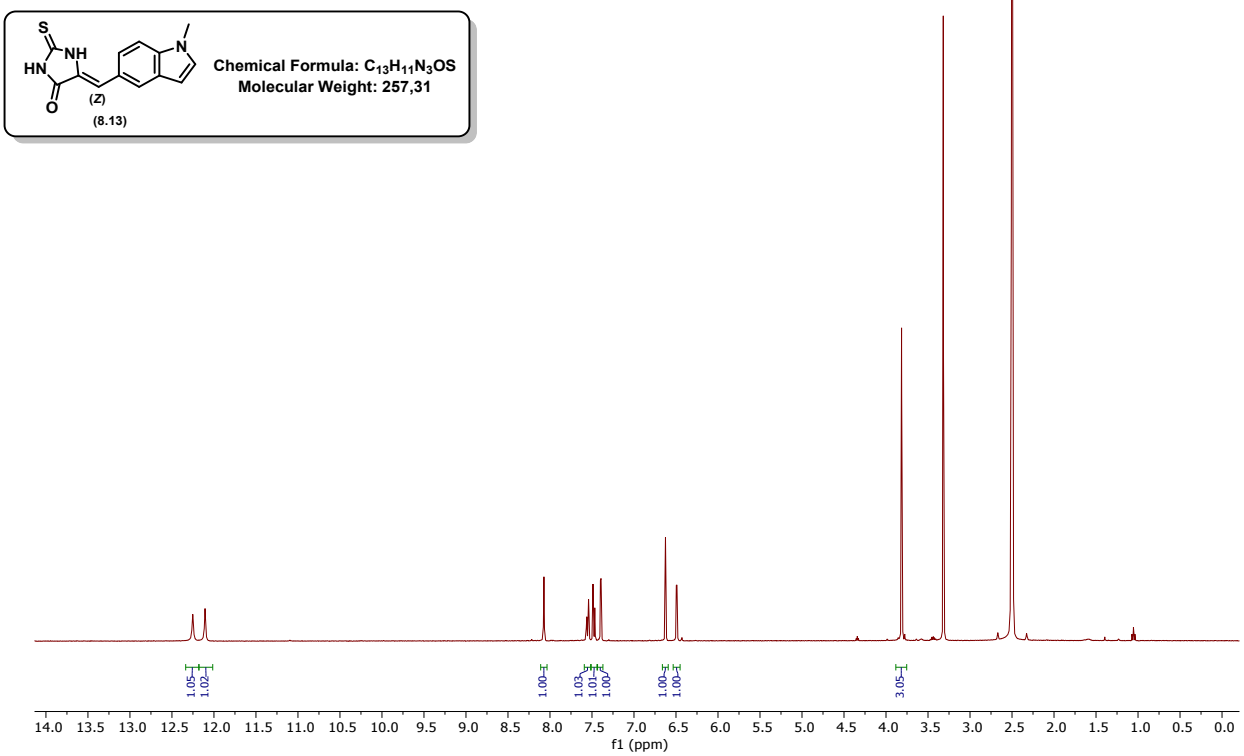

Chemical Formula: $C_{11}H_7N_3OS_2$
Molecular Weight: 261,32
(Z)
(8.4)
12.41
12.36
9.46
8.51
8.22
8.20
7.84
7.82
6.68
3.32
2.51
2.50
2.50
2.50
2.49
1.00
0.99
0.88
1.01
1.01
1.02
1.00
f1 (ppm)

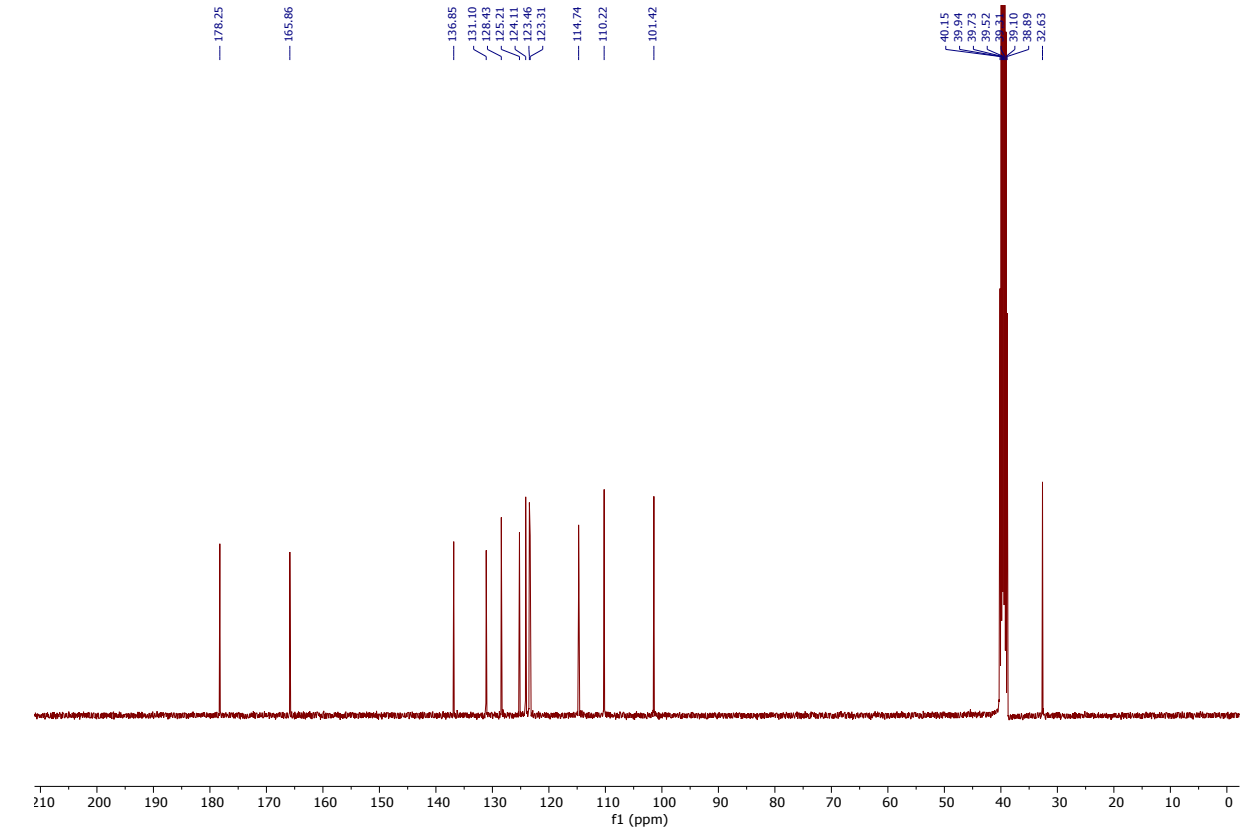

179.36
165.78
157.30
153.53
134.48
130.60
128.04
127.28
124.40
122.75
111.29
40.15
39.94
39.73
39.52
39.31
39.10
38.89
f1 (ppm)



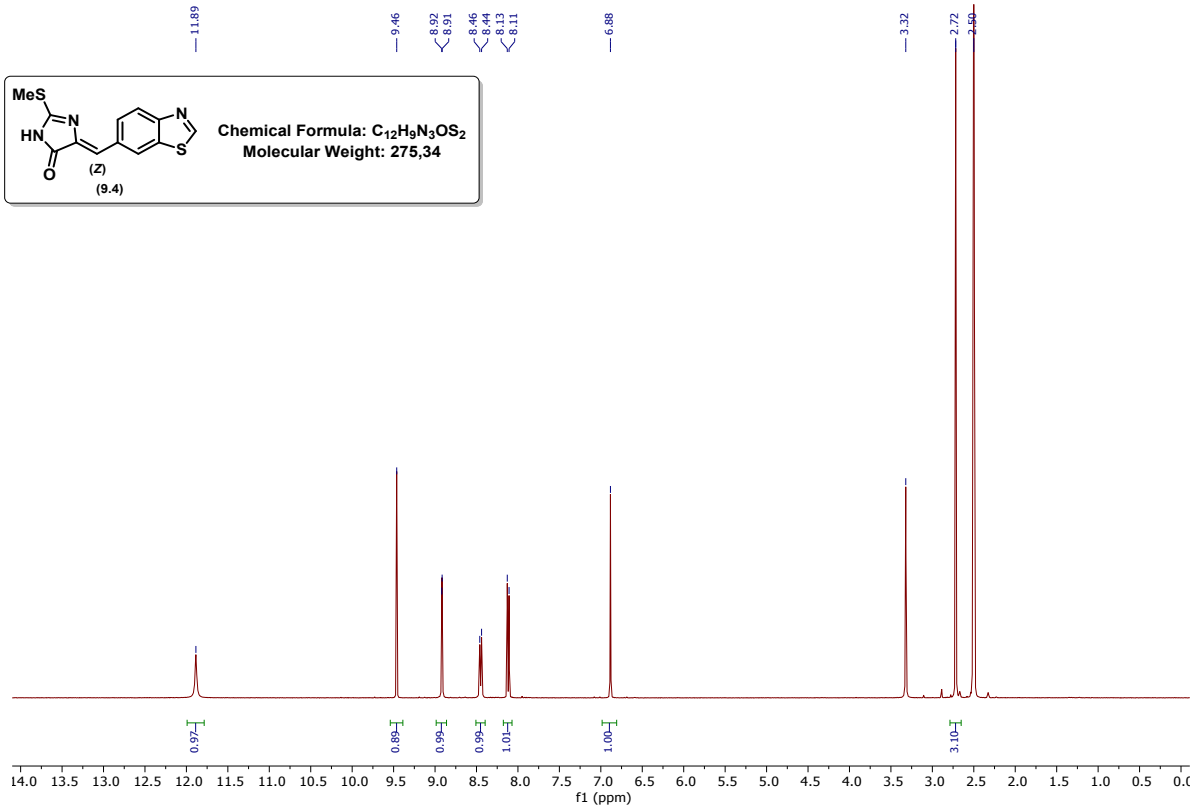
Chemical Formula: $C_{11}H_7N_3O_2S$
Molecular Weight: 245,26

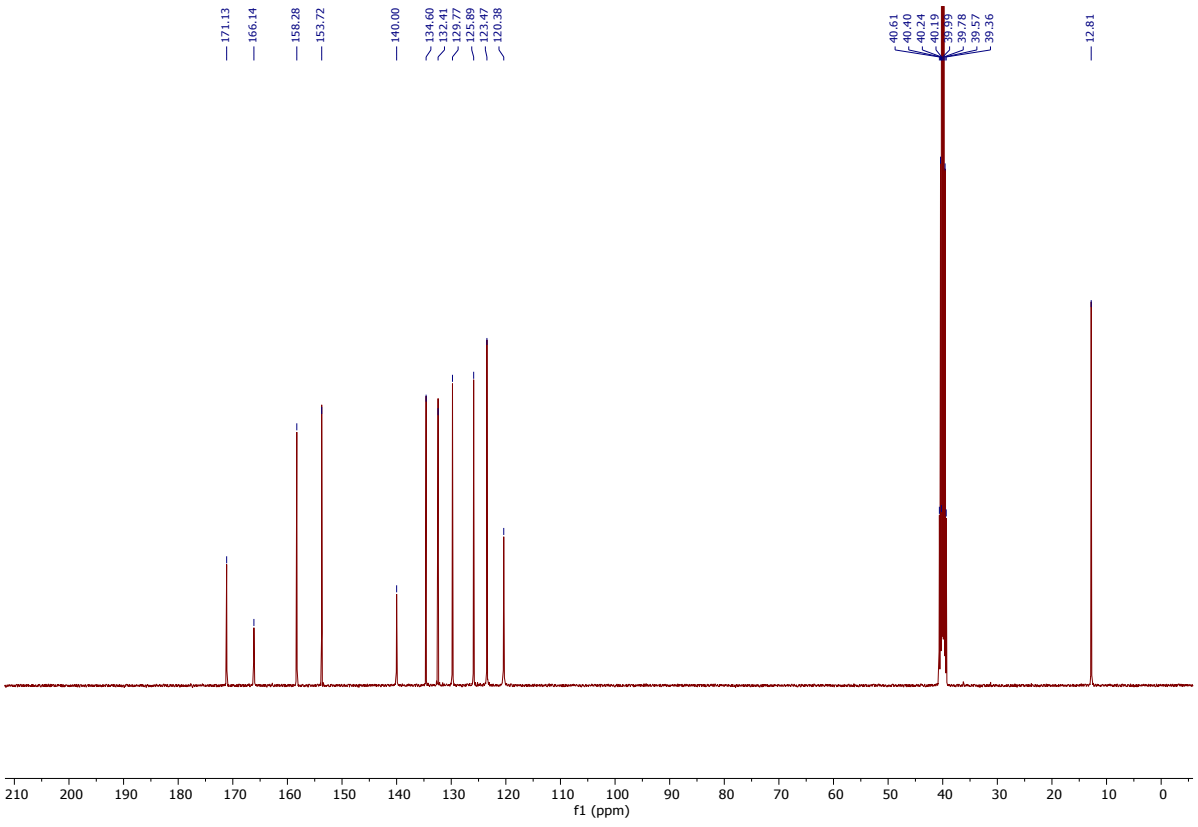


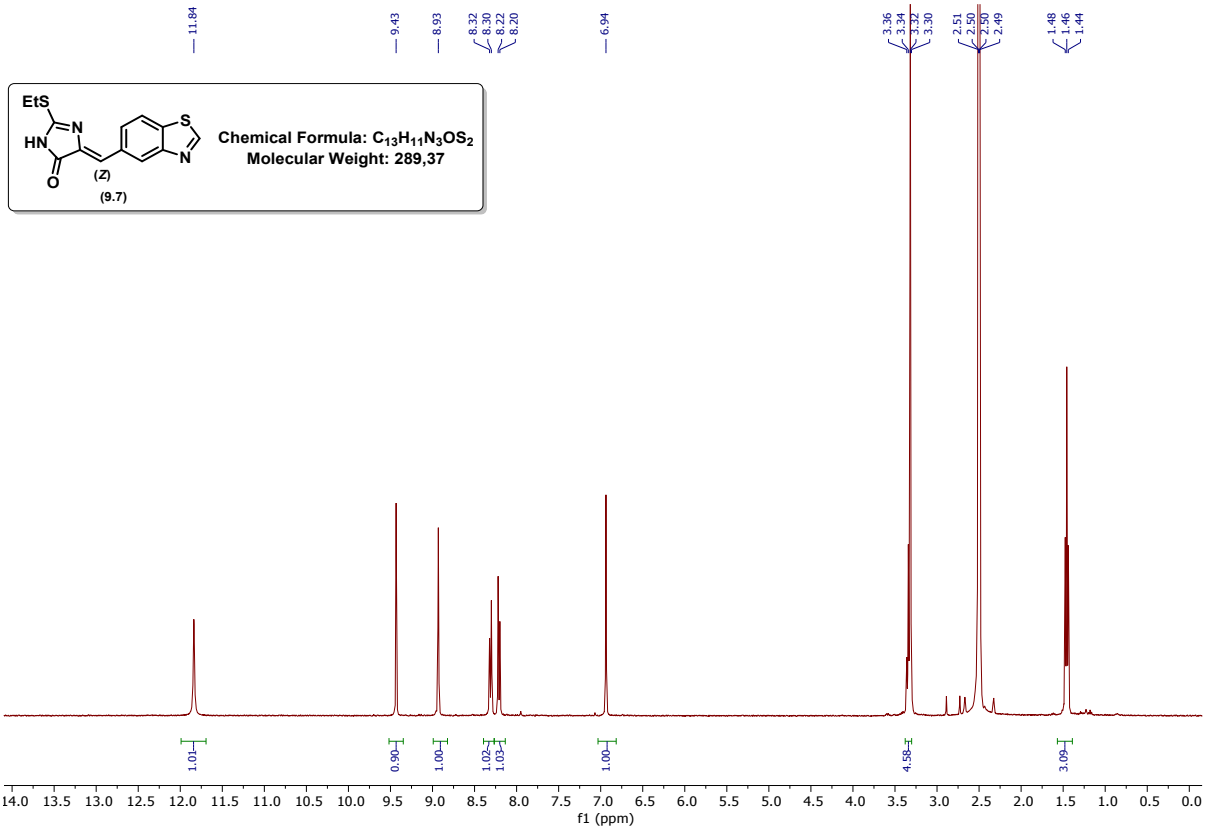

(Z)
(8.13)
Chemical Formula: C13H11N3OS
Molecular Weight: 257,31
f1 (ppm)

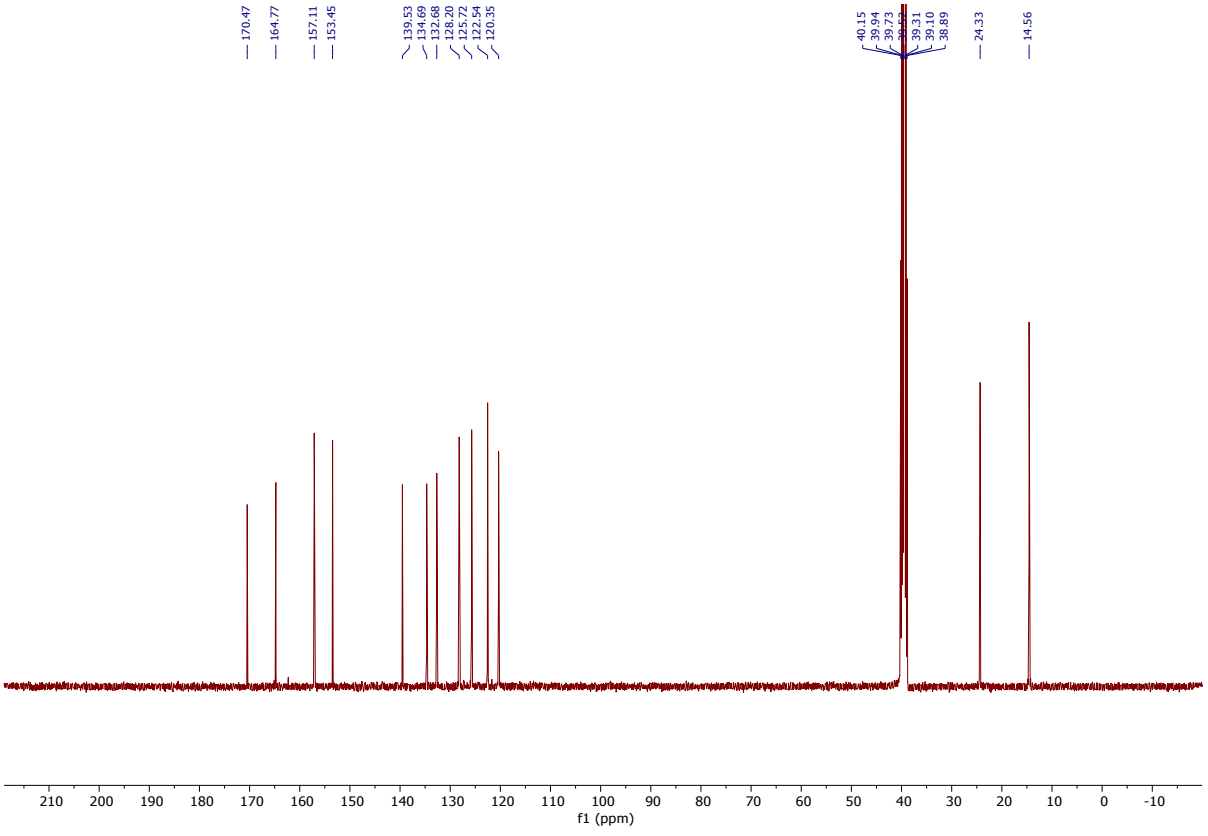

f1 (ppm)

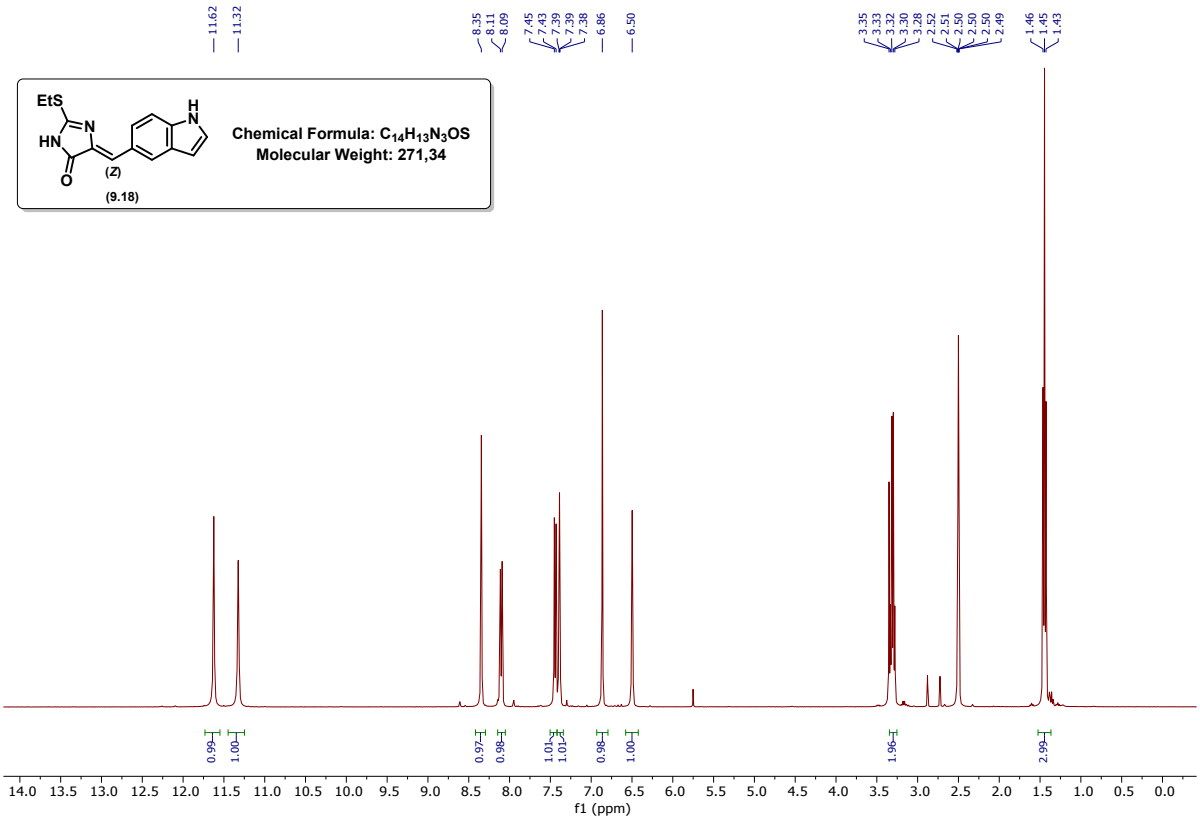
Selected examples of ^{1}H NMR + ^{13}C of intermediate compounds from GP9 (*S*-alkylation)

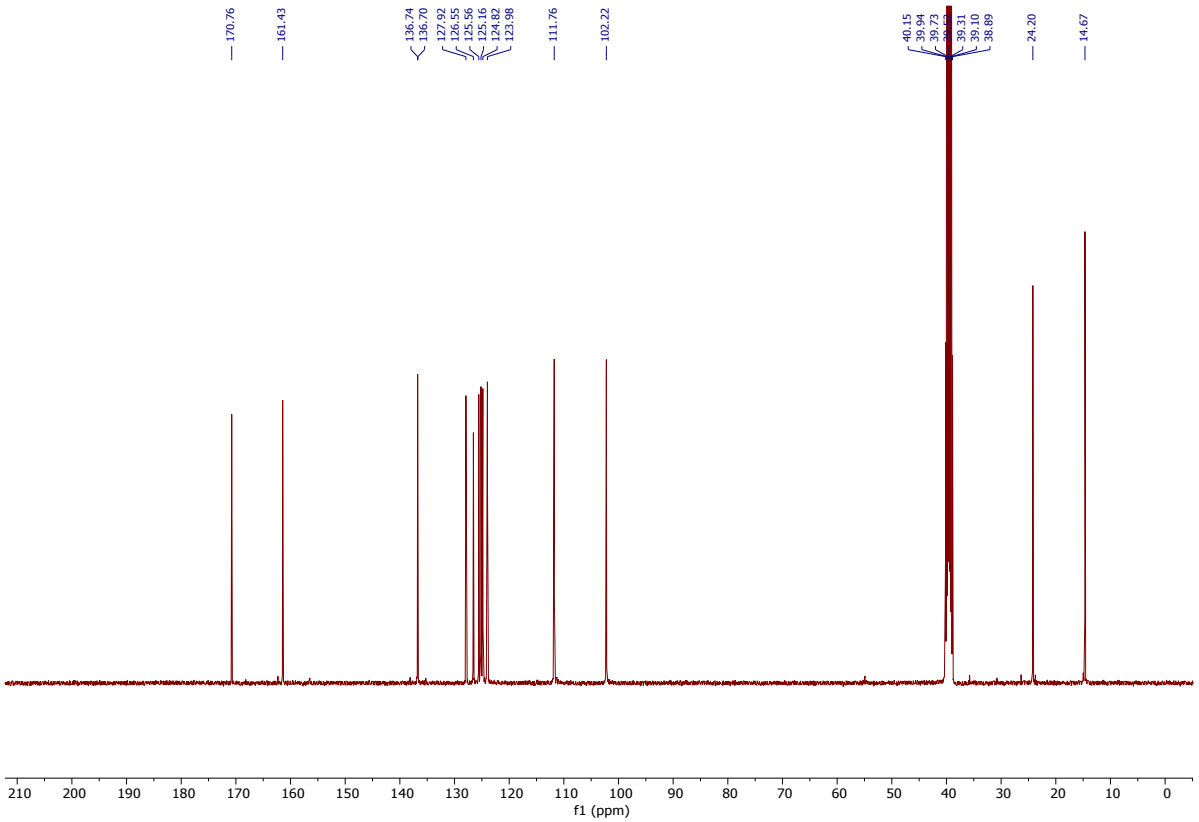




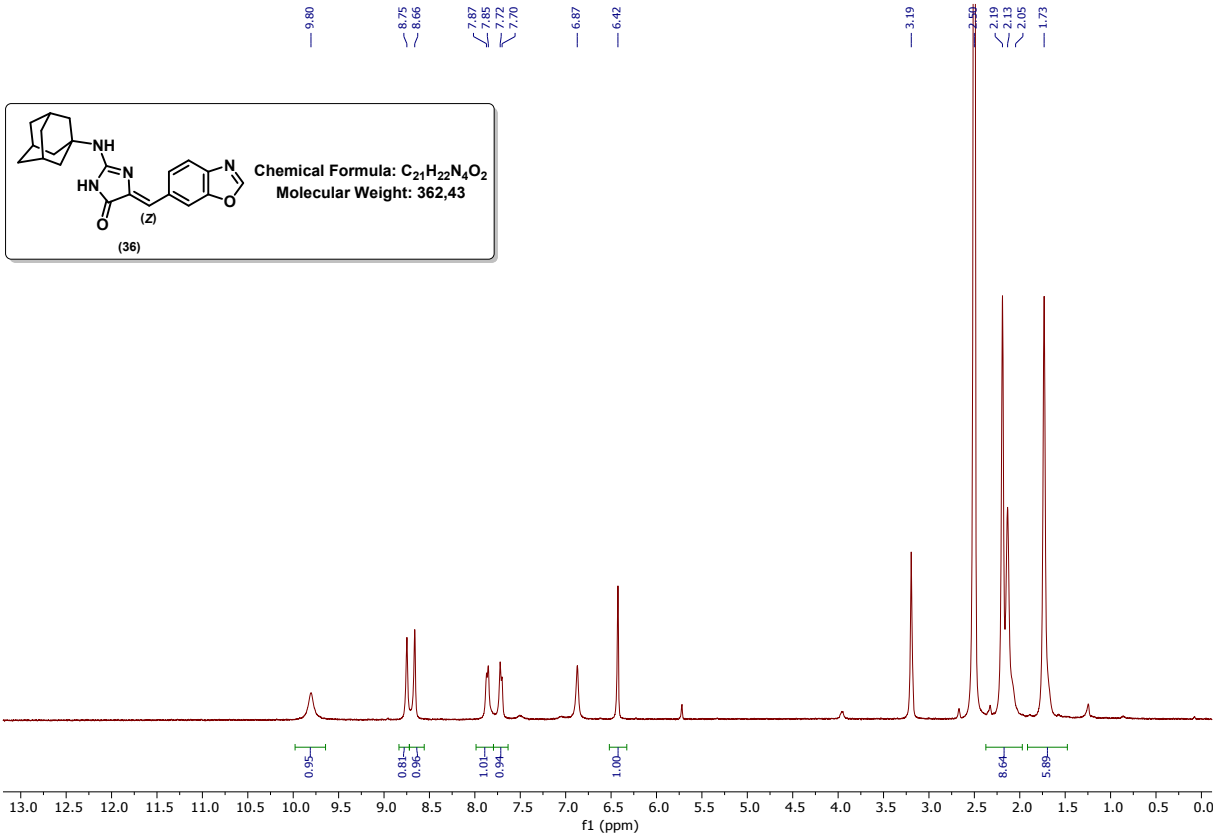

EtS
HN
O
(Z)
(9.7)
Chemical Formula: C13H11N3OS2
Molecular Weight: 289,37
11.84
9.43
8.93
8.32
8.30
8.22
8.20
6.94
3.36
3.34
3.32
3.30
2.51
2.50
2.50
2.49
1.48
1.46
1.44
1.01
0.90
1.00
1.02
1.03
1.00
4.58
3.09
f1 (ppm)

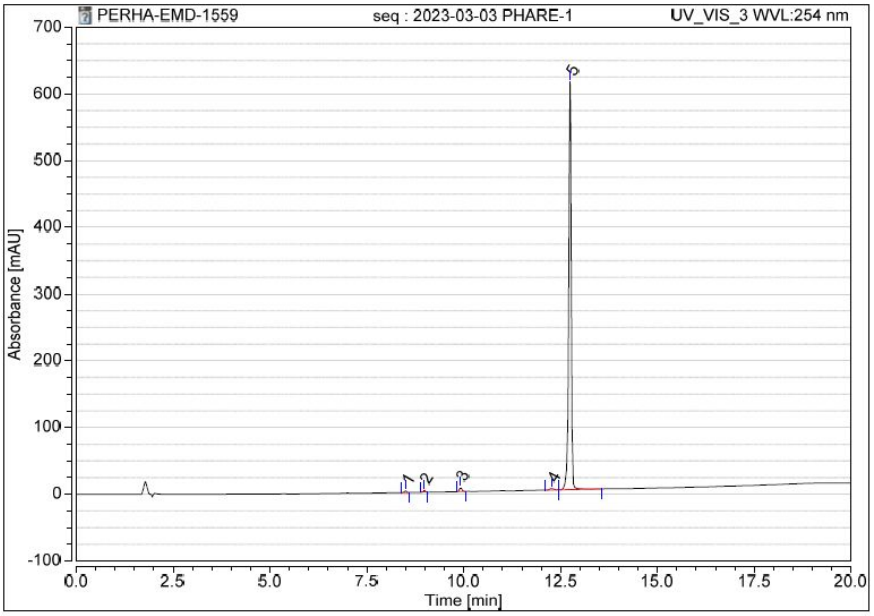

170.47
164.77
157.11
153.45
139.53
134.69
132.68
128.20
125.72
122.94
120.35
40.15
39.94
39.73
39.52
39.31
39.10
38.89
24.33
14.56
f1 (ppm)


EtS
HN
N
O
H
N
(Z)
(9.18)
Chemical Formula: C14H13N3OS
Molecular Weight: 271,34
f1 (ppm)

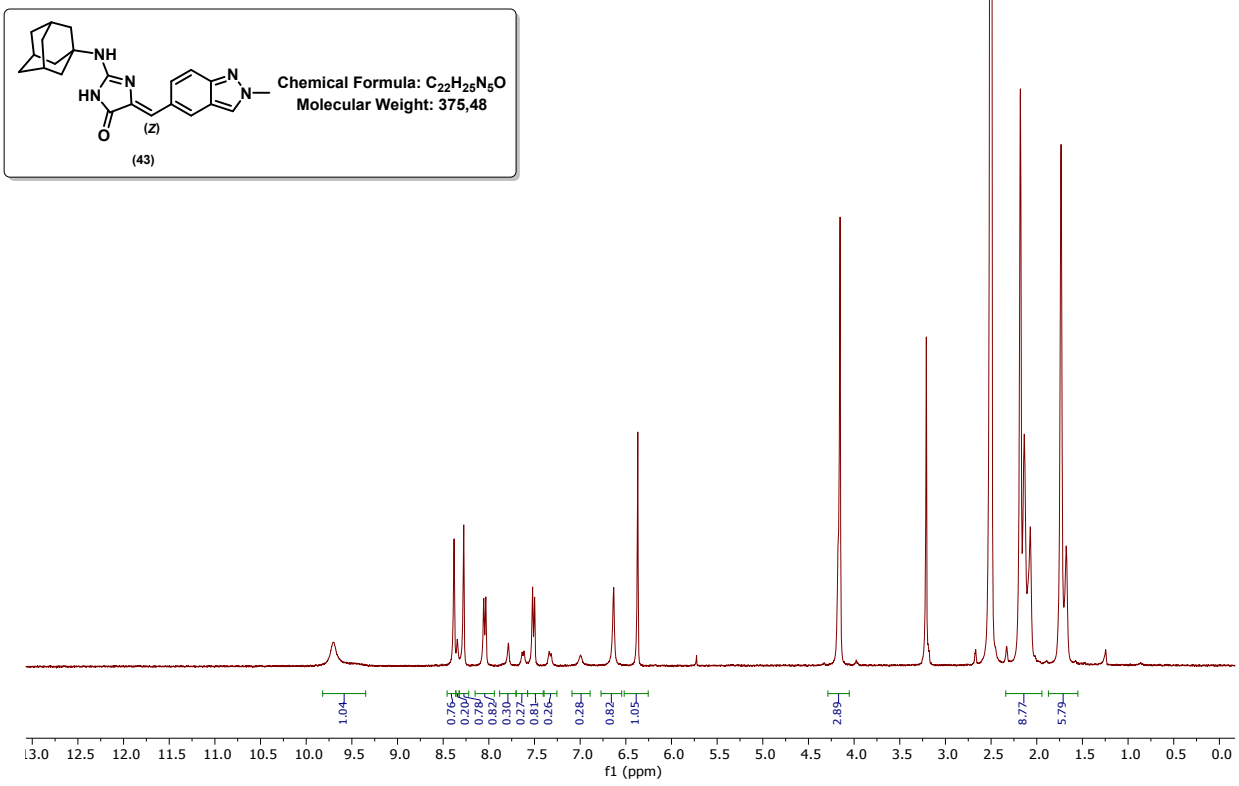

f1 (ppm)

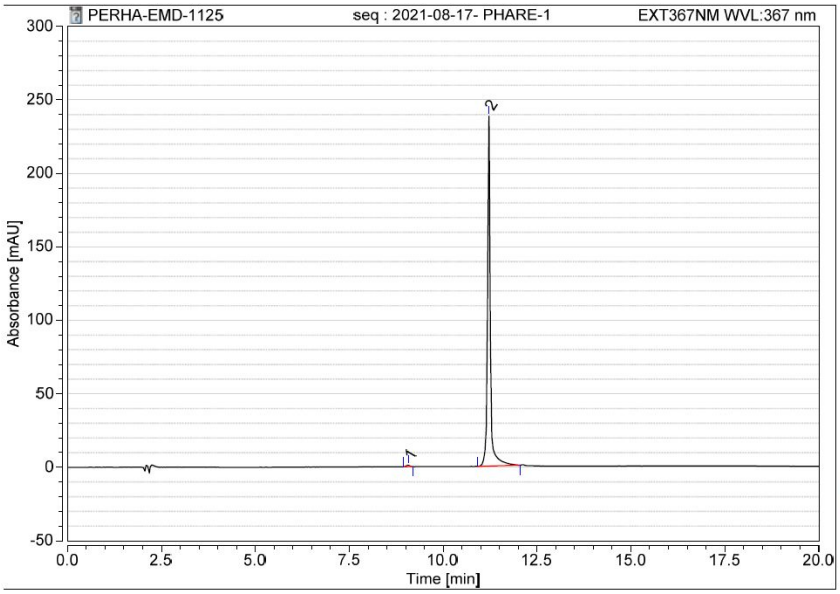
Selected examples of ^{1}H NMR + HPLC of final compounds in table 1





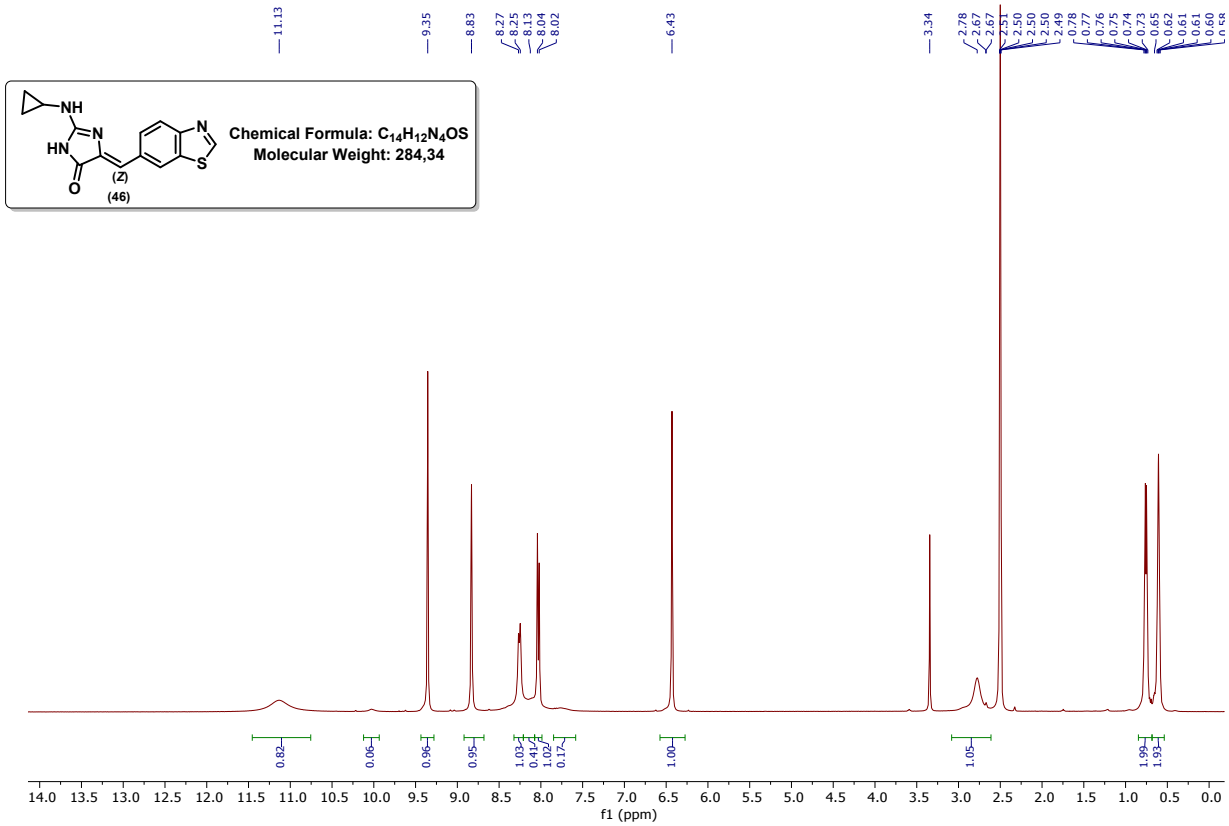
No.	Retention Time min	Area mAU*min	Relative Area %
1	8.50	0.2	0.3
2	8.98	0.2	0.3
3	9.92	0.4	0.9
4	12.26	0.3	0.6
5	12.75	45.7	97.8
Total:		**46.7**	**100.0**

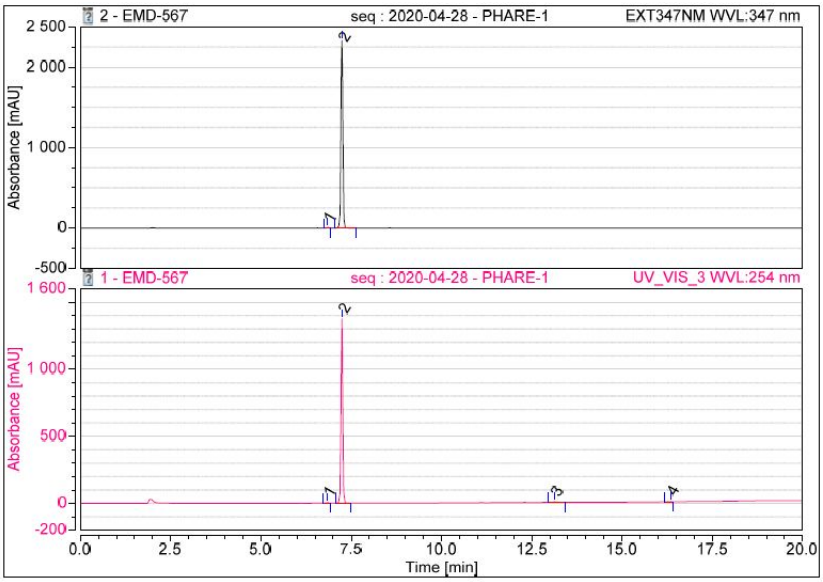




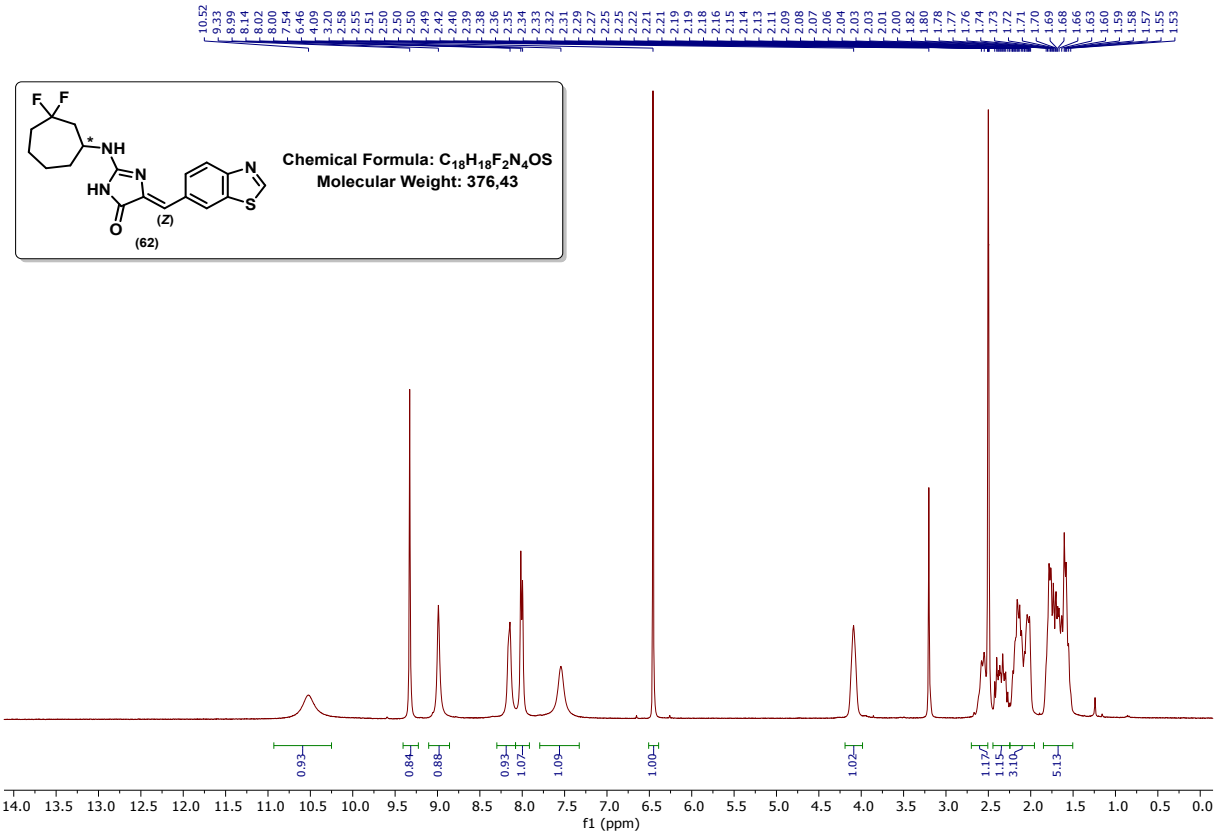
No.	etention Tim min	Area mAU*min	Relative Area %
1	9.07	0.1	0.5
2	11.22	21.1	99.5
Total:		**21.2**	**100.0**

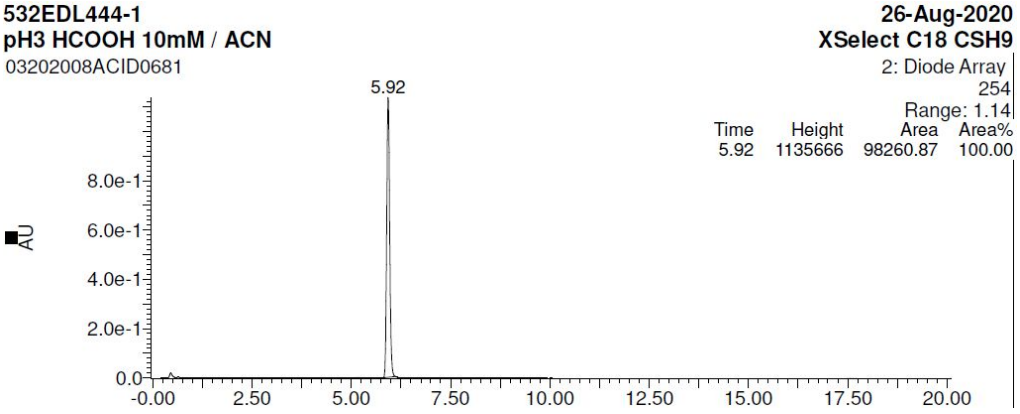
Selected examples of ^{1}H NMR + HPLC of final compounds in table 2



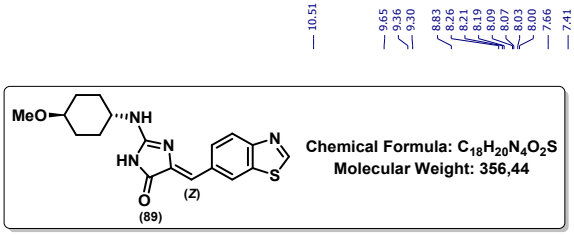


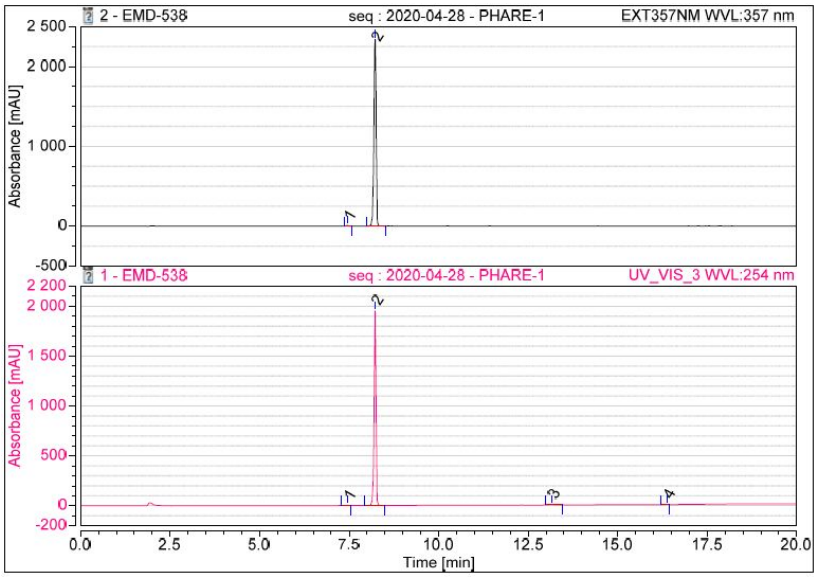
No.	Retention Time min	Area mAU*min	Relative Area %
1	6.85	0.4	0.3
2	7.24	145.7	99.7
Total:		**146.2**	**100.0**


Chemical Formula: C18H18F2N4OS
Molecular Weight: 376,43
(62)
f1 (ppm)

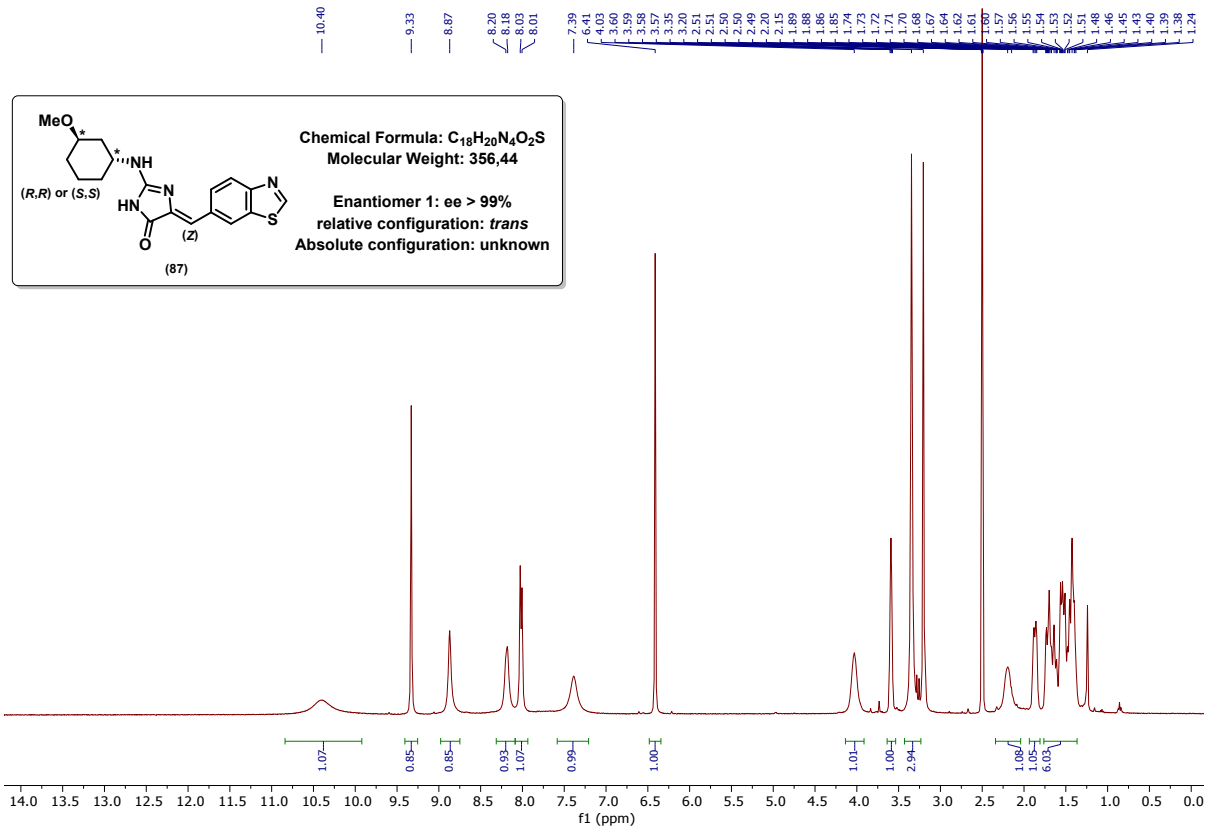

532EDL444-1
pH3 HCOOH 10mM / ACN
03202008ACID0681
26-Aug-2020
XSelect C18 CSH9
2: Diode Array
254
Range: 1.14
Time Height Area Area%
5.92 1135666 98260.87 100.00
5.92
AU
f1 (ppm)

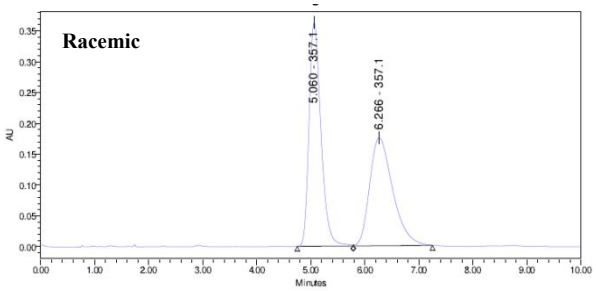
Selected examples of ^{1}H NMR + HPLC of final compounds in table 3



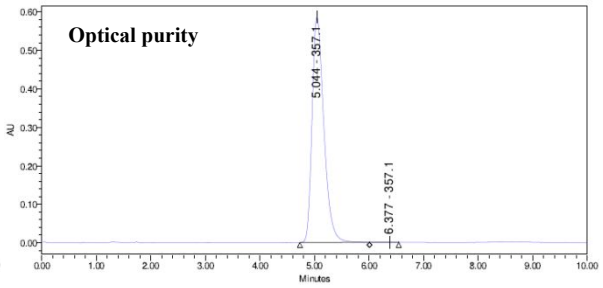


No.	etention Tim min	Area mAU*min	Relative Area %
1	7.45	0.4	0.3
2	8.23	168.1	99.7
Total:		**168.5**	**100.0**

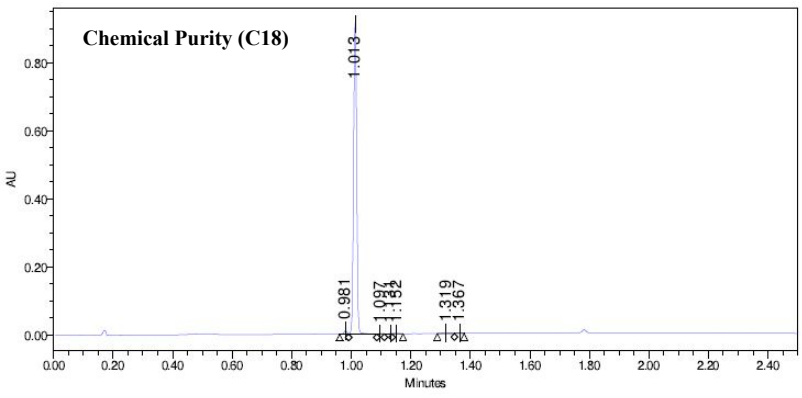




	Retention Time (min)	Area (µV*sec)	% Area	Width @ 50%
1	5.06	5542427	51.6	0.23072
2	6.27	5190448	48.4	0.45139

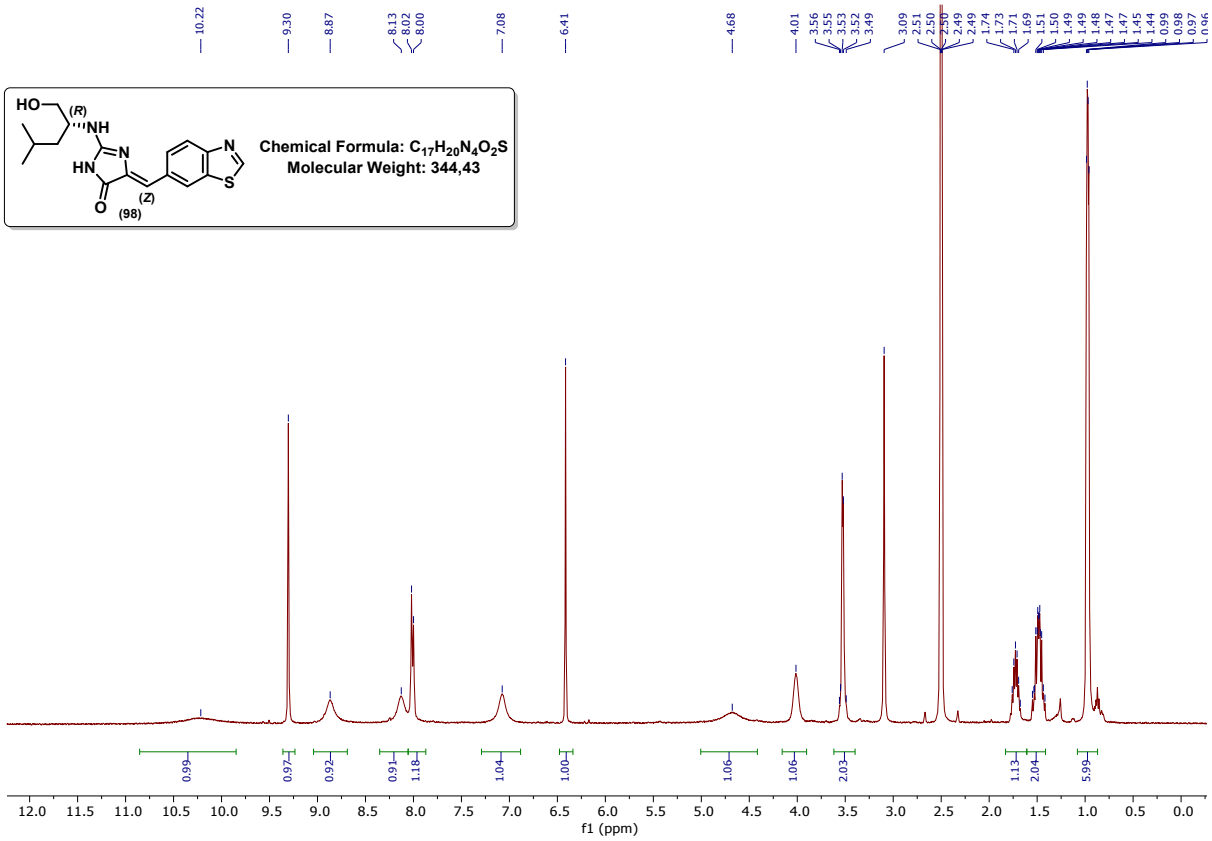


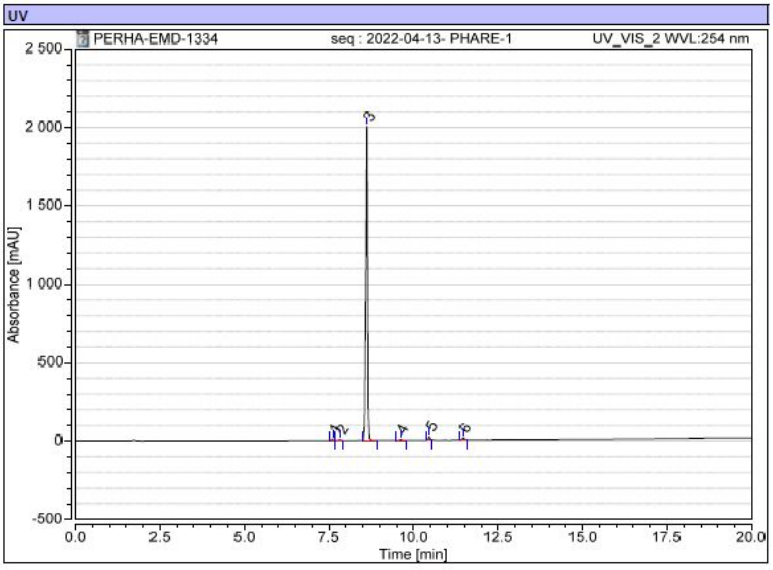
	Retention Time (min)	Area (µV*sec)	% Area	Width @ 50%
1	5.04	8780939	99.9	0.22680
2	6.38	10720	0.1	0.40852



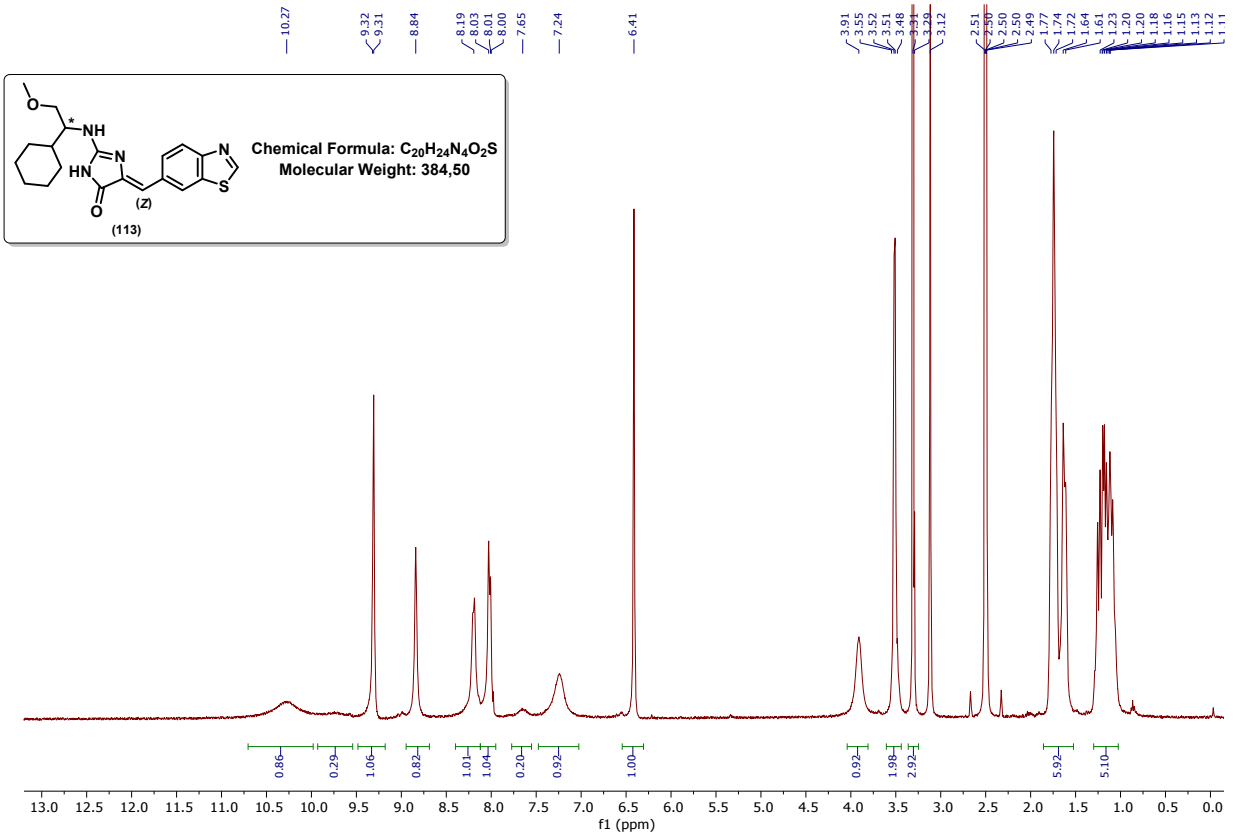
	Retention Time (min)	Area (µV*sec)	% Area	Width (sec)
1	0.98	6972	1.05	1.850
2	1.01	655154	98.41	5.650
3	1.10	523	0.08	1.500
4	1.13	683	0.10	1.600
5	1.15	929	0.14	2.200
6	1.32	1186	0.18	3.450
7	1.37	273	0.04	1.950

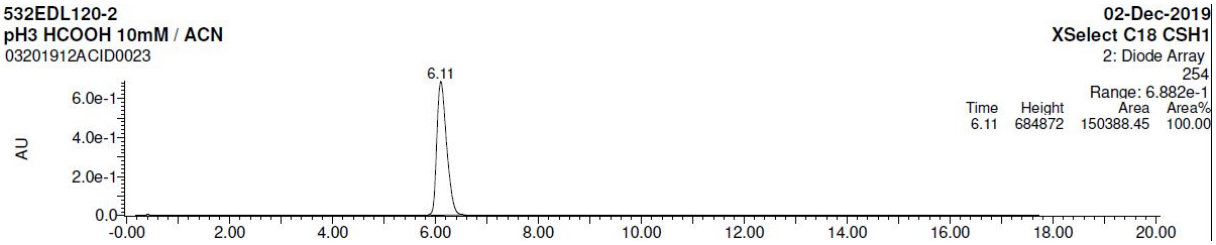
Selected examples of ^{1}H NMR + HPLC of final compounds in table 4



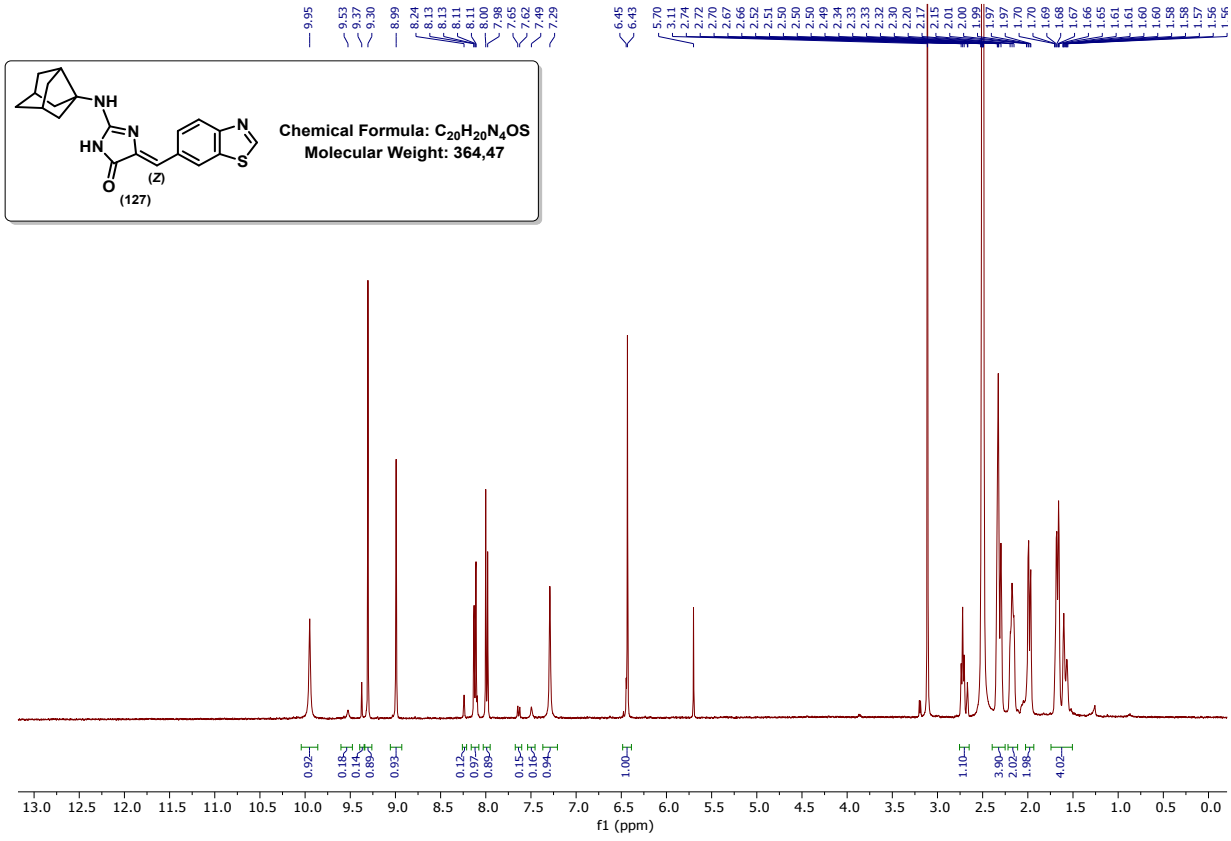


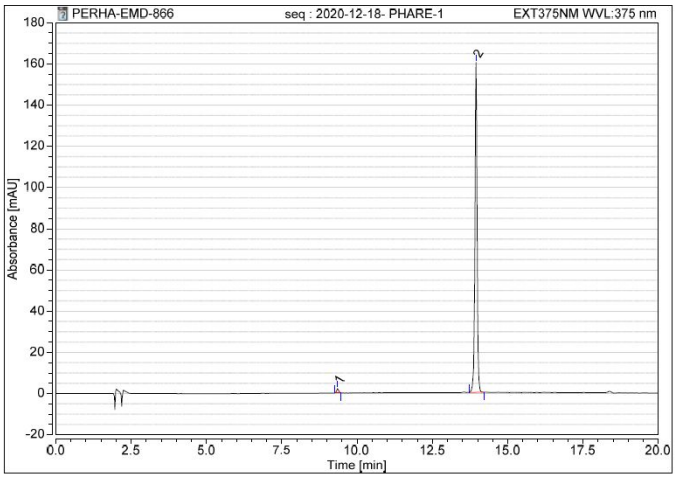
No.	Retention Time min	Area mAU*min	Relative Area %
1	7.62	0.8	0.6
2	7.82	0.5	0.4
3	8.62	123.7	96.9
4	9.62	0.4	0.3
5	10.46	1.2	0.9
6	11.46	1.0	0.8
Total:		127.7	100.0


Chemical Formula: C20H24N4O2S
Molecular Weight: 384,50
(Z)
(113)
f1 (ppm)

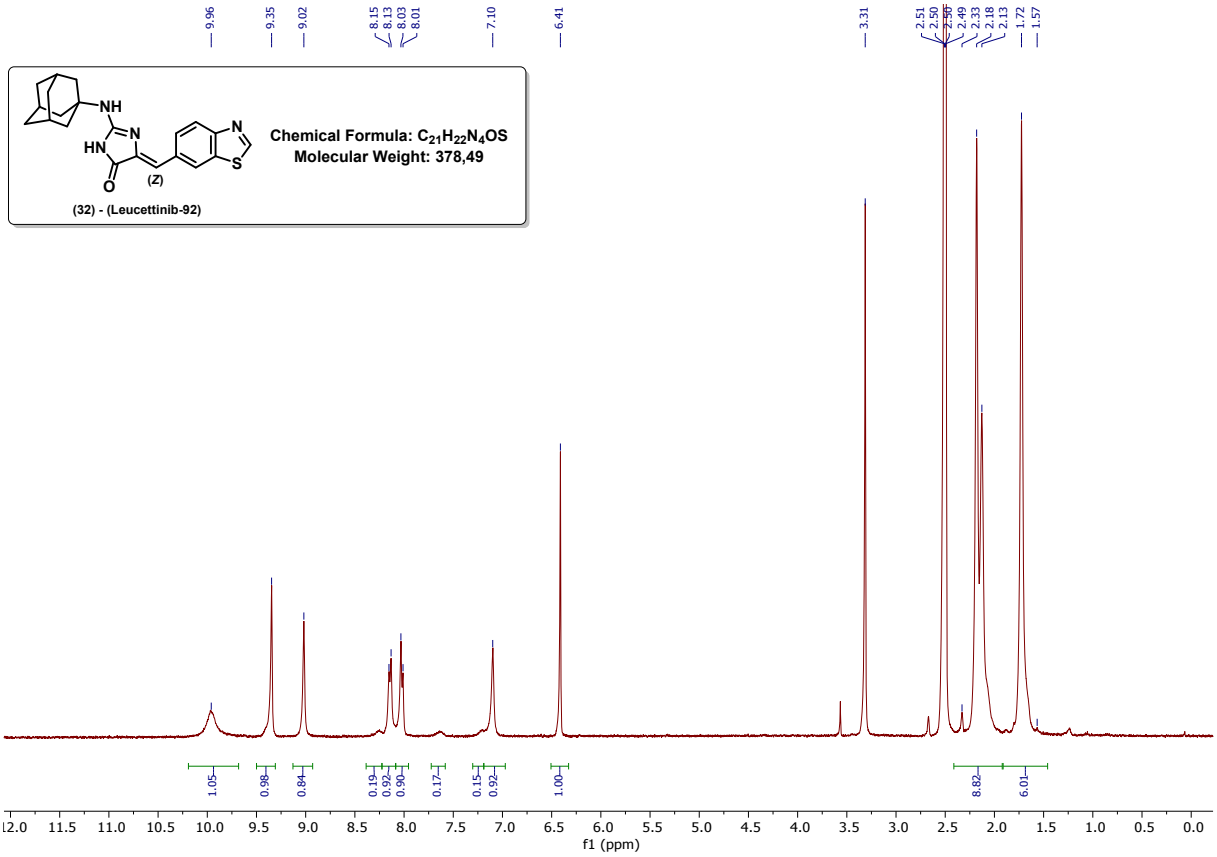

532EDL120-2
pH3 HCOOH 10mM / ACN
03201912ACID0023
02-Dec-2019
XSelect C18 CSH1
2: Diode Array
254
Range: 6.882e-1
Time Height Area Area%
6.11 684872 150388.45 100.00
6.11
AU
min

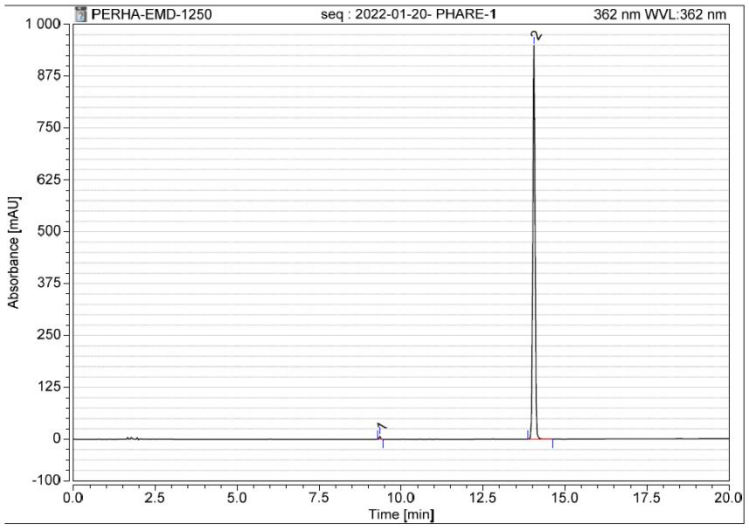
Selected examples of ^{1}H NMR + HPLC of final compounds in table 5



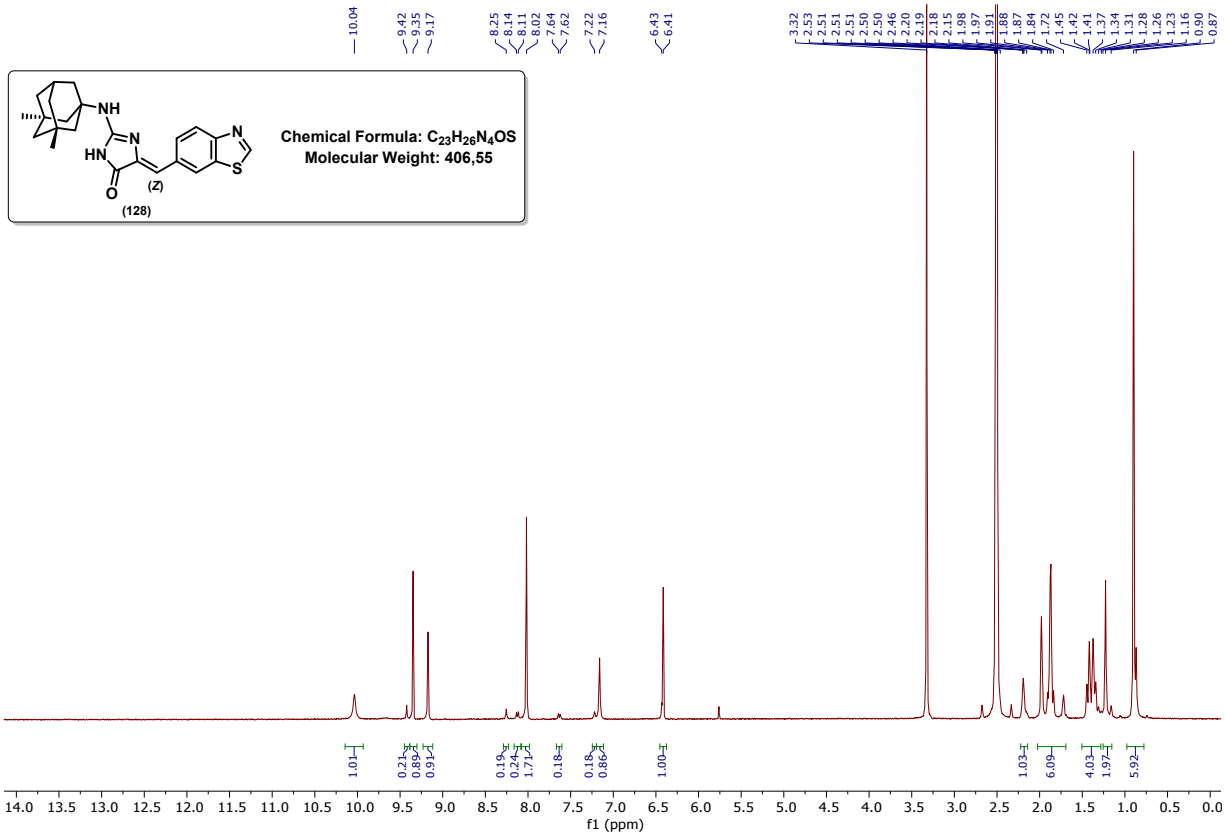


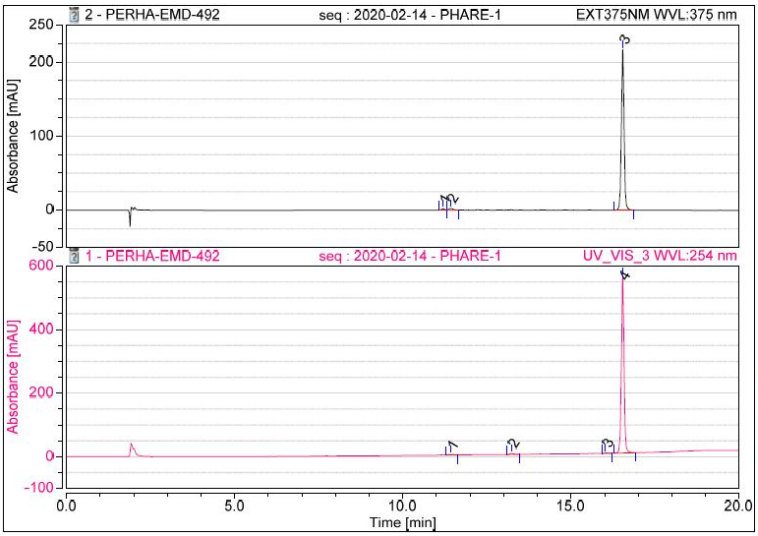
No.	Retention Time min	Area mAU*min	Relative Area %
1	9.36	0.2	1.2
2	13.95	13.4	98.8
Total:		**13.5**	**100.0**





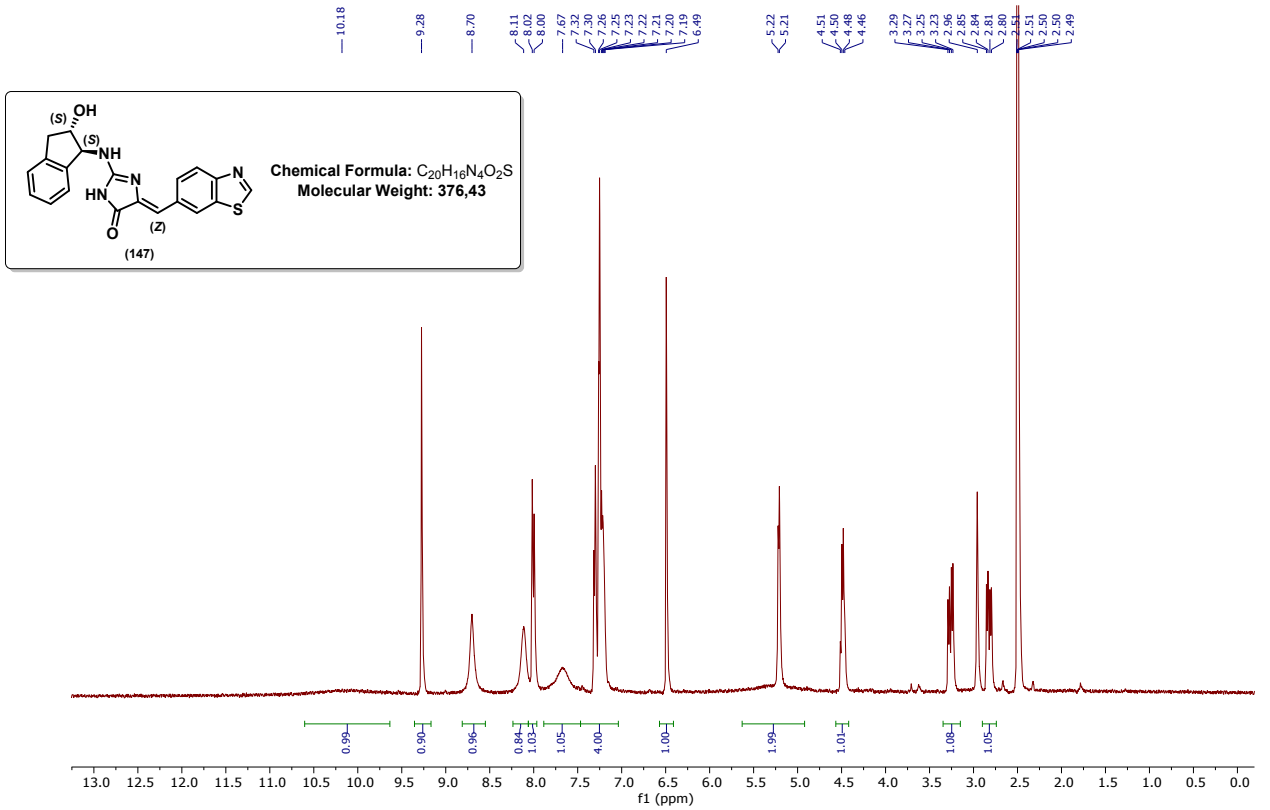
No.	etention Tim min	Area mAU*min	Relative Area %
1	9.35	0.4	0.5
2	14.05	76.9	99.5
Total:		**77.3**	**100.0**

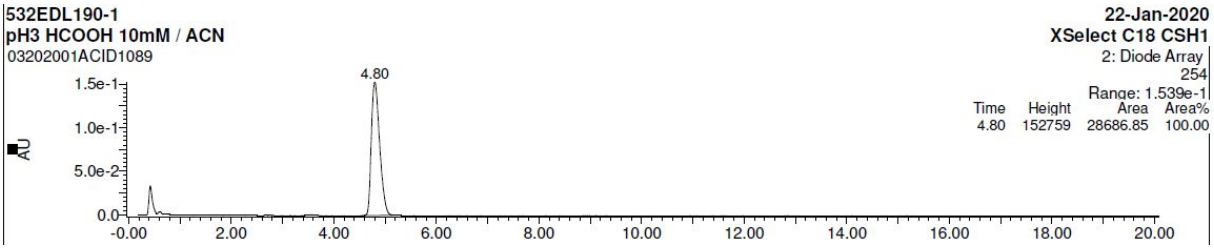


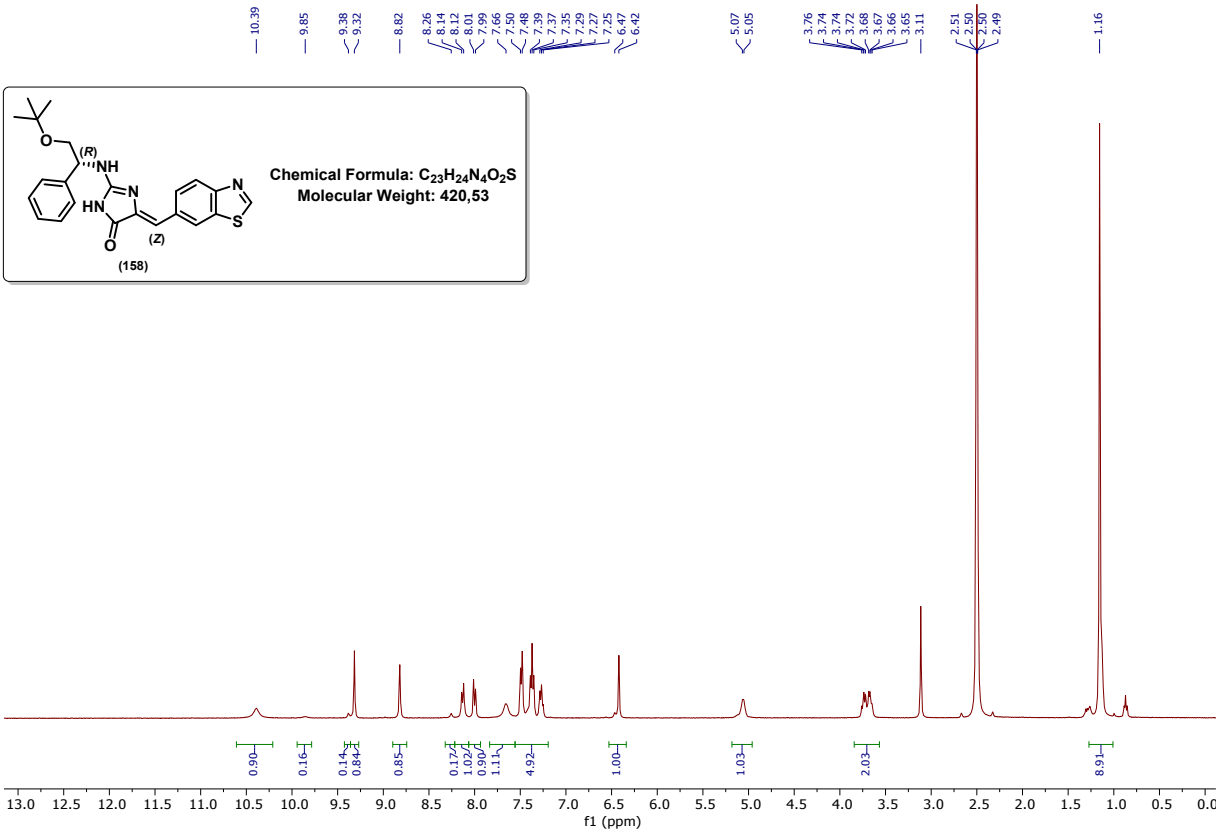


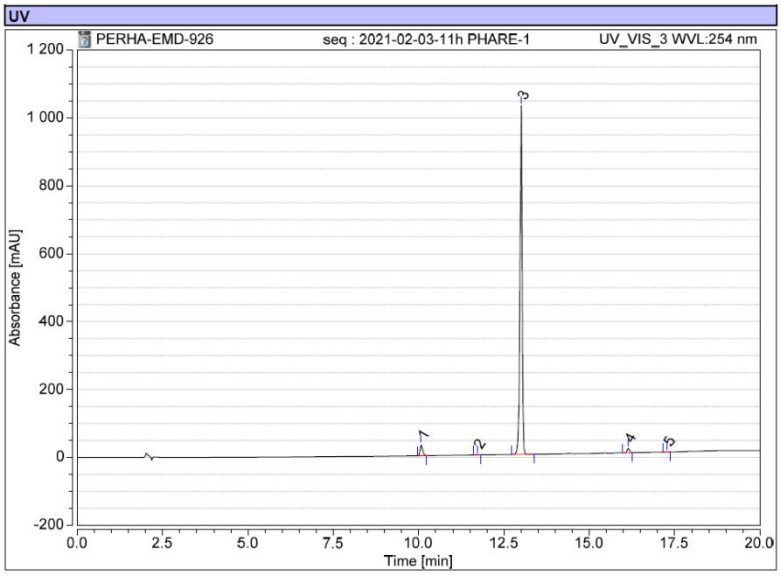
No.	Retention Time min	Area mAU*min	Relative Area %
1	11.20	0.2	1.0
2	11.42	0.4	1.8
3	16.54	20.0	97.2
Total:		**20.6**	**100.0**

Selected examples of ^{1}H NMR + HPLC of final compounds in table 6



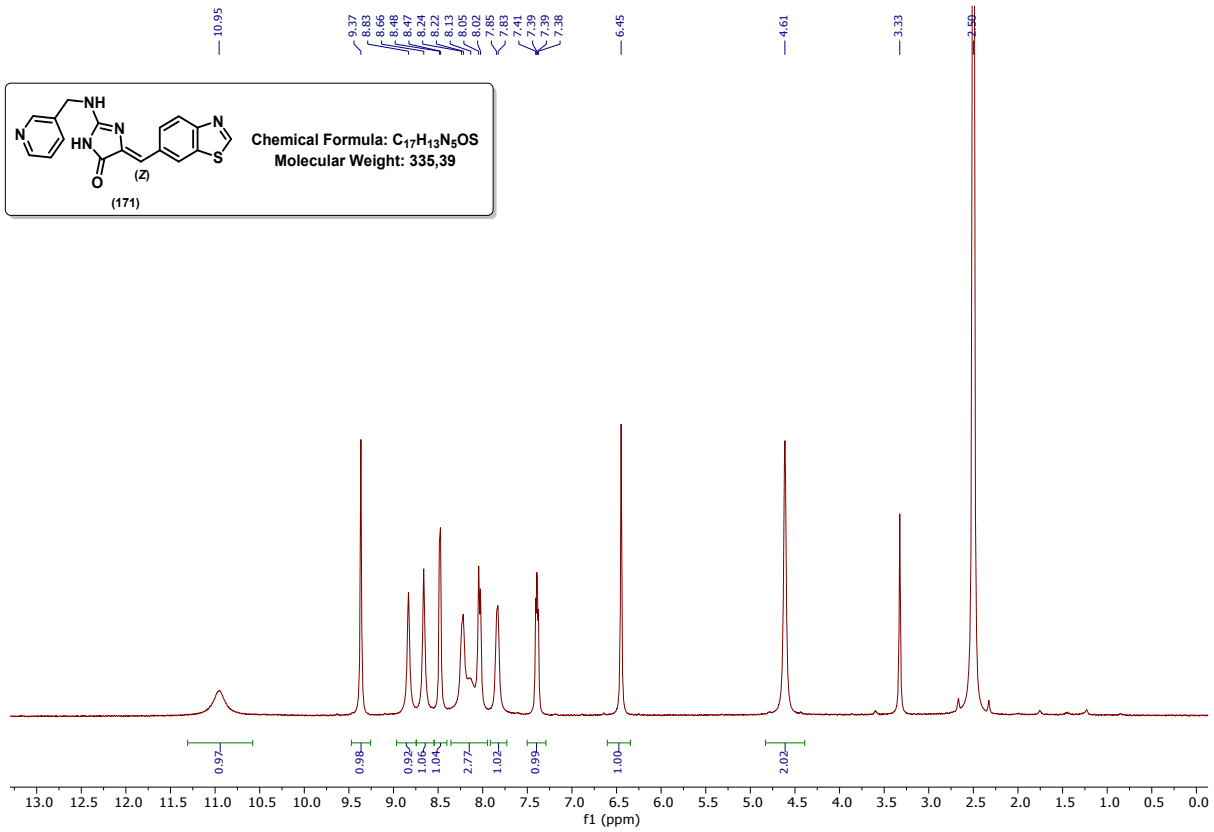


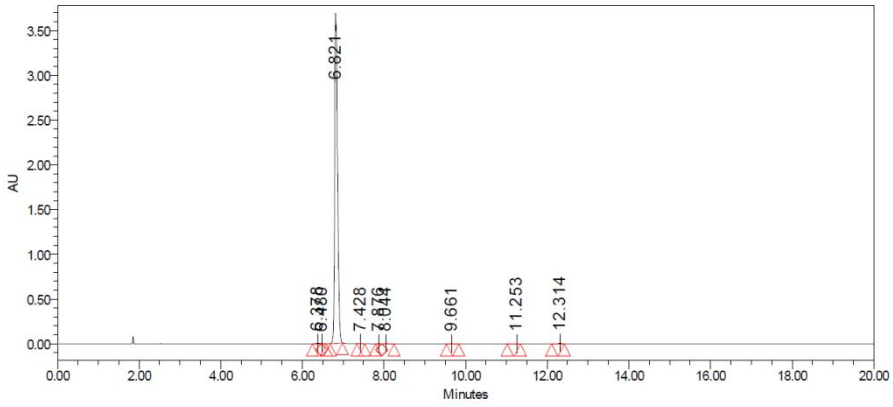




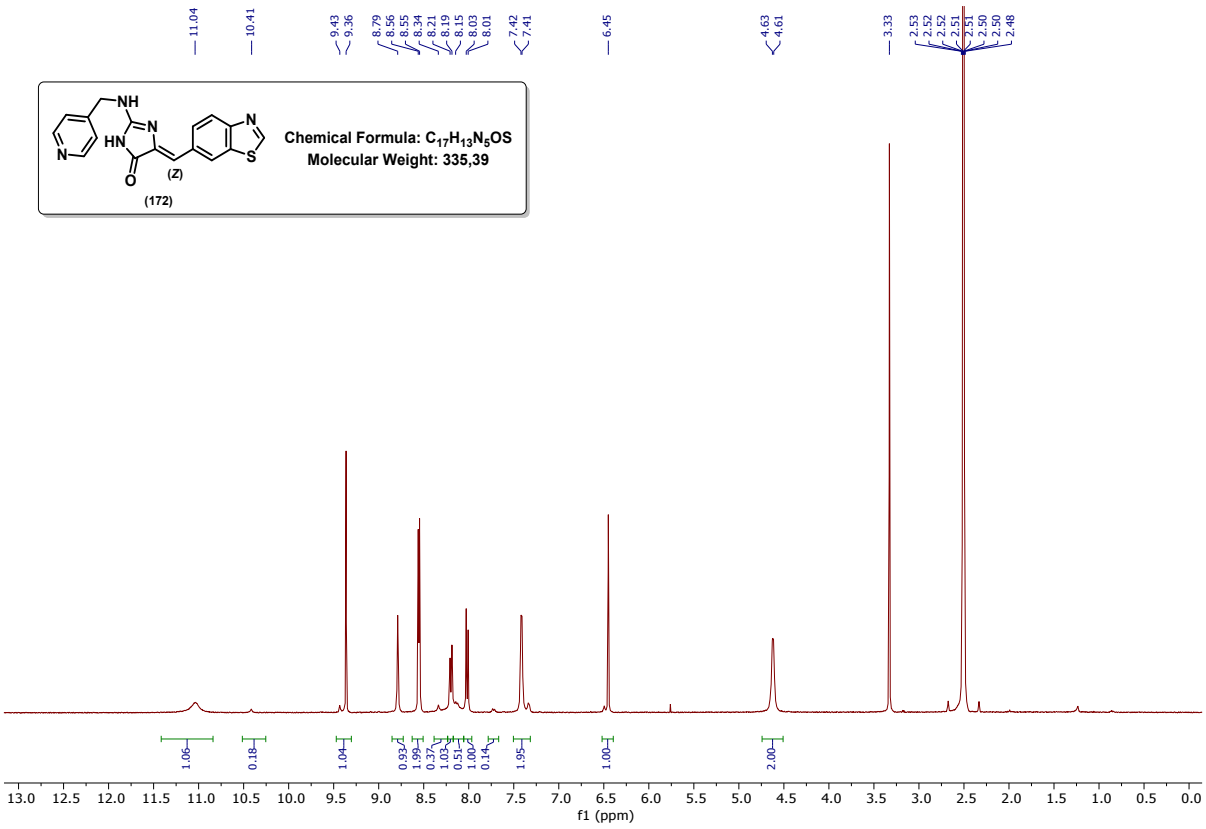
No.	Retention Time min	Area mAU*min	Relative Area %
1	10.08	2.7	3.3
2	11.72	0.1	0.2
3	13.01	77.4	95.1
4	16.14	1.0	1.3
5	17.29	0.1	0.1
Total:		**81.4**	**100.0**

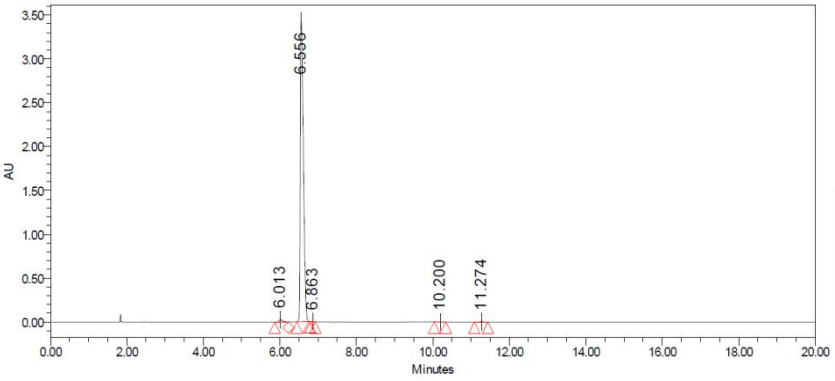
Selected examples of ^{1}H NMR + HPLC of final compounds in table 7





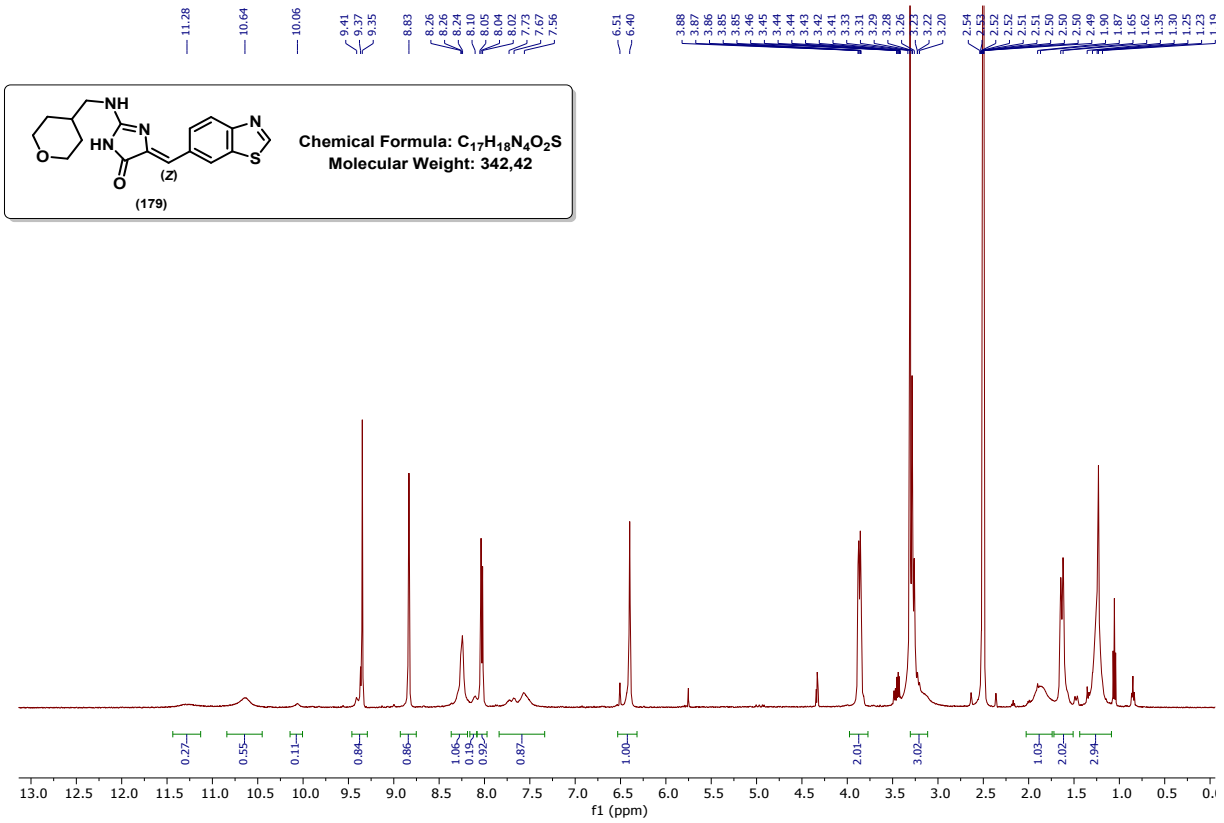
	Retention Time (min)	Area	% Area	Height
1	6.378	40821	0.22	5958
2	6.480	9589	0.05	3094
3	6.821	18114046	99.34	3592824
4	7.428	10828	0.06	3106
5	7.876	5468	0.03	1360
6	8.044	6761	0.04	712
7	9.661	6259	0.03	765
8	11.253	5395	0.03	509
9	12.314	35549	0.19	8246

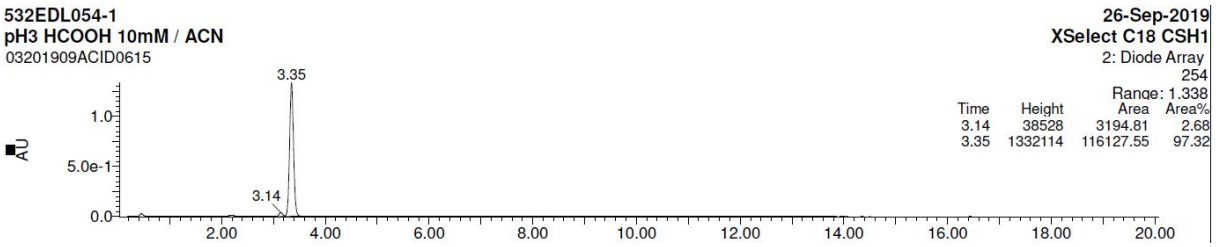


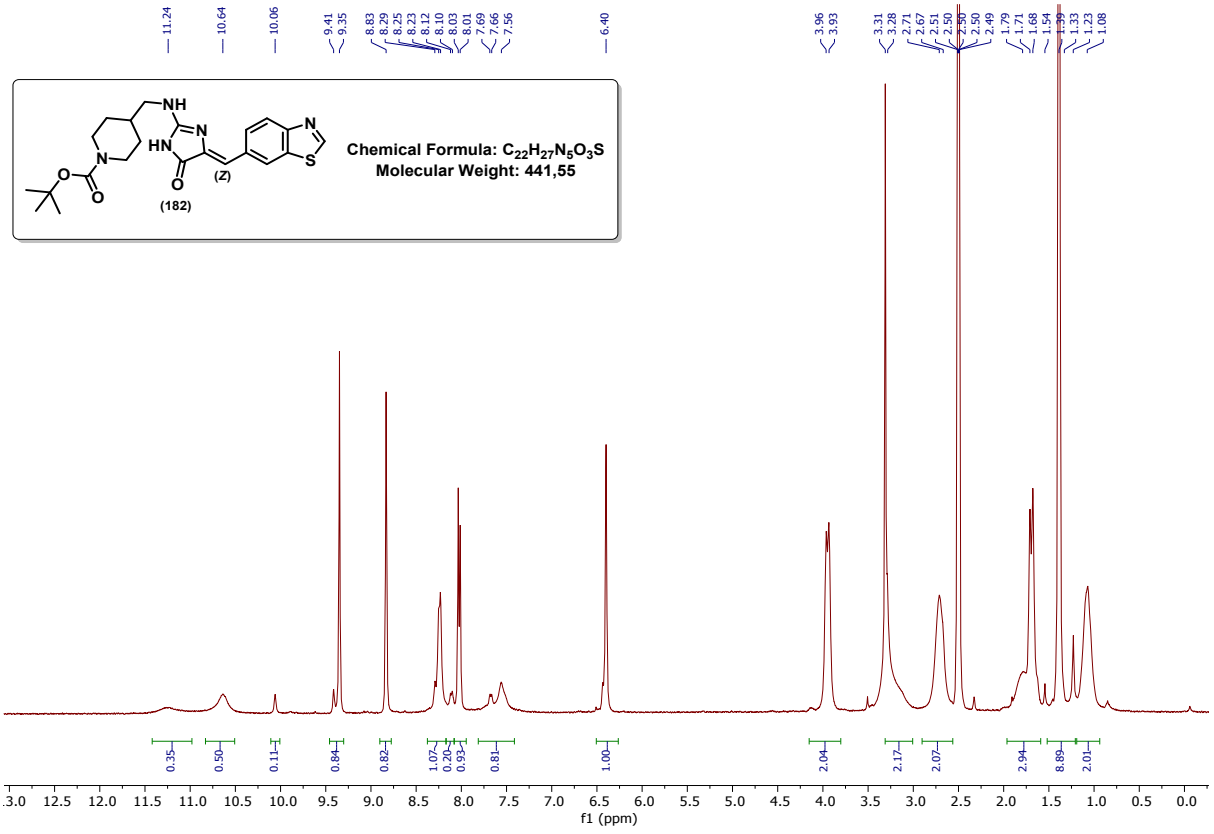


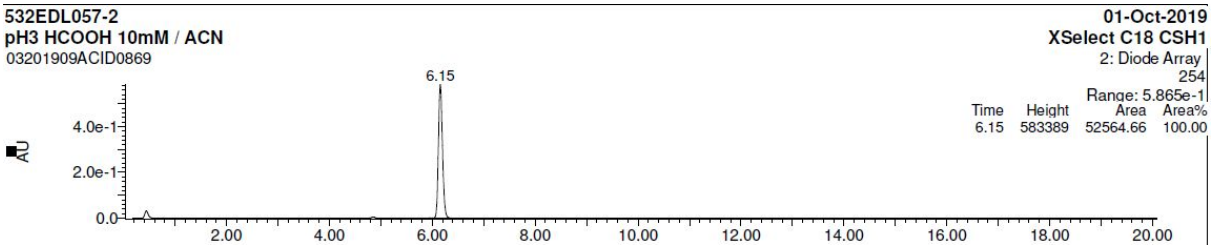
	Retention Time (min)	Area	% Area	Height
1	6.013	176410	0.89	28099
2	6.556	19529204	98.82	3437704
3	6.863	12885	0.07	3972
4	10.200	15594	0.08	2559
5	11.274	27390	0.14	4833

Selected examples of ^{1}H NMR + HPLC/MS of final compounds in table 8

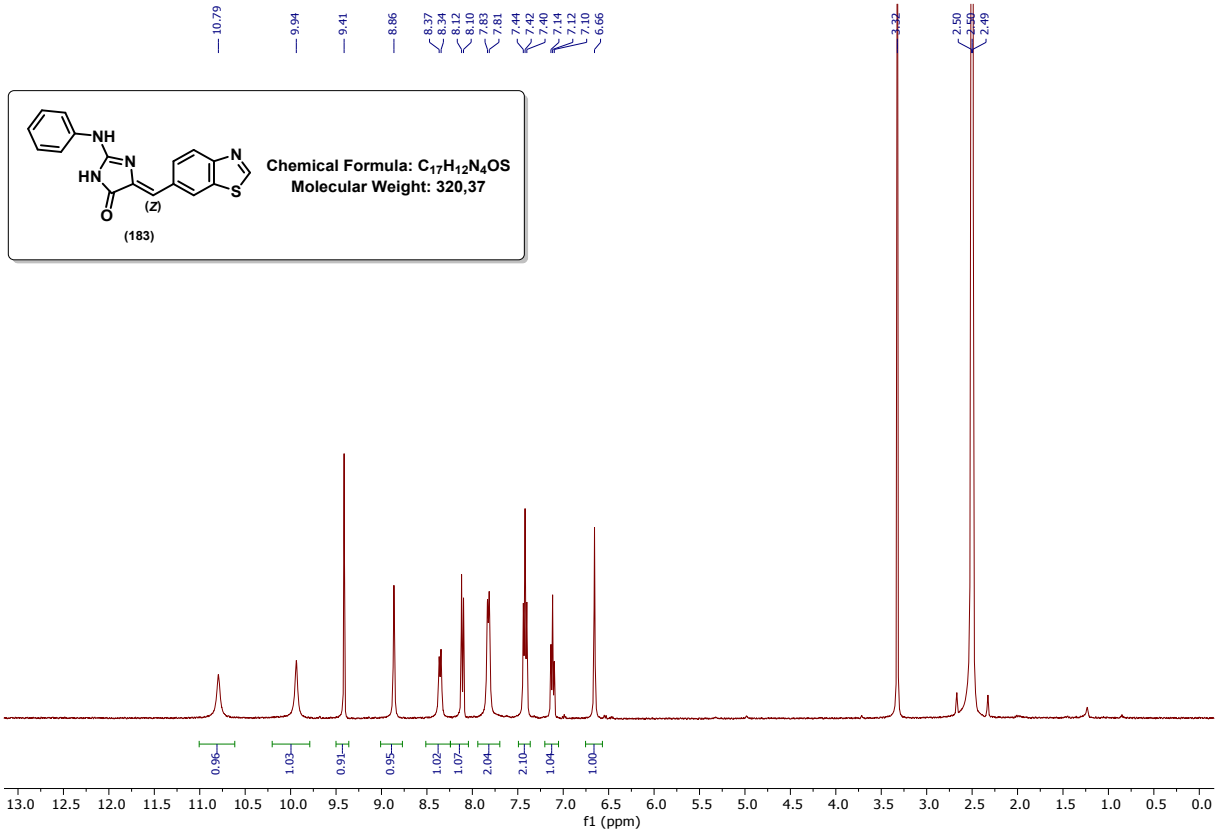


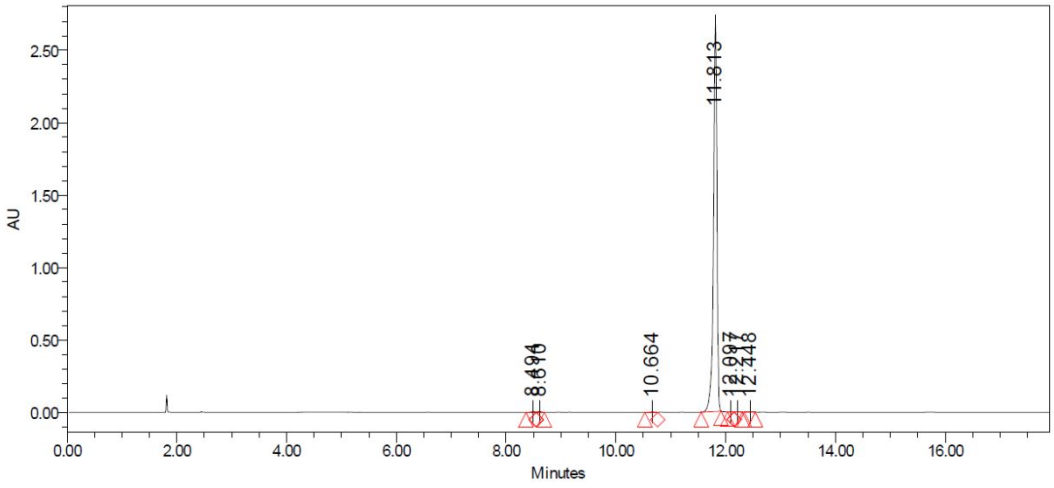



Chemical Formula: $C_{22}H_{27}N_5O_3S$
Molecular Weight: 441,55
(182)
(Z)
f1 (ppm)

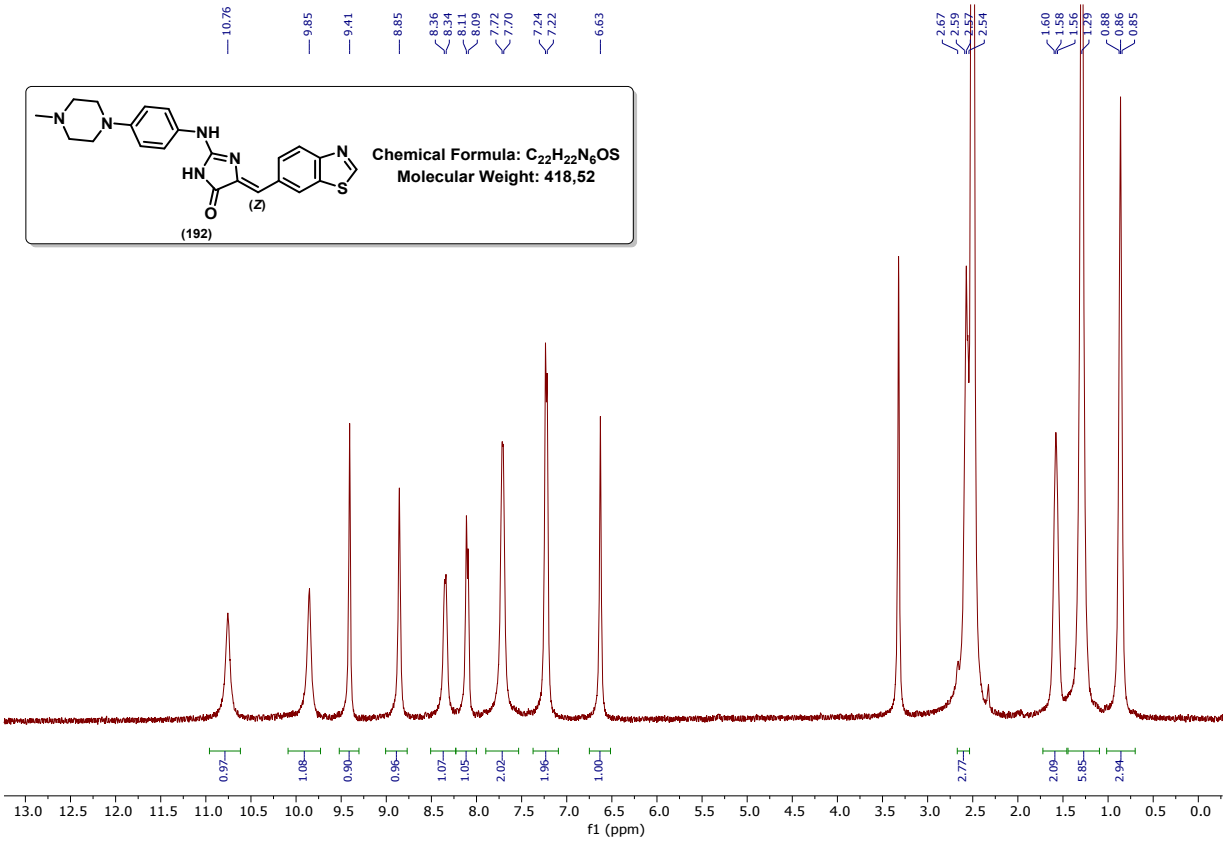

532EDL057-2
pH3 HCOOH 10mM / ACN
03201909ACID0869
01-Oct-2019
XSelect C18 CSH1
2: Diode Array
254
Range: 5.865e-1
Time Height Area Area%
6.15 583389 52564.66 100.00
6.15
AU
Minutes

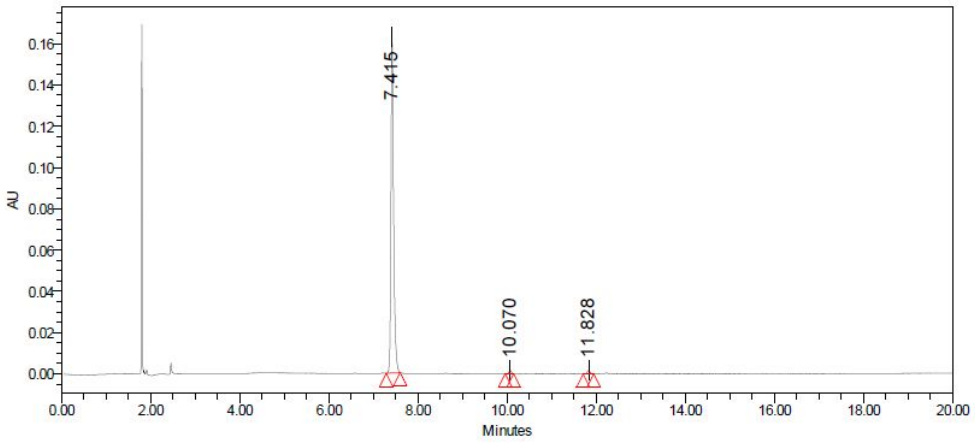
Selected examples of ^{1}H NMR + HPLC of final compounds in table 9





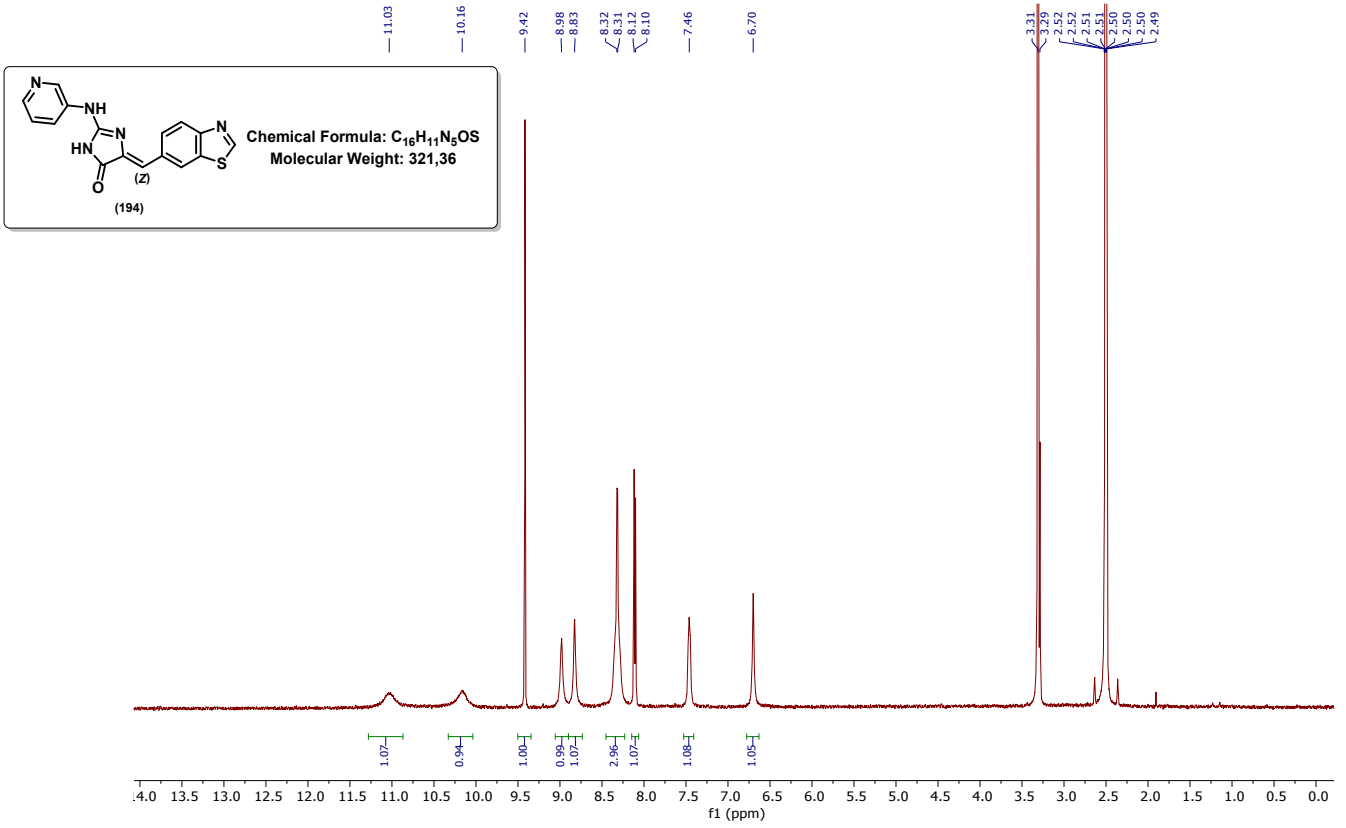
	Retention Time (min)	Area	% Area	Height
1	8.494	23269	0.20	6918
2	8.610	24242	0.21	6695
3	10.664	13379	0.11	3247
4	11.813	11705417	99.27	2666494
5	12.097	5571	0.05	1638
6	12.217	11571	0.10	2917
7	12.448	8128	0.07	1937

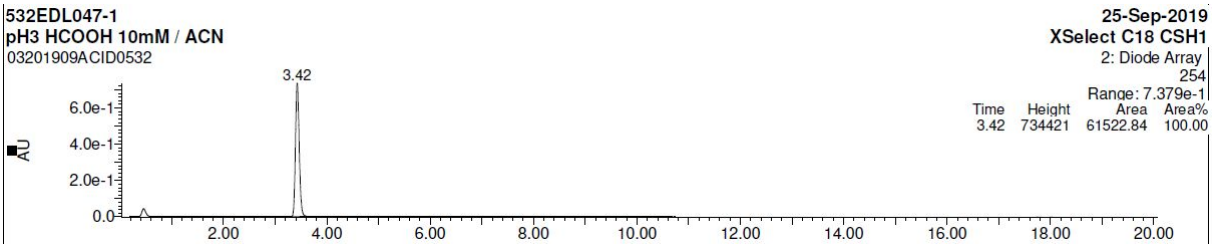


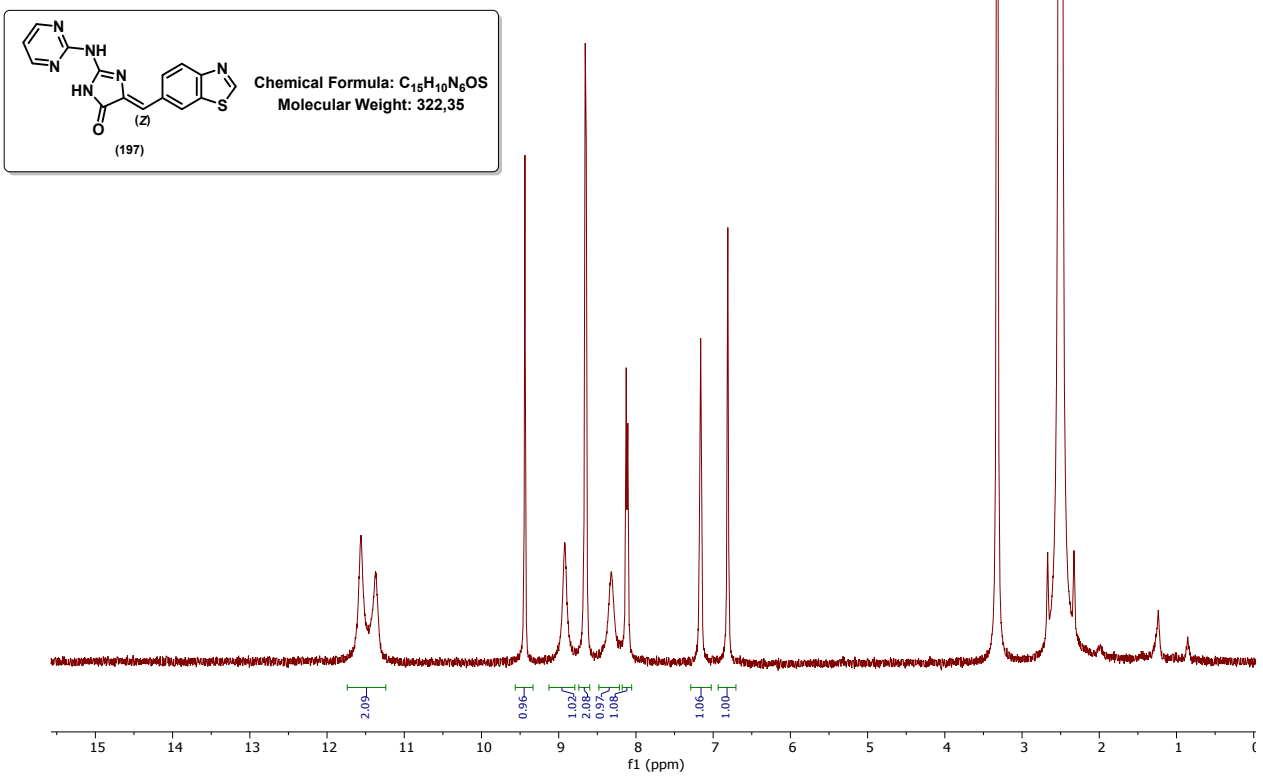


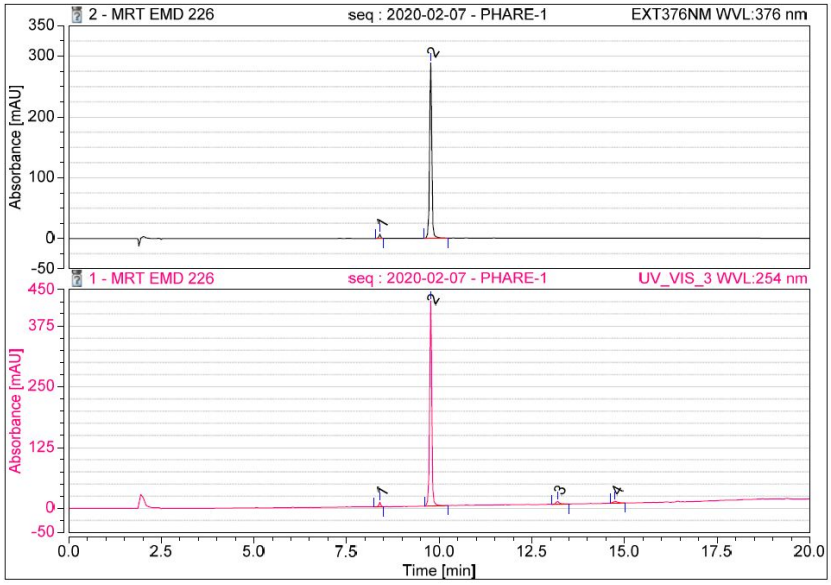
	Retention Time (min)	Area	% Area	Height
1	7.415	663146	97.94	163278
2	10.070	6281	0.93	1609
3	11.828	7672	1.13	1750

Selected examples of ^{1}H NMR + HPLC of final compounds in table 10

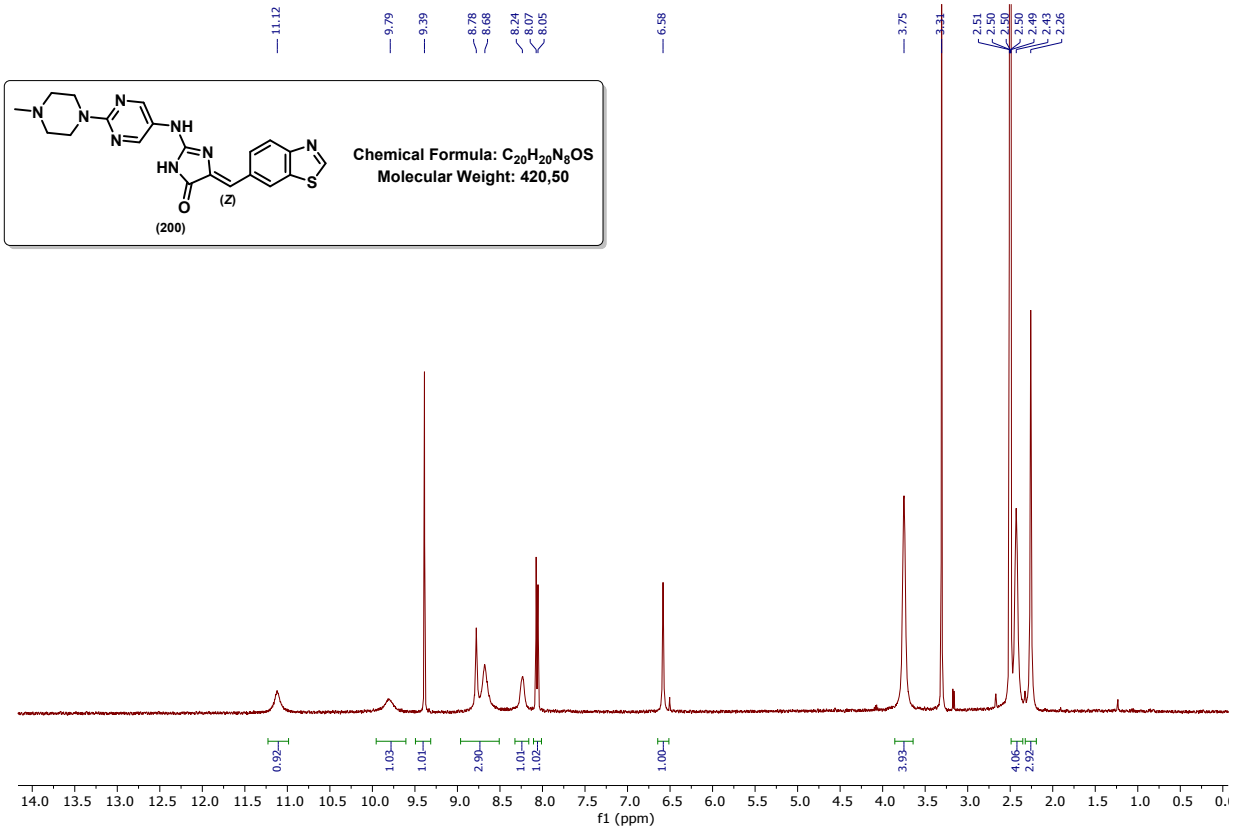


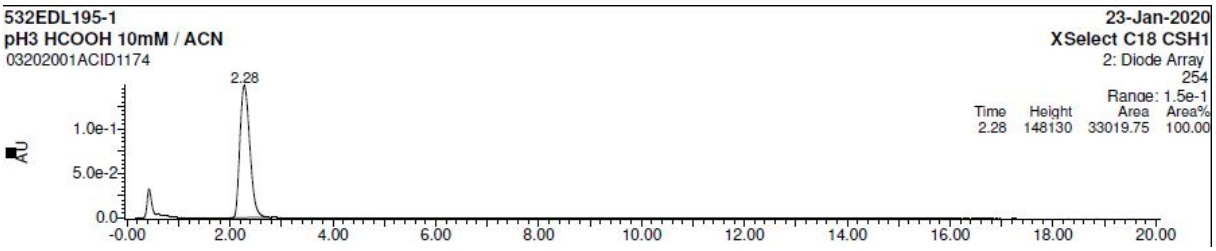




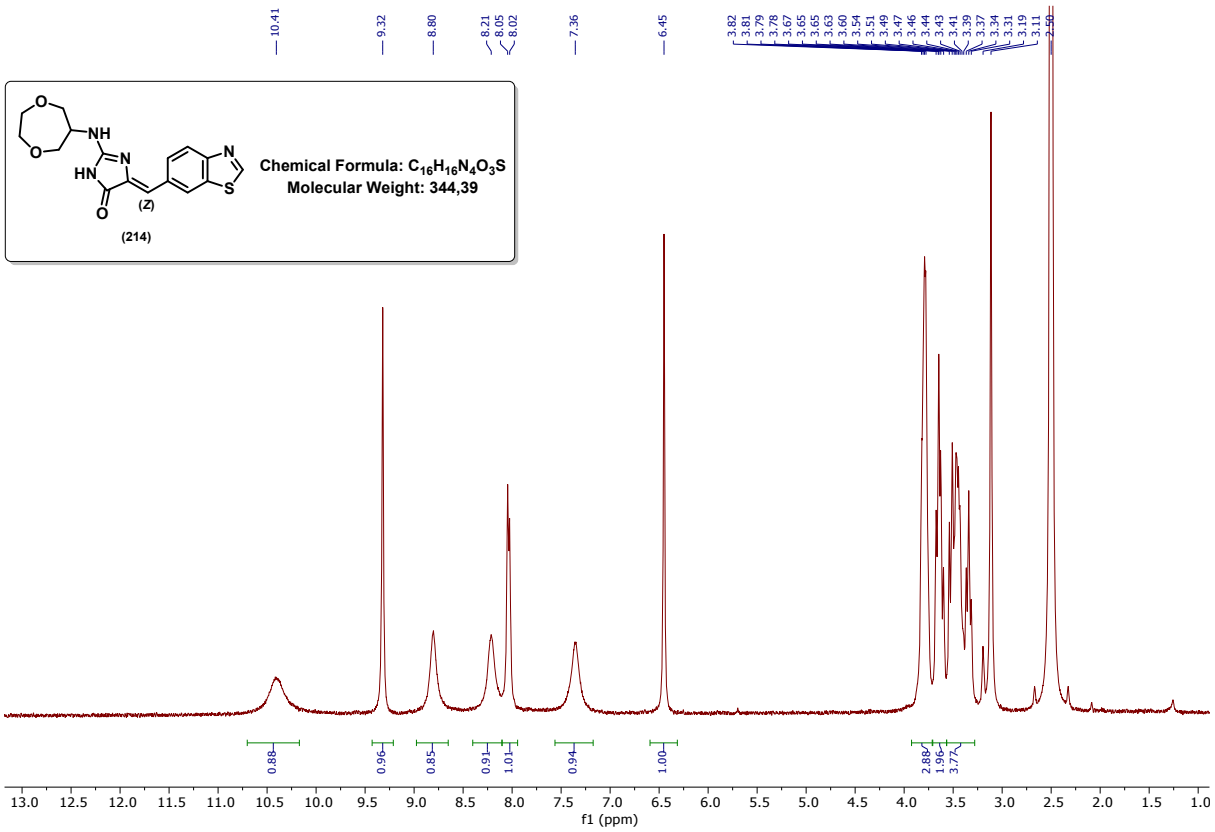


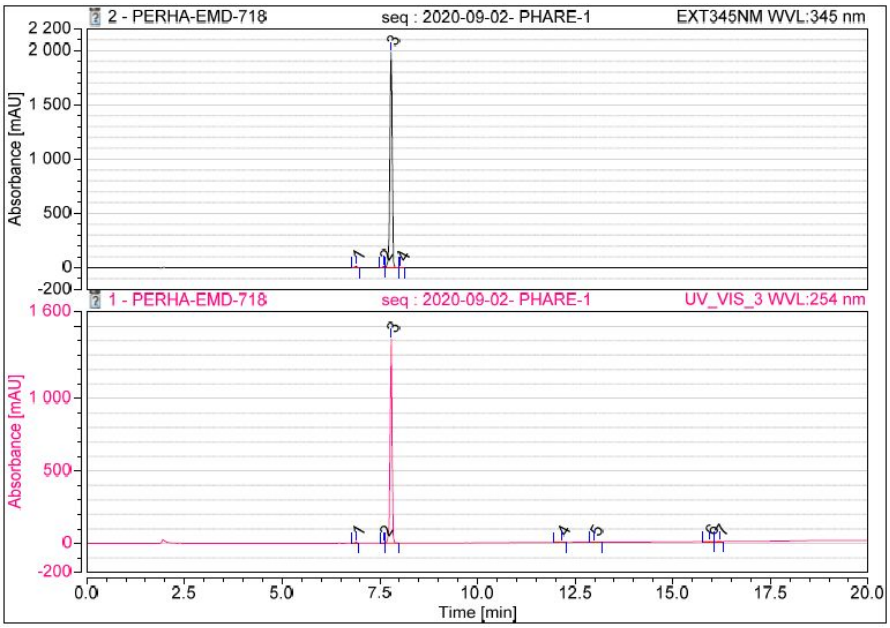
No.	etention Tim min	Area mAU*min	Relative Area %
1	8.40	0.4	2.0
2	9.77	19.2	98.0
Total:		**19.6**	**100.0**


11.12
9.79
9.39
8.78
8.68
8.24
8.07
8.05
6.58
3.75
3.31
2.51
2.50
2.50
2.50
2.49
2.43
2.26
(Z)
(200)
Chemical Formula: C20H20N8OS
Molecular Weight: 420,50
0.92
1.03
1.01
2.90
1.01
1.02
1.00
3.93
4.06
2.92
f1 (ppm)

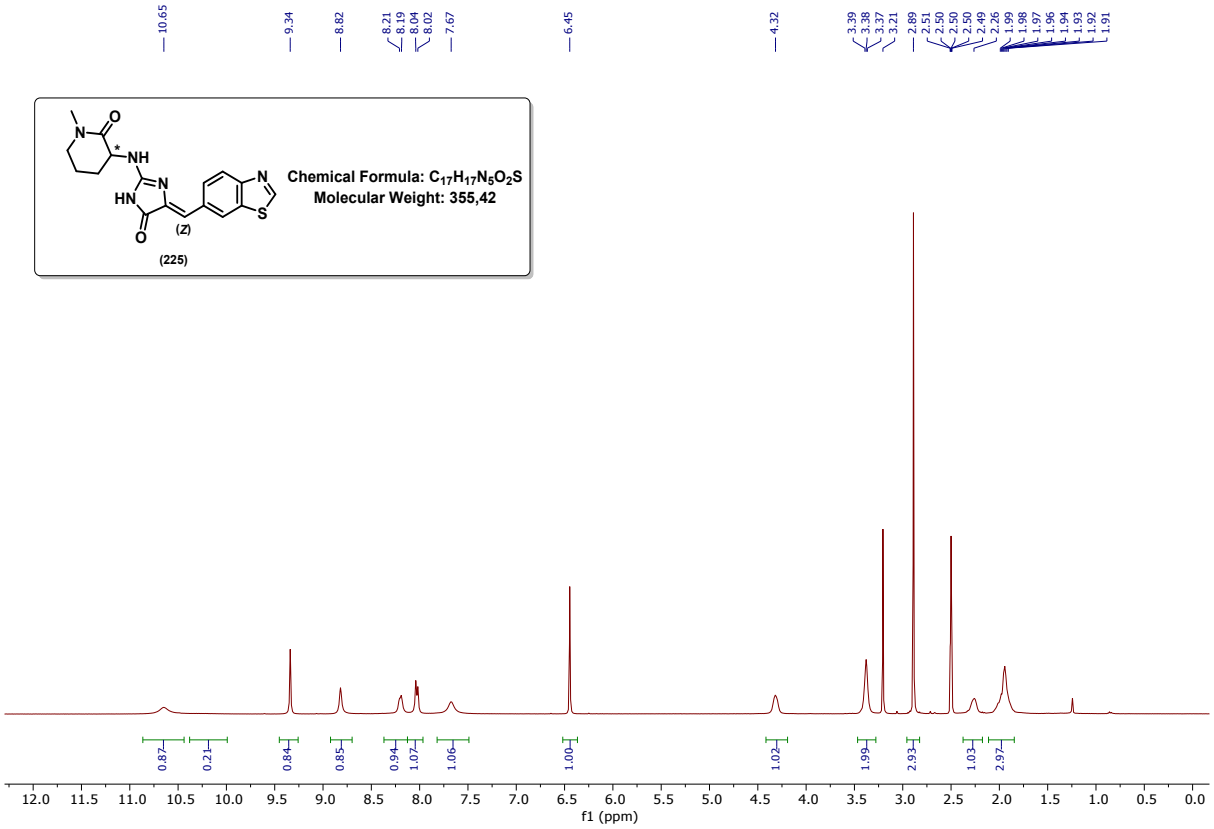

532EDL195-1
pH3 HCOOH 10mM / ACN
03202001ACID1174
23-Jan-2020
XSelect C18 CSH1
2: Diode Array
254
Range: 1.5e-1
Time Height Area Area%
2.28 148130 33019.75 100.00
2.28
AU

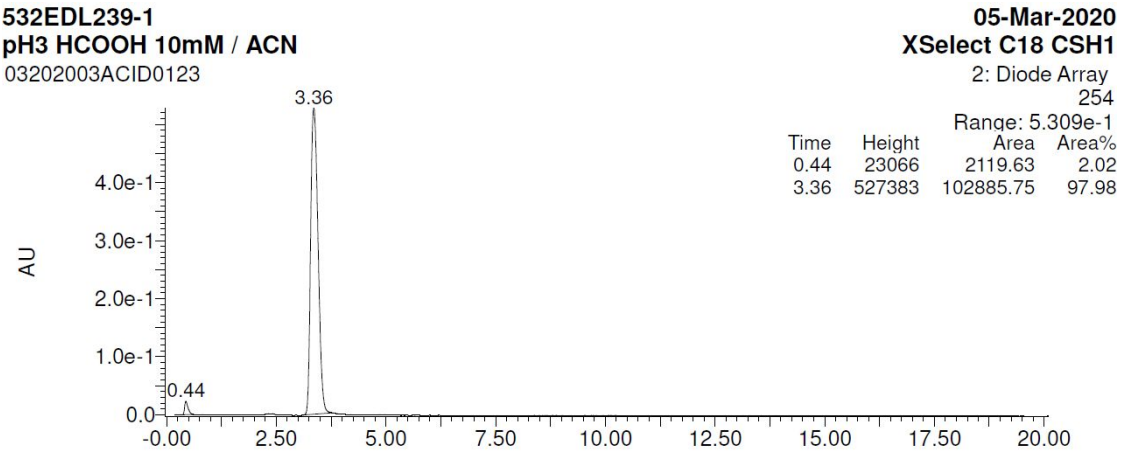
Selected examples of ^{1}H NMR + HPLC of final compounds in table 11





No.	etention Tim min	Area mAU*min	Relative Area %
1	6.89	0.8	0.6
2	7.61	0.7	0.5
3	7.79	129.4	98.8
4	8.03	0.1	0.1
Total:		**131.0**	**100.0**


10.65
9.34
8.82
8.21
8.19
8.04
8.02
7.67
6.45
4.32
3.39
3.38
3.37
3.21
2.89
2.51
2.50
2.50
2.50
2.49
2.26
1.99
1.98
1.97
1.96
1.94
1.93
1.92
1.91
Chemical Formula: C17H17N5O2S
Molecular Weight: 355,42
(Z)
(225)
0.87
0.21
0.84
0.85
0.94
1.07
1.06
1.00
1.02
1.99
2.93
1.03
2.97
12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0
f1 (ppm)


532EDL239-1
pH3 HCOOH 10mM / ACN
03202003ACID0123
05-Mar-2020
XSelect C18 CSH1
2: Diode Array
254
Range: 5.309e-1
Time Height Area Area%
0.44 23066 2119.63 2.02
3.36 527383 102885.75 97.98
AU
4.0e-1
3.0e-1
2.0e-1
1.0e-1
0.0
3.36
0.44
-0.00 2.50 5.00 7.50 10.00 12.50 15.00 17.50 20.00

9 Tables

Table S1. Assay parameters for the tested protein kinases in the *Reaction Biology* radiometric assays.

#	Kinase	Kinase concentration (ng/50 µL)	Kinase concentration (nM)	ATP concentration (µM)	Substrate	Substrate concentration (µg/50 µL)
1	CDK5/p25	15	3.3	0.3	RBERCHKtide	1.0
2	CK1ε	2	0.8	0.3	Casein	0.5
3	CLK1	200	46.1	0.3	H_20 (autophosphorylation)	0
4	CLK2	1	0.3	0.3	GSK3(14-27)	1.0
5	CLK3	8	2.7	0.3	S6-Peptide	1.0
6	CLK4	30	7.1	0.1	Myelin Basic Protein	1.0
7	DYRK1A	5	0.9	1.0	RBERCHKtide	2.0
8	DYRK1B	5	1.0	0.3	RBERCHKtide	2.0
9	DYRK2	3	0.7	1.0	RBERIRStide	2.0
10	DYRK3	3	0.6	0.3	RBERIRStide	1.0
11	DYRK4	20	4.5	0.1	RBERCHKtide	1.0
12	GSK3β	75	19.7	0.3	RBERCHKtide	1.0

Table S2. Evaluation of Leucettinib-92 (32) in the *Eurofins DiscovRx* KinomeScan kinase selectivity panel (468 kinases) (). Enzymes were prepared and assayed as described in Karaman et al. (2008). Enzymes were exposed to 1 µM of Leucettinib-92 (**32**). A semiquantitative scoring of this primary screen was estimated. Scores >10, between 1 and 10 and <1 indicate the probability of a being a false positive is <20%, < 10%, < 5%, respectively. Scores ≤10 are underlined in pink.

#	Kinase	Leucettinib 92
1	AAK1	45
2	ABL1(E255K)-phosphorylated	98
3	ABL1(F317I)-nonphosphorylated	100
4	ABL1(F317I)-phosphorylated	100
5	ABL1(F317L)-nonphosphorylated	100
6	ABL1(F317L)-phosphorylated	100
7	ABL1(H396P)-nonphosphorylated	85
8	ABL1(H396P)-phosphorylated	100
9	ABL1(M351T)-phosphorylated	100
10	ABL1(Q252H)-nonphosphorylated	80
11	ABL1(Q252H)-phosphorylated	95
12	ABL1(T315I)-nonphosphorylated	100
13	ABL1(T315I)-phosphorylated	100
14	ABL1(Y253F)-phosphorylated	100
15	ABL1-nonphosphorylated	92
16	ABL1-phosphorylated	100
17	ABL2	100
18	ACVR1	84
19	ACVR1B	65
20	ACVR2A	98
21	ACVR2B	87
22	ACVRL1	98
23	ADCK3	92
24	ADCK4	100
25	AKT1	80
26	AKT2	95
27	AKT3	2.7
28	ALK	96
29	ALK(C1156Y)	100
30	ALK(L1196M)	100
31	AMPK-alpha1	77
32	AMPK-alpha2	100
33	ANKK1	100
34	ARK5	95
35	ASK1	78
36	ASK2	100
37	AURKA	100
38	AURKB	100
39	AURKC	87
40	AXL	47
41	BIKE	73
42	BLK	71
43	BMPR1A	62
44	BMPR1B	81
45	BMPR2	77

#	Kinase	Leucettinib 92
46	BMX	86
47	BRAF	81
48	BRAF(V600E)	74
49	BRK	100
50	BRSK1	100
51	BRSK2	86
52	BTK	100
53	BUB1	87
54	CAMK1	95
55	CAMK1B	100
56	CAMK1D	98
57	CAMK1G	96
58	CAMK2A	77
59	CAMK2B	81
60	CAMK2D	100
61	CAMK2G	94
62	CAMK4	100
63	CAMKK1	94
64	CAMKK2	70
65	CASK	91
66	CDC2L1	98
67	CDC2L2	91
68	CDC2L5	100
69	CDK11	51
70	CDK2	100
71	CDK3	80
72	CDK4	94
73	CDK4-cyclinD1	94
74	CDK4-cyclinD3	100
75	CDK5	99
76	CDK7	60
77	CDK8	40
78	CDK9	18
79	CDKL1	70
80	CDKL2	20
81	CDKL3	49
82	CDKL5	100
83	CHEK1	100
84	CHEK2	100
85	CIT	0
86	CLK1	0.75
87	CLK2	0
88	CLK3	9
89	CLK4	2.1
90	CSF1R	79
91	CSF1R-autoinhibited	100
92	CSK	99
93	CSNK1A1	24
94	CSNK1A1L	57
95	CSNK1D	20
96	CSNK1E	3.7
97	CSNK1G1	81

#	Kinase	Leucettinib 92
98	CSNK1G2	54
99	CSNK1G3	53
100	CSNK2A1	1.3
101	CSNK2A2	0.6
102	CTK	94
103	DAPK1	88
104	DAPK2	71
105	DAPK3	72
106	DCAMKL1	100
107	DCAMKL2	92
108	DCAMKL3	99
109	DDR1	97
110	DDR2	100
111	DLK	100
112	DMPK	9.3
113	DMPK2	63
114	DRAK1	61
115	DRAK2	38
116	DYRK1A	0
117	DYRK1B	0
118	DYRK2	2.7
119	EGFR	77
120	EGFR(E746-A750del)	99
121	EGFR(G719C)	94
122	EGFR(G719S)	97
123	EGFR(L747-E749del, A750P)	62
124	EGFR(L747-S752del, P753S)	74
125	EGFR(L747-T751del,Sins)	77
126	EGFR(L858R)	76
127	EGFR(L858R,T790M)	100
128	EGFR(L861Q)	98
129	EGFR(S752-I759del)	88
130	EGFR(T790M)	96
131	EIF2AK1	100
132	EPHA1	81
133	EPHA2	85
134	EPHA3	96
135	EPHA4	100
136	EPHA5	95
137	EPHA6	90
138	EPHA7	100
139	EPHA8	100
140	EPHB1	98
141	EPHB2	94
142	EPHB3	99
143	EPHB4	86
144	EPHB6	73
145	ERBB2	100
146	ERBB3	100
147	ERBB4	92
148	ERK1	86
149	ERK2	100

#	Kinase	Leucettinib 92
150	ERK3	95
151	ERK4	100
152	ERK5	100
153	ERK8	18
154	ERN1	100
155	FAK	100
156	FER	97
157	FES	91
158	FGFR1	94
159	FGFR2	87
160	FGFR3	88
161	FGFR3(G697C)	95
162	FGFR4	99
163	FGR	92
164	FLT1	100
165	FLT3	63
166	FLT3(D835H)	58
167	FLT3(D835V)	1.6
168	FLT3(D835Y)	12
169	FLT3(ITD)	48
170	FLT3(ITD,D835V)	6.3
171	FLT3(ITD,F691L)	28
172	FLT3(K663Q)	51
173	FLT3(N841I)	28
174	FLT3(R834Q)	82
175	FLT3-autoinhibited	100
176	FLT4	98
177	FRK	98
178	FYN	92
179	GAK	89
180	GCN2(Kin.Dom.2,S808G)	79
181	GRK1	99
182	GRK2	100
183	GRK3	100
184	GRK4	71
185	GRK7	100
186	GSK3A	12
187	GSK3B	33
188	HASPIN	0.45
189	HCK	80
190	HIPK1	1.2
191	HIPK2	0.65
192	HIPK3	2.6
193	HIPK4	12
194	HPK1	100
195	HUNK	100
196	ICK	100
197	IGF1R	90
198	IKK-alpha	87
199	IKK-beta	100
200	IKK-epsilon	100
201	INSR	100

#	Kinase	Leucettinib 92
202	INSRR	100
203	IRAK1	2.4
204	IRAK3	74
205	IRAK4	67
206	ITK	99
207	JAK1(JH1domain-catalytic)	90
208	JAK1(JH2domain-pseudokinase)	98
209	JAK2(JH1domain-catalytic)	25
210	JAK3(JH1domain-catalytic)	4.1
211	JNK1	100
212	JNK2	100
213	JNK3	100
214	KIT	91
215	KIT(A829P)	95
216	KIT(D816H)	68
217	KIT(D816V)	61
218	KIT(L576P)	95
219	KIT(V559D)	97
220	KIT(V559D,T670I)	82
221	KIT(V559D,V654A)	83
222	KIT-autoinhibited	100
223	LATS1	49
224	LATS2	0
225	LCK	74
226	LIMK1	75
227	LIMK2	89
228	LKB1	82
229	LOK	91
230	LRRK2	46
231	LRRK2(G2019S)	83
232	LTK	100
233	LYN	84
234	LZK	91
235	MAK	77
236	MAP3K1	100
237	MAP3K15	100
238	MAP3K2	100
239	MAP3K3	100
240	MAP3K4	91
241	MAP4K2	27
242	MAP4K3	100
243	MAP4K4	16
244	MAP4K5	83
245	MAPKAPK2	100
246	MAPKAPK5	100
247	MARK1	100
248	MARK2	93
249	MARK3	100
250	MARK4	90
251	MAST1	96
252	MEK1	99
253	MEK2	100

#	Kinase	Leucettinib 92
254	MEK3	60
255	MEK4	100
256	MEK5	95
257	MEK6	99
258	MELK	44
259	MERTK	99
260	MET	66
261	MET(M1250T)	89
262	MET(Y1235D)	95
263	MINK	9.3
264	MKK7	100
265	MKNK1	100
266	MKNK2	100
267	MLCK	100
268	MLK1	78
269	MLK2	100
270	MLK3	94
271	MRCKA	47
272	MRCKB	4.9
273	MST1	100
274	MST1R	93
275	MST2	100
276	MST3	92
277	MST4	100
278	MTOR	93
279	MUSK	100
280	MYLK	84
281	MYLK2	95
282	MYLK4	90
283	MYO3A	100
284	MYO3B	100
285	NDR1	25
286	NDR2	79
287	NEK1	100
288	NEK10	100
289	NEK11	100
290	NEK2	100
291	NEK3	93
292	NEK4	99
293	NEK5	85
294	NEK6	100
295	NEK7	100
296	NEK9	100
297	NIK	61
298	NIM1	100
299	NLK	99
300	OSR1	100
301	p38-alpha	93
302	p38-beta	100
303	p38-delta	93
304	p38-gamma	87
305	PAK1	50

#	Kinase	Leucettinib 92
306	PAK2	30
307	PAK3	100
308	PAK4	86
309	PAK6	92
310	PAK7	97
311	PCTK1	100
312	PCTK2	89
313	PCTK3	100
314	PDGFRA	100
315	PDGFRB	91
316	PDPK1	67
317	PFCDPK1(P.falciparum)	100
318	PFPK5(P.falciparum)	100
319	PFTAIRE2	93
320	PFTK1	95
321	PHKG1	88
322	PHKG2	90
323	PIK3C2B	98
324	PIK3C2G	98
325	PIK3CA	100
326	PIK3CA(C420R)	100
327	PIK3CA(E542K)	97
328	PIK3CA(E545A)	100
329	PIK3CA(E545K)	100
330	PIK3CA(H1047L)	96
331	PIK3CA(H1047Y)	100
332	PIK3CA(I800L)	100
333	PIK3CA(M1043I)	100
334	PIK3CA(Q546K)	100
335	PIK3CB	89
336	PIK3CD	100
337	PIK3CG	91
338	PIK4CB	100
339	PIKFYVE	27
340	PIM1	26
341	PIM2	49
342	PIM3	25
343	PIP5K1A	94
344	PIP5K1C	100
345	PIP5K2B	92
346	PIP5K2C	90
347	PKAC-alpha	16
348	PKAC-beta	11
349	PKMYT1	100
350	PKN1	55
351	PKN2	100
352	PKNB(M.tuberculosis)	100
353	PLK1	100
354	PLK2	100
355	PLK3	100
356	PLK4	100
357	PRKCD	57

#	Kinase	Leucettinib 92
358	PRKCE	14
359	PRKCH	65
360	PRKCI	100
361	PRKCQ	24
362	PRKD1	100
363	PRKD2	100
364	PRKD3	100
365	PRKG1	50
366	PRKG2	2.1
367	PRKR	97
368	PRKX	27
369	PRP4	100
370	PYK2	97
371	QSK	100
372	RAF1	100
373	RET	90
374	RET(M918T)	100
375	RET(V804L)	96
376	RET(V804M)	95
377	RIOK1	100
378	RIOK2	80
379	RIOK3	70
380	RIPK1	94
381	RIPK2	91
382	RIPK4	97
383	RIPK5	100
384	ROCK1	57
385	ROCK2	91
386	ROS1	84
387	RPS6KA4(Kin.Dom.1-N-terminal)	100
388	RPS6KA4(Kin.Dom.2-C-terminal)	100
389	RPS6KA5(Kin.Dom.1-N-terminal)	98
390	RPS6KA5(Kin.Dom.2-C-terminal)	73
391	RSK1(Kin.Dom.1-N-terminal)	70
392	RSK1(Kin.Dom.2-C-terminal)	84
393	RSK2(Kin.Dom.1-N-terminal)	100
394	RSK2(Kin.Dom.2-C-terminal)	100
395	RSK3(Kin.Dom.1-N-terminal)	96
396	RSK3(Kin.Dom.2-C-terminal)	93
397	RSK4(Kin.Dom.1-N-terminal)	100
398	RSK4(Kin.Dom.2-C-terminal)	91
399	S6K1	100
400	SBK1	100
401	SGK	100
402	SgK110	80
403	SGK2	100
404	SGK3	94
405	SIK	100
406	SIK2	100
407	SLK	100
408	SNARK	66
409	SNRK	100

#	Kinase	Leucettinib 92
410	SRC	83
411	SRMS	100
412	SRPK1	100
413	SRPK2	100
414	SRPK3	100
415	STK16	39
416	STK33	100
417	STK35	98
418	STK36	85
419	STK39	97
420	SYK	100
421	TAK1	8.9
422	TAOK1	45
423	TAOK2	98
424	TAOK3	100
425	TBK1	98
426	TEC	100
427	TESK1	91
428	TGFBR1	95
429	TGFBR2	51
430	TIE1	99
431	TIE2	94
432	TLK1	95
433	TLK2	97
434	TNIK	20
435	TNK1	80
436	TNK2	86
437	TNNI3K	85
438	TRKA	100
439	TRKB	100
440	TRKC	100
441	TRPM6	98
442	TSSK1B	100
443	TSSK3	100
444	TTK	90
445	TXK	90
446	TYK2(JH1domain-catalytic)	56
447	TYK2(JH2domain-pseudokinase)	38
448	TYRO3	100
449	ULK1	100
450	ULK2	96
451	ULK3	100
452	VEGFR2	100
453	VPS34	99
454	VRK2	100
455	WEE1	100
456	WEE2	100
457	WNK1	100
458	WNK2	100
459	WNK3	100
460	WNK4	86
461	YANK1	100

#	Kinase	Leucettinib 92
462	YANK2	100
463	YANK3	100
464	YES	94
465	YSK1	98
466	YSK4	8.9
467	ZAK	87
468	ZAP70	100

Table S3. Thermal shift selectivity screen of Leucettinib-92 (32) and iso-Leucettinib-92 (35) tested at 0.1 µM with 95 human kinases. Thermal shifts superior to 8°C shift are underlined in pink.

#	Kinase	Leucettinib 92	Iso-Leucettinib-92
1	AAK1	6.1	0.0
2	ABL1	2.4	-0.2
3	AKT3	-0.3	0.0
4	AURKB	-0.6	-0.9
5	BMP2K	9.8	-0.1
6	BMPR2	4.9	0.0
7	BMX	-1.2	-2.6
8	BRAF	2.5	-0.7
9	BRD4	-0.1	-1.1
10	BRPF1B	-0.4	-1.5
11	CAMK1D	0.1	0.1
12	CAMK2B	-0.4	-0.6
13	CAMK2D	1.1	-0.5
14	CAMK4	0.9	-0.1
15	CAMKK2	10.2	-0.5
16	CASK	-0.6	-0.4
17	CDKL1	1.4	-0.9
18	CHEK2	-0.4	-0.9
19	CLK1	19.9	2.0
20	CLK3	9.7	-0.5
21	CSNK1D	5.0	1.4
22	CSNK1E	5.5	-2.5
23	CSNK2A1	9.7	0.3
24	DAPK1	3.0	-0.2
25	DAPK3	3.0	-1.4
26	DCAMKL1	2.9	-0.3
27	DMPK1	5.6	0.1
28	DYRK1A	18.1	3.2
29	DYRK2	12.4	0.0
30	EPHA2	2.5	-0.4
31	EPHA4	1.8	1.0
32	EPHA5	-2.1	-0.8
33	EPHA7	0.3	-0.2
34	EPHB1	1.4	0.3
35	EPHB3	0.4	-4.4
36	FES	-0.5	-0.2
37	FGFR1	0.4	-0.7
38	FGFR2	0.9	0.2
39	FGFR3	-2.1	-0.1

40	FLT1	3.1	0.5
41	GAK	2.7	0.0
42	GPRK5	1.4	-0.3
43	GSG2	7.6	-0.1
44	GSK3B	6.5	0.9
45	HIPK2HSF	5.2	-0.4
46	MAP2K1	0.6	0.1
47	MAP2K4	0.5	-0.1
48	MAP2K6	-0.3	-0.1
49	MAP2K7	-0.1	0.4
50	MAP3K5	3.7	-0.2
51	MAPK1	0.3	-0.8
52	MAPK10	2.9	-0.7
53	MAPK13	0.8	-0.4
54	MAPK14	-0.2	0.1
55	MAPK15HSD	10.3	-0.2
56	MAPK8	2.5	0.1
57	MAPK9	0.9	0.1
58	MAPKAPK2	0.3	0.8
59	MARK3	0.6	0.2
60	MARK4	0.5	-0.6
61	MELK	4.2	-0.5
62	MERTK	0.8	0.2
63	MSSK1	0.2	0.1
64	MST4	-1.1	-0.5
65	NEK1	-3.6	-1.4
66	NEK2	-1.8	-0.5
67	NEK7	-0.9	-0.4
68	NQO2	-7.3	-0.8
69	OSR1	0.0	-0.9
70	PAK1	1.0	-0.7
71	PAK4	3.0	-0.2
72	PCTK1	1.3	-0.6
73	PHKG2	1.7	-0.6
74	PIM1	4.4	1.0
75	PIM3	5.5	1.0
76	PLK4	3.3	0.3
77	RPS6KA5	3.1	0.0
78	SLK	0.7	-0.5
79	SRC	1.5	-0.1
80	SRPK1	-0.6	-2.7
81	SRPK2	-0.6	0.0
82	STK10	-0.3	-0.6
83	STK17A	4.8	0.0
84	STK3	-0.5	-1.6
85	STK38L	3.5	-0.1
86	STK39	0.9	0.9
87	STK4	-0.4	-0.9
88	STK6	7.5	-0.4
89	TIF1	0.7	-1.2
90	TLK1	0.5	-0.3
91	TTK	1.2	1.0
92	ULK1	1.0	-1.5

93	ULK3	2.7	-0.8
94	VRK1	1.0	-0.4
95	WNK1	0.8	-0.3

Table S4. Conservation, within CLKs and DYRKs, of the DYRK1A amino acids involved in the binding of Leucettinib-92 (32). The DYRK1A amino acids interacting with Leucettinib-92 (**32**) (Fig. 2) are indicated in full. Corresponding amino acids in CLKs and other DYRKs are shown.

CLK1	CLK2	CLK3	CLK4	DYRK1A	DYRK1B	DYRK2	DYRK3	DYRK4
V	V	V	V	V173	V	V	A	A
K	K	K	K	K188	K	K	K	K
E	E	E	E	E239	E	E	E	E
L	L	L	L	L241	L	L	L	L
L	L	L	L	L294	L	L	L	V
V	V	A	V	V306	V	I	I	I
D	D	D	D	D307	D	D	D	D

Table S5. Data collection and refinement statistics for CLK1-Leucettinib-92 and CSNK2A1-Leucettinib-92 co-crystal structures.

Data collection	CLK1-Leucettinib-92	CSNK2A1-Leucettinib-92
Beamline	X06SA/PXI SLS	X06SA/PXI SLS
Wavelength (Å)	0.99999	0.99999
Space group	C 1 2 1	P 4_3 2_1 2
Cell dimensions		
a, b, c (Å)	92.13, 64.03, 70.57	127.30, 127.30, 124.47
α, β, γ (°)	90.0, 118.5, 90.0	90.0, 90.0, 90.0
Resolution (Å)*	47.30-2.60 (2.72-2.60)	45.01-2.45 (2.55-2.45)
unique observations*		
*Rpim**	0.090 (0.478)	0.034 (0.596)
Completeness (%)*	95.6 (98.2)	100.0 (99.9)
Multiplicity*	2.4 (2.5)	13.4 (12.9)
mean I/σI*	9.0 (1.9)	15.1 (1.7)
CC1/2*	0.989 (0.594)	0.999 (0.858)
Refinement		
Rwork / Rfree	0.209 / 0.259	0.209 / 0.253
No. of atoms	2540	5563
overall B-factors (Å^2)	49.3	60.5
Rms deviations		
Bond lengths (Å)	0.003	0.008
Bond angles (°)	0.64	1.52
Ramachandran outlier (%)	0.3	0.0
Protein Data Bank entry	8P04	8P05

*Values for the highest resolution shell are shown in parentheses

Figure S1. Co-crystal structure of Leucettinib-92 (32) with CSNK2A1. A. The observed electron density map ($2F_o-F_c$), of the ligand contoured at 1σ. **B.** Binding of Leucettinib-92 (**32**) to CSNK2A1 in cartoon/stick representation. Possible hydrogen bonds are indicated as black dashed lines. Water molecules are shown as red spheres. **C.** Overlay of the CSNK2A1 and CLK1 structures with Leucettinib-92 (**32**). The active sites of both kinases are highly similar and Leucettinib-92 (**32**) adopts a similar binding.