Supporting Information

The Discovery of Orally Bioavailable Tyrosine Threonine Kinase (TTK) Inhibitors: 3-(4-(heterocyclyl)phenyl)-1H-indazole-5-carboxamides as Anticancer Agents

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SYNTHESIS of INTERMEDIATES:

Amide formation: Acetamide General Method A1. A DMF solution of 3-iodo-1H-indazol-5-amine 2,2,2-trifluoroacetate (1.0 equiv), DIPEA (3 equiv) and RCO_2H (1.05 equiv) at 0 ^oC was treated with TBTU (1.05 equiv) added in one portion. The reaction was stirred allowing slowly to warm to rt. After several h or overnight stirring the crude reaction was subsequently diluted with H_2O. In the majority of examples a filtration and washing (H_2O) of the precipitate provided the desired material with the required purity or alternatively the material was purified directly by prep-HPLC or/and flash chromatography.

Carboxamide and Formamide General Method A2. Alternatively, a DMF solution of 3-iodo-1H-indazole-5-carboxylic acid or formic acid (1.0 equiv), DIPEA (3–5 equiv) and RNH_2 or $RR'NH$ (1–1.05 equiv) at 0 ^oC or rt was treated with TBTU or BOP-Cl (1.05 equiv) added in one portion. The reaction was stirred and warmed slowly to rt. After several h or overnight stirring the crude reaction was subsequently diluted with H_2O. In the

majority of examples a filtration and washing (H_2O) of the precipitate provided the desired material with the required purity or alternatively the material was purified directly by prep-HPLC or/and flash chromatography.

Nucleophilic substitution on 1-fluoro-4-iodobenzene. General Method B. NaH (60 % in mineral oil, 1.2 mmol) was added portion-wise to a solution of the alcohol (1 mmol) and 1-fluoro-4-iodobenzene (1 mmol) in DMF (1.5 mL) at 0 ^oC. After 15 min, the reaction mixture was allowed to warm to rt, then heated at 80–85 ^oC for 6–14 h in an oil bath. The mixture was quenched by adding H_2O (10 mL) and the product was extracted with EtOAc (30 mL). The organic layer was washed with brine (10 mL), dried (Na_2SO_4 or $MgSO_4$), concentrated to dryness and purified by chromatography.

Copper catalyzed amination of arylhalide. General Method C. A microwave vial was charged with 1,4-diiodobenzene (1.0 equiv), CuI (20 mol%), BINOL (20 mol%), and K_3PO_4 (2 equiv). The vial was capped and then evacuated and backfilled with Ar. Dialklyamine (1.2 equiv) and DMF were then added. The resulting mixture was stirred at rt for 2–4 days. The mixture was diluted with EtOAc, filtered through a cake of Celite and the filtrate was concentrated to give the crude product. Crude product was purified by flash chromatography to give the title compound.

Tropinone derivatives synthesis using Robinson annulation. General Method D. To a solution of 3-oxopentanedioic acid (1.1 equiv) and glutaraldehyde or 2-(2,2-diethoxyethoxy)-1,1-diethoxyethane and in H_2O was added concentrated HCl (0.95 equiv). The resulting solution was stirred at rt for 30 min, then cooled to 0 ^oC. A solution of 4-bromoaniline (1 equiv in MeOH was added over 20 min. After addition, the resulting mixture was stirred O/N at rt. Conc. HCl (0.24 equiv was added and reaction was heated at 55 ^oC for 2 h to decarboxylate. After quenching with K_2CO_3/H_2O to pH about 7, it was stirred at rt. The precipitates were

collected by suction filtration, rinsed with H_2O, MeOH and dried to give the tropinone derivative or alternatively it was purified by flash chromatography.

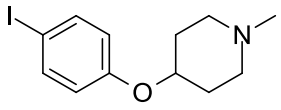
Preparation of boronic esters. General Procedure E. A mixture of aryliodide or arylbromide (1 equiv), bis(pinacolato)diboron (1.2–1.5 equiv), KOAc (3 equiv) and DMF or DMSO was purged with Ar for 10 min. $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (3–5 mol%) was added, the vial sealed and heated at 85–100 ^oC for 2–3 h. The product was partitioned between EtOAc and satd aq $NaHCO_3$ solution, washed with brine, dried over Na_2SO_4 or $MgSO_4$, filtered, and concentrated to dryness. The crude product was purified by flash chromatography to give the title compound. Or alternatively, to a solution of aryliodide or arylbromide (1.0 mmol) in Et_3N (3.0 mmol) and dioxane (1.0 mL) was added under Ar and HBpin(1.5 mmol), *S*-Phos (0.040 mmol) and $Cl_2Pd(CH_3CN)_2$ (0.010 mmol) and the reaction heated to 110 ^oC for 3 h. The mixture was then transferred to a separatory funnel with EtOAc and washed with satd aq $NaHCO_3$, H_2O, and brine. The organic layer was dried over $MgSO_4$, filtered and the solvent removed to yield pinacol boronic esters which were used directly for subsequent steps.

Synthesis of t-butylsulfinylimines. General Method F. Aryl or alkylaldehyde (1.2 equiv) was added to a stirred suspension of (*S*)-t-butylsulfinylamide (1.0 equiv) and flame-dried $CuSO_4$ (2.2 equiv) in dry CH_2Cl_2. The resulting mixture was stirred at rt for 2–3 days. The reaction mixture was filtered through a pad of Celite and the pad was extracted with CH_2Cl_2. The combined organic extracts were concentrated under reduced pressure yielding the crude product. Purification by repeated flash chromatography (SiO_2) using EtOAc-cyclohexane as eluent gave the desired product.

Deprotection of sulfonamides. General Method G. A solution of HCl (2.0 M in Et_2O, 2.0 equiv) was added carefully to a stirred 0 °C solution of sulfinamide (1.0 equiv) in MeOH. After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated

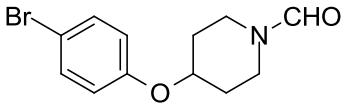
under reduced pressure and Et_2O was added and a white precipitation formed. The precipitate was filtered off and washed with Et_2O and dried under reduced pressure yielding the crude product.

4-(4-iodophenoxy)-1-methylpiperidine ***(5c).***



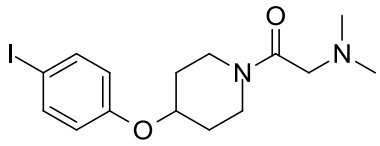
A solution of 1-methylpiperidin-4-ol (20.01 g, 174 mmol) in DMF (30 mL) was added via pipet to a cold (ice-bath) flask containing NaH (60% in mineral oil, 8.11 g, 203 mmol) suspended in DMF (100 mL) under Ar, and additional DMF (3 x 10 mL) was used to rinse the vial and pipet. After the mixture was stirred in ice bath for 30 min, 1-fluoro-4-iodobenzene (20.0 mL, 174 mmol) was added to the mixture and the reaction mixture was allowed to stir at rt for 30 min, then placed in an 85 ^oC oil bath. After a few min, due to excessive foaming, the flask was removed from the oil bath and allowed to stir at rt for 10 min. This was repeated 3 times until no longer foaming excessively on introduction to the oil bath, then the reaction flask was heated at 85 ^oC in oil bath for 24 h. After cooling to rt, H_2O (50 mL) was added dropwise at first, then rapidly when little gas evolution occurred. The reaction mass was then poured into H_2O (450 mL) and the resulting aq. suspension was cooled in ice bath, then the precipitate was collected by vacuum filtration, rinsing with H_2O (2 x 50 mL). The resulting solid was dissolved in MeOH and the solvent was removed, then EtOH was added and the solution was evaporated to yield **5c** as a tan solid (36.9 g, 67%). ^1H NMR (400 MHz, $CDCl_3$) δ 7.55 (d, J = 8.9 Hz, 2H), 6.69 (d, J = 8.9 Hz, 2H), 4.32–4.24 (m, 1H), 2.68 (br s, 2H), 2.31 (s, 3H), 2.29–2.23 (m, 2H), 2.03–1.94 (m, 2H), 1.88–1.78 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{16}INO + H]^+$ 318.0; found 318.0.

4-(4-bromophenoxy)piperidine-1-carbaldehyde ***(6a).***



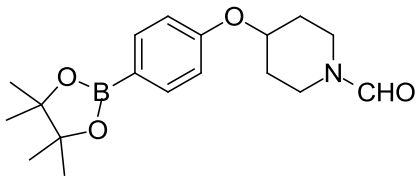
According to general method A2 using 4-(4-bromophenoxy)piperidine hydrochloride (1.0 g, 3.42 mmol) and formic acid (0.13 mL, 3.42 mmol), **6a** was obtained as a yellow solid (885 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (s, 1H), 7.58 (d, J = 8.78 Hz, 2H), 6.71 (d, J = 9.03 Hz, 2H), 4.61–4.54 (m, 1H), 3.68–3.56 (m, 3H), 3.40–3.29 (m, 1H), 1.98–1.76 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{14}BrNO_2 + H]^+$ 284.0; found 284.0.

2-(dimethylamino)-1-(4-(4-iodophenoxy)piperidin-1-yl)ethanone ***(6b).***



According to general method A2 using 4-(4-iodophenoxy)piperidine hydrochloride and 2-(dimethylamino)acetic acid, **6b** was obtained as a yellow solid (739 mg, 95%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60–7.52 (m, 2H), 6.73–6.66 (m, 2H), 4.50 (tt, J = 6.6, 3.5 Hz, 1H), 3.79 (dd, J = 8.8, 4.0 Hz, 2H), 3.66–3.57 (m, 1H), 3.57–3.48 (m, 1H), 3.13 (s, 2H), 2.29 (s, 6H), 2.00–1.73 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{15}H_{21}IN_2O_2 + H]^+$ 389.1; found 389.1.

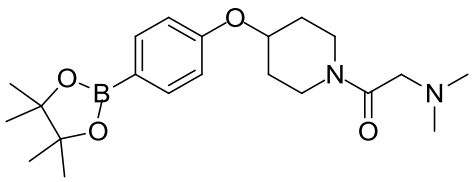
4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine-1-carbaldehyde ***(7a).***



A microwave oven vial was charged with 4-(4-bromophenoxy)piperidine-1-carbaldehyde (480 mg, 1.68 mmols), bis(pinacolato)diboron (513 mg, 2.02 mmols), KOAc (495 mg, 5.05 mmols) and DMF (8 mL). The mixture was purged with Ar for 2 min, then $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (69 mg, 0.05 mmol) was added and the vial was sealed. The resulting mixture was stirred at 85 ^{o}C for 2 h with microwave irradiation and then was filtered through Celite. The filtrate was concentrated under reduced pressure. The residue was purified by flash

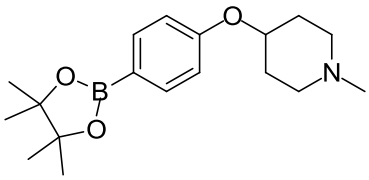
chromatography (0–100% EtOAc in hexanes) to give **7a** as a light yellow solid (473 mg, 85%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.06 (s, 1 H), 7.77 (d, J = 8.5 Hz, 2H), 6.94–6.88 (d, J = 8.5 Hz, 2H), 4.72–4.65 (m, 1H), 3.69–3.55 (m, 3H), 3.39–3.29 (m, 1H), 1.90 (m, 4H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{26}BNO_4 + H]^+$ 332.2; found 332.3.

2-(dimethylamino)-1-(4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidin-1-yl)ethanone ***(7b).***



According to general method E using 2-(dimethylamino)-1-(4-(4-iodophenoxy)piperidin-1-yl)ethanone, **7b** was obtained as a pale solid (380 mg, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, J = 8.5 Hz, 2H), 6.90 (d, J = 8.5 Hz, 2H), 4.62 (br s, 1H), 3.82–3.61 (m, 3H), 3.57–3.47 (m, 1H), 3.30 (m, 2H), 2.47–2.31 (m, 6H), 2.02–1.74 (m, 4H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{21}H_{33}BN_2O_4 + H]^+$ 389.3; found 389.1.

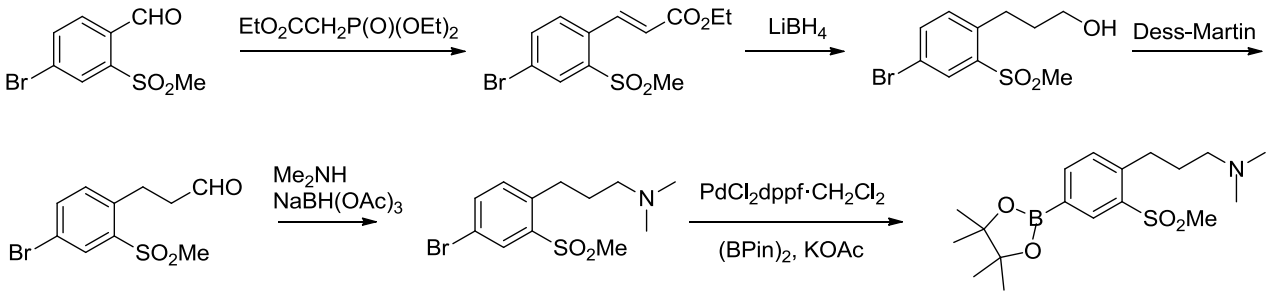
1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine ***(7c).***



According to general method E using 4-(4-iodophenoxy)-1-methylpiperidine (9.58g, 30.2 mmol) with S-Phos (379 mg, 0.92 mmol mmol) and $Cl_2Pd(CH_3CN)_2$ (60 mg, 0.23 mmol) at 110 ^{o}C for 6.5 h, MeOH (2 mL) was slowly added to quench excess borane, followed by DCM (200 mL) and satd aq $NaHCO_3$ (50 mL). After vacuum filtration through a pad of Celite and rinsing with DCM (150 mL) and satd aq $NaHCO_3$ (50 mL), the layers were separated and the aq. layer was extracted with with DCM (100 mL). The combined DCM layers were washed with H_2O (50 mL), and brine (50 mL), and dried (Na_2SO_4), filtered and the solvent removed to

yield the crude product. Purification by flash chromatography (0–15% MeOH in DCM) gave **7c** as a white solid (7.79 g, 90% pure, 73%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.0 Hz, 2H), 6.95 (d, J = 7.9 Hz, 2H), 4.54–4.41 (m, 1H), 2.80–2.68 (m, 2H), 2.48–2.35 (m, 2H), 2.33 (s, 3H), 2.10–1.98 (m, 2H), 1.93–1.77 (m, 2H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{28}BNO_3 + H]^+$ 318.2; found 318.1.

N,N-dimethyl-3-(2-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)propan-1-amine ***(7d)****.*



A stirred $PhCF_3$ (5 mL) solution of 4-bromo-2-(methylsulfonyl)benzaldehyde (0.50 g, 1.9 mmol) and EtONa (0.26 g, 3.8 mmol) was treated with triethyl phosphonoacetate (0.64 g, 0.57 mmol) at 0 ^{o}C. The reaction was warmed to rt and later heated under microwave irradiation for 10 min at 120 ^{o}C. After cooling the reaction was partitioned between EtOAc and H_2O. The organic layer was washed (H_2O, brine), dried (Na_2SO_4) and concentrated under reduced pressure to provide (E)-ethyl 3-(4-bromo-2-(methylsulfonyl)phenyl)acrylate as white powder (0.67 g), in a mixture (70 wt%) with triethyl phosphonoacetate. ^{1}H NMR (400 MHz, CD_3OD) δ 8.40 (d, J = 15.8 Hz, 1H), 8.15 (s, 1H), 7.88 (d, J = 8.5 Hz, 1H), 7.76 (d, J = 8.3 Hz, 1H), 6.53 (d, J = 15.8 Hz, 1H), 4.26 (q, J = 7.2 Hz, 2H), 3.11 (s, 3H), 1.24 (t, J = 7.0 Hz, 3H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{13}BrO_4S + H]^+$ 333.0; found 333.1.

To a solution of (E)-ethyl 3-(4-bromo-2-(methylsulfonyl)phenyl)acrylate (0.47 g, 70 wt%, 0.99 mmol) in anh THF (20 mL) was added $LiBH_4$ (108 mg, 4.9 mmol) at 0 ^{o}C. The reaction was allowed to warm to rt overnight. Later the reaction was heated at 50 ^{o}C for 1 h before it was cooled to rt and quenched with satd aq NH_4Cl. The mixture was extracted with DCM and combined organics extracts were washed (brine), dried and concentrated

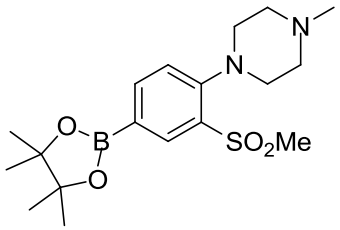
under reduced pressure. Purification by flash chromatography (0–20% MeOH in DCM) afforded 3-(4-bromo-2-(methylsulfonyl)phenyl)propan-1-ol as a clear oil (0.23 g, 79%). LCMS (ESI) *m/z* calcd for $[C_{10}H_{13}BrO_3S + H]^+$ 293.0; found 293.0.

This material (230 mg, 0.78 mmol) in DCM (5 mL) was treated with Dess-Martin periodinane (0.33 g, 0.77 mmol) at rt. The reaction was stirred for 1.5 h, diluted with Et_2O and treated with xs aq NaOH (1 M). After stirring for 5 min at rt, the layers were separated. The organic phase was washed (H_2O, brine), dried (Na_2SO_4) and concentrated under reduced pressure to yield 3-(4-bromo-2-(methylsulfonyl)phenyl)propanal as a clear gum (0.19 g, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.81 (s, 1 H), 8.17 (s, 1H), 7.68 (d, J = 8.0 Hz, 1H), 7.28 (d, J = 7.5 Hz, 1H), 3.25 (t, J = 7.5 Hz, 2H), 3.13 (s, 3H), 2.94 (t, J = 7.2 Hz, 2H).

A mixture of 3-(4-bromo-2-(methylsulfonyl)phenyl)propanal (89 mg, 0.31 mmol) in DMF (1 mL) and THF (5 mL) was treated with Me_2NH (2 M in THF, 0.6 mL, 1.2 mmol) and $NaBH(OAc)_3$ (0.19 g, 0.92 mmol) at rt. It was stirred for 1.5 h at rt, concentrated under reduced pressure to remove THF. Purification by prep-HPLC provided 3-(4-bromo-2-(methylsulfonyl)phenyl)-N,N-dimethylpropan-1-amine 2,2,2-trifluoroacetate as a clear gum (64 mg, 48%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.14 (s, 1H), 7.84 (d, J = 8.0 Hz, 1H), 7.48 (d, J = 8.0 Hz, 1H), 3.27–3.17 (m, 2H), 3.21 (s, 3H), 3.06 (t, J = 8.3 Hz, 2H), 2.91 (s, 6H), 2.13–1.96 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{18}BrNO_2S + H]^+$ 320.0; found 320.2.

A mixture of 3-(4-bromo-2-(methylsulfonyl)phenyl)-N,N-dimethylpropan-1-amine (64 mg, 0.15 mmol), 4,4,4',4',5,5,5',5'-octamethyl-2,2'-bi(1,3,2-dioxaborolane) (45 mg, 0.18 mmol), KOAc (58 mg, 0.59 mmol) in anh DMF (2.5 mL) was degassed with Ar, charged with $Pd(dppf)Cl_2 \cdot CH_2Cl_2$ (6 mg, 0.007 mmol) and heated sealed in a microwave reactor at 100 ^{o}C for 2 h. The crude **7d** in DMF solution was used without further purification. LCMS (ESI) *m/z* calcd for $[C_{18}H_{30}BNO_4S + H]^+$ 368.2; found 368.1.

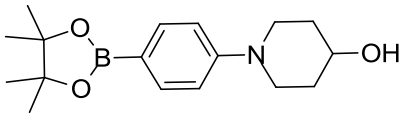
*1-methyl-4-(2-(methylsulfonyl)-4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl) phenyl) piperazine (**7e**)*



To a solution of 1-(4-chloro-2-(methylsulfonyl) phenyl) piperazine (800 mg, 2.91 mmol) in formic acid (15 mL) was added formalin (0.92 mL, 11.33 mmol). The solution was heated to 150 °C for 15 min under microwave irradiation. Solvents were removed in vacuo and the residue was dissolved in EtOAc (50 mL), washed with satd aq $NaHCO_3$ (10 mL x 2), brine (10 mL) and dried over Na_2SO_4 and concentrated to dryness. Purification by flash chromatography (0–10% MeOH in DCM) gave 1-(4-chloro-2-(methylsulfonyl) phenyl)-4-methyl piperazine as a cream solid (720 mg, 86%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 2.4 Hz, 1H), 7.58 (dd, J = 8.4, 2.4 Hz, 1H), 7.37 (d, J = 8.8 Hz, 1H), 3.59 (s, 3H), 3.11–3.08 (br s, 4H), 2.64–2.62 (br s, 4H), 2.38 (s, 3H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{17}ClN_2O_2S + H]^+$ 289.1; found, 289.1.

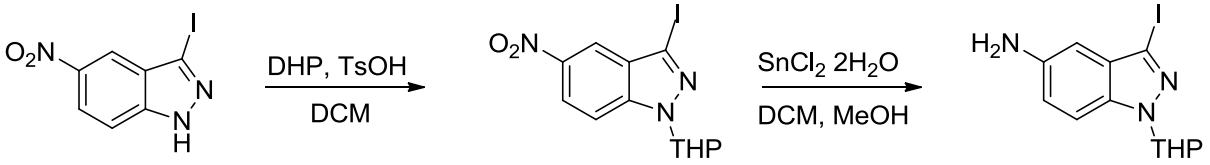
A mixture of *1*-(4-chloro-2-(methylsulfonyl) phenyl)-4-methyl piperazine (700 mg, 2.42 mmol), pinacolato diboron (666 mg, 2.67 mmol), KOAc (713 mg, 7.27 mmol) and dioxane (21 mL) was purged with argon for 10 min before $Pd(dba)_2$ (69 mg,0.121 mmol) and tricyclohexyl phosphine tetrafluoroborate (89 mg, 0.242 mmol) were added. The vial was sealed and heated it in oil bath to 80 °C for 18 h. the reaction mass was diluted using EtOAc (100 mL), washed with satd aq $NaHCO_3$ (20 mL x 2), brine (20 mL) and dried over Na_2SO_4 and concentrated to dryness. Purification by flash chromatography (0–30% MeOH in DCM) gave **7e** as a light brown solid (270 mg, 29%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (s, 1H), 8.02 (d, J = 8.0 Hz, 1H), 7.38 (d, J = 8.0 Hz, 1H), 3.32 (s, 3H), 3.12–3.08 (br s, 4H), 2.67–2.62 (br s, 4H), 2.38 (s, 3H), 1.33 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{29}BN_2O_4S + H]^+$ 381.2; found, 381.1.

*1-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)piperidin-4-ol (**7f**).*



According to general method E using 1-(4-bromophenyl)piperidin-4-one (1.49 g, 5.86 mmol) and excess HBpin (3 equiv) at 100 ^{o}C for 17 h, **7f** was obtained (1.59 g, 80% pure, 72%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 8.8 Hz, 2H), 6.91 (d, J = 8.8 Hz, 2H), 3.88 (tt, J = 8.6, 4.2 Hz, 1H), 3.68 (dt, J = 13.1, 4.1 Hz, 2H), 3.00 (ddd, J = 12.7, 10.1, 3.0 Hz, 2H), 2.04–1.92 (m, 2H), 1.73–1.60 (m, 2H), 1.33 (s, 12H).

*3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine (**9a**)*

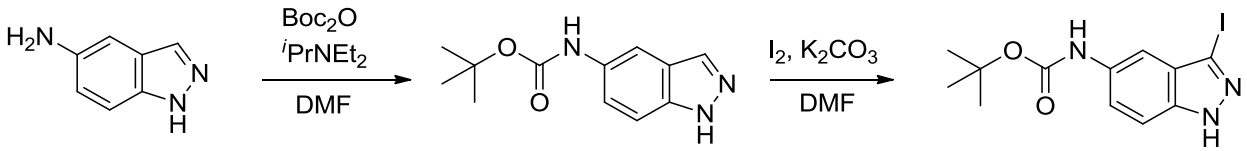


To a suspension of 3-iodo-5-nitro-1H-indazole (1.0 g, 3.46 mmol) in CH_2Cl_2 (15mL) was added 3,4-dihydro-2H-pyran (0.95 mL, 10.4 mmol) and *p*-TsOH (66mg, 0.346 mmol). The reaction was stirred for 24 hours and the diluted with CH_2Cl_2 (100 mL). The mixture was then washed with satd aq $NaHCO_3$ (2 x 50 mL), concentrated and purified by flash chromatography (14% EtOAc in hexanes) to give 3-iodo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole as a yellow solid (603 mg, 67%.) ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.47 (d, 1H, J = 2.0 Hz), 8.30 (dd, J = 9.2, 2.0 Hz, 1H), 7.68 (d, J = 9.6 Hz, 1H), 5.76–5.73 (m, 1H), 4.03–3.98 (m, 1H), 3.78–3.72 (m, 1H), 2.54–2.45 (m, 1H), 2.17–2.08 (m, 2H), 1.83–1.76 (m, 3H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{12}IN_3O_3 + Na]^+$ 396.0; found 396.0

To a solution of 3-iodo-5-nitro-1-(tetrahydro-2H-pyran-2-yl)-1H-indazole (828 mg, 2.22 mmol) in CH_2Cl_2 (7.0 mL) and MeOH (7.0 mL) was added tin(II) chloride dihydrate (3.0 g, 13.32 mmol) and the reaction stirred for 18 h. The mixture was diluted with CH_2Cl_2 (50 mL), cooled to 0 ^{o}C, and then quenched (carefully!) with satd aq Na_2CO_3 (25 mL). The mixture was allowed to stir for 1–2 h, separated, extracted with DCM and purified by flash chromatography (2% MeOH in DCM) to give **9a** as a pink solid (510 mg, 67%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 1H), 6.89 (dd, J = 8.8, 2.0 Hz, 1H), 6.65 (d, J = 2.0 Hz, 1H), 5.62–5.59 (m, 1H),

4.03–3.98 (m, 1H), 3.73–3.68 (m, 1H), 2.56–2.46 (m, 1H), 2.15–2.00 (m, 2H), 1.77–1.64 (m, 3H); MS ESI *m/z* calcd for $[C_{12}H_{14}IN_3O + H]^+$ 344.0; found 344.0.

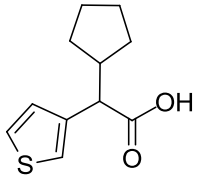
*tert-butyl 3-iodo-1H-indazol-5-ylcarbamate (**9b**)*



A DMF (15 mL) solution of aminoindazole (1.0 g, 7.5 mmol) and DIPEA (2.0 mL, 11 mmol) was treated with Boc_2O (1.7 g, 7.7 mmol) (50 % added in one portion as a solid, and 50 % as a solution in anh DMF (1 mL) at 0 ^oC. The reaction was stirred with the cooling for 1.5 h and then allowed to warm slowly to rt overnight. Later it was diluted with H_2O to about 100 mL. A tan precipitate was collected by filtration, washed with H_2O and dried to afford tert-butyl 1H-indazol-5-ylcarbamate as a light tan solid (1.7 g, 94%). ^1H NMR (400 MHz, DMSO-d_6) δ 12.90 (s, 1H), 9.27 (s, 1H), 7.94 (s, 1H), 7.87 (br s, 1H), 7.41 (d, J = 8.8 Hz, 1H), 7.33 (d, J = 9.2 Hz, 1H), 1.47 (s, 9H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{15}N_3O_2 + H]^+$ 234.0; found 233.9 .

To a cooled (0 ^oC) DMF (30 mL) solution tert-butyl 1H-indazol-5-ylcarbamate (1.6 g, 6.9 mmol) and K_2CO_3 (3.8 g, 27.6 mmol) was added I_2 (1.8 g, 7.1 mmol) in one portion. The reaction was stirred with cooling for 3 h and then treated with 10% aq $NaHSO_3$ (50 mL) and subsequently with H_2O (150 mL). A filtration and washing (H_2O) of the ppt provided crude material which after purification by flash chromatography (0–6% MeOH in DCM) and recrystallization from EtOAc/hexanes yielded **9b** as an off-white solid (1.9 g, 78%). ^1H NMR (400 MHz, acetone-d_6) δ 12.54 (br s, 1H), 8.51 (br s, 1H), 7.87 (br s, 1H), 7.66–7.24 (m, 2H), 1.51 (s, 9H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{14}IN_3O_2 + H]^+$ 360.0; found 359.9.

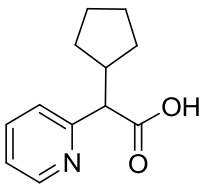
2-cyclopentyl-2-(thiophen-3-yl)acetic acid



NaH (0.26 g, 60% in mineral oil, 6.5 mmol) was added portion wise to a solution of ethyl 3-thiophene acetate (0.88 mL, 5.8 mmol) in DMF (20 mL) at rt under Ar. After stirring for 5 min, cyclopentyl bromide (0.70 mL, 6.9 mmol) was added and stirring was continued for 18 h at 25 °C. 20% aq NH_4Cl (50 mL) was added and the product was extracted using EtOAc (2 x 50 mL), and the combined EtOAc layers were washed with H_2O, brine and dried (Na_2SO_4) and concentrated under vacuum. Purification by flash chromatography (0–25% EtOAc in hexanes) gave ethyl 2-cyclopentyl-2-(thiophen-3-yl)acetate as colorless oil (1.04 g, 74%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.26–7.25 (m, 1H), 7.16–7.15 (m, 1H), 7.12 (dd, J = 4.8, 1.2 Hz, 1H), 4.18–4.06 (m, 2H), 3.45 (d, J = 10.8 Hz, 1H), 2.51–2.49 (m, 1H), 1.86–1.83 (m, 1H), 1.49–1.46 (m, 6H), 1.24 (t, J = 7.2 Hz, 3H), 1.12–1.05 (m, 1H).

Aq NaOH (2 M, 5.45 mL, 10.9 mmol) was added to a solution of ethyl 2-cyclopentyl-2-(thiophen-3-yl)acetate (1.04 g, 4.3 mmol) in MeOH (10.4 mL) at rt. The reaction mixture was refluxed for 2.5 h, and then concentrated under reduced pressure. The residue was acidified to pH 2 using conc. HCl and the product was extracted with DCM. The combined organic layer was washed with H_2O and brine, dried (Na_2SO_4) and concentrated under vacuum to give 2-cyclopentyl-2-(thiophen-3-yl)acetic acid as off white solid (0.89 g, 97%). 1H NMR (400 MHz, CDCl3) δ 7.29–7.27 (m, 1H), 7.18–7.17 (m, 1H), 7.12–7.10 (m, 1H), 3.47 (d, J = 10.8 Hz, 1H), 2.55–2.45 (m, 1H), 1.95–1.89 (m, 1H), 1.71–1.48 (m, 5H), 1.35–1.26 (m, 1H), 1.12–1.05 (m, 1H).

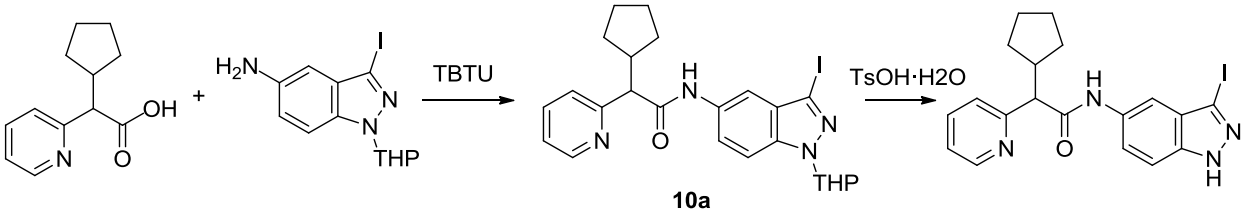
2-cyclopentyl-2-(pyridin-2-yl)acetic acid



A solution of ethyl 2-(pyridin-2-yl)acetate (2 g, 12.1 mmol) in anhydrous DMF (20 mL) was cooled down to 0 ^{o}C followed by adding of 60% NaH (581 mg, 14.5 mmol) in portions and bromocyclopentane (1.98 g, 13.3 mmol) dropwise. The resulting suspension was stirred at rt for 2 h before H_2O was added. The mixture was extracted with EtOAc. The organic layer was washed with H_2O (three times), brine, dried over Na_2SO_4 and concentrated under reduced pressure to give ethyl 2-cyclopentyl-2-(pyridin-2-yl)acetate as a yellow oil (370 mg, 52%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.55 (d, J = 4.8 Hz, 1 H), 7.65 (td, J = 7.7, 1.8 Hz, 1H), 7.40 (d, J = 8.0 Hz, 1H), 7.17 (ddd, J = 7.4, 5.0, 0.9 Hz, 1H), 4.23–4.04 (m, 2H), 3.58 (d, J = 11.0 Hz, 1H), 2.75–2.58 (m, 1H), 2.01–1.88 (m, 1H), 1.54–1.24 (m, 5H), 1.22 (t, J = 7.2 Hz, 3H), 1.07 (dq, J = 12.4, 8.2 Hz, 1H), 0.92–0.79 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{14}H_{19}NO_2 + H]^+$ 234.1; found 234.0.

According to the hydrolysis method used for 2-cyclopentyl-2-(thiophen-3-yl)acetic acid using ethyl 2-cyclopentyl-2-(pyridin-2-yl)acetate, 2-cyclopentyl-2-(pyridin-2-yl)acetic acid was obtained as colorless gel (216 mg, 43%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.75 (d, J = 5.3 Hz, 1H), 8.53–8.45 (m, 1H), 8.08 (d, J = 7.8 Hz, 1H), 7.95–7.86 (m, 1H), 3.85 (d, J = 11.0 Hz, 1H), 2.66 (m, 1H), 2.10–1.99 (m, 1H), 1.82–1.39 (m, 6H), 1.16–1.04 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{15}NO_2 + H]^+$ 206.1; found 206.1.

2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide

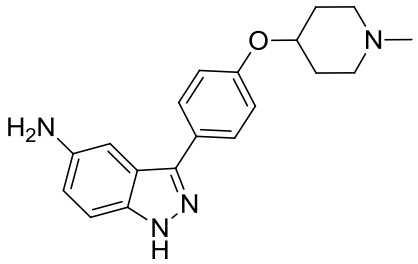


According to general method A1 using 2-cyclopentyl-2-(pyridin-2-yl)acetic acid and 3-iodo-1-(tetrahydro-2H-pyran-2-yl)-1H-indazol-5-amine, **10a** was obtained as a brown solid (178 mg, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (br s, 1H), 8.63 (d, J = 4.0 Hz, 1H), 7.80–7.64 (m, 2H), 7.58–7.43 (m, 2H), 7.38–7.20 (m, 2H), 5.64 (d, J = 8.0 Hz, 1H), 3.98 (d, J = 10.5 Hz, 1H), 3.70 (t, J = 9.3 Hz, 1H), 3.56–3.42 (m, 1H), 2.75–2.60 (m,

1H), 2.51 (d, *J* = 9.5 Hz, 1H), 2.21–1.88 (m, 3H), 1.82–1.33 (m, 9H), 1.15–1.00 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{24}H_{27}IN_4O_2 + H]^+$ 531.1; found 531.2.

The solution of **10a** (178mg, 0.34 mmol) and $TsOH \cdot H_2O$ (288 mg, 1.51 mmols) in MeOH (3 mL) was stirred at 125 ^oC for 3 h with microwave irradiation in a sealed vial before it was concentrated under reduced pressure. The residue was purified by flash chromatography (0–10% MeOH in DCM) to give 2-cyclopentyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide as a light yellow solid (104 mg, 69%). ^1H NMR (400 MHz, CD_3OD) δ 8.48 (dd, *J* = 4.9, 0.9 Hz, 1H), 7.85 (d, *J* = 1.3 Hz, 1H), 7.76 (td, *J* = 7.7, 1.8 Hz, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.51–7.40 (m, 2H), 7.27 (ddd, *J* = 7.5, 5.0, 1.0 Hz, 1H), 3.59 (d, *J* = 11.0 Hz, 1H), 2.84–2.68 (m, 1H), 1.94 (dd, *J* = 11.7, 4.6 Hz, 1H), 1.76–1.35 (m, 6H), 1.12–0.99 (m, 1H); MS ESI *m/z* $[C_{19}H_{19}IN_4O + H]^+$ 447.1; found 447.1.

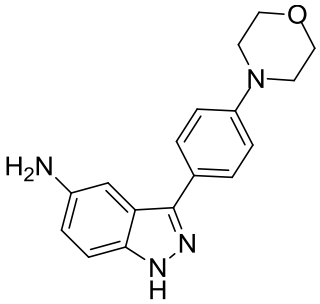
*3-(4-((1-methylpiperidin-4-yl)oxy)phenyl)-1H-indazol-5-amine (**11a**)*



tert-Butyl(3-iodo-1H-indazol-5-yl)carbamate (398 mg, 1.11 mmol), 1-methyl-4-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)piperidine (530 mg, 1.67 mmol), and LiCl (141 mg, 3.33 mmol) were dissolved in dioxane (7.0 mL) and 2 M aq Na_2CO_3 (2.8 mL) in a microwave vial. The mixture was purged with Ar for 15 min at which time $Pd(PPh_3)_4$ (96 mg, 0.083 mmol) was added. The vial was sealed and heated in the microwave at 120 ^oC for 3 h. The reaction was cooled, the solvent removed and the residue purified by column chromatography (10% MeOH in DCM) to give 230 mg of BOC protected material which was dissolved into CH_2Cl_2 (5 mL) and TFA (0.5 mL) was added. The reaction was stirred for 3 h. The solvent was removed and product precipitated with Et_2O to give **11a** as a brown solid (235 mg, 38%, di-TFA salt). ^1H NMR (400 MHz,

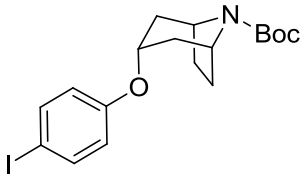
CD_3OD) δ 8.01 (s, 1 H), 7.90-7.86 (m, 2H), 7.73 (d, J = 8.8 Hz, 1 H), 7.42 (d, J = 9.0, 1H), 7.23–7.16 (m, 2H), 4.88 (br s, 1H), 3.66–3.39 (m, 2H), 3.39–3.00 (m, 2H), 2.95–2.89 (m, 3H), 2.46–2.29 (m, 2H), 2.17–1.90 (m, 2H); LCMS (ESI) *m/z* calcd for $[C_{19}H_{22}N_4O + H]^+$ 323.1; found 323.1.

*3-(4-morpholinophenyl)-1H-indazol-5-amine (**11b**)*



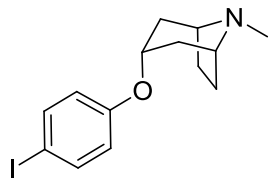
To a mixture of tert-butyl (3-iodo-1H-indazol-5-yl)carbamate (1.077 g, 3 mmol) and (4-morpholinophenyl)boronic acid (652 mg, 3.15 mmol) in EtOH (12 mL) was added 2 M aq Na_2CO_3 (3 mL, 6 mmol), followed by $Pd(PPh_3)_4$ (104 mg, 0.09 mmol). The resulting mixture was purged with Ar and microwaved 3 h at 125 ^oC. Repeated this reaction twice on the same scale. All three reactions were combined, diluted with H_2O, extracted with EtOAc and purified by flash chromatography (0–25 % MeOH in DCM) to give 4.20 g of brown solid. It was redissolved in DCM (20 mL) and treated with TFA (10 mL). After stirring for 3 h at rt, it was concentrated and purified by biotage RP column (5–90 % MeOH in 0.1% TFA-H_2O) to give **11b** as a light puple solid (866 mg, 55%, di-TFA salt). ^1H NMR (400 MHz, CD_3OD) δ 8.05 (s, 1H), 7.84 (d, J = 7.2 Hz, 2H), 7.72 (d, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 1H), 7.17 (d, J = 7.2 Hz, 2H), 4.00–3.80 (m, 4H), 3.40–3.20 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{17}H_{18}N_4O + H]^+$ 295.1; found 259.0.

*tert-butyl endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane-8-carboxylate **(23a).***



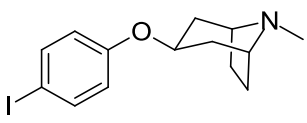
The suspension of NaH (60%, 317 mg, 7.9 mmol) in DMF (10 mL) was degassed with Ar followed by addition of tert-butyl endo-3-hydroxy-8-azabicyclo[3.2.1]octane-8-carboxylate (2.0 g, 7.2 mmol) at rt. The resulting mixture was degassed with Ar again and slowly warmed up. The solution began bubbling at 45 ^{o}C and finished at 60 ^{o}C. At 70 ^{o}C, 1-fluoro-4-iodobenzene (0.83 mL, 7.2 mmol) was added dropwise and the reaction mixture was stirred at 85 ^{o}C overnight. After cooling to rt, H_2O and EtOAc were added. The organic phase was washed with H_2O and brine and dried (Na_2SO_4) and concentrated. The residue was purified by flash chromatography (10–35% EtOAc in hexanes) to yield **23a** as a white solid (1.5 g, 54%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61–7.51 (m, 2H), 6.62 (d, J = 9.0 Hz, 2H), 4.59 (br s, 1H), 4.32–4.09 (m, 2H), 2.23–2.02 (m, 4H), 2.00–1.89 (m, 4H), 1.48 (s, 9H). LCMS (ESI) *m/z* calcd for$[C_{18}H_{24}INO_3 - C_4H_9]^+$ 374.0; found 374.0.

endo-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane ***(23b).***



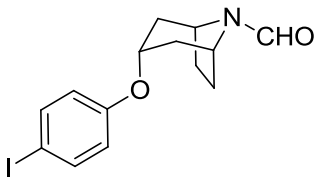
According to general method B using endo-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (28.24 g, 200 mmol), DMF (150 mL), 60% NaH (9.90 g, 248 mmol) and 1-fluoro-4-iodobenzene (44.4 g, 200 mmol) at 85 ^{o}C, **23b** was obtained as a beige solid (27.76 g, 40%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 4.65 (t, J = 4.9 Hz, 1H), 3.79 (br s, 2H), 2.83–2.71 (m, 5H), 2.55–2.47 (m, 2H), 2.32–2.15 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{14}H_{18}INO + H]^+$ 344.0; found 344.0.

exo-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane ***(23c).***



According to general method B using exo-8-methyl-8-azabicyclo[3.2.1]octan-3-ol (7.05 g, 50 mmol) and 1-fluoro-4-iodobenzene (11.1 g, 50 mmol), **23c** was obtained as a beige solid (9.36 g, 55%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.53 (d, J = 9.2 Hz, 2H), 6.67 (d, J = 8.8 Hz, 2H), 4.50–4.40 (m, 1H), 3.28–3.24 (m, 2H), 2.37 (s, 3H), 2.12–2.05 (m, 2H), 1.98–1.89 (m, 2H), 1.87–1.77 (m, 2H), 1.66–1.58 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{14}H_{18}INO + H]^+$ 344.0; found 344.0.

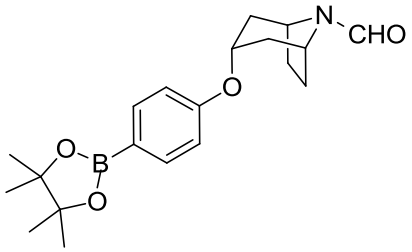
endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde ***(24).***



To a solution of tert-butyl endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane-8-carboxylate (1.0 g, 429 mmol) in DCM (3 mL) was added TFA (3 mL) and the reaction mixture was stirred at rt for 6 h. After evaporation of solvents, the residue was washed with satd $NaHCO_3$ and extracted with EtOAc. The combined EtOAc portions was dried over Na_2SO_4 and concentrated to endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane as a white solid (767 mg, quant.). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 (d, J = 9.0 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 4.59 (t, J = 4.3 Hz, 1H), 4.50–4.10 (m, 1H), 3.75 (br s, 2H), 2.30–2.20 (m, 4H), 2.06 (d, J = 14.8 Hz, 2H), 2.02–1.94 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{13}H_{16}INO + H]^+$ 330.0; found 330.0.

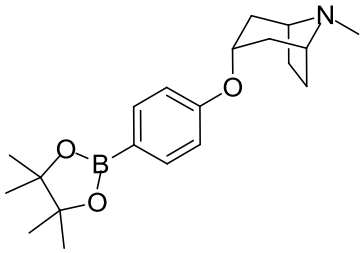
According to general method A2 using endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane (2.75 g, 8.36 mmol), and HCOOH (0.35 mL, 9.19 mmol), **24** was obtained as a white solid (1.0 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.58 (d, J = 8.8 Hz, 2H), 6.62 (d, J = 8.8 Hz, 2H), 4.63 (br s, 2H) 4.08 (br s, 1H), 2.28–1.90 (m, 8H). LCMS (ESI) *m/z* calcd for $[C_{14}H_{16}INO_2 + H]^+$ 358.0; found 358.1.

endo-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde ***(25a).***



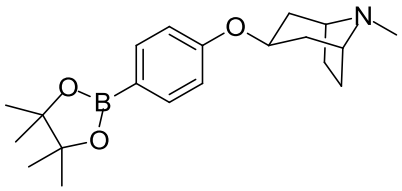
According to general method E using endo-3-(4-iodophenoxy)-8-azabicyclo[3.2.1]octane-8-carbaldehyde (110mg, 0.31 mmol), **25a** was obtained as an off-white solid (68 mg (62%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.77 (d, J = 8.5 Hz, 2H), 6.83 (d, J = 8.5 Hz, 2H), 4.77–4.69 (m, 1H), 4.66–4.58 (m, 1H), 4.11–4.04 (m, 1H), 2.25 (s, 6H), 2.01–1.89 (m, 2H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{20}H_{28}INO_4 + H]^+$ 358.2; found 358.3.

endo-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane ***(25b).***



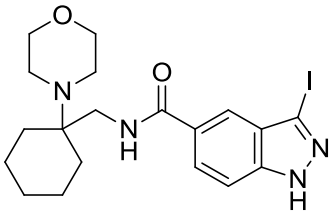
According to general method E using endo-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1]octane (6.86 g, 20 mmol) and HBpin (3.77 ml, 26 mmol), **25b** was obtained as a light yellow solid (2.56 g, 37%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.5 Hz, 2H), 6.84 (d, J = 8.8 Hz, 2H), 4.81 (br s, 1H), 3.82 (br s, 2H), 3.38–3.18 (m, 2H), 2.77 (s, 3H), 2.63–2.54 (m, 2H), 2.36–2.21 (m, 4H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{20}H_{30}BNO_3 + H]^+$ 344.2; found 344.2.

exo-8-methyl-3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenoxy)-8-azabicyclo[3.2.1]octane ***(25c).***



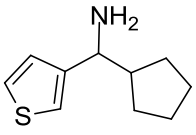
According to general method E using exo-3-(4-iodophenoxy)-8-methyl-8-azabicyclo[3.2.1] octane (6.86 g, 20 mmol) and HBpin (3.77 ml, 26 mmol), **25c** was obtained as a light yellow solid (5.14 g, 75%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.20 (d, J = 8.0 Hz, 2H), 6.88 (d, J = 8.4 Hz, 2H), 4.62–4.52 (m, 1H), 3.33–3.27 (m, 2H), 3.40 (s, 3H), 2.15–1.85 (m, 6H), 1.72–1.65 (m, 2H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{20}H_{30}BNO_3 + H]^+$ 344.2; found 344.2.

3-iodo-N-((1-morpholinocyclohexyl)methyl)-1H-indazole-5-carboxamide ***(28).***



According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (90 mg, 0.31 mmol) and (1-morpholino cyclohexyl)methanamine (62 mg, 0.31 mmol), **28** was obtained as a colorless solid (TFA salt, 148 mg, 81%). ^{1}H NMR (free base, 400 MHz, CD_3OD) δ 8.01 (s, 1 H), 7.92 (d, J = 8.8 Hz, 1H), 7.61 (d, J = 8.8 Hz, 1H), 3.72 (br s, 4H), 3.52 (s, 2H), 2.78 (br s, 4H), 1.45 (br s, 10H). LCMS (ESI) *m/z* calcd for $[C_{19}H_{25}IN_4O_2 + H]^+$ 469.1; found 469.2.

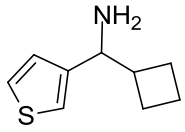
Cyclopentyl(thiophen-3-yl)methanamine ***(31a).***



According to the method used for cyclobutyl(thiophen-3-yl)methanamine by using cyclopentyl-3-thienyl ketone (3.5 g, 19.4 mmol) at 60 °C for 24 h, **31a** was obtained as a colorless oil (3.25 g, 93%). ^{1}H NMR (400 MHz,

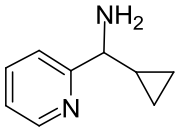
DMSO-d_6) δ 7.44–7.42 (m, 1H), 7.27 (t, J = 2 Hz,1H), 7.12–7.10 (m, 1H), 3.74 (t, J = 8.4 Hz, 1H), 2.09–1.99 (m, 1H), 1.76–1.68 (m, 1H), 1.58–1.29 (m, 8H), 1.16–1.14 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{10}H_{15}NS + H]^+$ 182.1; found 182.1.

cyclobutyl(thiophen-3-yl)methanamine ***(31b).***



A mixture of cyclobutyl(thiophen-3-yl)methanone (1.04 g, 6.27 mmol), NH_4OAc (5.85 g, 75.24 mmol) and $NaCNBH_3$ (1.58 g, 25.08 mmol) in MeOH (30 mL) was heated at 65 ^oC for 3 h, then left O/N at 65 ^oC. After removal of solvent, it was purifed by flash chromatography (0–30% MeOH in DCM) to give **31b** as colorless oil (1.194 g, quantivative). ^1H NMR (400 MHz, CD_3OD) δ 7.55–7.50 (m, 2H), 7.17 (dd, J = 4.8 Hz, 1.2 Hz, 1H), 4.37 (d, J = 10.0 Hz, 1H), 2.93–2.82 (m, 1H), 2.29–2.19 (m, 1H), 2.05–1.75 (m, 5H). LCMS (ESI) *m/z* calcd for $[C_9H_{13}NS – NH_2]^+$ 151.1; found 151.0.

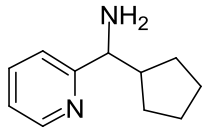
cyclopropyl(pyridin-2-yl)methanamine ***(31c).***



To a 20 mL microwave vial charged with Mg powder (240 mg, 10 mmol) and THF (10 mL) was added bromocyclopropane (1.21 g, 10 mmol). The resulting mixture was stirred for 30 min at rt before a solution of picolinonitrile (520 mg, 5 mmol) in THF (3 mL) was added. It was microwaved 10 min at 100 ^oC, cooled to rt and added dropwise to a cold solution of $NaBH_4$ (380 mg, 10 mmol) in MeOH (30 mL) at 0 ^oC. The resulting mixture was stirred for 15 min at rt, quenched with H_2O, extracted with DCM and purified by flash chromatography (0–30% MeOH in DCM) to give **31c** as light brown oil (590 mg, 79%). ^1H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, J = 4.0 Hz, 1H), 7.82 (dt, J = 7.6 Hz, 1.6 Hz, 1H), 7.50 (d, J = 8.0 Hz, 1H), 7.39–7.34 (m,

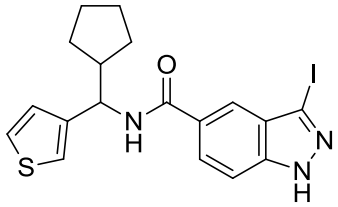
1H), 3.25 (d, *J* = 8.8 Hz, 1H), 1.18–1.10 (m, 1H), 0.70–0.62 (m, 1H), 0.54–0.42 (m, 2H), 0.40–0.34 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_9H_{12}N_2 - NH_2]^+$ 132.1; found 132.0.

cyclopentyl(pyridin-2-yl)methanamine ***(31d).***



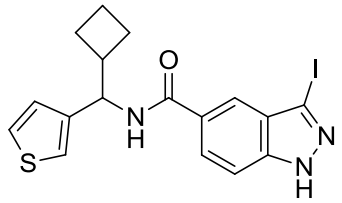
According to the method used for cyclobutyl(thiophen-3-yl)methanamine by using cyclopentyl-2-pyridyl ketone (1.0 g, 5.7 mmol), NH_4OAc (5.3 g, 69 mmol), $NaCNBH_3$ (1.4 g, 23 mmol) and MeOH (20 mL), **31d** was obtained as a clear oil (931 mg, 93%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.50 (d, *J* = 4.0 Hz, 1H), 7.80 (t, *J* = 7.9 Hz, 1H), 7.41 (d, *J* = 8.0 Hz, 1H), 7.31 (t, *J* = 5.0 Hz, 1H), 3.76 (d, *J* = 8.8 Hz, 1H), 2.27–2.14 (m, 1H), 1.99–1.88 (m, 1H), 1.75–1.36 (m, 5H), 1.35–1.25 (m, 1H), 1.24–1.12 (m, 1H).

N-(cyclopentyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32a).***



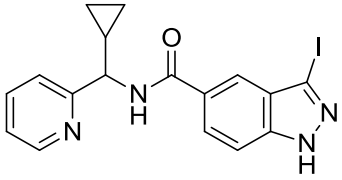
According to general method A2 using cyclopentyl(thiophen-3-yl)methanamine (3.25 g, 17.9 mmol) and 3-iodo-1H-indazol-5-carboxylic acid (5.16 g, 17.9 mmol), **32a** was obtained as a cream solid (7.95 g, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.72 (br s, 1H), 8.86 (t, *J* = 8.8 H_Z, 1H), 8.09 (s, 1H), 7.92–7.90 (m, 1H), 7.58 (t, *J* = 8.8 H_Z, 1H), 7.46–7.44 (m, 1H), 7.39–7.38 (m, 1H), 7.22 (d, *J* = 4.8 Hz, 1H), 4.98 (t, *J* = 9.6 Hz, 1H), 1.81–1.78 (m, 1H), 1.61–1.32 (m, 7H), 1.20–1.17 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{18}IN_3OS + H]^+$ 452.0, found 452.0.

N-(cyclobutyl(thiophen-3-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32b).***



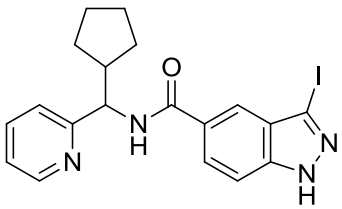
To a solution of cyclobutyl(thiophen-3-yl)methanamine (1.194 g, 6.27 mmol), 3-iodo-1H-indazole-5-carboxamide (1.81 g, 6.27 mmol) in DMF (20 mL) at 0 ^{o}C was added TBTU (2.01 g, 6.27 mmol), followed by $^{i}Pr_2NEt$ (2.18 mL, 12.54 mmol). The resulting mixture was stirred at 0 ^{o}C for 1 h, quenched with H_2O (70 mL) and stirred for 1.5 h at rt. Suction filtration gave crude **32b** as a light beige solid (2.512 g, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.69 (s, 1H), 8.75 (d, J = 8.8 Hz, 1H), 8.04 (s, 1H), 7.94 (dd, J = 4.6, 1.4 Hz, 1H), 7.58 (d, J = 8.8 Hz, 1H), 7.45 (dd, J = 4.8, 2.8 Hz, 1H), 7.35 (d, J = 3.2 Hz, 1H), 7.14 (dd, J = 4.8, 0.8 Hz, 1H), 5.19 (t, J = 9.4 Hz, 1H), 2.10–2.00 (m, 1H), 2.00–1.88 (m, 1H), 1.86–1.70 (m, 5H). LCMS (ESI) *m/z* calcd for $[C_{17}H_{16}IN_3OS + H]^+$ 438.0; found 438.0.

N-(cyclopropyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32c).***



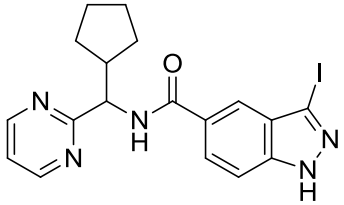
According to general method A2 using cyclopropyl(pyridin-2-yl)methanamine (575 mg, 3.94 mmol), 3-iodo-1H-indazole-5-carboxamide (1.14 g, 3.94mmol) and TBTU (1.27 g, 3.94 mmol), **32c** was obtained as a pale yellow solid (1.290 g, 78%) with ^{1}H NMR and LCMS as described for **32c-*R*.**

N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32d).***



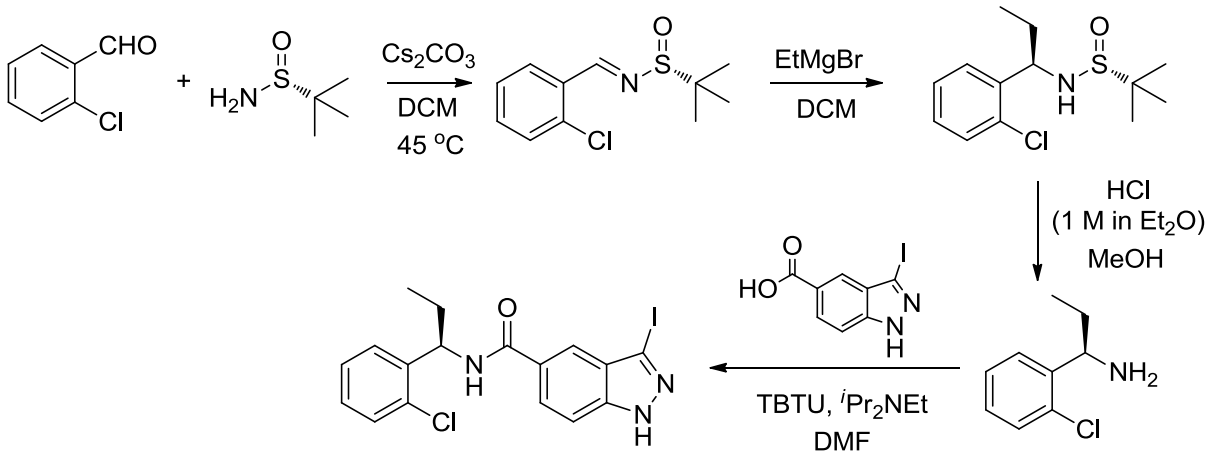
According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (1.52 g, 5.28 mmol), cyclopentyl(pyridin-2-yl)methanamine (930 mg, 5.28 mmol), TBTU (1.69 mg, 5.28 mmol), DIPEA (2.75 mL, 15.8 mmol) and DMF (10 mL), **32d** was obtained as a pale yellow solid (1.76 g, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.57–8.50 (m, 1H), 8.07 (s, 1H), 7.93 (d, J = 9.3 Hz, 1H), 7.82 (t, J = 7.4 Hz, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.51 (d, J = 7.5 Hz, 1H), 7.32 (dd, J = 6.6, 5.4 Hz, 1H), 5.01 (d, J = 9.8 Hz, 1H), 2.62–2.48 (m, 1H), 2.05–1.94 (m, 1H), 1.78–1.48 (m, 5H), 1.42–1.23 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{19}H_{19}IN_4O + H]^+$ 447.1; found 447.1.

N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32e).***



According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (325 mg, 1.1 mmol) and cyclopentyl(pyrimidin-2-yl)methanamine (200 mg, 1.1 mmol), **32e** was obtained as an off white solid (0.38 g, 75%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.67 (s, 1H), 8.97 (d, J = 8.3 Hz, 1H), 8.78 (d, J = 4.8 Hz, 2H), 8.11 (s, 1H), 7.94 (d, J = 8.8 Hz, 1H), 7.57 (d, J = 8.5 Hz, 1H), 7.38 (t, J = 4.9 Hz, 1H), 5.01 (t, J = 8.78 Hz, 1H), 2.63–2.52 (m, 1H), 1.94–1.81 (m, 1H), 1.71–1.38 (m, 5H), 1.36–1.20 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{18}IN_5O + H]^+$ 448.1; found 448.1.

(R)-N-(1-(2-chlorophenyl)propyl)-3-iodo-1H-indazole-5-carboxamide ***(32f).***



To a mixture of (*R*)-2-methylpropane-2-sulfinamide (364 mg, 3.0 mmol) and Cs_2CO_3 (977 mg, 3 mmol) in DCM (8 mL) was added 2-chlorobenzaldehyde (0.34 mL, 3 mmol) and the resulting mixture was heated at 45 ^oC for 18 h. After filtering through celite, the reaction mixture was concentrated and purified by flash chromatography (5% EtOAc in hexanes) to give (*R,E*)-N-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide as pale yellow oil (635 mg, 87%). ^1H NMR (400 MHz, $CDCl_3$) δ 9.04 (s, 1H), 8.06 (dd, J = 7.3, 1.5 Hz, 1H), 7.48–7.39 (m, 2H), 7.37–7.31 (m, 1H), 1.27 (s, 9H). LCMS (ESI) *m/z* calcd for $[C_{11}H_{14}ClNOS + H]^+$ 244.1; found 244.0.

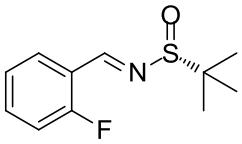
To a solution of (*R,E*)-N-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide (635 mg, 2.6 mmol) in DCM (13 mL) at -48 ^oC was added EtMgBr (3.0 M in Et_2O, 1.7 mL, 5.2 mmol) slowly. After stirring for 4 h at -48 ^oC, it was warmed up to rt, stirred O/N, quenched with satd aq NH_4Cl, extracted with EtOAc and purifed by RP Biotage to give (*R*)-N-((*R*)-1-(2-chlorophenyl)propyl)-2-methylpropane-2-sulfinamide (438 mg, 62%, 36 %de determined by ^1H NMR based on intergrations of benzylic protons). ^1H NMR (2.2 : 1.0 diastereomeric mixture, 400 MHz, $CDCl_3$) δ 7.40–7.34 (m, 3H), 7.31–7.24 (m, 1.5H), 7.24–7.17 (m, 1.5H), 4.86 (t, J = 6.80 Hz, 1H), 4.77 (t, J = 6.50 Hz, 0.46 H), 2.03–1.84 (m, 3H), 1.24 (s, 4H), 1.20 (s, 9H), 0.95–0.86 (m, 4.5H).

(*R*)-N-((*R*)-1-(2-chlorophenyl)propyl)-2-methylpropane-2-sulfinamide (438 mg, 36 %de) was dissoved in 3.5 mL of MeOH and 1.0 M HCl in Et_2O (3.3 mL, 3.3 mmol) was added. The resulting mixture was stirred at rt for 2 h and concentrated to dryness. Trituration with Et_2O afforded (*R*)-1-(2-chlorophenyl)propan-1-amine hydrochloride (224 mg, 42%, 36 %ee based upon %de). ^1H NMR (400 MHz, CD_3OD) δ 7.58–7.51 (m, 2H),

7.51–7.36 (m, 2H), 4.75 (dd, *J* = 8.8, 6.5 Hz, 1H), 2.11–1.94 (m, 2H), 0.94 (t, *J* = 7.4 Hz, 3H). LCMS (ESI) *m/z* calcd for $[C_9H_{12}ClN - NH_2]^+$ 153.0; found 152.9.

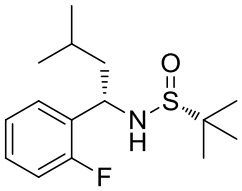
According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (489 mg, 1.7 mmol) and (*R*)-1-(2-chlorophenyl)propan-1-amine hydrochloride (349 mg, 36 %ee, 1.7 mmol), **32f** was obtained as a white solid (650 mg, 83 %, 36 %ee). ^{1}H NMR (400 MHz, CD_3OD) δ 8.11 (s, 1H), 7.95 (dd, *J* = 8.9, 1.6 Hz, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.51 (dd, *J* = 7.7, 1.4 Hz, 1H), 7.41 (dd, *J* = 7.8, 1.4 Hz, 1H), 7.31 (td, *J* = 7.5, 1.5 Hz, 1H), 7.27–7.21 (m, 1H), 5.46 (dd, *J* = 8.9, 5.9 Hz, 1H), 2.01–1.87 (m, 2H), 1.09 (t, *J* = 7.3 Hz, 3H). LCMS (ESI) *m/z* calcd for $[C_{17}H_{15}ClIN_3O + H]^+$ 440.0; found 440.2.

(R,E)-N-(2-fluorobenzylidene)-2-methylpropane-2-sulfinamide ***(53a).***



According to general method F using 2-fluorobenzaldehyde (10.0 g, 80.5 mmol), (*R*)-t-butylsulfinylamide (12.2 g, 100 mmol), flame-dried $CuSO_4$ (16 g, 100 mmol) and $MgSO_4$ (29 g, 240 mmol) in DCM (150 mL), **53a** was obtained as a clear pale yellow oil (11.3 g, 61%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.91 (s, 1H), 8.01 (dt, *J* = 7.6, 1.6 Hz, 1H), 7.48–7.54 (m, 1H), 7.23–7.27 (m, 1H), 7.14–7.19 (m, 1H), 1.28 (s, 9H).

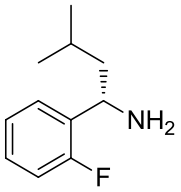
(R)-N-((S)-1-(2-fluorophenyl)-3-methylbutyl)-2-methylpropane-2-sulfinamide ***(54a).***



Isobutyl magnesium bromide (2.0 M in Et_2O, 8.25 mL, 16.5 mmol) was added carefully to stirred dimethylzinc (1.2 M in toluene, 15.6 mL, 18.7 mmol) at rt. Dry THF (30 mL) was added and the mixture was stirred at rt for 30 min before being added slowly, drop wise over 30 min to a stirred -78 °C solution of (*R*,*E*)-

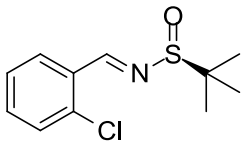
N-(2-fluorobenzylidene)-2-methylpropane-2-sulfinamide (2.5 g, 11 mmol) in dry THF (30 mL). Once the addition was complete the mixture was stirred at this temperature for 3 h. The reaction was quenched by addition of saturated aq NH_4Cl (50 mL). H_2O (200 mL) was added and the mixture was extracted with Et_2O (2 x 75 mL). The combined organic extracts were washed with brine (50 mL), dried (Na_2SO_4) and concentrated under reduced pressure to yield crude **54a** as clear yellow oil (3.05 g, 97%, 4:1 mixture of product and methylated by-product). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33–7.29 (m, 1H), 7.29–7.22 (m, 1H), 7.17–7.11 (m, 1H), 7.06–7.02 (m, 1H), 4.61–4.56 (m, 1H), 3.53 (m, 1H), 1.60–1.55 (m, 1H), 1.54–1.44 (m, 1H), 1.21 (s, 9H), 0.95–0.90 (m, 6H).

(S)-1-(2-fluorophenyl)-3-methylbutan-1-amine hydrochloride ***(55a-S).***



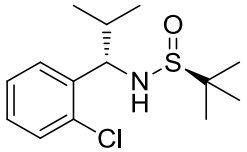
The deprotection of chiral auxiliary carried out by using HCl (2.0 M in Et_2O, 25 mL) and a solution of (*R*)-N-((*S*)-1-(2-fluorophenyl)-3-methylbutyl)-2-methylpropane-2-sulfinamide (3.05 g, 10.6 mmol) in MeOH (30 mL). After stirring at rt for 1 h, the reaction mixture was concentrated under reduced pressure to give a crude pale yellow solid (3.0 g). Purification by flash chromatography (C18, 5–80% MeOH in H_2O) gave **55a**-*S* as a white solid HCl salt (1.52 g, 64%, 97 %ee (*S*)). ^{1}H NMR (400 MHz, CD_3OD) δ 7.52–7.46 (m, 2H), 7.32 (t, J = 7.6 Hz, 1H), 7.26–7.22 (m, 1H), 4.66–4.62 (m, 1H), 1.98–1.93 (m, 1H), 1.86–1.79 (m, 1H), 1.47–1.37 (m, 1H), 0.98–1.93 (m, 6H). Chiral HPLC retention time, 6.89 min (S), 6.08 min (R); Daicel Chiralpak OD-H (250 mm × 4.6 mm); isocratic 3% ^{i}PrOH (0.5% Et_2NH) in n-heptane; 1 mL/min, λ = 254 nm.

(S,E)-N-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide ***(53b).***



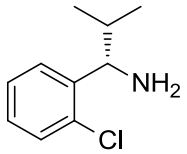
According to general method F using 2-chlorobenzaldehyde (20.9 g, 149 mmol), (*S*)-t-butylsulfinylamide (15.0 g, 124 mmol), **53b** was obtained as a clear pale yellow oil **(**26.9 g, 89%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 9.05 (s, 1H), 8.06 (d, J = 7.5 Hz, 1H), 7.48–7.39 (m, 2H), 7.38–7.31 (m, 1H), 1.28 (s, 9H).

(S)-N-((S)-1-(2-chlorophenyl)-2-methylpropyl)-2-methylpropane-2-sulfinamide ***(54b).***



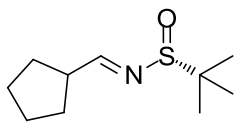
^{i}PrMgCl (2.0 M in THF, 46.2 mL, 92.3 mmol) was added carefully to stirred Me_2Zn (1.2 M in PhMe, 82 mL, 98.4 mmol) at rt. The resulting solution was stirred at rt for 30 min before being added dropwise, over 30 min, to a stirred -78 °C solution of (*S*,*E*)-*N*-(2-chlorobenzylidene)-2-methylpropane-2-sulfinamide(15.0 g, 61.5 mmol) in dry THF (350 mL). After the addition was complete the reaction mixture was stirred at -78 °C for 3 h before being quenched by careful addition of satd aq NH_4Cl (200 mL). The mixture was extracted with Et_2O (3 x 100 mL). The combined organic extracts were washed with brine (100 mL) and were dried (Na_2SO_4). The organic layer was concentrated under reduced pressure yielding the crude product **54b** (17.9 g, quantitative yield, 16:1 d.r. (S_S,*S*)-(S_S,*R*) as a white solid which was used without any further purification. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.38–7.15 (m, 4H), 4.46 (t, J = 8.0 Hz, 1H), 3.75 (br d, J = 8.0 Hz, 1H), 2.28–2.15 (m, 1H), 1.22 (s, 9H), 1.01 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H).

(S)-1-(2-chlorophenyl)-1-isopropylmethylamine hydrochloride ***(55b-S).***



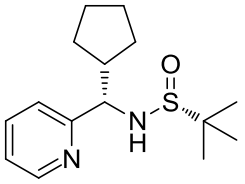
It was synthesized according to general method G utilizing HCl (2.0 M in Et_2O, 61.0 mL, 122.0 mmol) and a solution of (*S*)-N-((*S*)-1-(2-chlorophenyl)-2-methylpropyl)-2-methylpropane-2-sulfinamide (17.8 g, 61.0 mmol) in MeOH (175 mL). After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and Et_2O (250 mL) was added and a white precipitation formed. The precipitation was filtered off and washed with Et_2O (2 x 200 mL) and dried under reduced pressure yielding the crude (*S*)-1-(2-chlorophenyl)-1-isopropylmethylamine (11.8 g, 88.7% ee (*S*)) as a white solid. The crude product was recrystallised from ^{t}BuOMe (300 mL) and MeOH (48 mL) at 80 °C. After having cooled down over night only a small amount of crystals had been formed which were removed by filtration. The filtrate was concentrated under reduced pressure and after roughly half the volume had been removed a second crop of solids appeared which was also removed by filtration. The two crops of crystals were found to be racemic by chiral HPLC. The filtrate was concentrated to dryness and recrystallised again from ^{t}BuOMe (300 mL) and MeOH (33 mL) at 80 °C. Again only a small amount of crystals were formed as the solution cooled down which were removed by filtration, as was a second crop of solids formed when the solution was concentrated under reduced pressure. The remaining filtrate was concentrated to dryness and was suspended in ^{t}BuOMe (200 mL) and filtered off. The resulting white solid was washed with Et_2O (3 x 150 mL) and was dried under reduced pressure yielding **55b**-*S* (9.0 g, 67%, 97 %ee (*S*)) as a white solid. ^{1}H NMR (400 MHz, D_2O + NaOH) δ 7.59–7.41 (m, 4H), 4.60 (d, J = 9.5 Hz, 1H), 2.44–2.30 (m, 1H), 1.18 (d, J = 6.5 Hz, 3H), 0.85 (d, J = 6.5 Hz, 3H). HPLC: Daicel Chiralpak AD-H, 97:3 v/v heptane-EtOH (0.1% Et_3N), 1.0 mL/min, λ = 280 nm, R_t = 6.0 min (*S*), R_t = 7.3 min (*R*).

(R,E)-N-(Cyclopentylmethylene)-2-methylpropane-2-sulfinamide ***(56).***



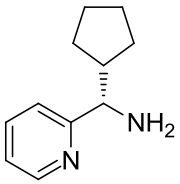
According to general method F using cyclopentanecarboxaldehyde (15.0 g, 152.8 mmol, 1.0 eq.), (*R*)-t-butylsulfinylamide (24.1 g, 198.7 mmol, 1.3 eq.) and flame-dried $CuSO_4$ (73.2 g, 458.5 mmol, 3.0 eq.), **56** was obtained as a pale yellow oil (23.8 g, 78%). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.99 (d, J = 5.5 Hz, 1H), 3.02–2.87 (m, 1H), 1.97–1.78 (m, 2H), 1.78–1.55 (m, 6H), 1.18 (s, 9H).

(R)-N-((S)-cyclopentyl(pyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide ***(57).***



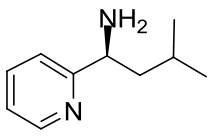
A solution of 2-bromopyridine (11.8 mL, 19.5 g, 123.5 mmolin dry THF (50 mL) was added carefully to ^{i}PrMgCl·LiCl (1.3 M in THF, 95.0 mL, 123.5 mmol). The resulting solution was stirred at rt for 3 h after which it was added dropwise, over 45 min, to a -48 °C solution of (*R*,*E*)-N-(cyclopentylmethylene)-2-methylpropane-2-sulfinamide (19.1 g, 95.0 mmol) in dry CH_2Cl_2 (250 mL). The resulting mixture was stirred at -48 °C for 1 h before being allowed to slowly warm up to rt over 16 h. The reaction was quenched by addition of saturated aq NH_4Cl (200 mL). H_2O (200 mL) was added and the mixture was extracted with CH_2Cl_2 (3 x 100 mL). The combined organic extracts were washed with brine (150 mL). The organic layer was dried (Na_2SO_4) and was concentrated under reduced pressure yielding the crude product (28.6 g, 5:1 d.r. (R_S,*S*)-(R_S,*R*)) as a clear red oil. The crude product was purified by repeated flash chromatography (5% MeOH in EtOAc) in combination with trituration of the obtained solids with cyclohexane which eventually gave **57** as a white solid (8.80 g, 33%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.56 (d, J = 4.5 Hz, 1H), 7.63 (dt, J = 1.0, 7.5 Hz, 1H), 7.22 (d, J = 7.5 Hz, 1H), 7.16 (dd, J = 4.5, 7.5 Hz, 1H), 4.26 (dd, J = 5.0, 8.5 Hz, 1H), 3.95 (d, J = 5.0 Hz, 1H), 2.44–2.31 (m, 1H), 1.94–1.83 (m, 1H), 1.68–1.44 (m, 5H), 1.44–1.32 (m, 1H), 1.30–1.17 (m, 1H), 1.13 (s, 9H).

(S)-1-(Cyclopentyl)-1-(2-pyridinyl)methylamine hydrochloride ***(55c-S).***

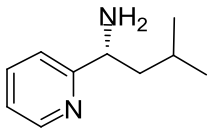


The HCl salt of **55c**-*S* was synthesized according to general method G using HCl (2.0 M in Et_2O, 31.4 mL, 62.8 mmol) and a solution of (R_S)-N-((*S*)-cyclopentyl(pyridin-2-yl)methyl)-2-methylpropane-2-sulfinamide (8.8 g, 31.4 mmol) in MeOH (100 mL). After the addition was complete the cooling bath was removed and the mixture was stirred at rt for 1 h. The reaction mixture was concentrated under reduced pressure and the residue was suspended in Et_2O (125 mL). The precipitation was filtered off and washed with Et_2O (2 x 125 mL) and dried under reduced pressure yielding the crude product (7.7 g, 95.0 %ee (*S*)) as a white solid. The crude product was recrystallised from ^{t}BuOMe (150 mL), EtOH (200 mL) and MeOH (170 mL) at 80 °C. The crystals formed after the solution cooled down were collected by filtration (3.3 g, 99.0 %ee (*S*)) and the filtrate was concentrated under reduced pressure and was recrystallised again from ^{t}BuOMe (100 mL) and MeOH (150 mL). The second crop of crystals was collected by filtration (1.3 g, resulting in a combined yield of 4.6 g, 69%, 98.0 %ee (*S*)). ^{1}H NMR (400 MHz, D_2O + NaOH) δ 8.81 (d, J = 5.5 Hz, 1H), 8.55 (t, J = 8.0 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 7.99 (t, J = 6.5 Hz, 1H), 4.53 (d, J = 10.5 Hz, 1H), 2.63–2.50 (m, 1H), 2.11–2.01 (m, 1H), 1.84–1.40 (m, 6H), 1.24–1.12 (m, 1H). The ee of the compound was determined by acetylating small samples with AcCl and analysing the products, (*S*)- and (*R*)-N-(Cyclopentyl(pyridin-2-yl)methyl)acetamides, by chiral HPLC: chiral HPLC retention time, 25.4 min (*S*), 9.5 min (*R*); Daicel Chiralpak AD-H (250 mm × 4.6 mm); isocratic 20% EtOH (0.5% Et_2NH) in n-heptane; 1 mL/min, λ = 254 nm.

(S)-3-Methyl-1-(pyridin-2-yl)butan-1-amine (L)-DBTA salt and (R)-3-Methyl-1-(pyridin-2-yl)butan-1-amine (D)-DBTA salt



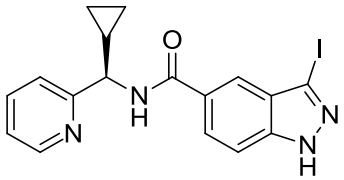
(L)-DBTA salt



(D)-DBTA salt

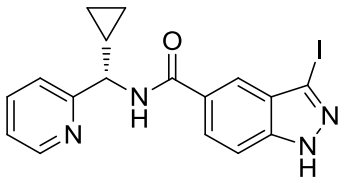
To a boiling solution of (-)-dibenzoyl-L-tartaric acid ((L)-DBTA, 11.0 g, 30.5 mmol) in MeOH (120 mL) with stirring was added a solution of racemic 3-methyl-1-(pyridin-2-yl)butan-1-amine (5.0 g, 30.5 mmol) in MeOH (30 mL) dropwise. After the addition, the resulting suspension was stirred for 5 min under reflux and cooled in air for about 5 min. The resulting precipitate was collected by vacuum filtration, washed with cold MeOH, air-dried and recrystallized from MeOH (300 mL) to give (L)-DBTA salt of (*S*)-3-methyl-1-(pyridin-2-yl)butan-1-amine as a white solid (3.54 g, 22%, 97 %ee). The two mother liquors were combined, concentrated to dryness and treated with 0.5 M aq NaOH to pH about 8. It was extracted with DCM (100 mL x 2), combined, dried and evaporated to give light brown oil which was redissoved in MeOH (30 mL). It was added slowly to a boiling solution of (D)-DBTA (8.25 g, 22.9 mmol) in MeOH (100 mL). After refluxing for 5 min, it was cooled to rt slowly. The resulting filtered cake was collected by suction filitration and crystallized by redissolving in boiling MeOH (200 mL) to give (D)-DBTA salt of (*R*)-3-methyl-1-(pyridin-2-yl)butan-1-amine as a white solid (2.25 g, 14%, 97 %ee). The ee of the compound was determined by acetylating small samples with acetyl chloride and analyzing the products by chiral HPLC: chiral HPLC retention time, 8.6 min (*S*), 6.4 min (*R*); Daicel Chiralpak AD-H (250 mm × 4.6 mm); isocratic 10% ^{i}PrOH (0.5% Et_2NH) in hexanes; 1 mL/min, $\lambda = 254$ nm.

(R)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide ***(32c-R).***



According to general method A2 using (*R*)-cyclopropyl(pyridin-2-yl)methanamine, **32c**-*R* was obtained as a light yellow solid (334 mg, 80%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.55–8.51 (m, 1H), 8.13-8.16 (m, 1H), 8.00–7.95 (m, 1H), 7.86–7.81 (m, 1H), 7.61–7.53 (m, 2H), 7.36–7.30 (m, 1H), 4.53–4.49 (m, 1H), 1.48–1.38 (m, 1H), 0.75–0.68 (m, 1H), 0.64–0.51 (m, 3H). LCMS (ESI) *m/z* calcd for $[C_{17}H_{15}INO_4 + H]^+$ 419.0; found 419.0.

(S)-2-cyclopropyl-N-(3-iodo-1H-indazol-5-yl)-2-(pyridin-2-yl)acetamide ***(32c-S).***



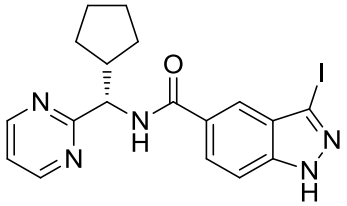
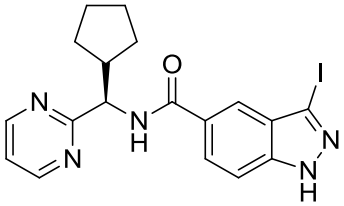
According to general method A2 using (*S*)-cyclopropyl(pyridin-2-yl)methanamine, **32c**-*S* was obtained as a yellow solid (874 mg, 77%) with ^{1}H NMR and LCMS as described for **32c**-*R*.

(S)-N-(cyclopentyl (pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32d-S)*** *and (R)-N-(cyclopentyl (pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide* ***(32d-R).***

Method 1: According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (3.31 g, 11.5 mmol) and (*S*)-cyclopentyl(pyridin-2-yl)methanamine dihydrochloride (2.85 g, 11.5 mmol), **32d**-*S* was obtained a beige solid (3.64 g, 71%) with ^{1}H NMR and LCMS as described for **32d**.

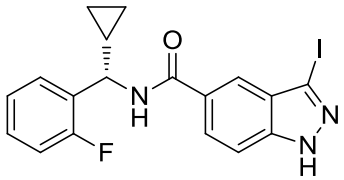
Method 2: Prepared by separating racemic compounds using preparative, chiral supercritical fluid chromatography (SFC). Preparative HPLC method: AD-H (2 x 15 cm); 25% EtOH(0.1% Et_2NH) in CO_2, 100 bar; 65 mL/min, λ = 220 nm. Using N-(cyclopentyl(pyridin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (7.9 g, 18 mmol), **32d**-*S* and **32d**-*R* were both obtained as a yellow solid (3.6 g, 46%, > 99 %ee for *S*; 3.5 g, 44%, > 99 %ee for *R*). LCMS (ESI) *m/z* calcd for $[C_{19}H_{19}IN_4O + H]^+$ 447.1; found 447.1 (both). Chiral HPLC retention time, 2.14 min (*S*) and 1.36 min (*R*); Daicel Chiralpak AD-H (25 x 0.46 cm); isocratic 40% EtOH (Et_2NH) in CO_2; 3 mL/min, λ = 254 nm.

(S)-N-(cyclopentyl (pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32e-S)*** *and (R)-N-(cyclopentyl (pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide* ***(32e-R).***

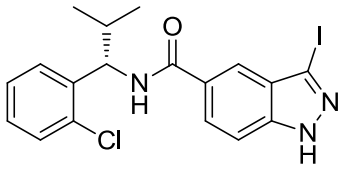
Prepared by separating racemic compounds using preparative, chiral supercritical fluid chromatography (SFC). Preparative HPLC method: AD-H (2 x 25 cm); 30% EtOH (0.1% Et_2NH) in CO_2, 100 bar; 65 mL/min, λ = 220 nm. Using N-(cyclopentyl(pyrimidin-2-yl)methyl)-3-iodo-1H-indazole-5-carboxamide (1.1 g, 2.4 mmol), **32e**-*S* and **32e**-*R* were both obtained as a yellow solid (475 mg, 45%, > 99 %ee for *S*; 468 mg, 44%, > 99 %ee for *R*). LCMS (ESI) *m/z* calcd for $[C_{18}H_{18}IN_5O+H]^+$ 448.1; found 448.4 (*S*) and 448.1 (*R*). Chiral HPLC retention time, 2.09 min (*S*) and 2.95 min (*R*); Daicel Chiralpak AD-H (25 x 0.46 cm); isocratic 40% EtOH (Et_2NH) in CO_2; 3 mL/min, λ = 254 nm.

(S)-N-(cyclopropyl(2-fluorophenyl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32g-S).***



According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (358 mg, 1.23 mmol), (*S*)-cyclopropyl(2-fluorophenyl) methanamine hydrochloride (250 mg, 1.23 mmol), BOP-Cl (576 mg, 1.3 mmol), DIPEA (1.08 mL, 6.19 mmol) and DMF (5 mL), **32g**-*S* was obtained as an off-white solid (405 mg, 75%). ^{1}H NMR (400 MHz, CD_3OD) δ 8.08 (s, 1 H), 7.95 (dd, *J* = 8.8, 1.6 Hz, 1H), 7.58–7.56 (m, 2H), 7.31–7.26 (m, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 7.09 (t, *J* = 10.0 Hz, 1H), 4.76 (d, *J* = 9.2 Hz, 1H), 1.50–1.41 (m, 1H), 0.72–0.66 (m, 1H), 0.62–0.58 (m, 1H), 0.56–0.50 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{15}FIN_3O + H]^+$ 436.0; found 436.2.

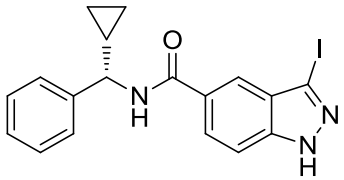
(S)-N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide ***(32h-S).***



Method 1: According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (10.08 g, 35 mmol) and (*S*)-1-(2-chlorophenyl)-2-methylpropan-1-amine hydrochloride (7.70 g, 35 mmol), **32h**-*S* was obtained as a beige solid (12.56 g, 79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.76 (s, 1H), 8.91 (d, J = 8.8 Hz, 1H), 7.91 (d, J = 9.2 Hz, 1H), 7.74–7.66 (m, 1H), 7.59 (d, J = 8.8 Hz, 1H), 7.46–7.22 (m, 4H), 5.27 (t, J = 9.2 Hz, 1H), 2.20–2.15 (m, 1H), 1.08 (d, J = 6.0 Hz, 3H), 0.79 (d, J = 6.8 Hz, 3H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{17}ClIN_3O + H]^+$ 454.0; found 454.0.

Method 2: Prepared by separating racemic compounds using preparative, chiral supercritical fluid chromatography (SFC). Preparative HPLC method: IC (2 x 15 cm); 30% ^{i}PrOH in CO_2, 100 bar; 65 mL/min, λ = 220 nm. Using N-(1-(2-chlorophenyl)-2-methylpropyl)-3-iodo-1H-indazole-5-carboxamide (1.0 g, 2.2 mmol), **32h**-*S* was obtained as a yellow solid (454 mg, 46%, > 99 %ee). LCMS (ESI) *m/z* calcd for $[C_{18}H_{17}ClIN_3O + H]^+$ 454.0; found 454.0. Chiral HPLC retention time, 4.57 min (*S*) and 6.32 min (*R*); Daicel Chiralpak IC (15 x 0.46 cm); isocratic 30% EtOH (Et_2NH) in CO_2; 3 mL/min, λ = 254 nm.

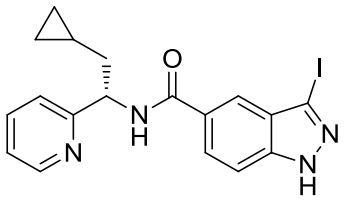
(S)-N-(cyclopropyl(phenyl)methyl)-3-iodo-1H-indazole-5-carboxamide ***(32i-S).***



According to general method A2 using 3-iodo-1H-indazole-5-carboxylic acid (79 mg, 0.79 mmol), (*S*)-cyclopropyl(phenyl)methanamine hydrochloride (50 mg, 0.27 mmol), TBTU (87 mg, 0.27 mmol), DIPEA (0.14 mL, 0.81 mmol) and DMF (4 mL), **32i**-*S* was obtained as an orange solid (110 mg, 98%). ^{1}H NMR (400 MHz,

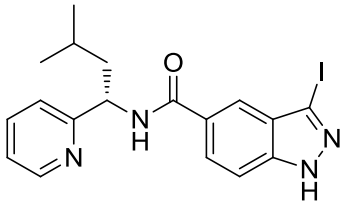
CD_3OD) δ 8.09 (s, 1 H), 7.95 (dd, J = 8.9, 1.6 Hz, 1H), 7.56 (d, J = 8.8 Hz, 1 H), 7.50–7.43 (m, 2H), 7.33 (t, J = 7.6 Hz, 2H), 7.24 (t, J = 7.3 Hz, 1H), 4.46 (d, J = 9.5 Hz, 1H), 1.46–1.34 (m, 1H), 0.66 (d, J = 8.0 Hz, 2H), 0.48 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{16}IN_3O + H]^+$ 418.0; found 418.1.

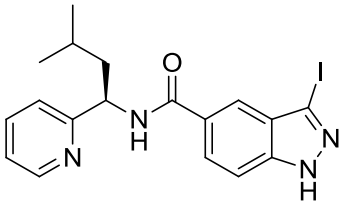
(S)-N-(2-cyclopropyl-1-(pyridin-2-yl)ethyl)-3-iodo-1H-indazole-5-carboxamide ***(32j-S).***



According to general method A2 using (*S*)-2-cyclopropyl-1-(pyridin-2-yl)ethanamine hydrochloride (1.99 g, 10 mmol) and 3-iodo-1H-indazole-5-carboxylic acid (2.88 g, 10 mmol), **32j**-*S* was obtained as an off white solid (3.346 g, 77%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.71 (s, 1H), 8.97 (d, J = 8.0 Hz, 1H), 8.51 (d, J = 4.4 Hz, 1H), 8.14 (s, 1H), 7.98 (d, J = 8.8 Hz, 1H), 7.75 (t, J = 7.6 Hz, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.42 (d, J = 8.0 Hz, 1H), 7.27–7.21 (m, 1H), 5.27–5.17 (m, 1H), 1.97–1.85 (m, 1H), 1.78–1.69 (m, 1H), 0.85–0.73 (m, 1H), 0.47–0.31 (m, 2H), 0.25–0.16 (m, 1H), 0.07–-0.02 (m, 1H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{17}IN_4O + H]^+$ 433.3; found 433.1.

(S)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide ***(32k-S)*** *and (R)-3-iodo-N-(3-methyl-1-(pyridin-2-yl)butyl)-1H-indazole-5-carboxamide* ***(32k-R).***

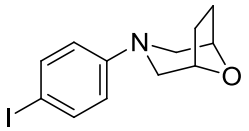




To a suspension of (*S*)-3-methyl-1-(pyridin-2-yl)butan-1-amine (L)-DBTA salt (3.54 g, 6.8 mmol) in MeOH (15 mL) was added 0.5 M aq NaOH slowly until pH about 9. It was extracted with DCM and evaporated. According to general method A2, the crude (*S*)-3-methyl-1-(pyridin-2-yl)butan-1-amine obtained was coupled with 3-iodo-

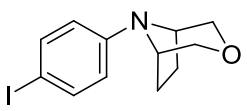
1H-indazole-5-carboxylic acid (1.87 g, 6.5 mmol) to give **32k**-*R* as a beige solid (2.27 g, 79%). Using the similar method used for **32k**-*R*, **32k**-*S* was obtained as a yellow solid (1.21 g, 80%) by using (*R*)-3-methyl-1-(pyridin-2-yl)butan-1-amine (D)-DBTA salt (1.90 g, 3.5 mmol) and 3-iodo-1H-indazole-5-carboxylic acid (1.008 g, 3.5 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 13.69 (s, 1H), 8.94 (d, J = 8.4 Hz, 1H), 8.53–8.50 (m, 1H), 8.14–8.12 (m, 1H), 7.98 (dd, J = 8.8, 1.6 Hz, 1H), 7.75 (dd, J = 7.6, 2.0 Hz, 1H), 7.59 (d, J = 8.8, Hz, 1H), 7.43 (d, J = 8.0 Hz, 1H), 7.27–7.22 (m, 1H), 5.26–5.16 (m, 1H), 1.91–1.83 (m, 1H), 1.76–1.65 (m, 2H), 0.95 (d, J = 6.8 Hz, 3H), 0.93 (d, J = 6.4 Hz, 3H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{19}IN_4O + H]^+$ 435.1; found 435.1 (both).

3-(4-iodophenyl)-8-oxa-3-azabicyclo[3.2.1]octane



According to the general method C using 8-oxa-3-azabicyclo [3.2.1] octane HCl salt (100 mg, 0.66 mmol), 1,4-diiodobenzene (330 mg, 1.0 mmol), K_3PO_4 (567 mg, 2.67 mmol), BINOL (38 mg, 0.13 mmol), CuI (26 mg, 0.13 mmol) and DMF (6 mL) at 24 °C for 48 h, 3-(4-iodophenyl)-8-oxa-3-azabicyclo[3.2.1]octane was obtained as a white solid (95 mg, 45%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.51 (d, J = 8.3 Hz, 2H), 6.58 (d, J = 8.3 Hz, 2H), 4.49 (br s, 2H), 3.28 (d, J = 11.3 Hz, 2H), 3.00 (d, J = 11.3 Hz, 2H), 2.05–1.84 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{14}INO+H]^+$ 316.0; found 316.0.

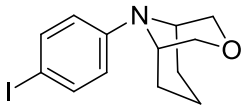
8-(4-iodophenyl)-3-oxa-8-azabicyclo[3.2.1]octane **(59a)**.



According to general method C using 1,4-diiodobenzene (6.6 g, 20 mmol) and 3-oxa-8-azabicyclo[3.2.1]octane hydrochloride (3.0 g, 20 mmol), **59a** was obtained as a white solid (1.48 g, 23%). ^{1}H NMR (400 MHz, $CDCl_3$) δ

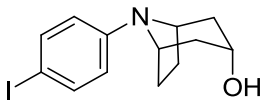
7.53–7.46 (m, 2H), 6.60–6.52 (m, 2H), 4.03–3.98 (m, 2H), 3.88 (d, *J* = 10.8 Hz, 2H), 3.51 (dt, *J* = 11.5, 1.1 Hz, 2H), 2.12–1.95 (m, 4H). LCMS (ESI) *m/z* calcd for $[C_{12}H_{14}INO + H]^+$ 316.0; found 316.2.

*9-(4-iodophenyl)-3-oxa-9-azabicyclo[3.3.1]nonane **(59b)***.



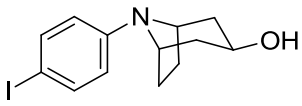
According to general method C using 1,4-diiodobenzene (7.80 g, 23.6 mmol) and 3-oxa-9-azabicyclo[3.3.1]nonane hydrochloride (3.85 g, 23.6 mmol), **59b** was obtained as a brown solid (650 mg, 8%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.49 (d, *J* = 9.0 Hz, 2H), 6.58 (d, *J* = 9.3 Hz, 2H), 4.04–3.92 (m, 4H), 3.70 (br s, 2H), 2.68–2.52 (m, 1H), 2.04–1.92 (m, 2H), 1.75–1.64 (m, 2H), 1.59 (dt, *J* = 12.8, 6.1 Hz, 1H). LCMS (ESI) *m/z* calcd for $[C_{13}H_{16}INO + H]^+$ 330.0; found 330.1.

*endo-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol **(59c)***.



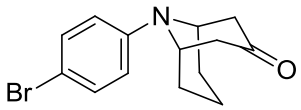
According to general method C using nortropine (2.0 g, 15.7 mmol) and 1,4-diiodobenzene (7.78 g, 23.5 mmol), K_3PO_4 (10 g, 47 mmol) at 45°C for 18 h, **59c**-*endo* was obtained as a light pink solid (2.26 g, 44%).^{1}H NMR (400 MHz, $CDCl_3$) δ 7.48–7.45 (m, 2H), 6.55–6.52 (m, 2H), 4.14 (br s, 2H), 4.01 (br m, 1H), 2.34–2.29 (m, 2H), 2.23–2.17 (m, 2H), 2.07–2.05 (m, 2H), 1.60–1.56 (m, 2H), 1.42 (d, *J* = 2.4 Hz, 1H). LCMS (ESI) *m/z* calcd for $[C_{13}H_{16}INO+H]^+$ 330.0; found 330.0.

*exo-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol **(59d)***.



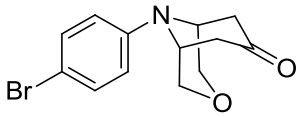
According to general method C using exo-8-azabicyclo[3.2.1]octan-3-ol hydrochloride (3.27 g, 20 mmol) and 1,4-diiodobenzene (6.60 g, 20 mmol), **59d** was obtained as a yellow solid (2.36 g, 36%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.52–7.47 (m, 2H), 6.60–6.56 (m, 2H), 4.25-4.21 (m, 2H), 4.17 (tt, J = 11.0, 5.8 Hz, 1H), 2.11–2.04 (m, 2H), 1.88–1.82 (m, 2H), 1.81–1.73 (m, 2H), 1.69–1.61 (m, 2H), 1.18 (d, J = 6.4 Hz, 1H). LCMS (ESI) *m/z* calcd for $[C_{13}H_{16}INO + H]^+$ 330.2; found 330.0.

*9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one (**62e**).*



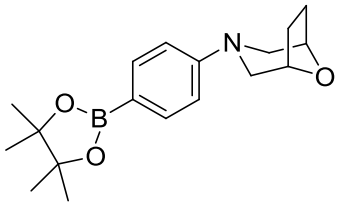
According to general method D using glutaraldehyde (50% wt in H_2O, 20 mL, 110 mmol), 3-oxopentanedioic acid (16.8 g, 115 mmol), 4-bromoaniline (17.2 g, 100 mmol), **62e** was obtained upon filtration as a brown solid (2.97 g, 10%, together with 6.2 g of crude brown oil which was used directly for reduction without further purification). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.37 (d, J = 8.8 Hz, 2H), 6.85 (d, J = 9.2 Hz, 2H), 4.45–4.38 (m, 2H), 2.65 (dd, J = 16.4, 6.4 Hz, 2H), 2.41 (d, J = 16.4 Hz, 2H), 2.02–1.90 (m, 2H), 1.80–1.73 (m, 2H), 1.70–1.61 (m, 2H). LCMS (ESI) *m/z* calcd for $[C_{14}H_{16}BrNO + H]^+$ 294.0; found 294.0.

*9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-one **(62f)**.*



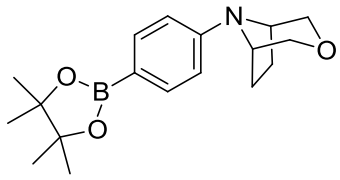
According to general method D using 2-(2,2-diethoxyethoxy)-1,1-diethoxyethane (5.00 g, 20 mmol), 3-oxopentanedioic acid (1.61 g, 22 mmol) and 4-bromoaniline (3.44 g, 20 mmol), **62f** was obtained as a light brown solid (0.88 g, 15%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.42 (d, J = 9.2 Hz, 2H), 6.83 (d, J = 9.2 Hz, 2H), 4.19 (d, J = 5.6 Hz, 2H), 3.94 (d, J = 11.2 Hz, 2H), 3.88 (d, J = 11.2 Hz, 2H), 2.59 (dd, J = 15.6, 5.6 Hz, 2H), 2.48 (d, J = 15.2 Hz, 2H). LCMS (ESI) *m/z* calcd for $[C_{13}H_{14}BrNO_2 + H]^+$ 296.0; found 296.0.

3-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-oxa-3-azabicyclo[3.2.1]-octane.



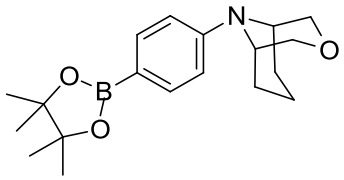
According to the general method E using 8-(4-iodophenyl)-3-oxa-8-azabicyclo[3.2.1]octane (95 mg, 0.30 mmol), bis (pinacolato)diboron (115 mg, 0.45 mmol), KOAc (89 mg, 0.90 mmol), $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (24 mg, 0.029 mmol) and DMF (3 mL), the title compound was obtained as a white solid (58 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.49 (br s, 2H), 3.41 (d, J = 11.3 Hz, 2H), 3.07 (s, 2H), 1.93 (br s, 4H), 1.36–1.31 (m, 12H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{26}BNO_3 + H]^+$ 316.2; found 316.2.

*8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-8-azabicyclo[3.2.1]octane (**60a**).*



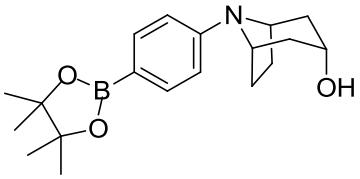
According to general method E using 3-(4-iodophenyl)-8-oxa-3-azabicyclo[3.2.1]octane (95 mg, 0.30 mmol), B_2pin_2 (115 mg, 0.45 mmol) and $Pd(dppf)Cl_2{\cdot}CH_2Cl_2$ (24 mg, 0.029 mmol), **60b** was obtained as a white solid (58 mg, 61%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.5 Hz, 2H), 6.79 (d, J = 8.5 Hz, 2H), 4.49 (br s, 2H), 3.41 (d, J = 11.3 Hz, 2H), 3.07 (s, 2H), 1.93 (br s, 4H), 1.36–1.31 (m, 12H). LCMS (ESI) *m/z* calcd for $[C_{18}H_{26}BNO_3 + H]^+$ 316.2; found 316.2.

*9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonane (**60b**).*



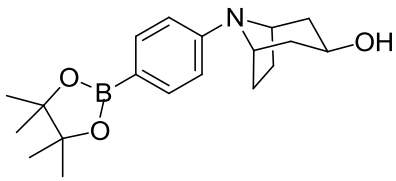
According to general method E using 9-(4-iodophenyl)-3-oxa-9-azabicyclo[3.3.1]nonane (650 mg, 1.97 mmol), **60b** was obtained as an off-white solid (284 mg, 44%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.71 (d, J = 8.8 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 4.04–3.93 (m, 4H), 3.84 (br s, 2H), 2.68–2.54 (m, 1H), 2.06–1.93 (m, 2H), 1.71 (dd, J = 13.2, 5.4 Hz, 2H), 1.62–1.55 (m, 1H), 1.33 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{19}H_{28}BNO_3+H]^+$ 330.2; found 330.2.

*endo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (**60c**).*



According to general method E using endo-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol (6.58 g, 20 mmol) and HBpin (8.7 ml, 60 mmol), **60c** was obtained as a light purplish white solid (6.70 g, 100%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (d, J = 8.4 Hz, 2H), 6.74 (d, J = 8.8 Hz, 2H), 4.28–4.23 (m, 2H), 4.03–3.97 (m, 1H), 2.36–2.28 (m, 2H), 2.27–2.19 (m, 2H), 2.11–2.05 (m, 2H), 1.60 (d, J = 14.8 Hz, 2H), 1.33 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{19}H_{28}BNO_3 + H]^+$ 330.2; found 330.1.

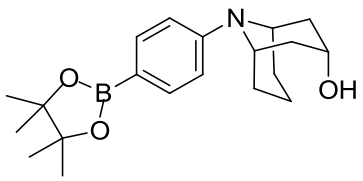
*exo-8-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-8-azabicyclo[3.2.1]octan-3-ol (**60d**).*



According to general method E using exo-8-(4-iodophenyl)-8-azabicyclo[3.2.1]octan-3-ol (2.35 g, 7 mmol) and HBpin (3.05 ml, 21 mmol), **60d** was obtained as an off white solid (2.05 g, 87%). ^{1}H NMR (400 MHz, $CDCl_3$)

δ 7.70 (d, J = 8.4 Hz, 2H), 6.77 (d, J = 8.4 Hz, 2H), 4.36–4.31 (m, 2H), 4.22–4.11 (m, 1H), 2.11–2.04 (m, 2H), 1.91–1.83 (m, 2H), 1.80–1.74 (m, 2H), 1.70–1.61 (m, 2H), 1.34 (s, 12H), 1.13 (d, J = 6.4 Hz, 1H, OH). LCMS (ESI) *m/z* calcd for $[C_{19}H_{28}BNO_3 + H]^+$ 330.2; found 330.1.

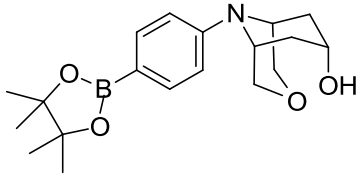
*endo-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-9-azabicyclo[3.3.1]nonan-3-ol (**60e**).*



To a solution of 9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-one (6.2 g, crude) in DCM (100 mL) and MeOH (60 mL) at 0 ^oC was added $NaBH_4$ (5.7 g, 15 mmol). The resulting mixture was stirred at 0 ^oC for 10 min, then rt for 30 min. After aqueous workup, the residue was purified by flash chromatography (0–10% EtOAc in DCM) to give endo-9-(4-bromophenyl)-9-azabicyclo[3.3.1]nonan-3-ol **63e** as brown solid (1.30 g). LCMS (ESI) *m/z* calcd for $[C_{14}H_{18}BrNO + H]^+$ 296.1; found 295.9.

According to general method E using **63e** (1.30 g, 4.4 mmol) and HBpin (1.9 mL), **60e** was obtained as a beige solid (727 mg, 10% over 2 steps). ^1H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, J = 8.8 Hz, 2H), 6.82 (d, J = 8.8 Hz, 2H), 4.36–4.27 (m, 2H), 3.85-3.75 (m, 1H), 2.48–2.38 (m, 2H), 1.83–1.73 (m, 2H), 1.63–1.43 (m, 6H), 1.33 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{20}H_{30}BNO_3 + H]^+$ 344.2; found 344.1.

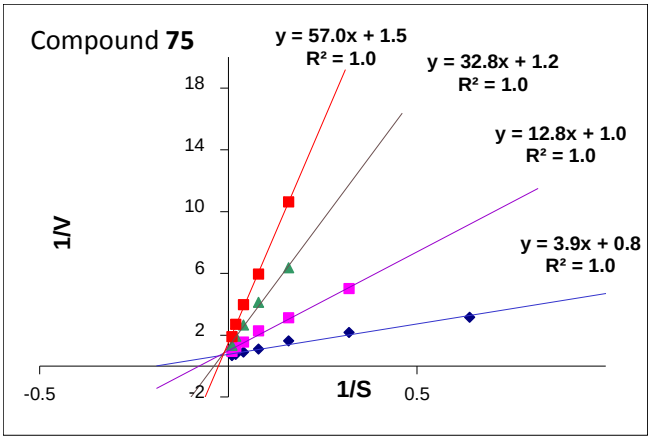
*endo-9-(4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)phenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol (**60f**).*



To a solution of 9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-one (0.98 g, 3.34 mmol) in THF (20 mL) and MeOH (0.5 mL) at 0 °C was added $NaBH_4$ (380 mL, 10 mmol). The resulting mixture was heated at

50 °C for 30 min. After cooling to rt, it was diluted with H_2O and extracted with DCM to give endo-9-(4-bromophenyl)-3-oxa-9-azabicyclo[3.3.1]nonan-7-ol **63f** as greenish yellow solid. LCMS (ESI) *m/z* calcd for $[C_{13}H_{16}BrNO_2 + H]^+$ 298.0; found 298.0.

According to general method E using **63f** and HBpin (1.45 mL, 10 mmol), **60f** was obtained as an off white solid (336 mg, 29% over 2 steps). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (d, J = 8.4 Hz, 2H), 6.79 (d, J = 8.8 Hz, 2H), 5.65 (d, J = 12.4 Hz, 1H), 4.02–3.92 (m, 6H), 2.32–2.24 (m, 2H), 1.78 (d, J = 14.8 Hz, 2H), 1.34 (s, 12H). LCMS (ESI) *m/z* calcd for $[C_{19}H_{28}BNO_4 + H]^+$ 346.2; found 346.1.



[Compound **75**] nM	0	2.2	6.6	11
V_{max}	1.57	1.25	1.02	0.77
Km_{App} (μM)	8.42	20.9	41.1	48.8
R^2	1.0	1.0	1.0	1.0

Figure S1. Left panel: Double Reciprocal plot of compound **75** inhibition of TTK. Red squares indicate no inhibitor; green triangles, 2.2 nM; pink squares, 6.6 nM & blue diamonds 11 nM. Right panel: Tabulation of V_{max} and Km_{App} indicates compound **75** is competitive with ATP (K_i = 0.7 $\pm$ 0.5 nM) but kinetics show some mixed behavior i.e. variable V_{max}.

Table S1. % Inhibition of 278 Kinase Panel by **75** at 1.0 μM (Millipore Radiometric Assay)

Kinase	% Inhib.	Kinase	% Inhib.	Kinase	% Inhib.
Abl(h)	3	cKit(D816H)(h)	24	HIPK2(h)	-1
Abl(m)	0	cKit(V560G)(h)	48	HIPK3(h)	-16
Abl (H396P) (h)	-9	cKit(V654A)(h)	3	IGF-1R(h)	-2
Abl (M351T)(h)	-5	CSK(h)	-5	IGF-1R(h), activated	-12
Abl (Q252H) (h)	-9	c-RAF(h)	-1	IKKα(h)	-4
Abl(T315I)(h)	-3	cSRC(h)	-11	IKKβ(h)	-11
Abl(Y253F)(h)	-11	DAPK1(h)	1	IR(h)	-4
ACK1(h)	-2	DAPK2(h)	-2	IR(h), activated	-6
ALK(h)	6	DCAMKL2(h)	11	IRR(h)	3
ALK4(h)	7	DDR2(h)	-9	IRAK1(h)	9
Arg(h)	0	DMPK(h)	-8	IRAK4(h)	-6
AMPKα1(h)	17	DRAK1(h)	72	Itk(h)	9
AMPKα2(h)	6	DYRK2(h)	1	JAK2(h)	-18
Arg(m)	-14	eEF-2K(h)	1	JAK3(h)	56
ARK5(h)	8	EGFR(h)	-8	JNK1α1(h)	26
ASK1(h)	-8	EGFR(L858R)(h)	0	JNK2α2(h)	21
Aurora-A(h)	56	EGFR(L861Q)(h)	-9	JNK3(h)	90
Aurora-B(h)	75	EGFR(T790M)(h)	0	KDR(h)	19
Aurora-C(h)	39	EGFR(T790M,L858R)(h)	0	Lck(h)	2
Axl(h)	31	EphA1(h)	2	Lck(h) activated	15
Blk(h)	16	EphA2(h)	-5	LIMK1(h)	2
Blk(m)	9	EphA3(h)	5	LKB1(h)	0
Bmx(h)	1	EphA4(h)	8	LOK(h)	-11
BRK(h)	-12	EphA5(h)	1	Lyn(h)	6
BrSK1(h)	-5	EphA7(h)	5	Lyn(m)	0
BrSK2(h)	-2	EphA8(h)	0	MAPK1(h)	75
BTK(h)	-1	EphB2(h)	-9	MAPK2(h)	90
BTK(R28H)(h)	5	EphB1(h)	-14	MAPK2(m)	90
CaMKI(h)	-13	EphB3(h)	-3	MAPKAP-K2(h)	-11
CaMKIIβ(h)	-3	EphB4(h)	-2	MAPKAP-K3(h)	-11
CaMKIIγ(h)	-5	ErbB4(h)	-2	MEK1(h)	41
CaMKIδ(h)	2	FAK(h)	5	MARK1(h)	7
CaMKIIδ(h)	-2	Fer(h)	-2	MELK(h)	80
CaMKIV(h)	1	Fes(h)	-3	Mer(h)	16
CDK1/cyclinB(h)	25	FGFR1(h)	5	Met(h)	20
CDK2/cyclinA(h)	6	FGFR1(V561M)(h)	6	Met(D1246H)(h)	17
CDK2/cyclinE(h)	6	FGFR2(h)	8	Met(D1246N)(h)	1
CDK3/cyclinE(h)	9	FGFR2(N549H)(h)	10	Met(M1268T)(h)	20
CDK5/p25(h)	16	FGFR3(h)	21	Met(Y1248C)(h)	23
CDK5/p35(h)	5	FGFR4(h)	4	Met(Y1248D)(h)	18
CDK6/cyclinD3(h)	6	Fgr(h)	11	Met(Y1248H)(h)	11
CDK7/cyclinH/MAT1(h)	65	Flt1(h)	12	MINK(h)	9
CDK9/cyclin T1(h)	-7	Flt3(D835Y)(h)	66	MKK4(m)	-20
CHK1(h)	10	Flt3(h)	10	MKK6(h)	21
CHK2(h)	19	Flt4(h)	35	MKK7β(h)	30
CHK2(I157T)(h)	1	Fms(h)	29	MLCK(h)	4
CHK2(R145W)(h)	2	Fms(Y969C)(h)	42	MLK1(h)	33
CK1γ1(h)	27	Fyn(h)	-1	Mnk2(h)	27
CK1γ2(h)	53	GCK(h)	14	MRCKα(h)	3
CK1γ3(h)	22	GRK5(h)	0	MRCKβ(h)	0
CK1δ(h)	-7	GRK6(h)	-2	MSK1(h)	1
CK1(y)	66	GRK7(h)	-7	MSK2(h)	12
CK2(h)	-2	GSK3α(h)	-6	MSSK1(h)	21
CK2α2(h)	2	GSK3β(h)	10	MST1(h)	-6
CLK2(h)	30	Haspin(h)	7	MST2(h)	2
CLK3(h)	5	Hck(h)	-2	MST3(h)	6
cKit(h)	-4	Hck(h) activated	-3	mTOR(h)	-3
cKit(D816V)(h)	0	HIPK1(h)	-9	mTOR/FKBP12(h)	-4

MuSK(h)	53	PKCη(h)	-18	SGK(h)	16
NEK2(h)	-17	PKCι(h)	-3	SGK2(h)	8
NEK3(h)	-3	PKCμ(h)	74	SGK3(h)	-11
NEK6(h)	-10	PKCθ(h)	8	SIK(h)	-4
NEK7(h)	-6	PKCζ(h)	-8	Snk(h)	-7
NEK11(h)	-1	PKD2(h)	3	Src(1-530)(h)	6
NLK(h)	2	PKG1α(h)	-4	Src(T341M)(h)	36
p70S6K(h)	26	PKG1β(h)	-5	SRPK1(h)	-3
NEK2(h)	-17	Plk1(h)	0	SRPK2(h)	-6
PAK2(h)	-4	Plk3(h)	-5	STK33(h)	6
PAK4(h)	-2	PRAK(h)	14	Syk(h)	-6
PAK5(h)	4	PRK2(h)	39	TAK1(h)	1
PAK6(h)	2	PrKX(h)	12	TAO1(h)	4
PAR-1Bα(h)	18	PTK5(h)	-4	TAO2(h)	-1
PASK(h)	-2	Pyk2(h)	17	TAO3(h)	11
PEK(h)	0	Ret(h)	26	TBK1(h)	67
PDGFRα(h)	-1	Ret (V804L)(h)	79	Tec(h) activated	9
PDGFRα(D842V)(h)	9	Ret(V804M)(h)	79	TGFBR1(h)	-3
PDGFRα(V561D)(h)	-1	RIPK2(h)	-1	Tie2 (h)	26
PDGFRβ(h)	6	ROCK-I(h)	4	Tie2(R849W)(h)	-5
PDK1(h)	40	ROCK-II(h)	50	Tie2(Y897S)(h)	-5
PhKγ2(h)	2	ROCK-II(r)	56	TLK2(h)	-4
Pim-1(h)	30	Ron(h)	3	TrkA(h)	-16
Pim-2(h)	4	Ros(h)	-13	TrkB(h)	24
Pim-3(h)	-17	Rse(h)	-3	TSSK1(h)	62
PKA(h)	-10	Rsk1(h)	20	TSSK2(h)	-12
PKBα(h)	-4	Rsk1(r)	13	Txk(h)	6
PKBβ(h)	-1	Rsk2(h)	15	ULK2(h)	34
PKBγ(h)	-3	Rsk3(h)	24	ULK3(h)	28
PKCα(h)	-12	Rsk4(h)	11	WNK2(h)	-7
PKCβI(h)	-11	SAPK2a(h)	0	WNK3(h)	3
PKCβII(h)	1	SAPK2a(T106M)(h)	62	VRK2(h)	6
PKCγ(h)	-4	SAPK2b(h)	66	Yes(h)	1
PKCδ(h)	1	SAPK3(h)	29	ZAP-70(h)	-9
PKCε(h)	-8	SAPK4(h)	44	ZIPK(h)	4

Table S2. TTK-Compound **51** Co-complex Crystallographic Data and Refinement Statistics

Data Collection			*Refinement and Statistics*	
Resolution, (Å)	2.38 (2.47-2.38)*		R_{cryst}, (%)	20.97
Space group	C2		R_{free}, (%)	24.99
a, (Å)	153.2		CC(1/2)	0.999 (0.896)*
b, (Å)	70.3		RMSD from idea geometry:	
c, (Å)	106.9		Bond lengths, (Å)	0.009
β, (°)	133.1		Bond angles, (°)	1.268
Molecules per asymmetric unit	2		Numbers of atoms:	
Unique reflections	33,447		Protein (non-hydrogen)	4,269
Multiplicity	6.7 (6.6)*		Water oxygen atoms	67
Average I/σ(I)	14.5 (2.0)*		Ligand atoms	72
R_{merge}, (%)	6.56 (50.8)*		PDB ID	4O6L
Completeness, (%)	99.3 (98.2)*			

*Outershell data in brackets

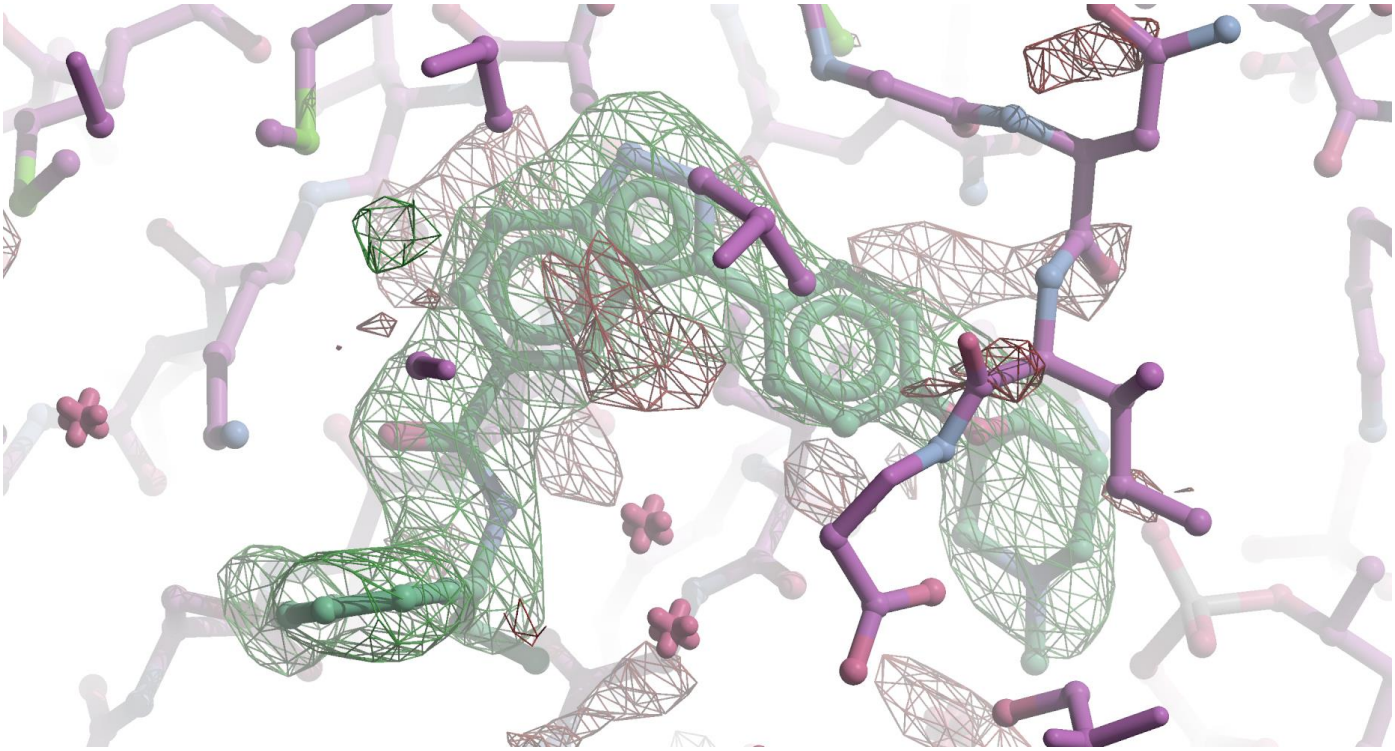


Figure S2. Omit map for TTK-Compound **51** Co-complex contoured at 3σ and shown in green

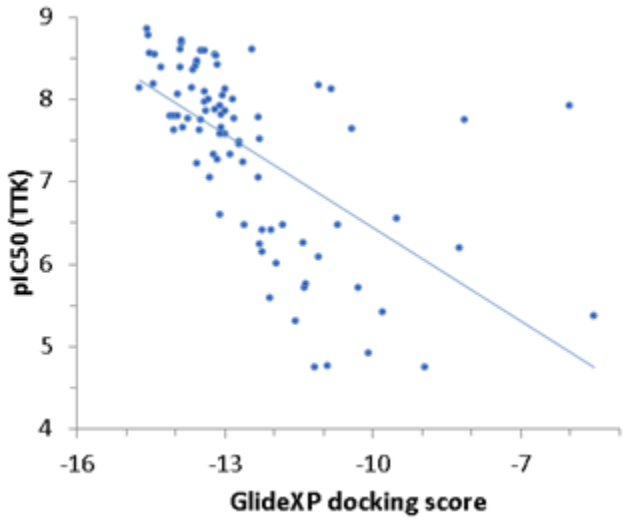


Figure S3. Predictive model using the 4O6L x-ray structure: pIC_{50} (TTK) vs GlideXP docking scores wherein the best GlideXP score (from docking multiple conformers) is selected as the docked structure. (R^2=0.37, rmse=0.86, n=86). Compounds from this work and Laufer, R.; Ng, G.; Liu, Y.; Patel, N. K.; Edwards, L.; Lang, Y.; Li, S.-W.; Feher, M.; Awrey, D.; Leung, G.; Beletskaya, I.; Plotnikova, O.; Mason, J.; Hodgson, R.; Wei, X. Mao, G; Luo, X.; Huang, P.; Green, E.; Kiarash, R.; Lin, D. C.-C.; Harris-Brandts, M.; Nadeem, V.; Mak, T. W.; Pan, J. G.; Qui, W.; Chirgadze, N.Y.; Pauls, H. W. Discovery of inhibitors of the mitotic kinase TTK based on N-(3-(3-sulfamoylphenyl)-1H-indazol-5-yl)-acetamides and carboxamides. *Bioorg. Med. Chem.* **2014**, *22*, 4968-4997.

Table S3. Cell seeding Data for Cancer Cell Lines (cells per 80 μL)

HMEC	Breast					Ovarian				
	MDA-MB-231	BT-474	SKBr-3	MCF-7	T-47D	A2780	OVCAR-3	OV-90	SKOV-3	TOV-21G
4,000	2,500	8,000	4,000	4,000	4,000	2,500	6,000	5,000	4,000	2,500

Colon					Prostate		Melanoma		Lung	
COLO-205	HT29	HCT-116	SW48	SW620	PC-3	DU145	SK-MEL-5	SK-MEL-28	A549	H23
2,000	1,500	800	2,500	1,500	2,500	2,500	2,500	3,000	1,000	4,000

Table S4. Compound **75** eADME data

*Human CYP_{450} IC_{50} (μM)						**Microsomal $T_{1/2}$ (min)				***hERG % Inhibition	
1A2	2C9	2C19	2D6	3A4 (BFC)	3A4 (DBF)	H	D	R	M	1 μM	10 μM
>20	2.4	8.2	>20	1.3	>10	>60	>60	>60	>60	3.2	12

*Methods described in Laufer, R.; Forrest, B.; Li, S-W.; Sampson, P.; Liu, Y.; Edwards, L.; Lang, Y.; Awrey, D.; Mao, V.; Plotnikova, O.; Leung, G.; Hodgson, R.; Beletskaya, I.; Mason, J.; Wei, S.; Luo, X.; Nadeem, V.; Feher, M.; Kiarash, R.; Green, E.; Mak, T.W.; Pan, J.G.; Pauls, H.W. The Discovery of PLK4 Inhibitors: (E)-3-((1H-indazol-6-yl)methylene)indolin-2-ones as novel anti-proliferative agents. *J. Med. Chem.* **2013**, *56*, 6069–6087. **Methods described in Sampson, P.B.; Liu, Y.; Patel, N.K.; Forrest, B.; Li, S-W.; Edwards, L.; Laufer, R.; Lang, Y.; Feher, M.; Ban, F.; Awrey, D.; Mao, G.; Plotnikova, O.; Leung, G.; Hodgson, R.; Beletskaya, I.; Mason, J.; Wei, X.; Luo, X.; Nadeem, V.; Kiarash, R.; Green, E.; Qiu, W.; Chirgadze, N.Y.; Mak, T.W.; Pan, G.; Pauls, H.W.; The discovery of PLK4 inhibitors: Design and optimization of spiro[cyclopropane-1,3'[3*H*]-indol]-2'(1'H)-ones as anti-cancer agents. *J. Med. Chem*. **2015**, *58*, 130–146. ***Patch clamp assay performed by ChanTest Corporation (Cleveland, OH) according to the CRO's protocol.

Table S5. Mouse weights upon oral QD dosing of compounds **69**, **75** and **86** for 21 days

Study	MTD**			Xenograft							
	69	**75**	**86**	HCT116				MDA-MB-468		SW48	
				Vehicle	**69**	**75**	**86**	Vehicle	**75**	Vehicle	**75**
Dose (mg/kg)	35	35	150	nil	35**	35****	150****	nil	30	nil	30
Start Weight*	21.5 ±1.8	22. ±0.4	26.7 ±0.8	21.8 ±0.4	23.2 ±1.1	20.4 ±1.2	24.1 ±1.0	25.6 ±1.3	24.3 ±1.8	22.3 ±1.5	21.8 ±1.8
End Weight*	21. ± 1.4	23.0 ±1.0	25.9 ±1.2	24.1 ±1.1	22.1 ±2.2	19.7 ±0.9	22.3 ±1.8	27.1 ±1.1	23.0 ±2.5	24.3 ±1.7	22.6 ±2.2
n	3	3	3	8	8	8	8	8	8	8	8

*with standard deviations **Maximum Tolerated Dose ***2/8 & ****1/8 animals were lost during the study