Supporting Information

Exploration and Optimization of Substituted Triazolothiadiazines and Triazolopyridazines as PDE4 Inhibitors

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Table S1. PDE4A inhibition by compounds XXX

Analogue #	**PDE4A** IC_{50} *(nM)*	Analogue #	**PDE4A** IC_{50} *(nM)*
5	6.7 ± 0.4	**28**	26 ± 2
6	13 ± 0.8	**29**	21 ± 1
7	6.1 ± 0.9	**30**	37 ± 2
8	11 ± 0.7	**31**	9.8 ± 0.5
9	3.4 ± 0.4	**32**	3.8 ± 0.3
10	3.0 ± 0.2	**33**	95 ± 6
17	7.3 ± 3.8	**34**	33 ± 3
18	1.5 ± 0.7	**35**	53 ± 3
21	46 ± 4	**36**	11 ± 0.5
22	32 ± 3	**37**	8.6 ± 0.8
23	35 ± 2	**38**	13 ± 0.8
24	35 ± 3	**39**	45 ± 3
25	20 ± 0.9	**40**	80 ± 6
26	11 ± 0.7	**41**	7.1 ± 0.7
27	22 ± 1	**42**	6.7 ± 0.8

* data represents the results from three seperate experiments.

Cyclic nucleotide-gated cation channel assay. The PDE4 cell line (BD Biosciences, Rockville, MD) assay was conducted as described in reference 18. **Cell culture**: Cells were plated at a density of 1000 cells/well in black, clear bottom, tissue culture treated, 1536 well plates (Kalypsys, San Diego, CA) in 3 μL assay medium containing DMEM, 50 units/mL penicillin and 50 μg/mL streptomycin, and 2%, 5%, 10%, or 20% fetal calf serum and were incubated 12 hr at 37 °C with 5% CO_2 prior to compound screening. 3 μl/well of 1 × membrane potential dye was added and incubated for 1 hr at the room temperature. 23 nL/well of compounds in DMSO solution or the positive control (**1**) was added with a Pintool station (Kalypsys, San Diego, CA). **Fluorescence assay**: After 30 min room temperature incubation with compounds, the assay plate was measured in a fluorescence plate reader in the bottom reading mode (Envision, PerkinElmer)

with an excitation of 535 (±20) nm and emission of 590 (±20) nm. A flying reagent dispensing (FRD) workstation (Aurora Discovery, San Diego) was used to dispense cells and reagents to 1536-well plates. The compounds were serially diluted in DMSO in 384-well plates first and reformatted into 1536-well plates at 7 μL/well using a Cybi-well dispensing station with a 384-well head (Cybio, Inc. Woburn, MA). A Pintool station was used to transfer 23 nL of compounds in DMSO solution to the 1536-well assay plates. The final DMSO concentration in the assay plates was under 0.5%. During compound library screening, all plate manipulations were done on an automated robotic system (Kalypsys, San Diego, CA). **1** was used as the positive control and data was normalized to 10 μM **1** response (100% activity). All samples were tested in duplicate.

Protein-fragmentation complementation assays. Reagents and general assay procedures and conditions were performed in a similar manner as described in reference 19. **Cell culture**: Stable β2AR-HEK293 cells were plated into 96-well white walled microtiter plates (Corning) and grown in DMEM (Invitrogen) supplemented with 10% fetal bovine serum. Transient transfections of plasmids harboring the *Rluc* PCA PKA reporter were performed with FuGENE-6 reagent (Roche). 48 hours following transfection, cells were treated with **19**, **20**, **1** (Sigma) or indicated compounds. **Bioluminescence assay**: Immediately after treatment, exchange of medium and addition of 100 μl PBS to the 96-well white walled plates (Corning) the bioluminescence analysis was sperformed on a LMax^{TM}II^{384} luminometer (Molecular Devices). *Rluc* activities were monitored for the first 10 seconds after addition of the substrate benzyl-coelenterazine (5 μM, Nanolight).

Molecular Docking. Three-dimensional coordinates of the crystallized structure of phosphodiesterase 4B (PDE-4B) were obtained from the Protein Data Bank (PDB ID: 1XMY).[7]

AutoDock software version 4.0 was used for all docking simulations.[27] The AutoDock Tool was applied to prepare ligands in docking format and to visualize the results. Gasteiger atomic charges were assigned and the flexibility of the molecule was determined using the AutoDock module AutoTors. All 7 torsion angles were defined so that they could be explored during the docking process. Nonpolar hydrogens, including their partial charges, were merged to parent atoms. The atomic solvation variables were assigned by the AutoDock module Addsol. Atomic interaction energy grids were calculated with the AutoDock module AutoGrid for atom probes corresponding to each atom type in the ligand. The grid box included the entire active site as observed in previous PDE4B inhibitors complexes providing sufficient space for ligand translational and rotational movement. The side chain dihedral angles of a conserved glutamine known to interact with many PDE4B inhibitors were allowed to rotate during the docking process. The Mg^{2+} and Zn^{2+} cations were included in the active site and nearby histidines were protonated accordingly. The Lamarckian genetic algorithm as implemented in AutoDock 4.0 for the docking simulations. In general, the default variables of AutoDock were used. The docked compounds were clustered into groups using an RMS deviation versus X-ray atom positions <1.0 Å. Twenty runs were executed and the most favorable free binding energy conformer was chosen for analysis. Binding constants (K_i) were estimated within the AutoDock scoring function; the most favorable conformations had a *Ki* in the low nanomolar range.

General synthetic materials and methods. All reactions were performed under a nitrogen atmosphere passed over Drierite® (calcium sulfate) using oven-dried glassware. All commercially available reagents and solvents (anhydrous and non-anhydrous) were purchased from Aldrich (Milwaukee, WI), Acros (Pittsburgh, PA), Sigma (St. Louis, MO), Strem (Newburyport, MA), and Fisher Scientific (Fair Lawn, NJ) and used as obtained. All reactions

were stirred *via* a Teflon-coated stirbar on a magnetic stirplate. Air and moisture sensitive reagents were transferred *via* syringe and introduced into reaction vessels through rubber septa. All microwave reactions were carried out in heavy-walled tubes containing a Teflon-coated stirbar and crimped top using an Initiator microwave (Biotage). Reaction progress was monitored by analytical TLC using 250 μm thick 60Å silica gel plates with fluorescent indicator (Aldrich). Developed plates were visualized by UV light (254 nm) and/or treatment with PMA (phosphomolybdic acid), ninhydrin, or vanillin stain. Purification of certain compounds under acidic conditions used a Waters semi-preparative HPLC equipped with a Phenomenex Luna® C18 reverse phase (5 micron, 30 x 75 mm) column having a flow rate of 45 mL/min. The mobile phase was a mixture of acetonitrile and H_2O each containing 0.1% trifluoroacetic acid. Purification of certain compounds under basic conditions used a Waters semi-preparative HPLC equipped with a Phenomenex Gemini® C18 reverse phase (5 micron, 30 x 75 mm) column having a flow rate of 45 mL/min. The mobile phase was a mixture of acetonitrile and H_2O (0.1% NH_4OH). During purification under either acidic or basic conditions, a gradient of 20% to 60% acetonitrile over 8 minutes was used with fraction collection triggered by UV detection (220 nM). Pure fractions were concentrated and dried using Glas-Col N_2 blowdown unit at 40 °C.

Melting points were determined with a Mel-Temp® capillary apparatus (Electrothermal). Infrared (IR) spectra were obtained using a Spectrum 100 FT-IR spectrometer (PerkinElmer) and reported in cm^{-1}. ^1H and ^{13}C NMR spectra were recorded using an Inova 400 (100) MHz spectrometer (Varian). Chemical shifts are reported in δ (ppm) units using ^1H (residual) and ^{13}C signals from $CDCl_3$ (7.26 and 77.23, respectively) or d_6-DMSO (2.50 and 39.51, respectively) as internal standard. Data are reported as follows: chemical shift, integration, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), coupling constant.

Samples were analyzed for purity on an Agilent 1200 series LC/MS equipped with a Zorbax™ Eclipse XDB-C18 reverse phase (5 micron, 4.6 x 150 mm) column having a flow rate of 1.1 mL/min. The mobile phase was a mixture of acetonitrile and H_2O each containing 0.05% trifluoroacetic acid. A gradient of 5% to 100% acetonitrile over 8 minutes was used during analytical analysis. Purity of final compounds was determined to be >95%, using a 5 μL injection with quantitation by AUC at 220 and 254 nM. High-resolution mass spectra (HRMS) were measured on a time-of-flight (TOF) mass spectrometer (Agilent). All yields refer to chromatographically and spectroscopically pure compounds.

Formation of Substituted Benzoates: General Procedure A: To a solution of benzoic acid (1.0 eq) in methanol (1.0M) was added sulfuric acid (catalytic). The solution was stirred at room temperature for 12 h, at which time the solvent was removed by rotary evaporation. The crude reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the organic extracts were combined, washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude product was purified by column chromatography to give the substituted benzoates in >80% yield.

Formation of Substituted Aryldithiocarbazates: General Procedure B: To a solution of methyl benzoate (1.0 eq) in ethanol (0.55M) was added hydrazine (4.0 eq). The solution was heated to reflux with stirring until TLC showed full consumption of starting materials (12 h), then cooled. The solvent was removed by rotary evaporation and the crude reaction mixture was partitioned between ethyl acetate and water. The aqueous layer was extracted twice with ethyl acetate and the organic extracts were combined, washed with water and brine, dried over Na_2SO_4, and concentrated by rotary evaporation. The crude hydrazide (1.0 eq) was taken up in ethanol (0.5M). Potassium hydroxide (1.5 eq) was added, and stirred to dissolve. To this

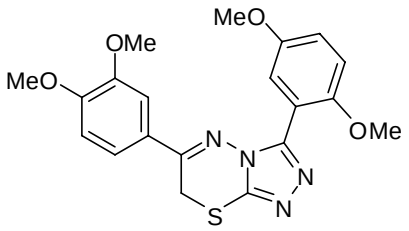
solution, carbon disulfide (1.5 eq) was added in a drop-wise fashion. Within a period of 1-10 min, the potassium salt precipitated from solution, and was allowed to stir as a suspension for 12 h. The suspension was filtered and dried to give the potassium aryldithiocarbazates as pale yellow powders in >85%.

Formation of Substituted triazoles: General Procedure C: To a mixture of aryldithiocarbazate (1.0 eq) in water (10.0M) was added hydrazine monohydrate (2.0 eq). The mixture was heated to 113 °C to induce cyclization to the triazole with formation of hydrogen sulfide gas (reaction mixture turned greenish brown). After 0.75 h, the reaction mixture was cooled and ice chips were added. Acidification with conc. hydrochloric acid precipitated a white solid. The product was filtered and washed with 2 x 20 mL portions of cold water to give the triazoles. If necessary, recrystallization from 95% ethanol garnered analytically pure products. Final yields ranged from 75-90%.

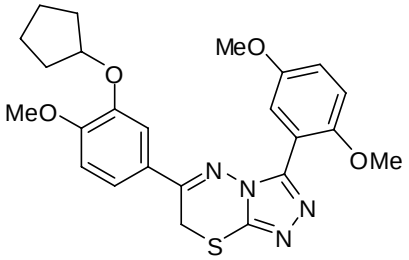
Formation of Substituted 2-bromoacetophenones: General Procedure D: To a solution of substituted acetophenone in chloroform (0.35M) was added bromine (1.2 eq). The solution was stirred at room temperature for 0.5 h, then heated to reflux for another 0.5-2 h until TLC showed full consumption of starting materials. The reaction mixture was concentrated by rotary evaporation and the crude product was purified by column chromatography. Final yields ranged from 50-95%.

Formation of Substituted 3,6-diphenyl-7*H*-[1,2,4]-triazolo[3,4-*b*][1,3,4]thiadiazines: General Procedure E: To a mixture of triazole (1.0 eq) and substituted 2-bromoacetophenone (1.0 eq) was added ethanol (0.1M). The reaction mixture was sealed in a crimp-top high pressure vessel and stirred at 105 °C for 4 h. The crude reaction mixture was partitioned between methylene chloride and water. The aqueous layer was removed and the organic layer

was washed with a mixture of water and brine, then concentrated by rotary evaporation. The crude product was purified by semi-preparative HPLC (see General Experimental for details).

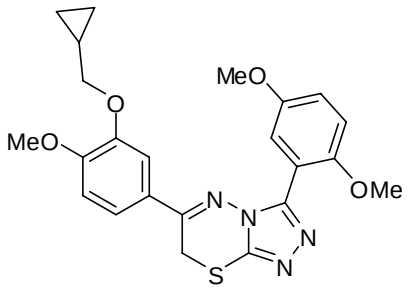


3-(2,5-dimethoxyphenyl)-6-(3,4-dimethoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (5). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.43 (d, 1H, *J* = 2.0 Hz), 7.40 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.23 (d, 1H, *J* = 3.2 Hz), 7.06 (dd, 1H, *J* = 3.2, 9.2 Hz), 6.93 (dd, 2H, *J* = 3.2, 12.0 Hz), 4.04 (s, 3H), 3.93 (s, 3H), 3.84 (s, 3H), 3.79 (s, 3H), 3.69 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 152.4, 152.2, 152.1, 151.6, 149.3, 141.4, 126.0, 121.1, 117.7, 116.3, 115.9, 112.6, 110.5, 109.2, 56.4, 56.0, 55.9, 55.8, 23.2. LC/MS: RT (min) = 5.06; (MH^+) 413.1. HRMS: (CI+, *m/z*), calcd for $C_{20}H_{21}N_4O_4S$ (MH^+), 413.1205; found, 413.1289.

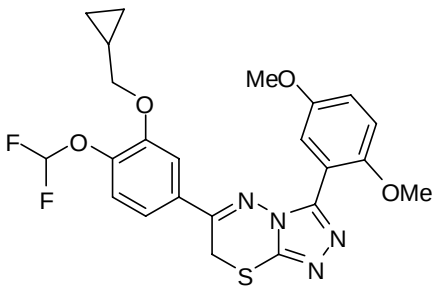


6-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(2,5-dimethoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (6). pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.44 (d, 1H, *J* = 2.0 Hz), 7.31 (dd, 1H, *J* = 2.2, 8.4 Hz), 7.22 (d, 1H, *J* = 3.1 Hz), 7.05 (dd, 1H, *J* = 3.1, 9.2 Hz), 6.94 (d, 1H, *J* = 9.2 Hz), 6.89 (d, 1H, *J* = 8.2 Hz), 4.68-4.72 (m, 1H), 3.97 (s, 2H), 3.90 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H) 1.79-1.89 (m, 6H), 1.57-1.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.6,

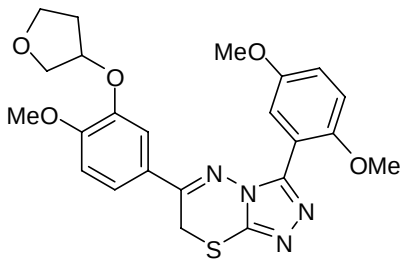
153.3, 152.7, 152.2, 148.1, 141.6, 125.5, 120.9, 118.0, 116.4, 115.2, 112.7, 112.4, 110.9, 80.7, 56.3, 56.1, 55.9, 32.7, 24.1, 22.9. LC/MS: RT (min) = 5.95; (MH^+) 467.1. HRMS: (CI+, *m/z*), calcd for $C_{24}H_{27}N_4O_4S$ (MH^+), 467.1675; found, 467.1757.



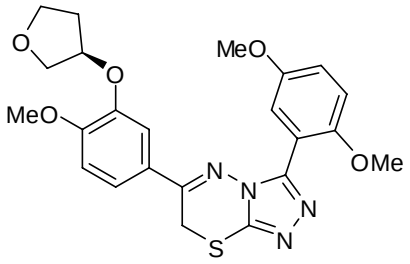
6-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-3-(2,5-dimethoxyphenyl)-7*H*-[1.2.4]triazolo[3,4-*b*][1.3.4]thiadiazine (7): pale yellow oil; ^{1}H NMR (CDCl3, 400 MHz) 7.46 (d, *J* = 1.96 Hz, 1H), 7.35 (dd, *J* = 2.15, 8.24 Hz, 1H), 7.22 (d, *J* = 3.13 Hz, 1H), 7.07-7.04 (m, 1H), 6.96-6.90 (m, 2H) 3.97 (s, 2H), 3.94 (s, 3H), 3.83 (d, *J* = 6.65 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 1.32-1.26 (m, 1H), 0.66-0.61 (m, 2H), 0.35-0.31 (m, 2H); ^{13}C NMR ($CDCl_3$, 150 MHz) δ 153.4, 153.1, 152.6, 152.2, 151.3, 148.8, 141.5, 125.7, 121.2, 118.0, 116.4, 115.3, 112.7, 111.4, 110.9, 74.1, 56.3, 56.0, 55.9, 23.1, 10.1, 3.47; LC-MS: RT (min) = 5.63; $[M + H]^+$ 453.1; HRMS calcd for $C_{23}H_{25}N_4O_4S$ (M + H) 453.1518, found 453.1595.



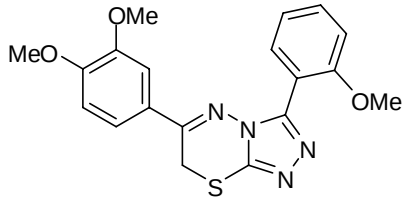
6-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-(2,5-dimethoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (8). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.46 (d, 1H, *J* = 2.0 Hz), 7.33 (dd, 1H, *J* = 2.4, 8.6 Hz), 7.24 (d, 1H, *J* = 8.2 Hz), 7.20 (d, 1H, *J* = 3.1 Hz), 7.06 (dd, 1H, *J* = 3.1, 9.0 Hz), 6.94 (d, 1H, *J* = 9.0 Hz), 6.70 (t, 1H, *J* = 74.7 Hz), 4.00 (s, 2H), 3.87 (d, 2H, *J* = 7.0 Hz, 2H), 3.81 (s, 3H), 3.70 (s, 3H), 1.22-1.30 (m, 1H), 0.62-0.68 (m, 2H), 0.31-0.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 152.6, 152.4, 151.8, 151.1, 143.6, 141.8, 131.9, 122.6, 120.7, 118.4, 116.7, 115.9, 115.3, 113.1, 113.0, 74.4, 56.6, 56.2, 23.7, 10.2, 3.5. LC/MS: RT (min) = 6.10; (MH^+) 489.1. HRMS: (CI+, *m/z*), calcd for $C_{23}H_{23}F_2N_4O_4S$ (MH^+), 489.1330; found, 489.1400.



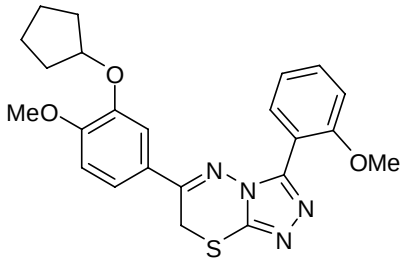
3-(2,5-dimethoxyphenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (9). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, *J* = 2.0 Hz), 7.38 (dd, 1H, *J* = 2.4, 8.6 Hz), 7.22 (d, 1H, *J* = 3.1 Hz), 7.06 (dd, 1H, *J* = 3.1, 9.0 Hz) 6.94 (dd, 2H, *J* = 8.8, 11.2 Hz), 4.90 (m, 1H), 3.86-4.04 (m, 4H), 3.98 (s, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 2.11-2.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 153.6, 152.8, 152.4, 151.4, 147.6, 141.9, 125.7, 122.2, 118.1, 116.9, 115.3, 113.1, 113.0, 111.4, 79.1, 73.0, 67.4, 56.6, 56.3, 56.1, 33.2, 23.1. LC/MS: RT (min) = 5.05; (MH^+) 469.1. HRMS: (CI+, *m/z*), calcd for $C_{23}H_{25}N_4O_5S$ (MH^+), 469.1467; found, 469.1544.



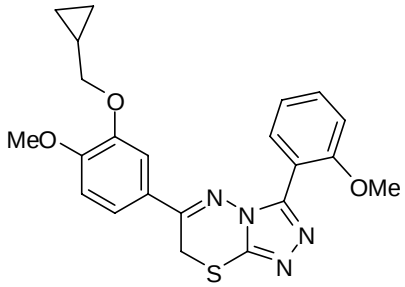
(*R*)-3-(2,5-dimethoxyphenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (10). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.41 (d, 1H, *J* = 2.0 Hz), 7.38 (dd, 1H, *J* = 2.4, 8.6 Hz), 7.22 (d, 1H, *J* = 3.1 Hz), 7.06 (dd, 1H, *J* = 3.1, 9.0 Hz) 6.94 (dd, 2H, *J* = 8.8, 11.2 Hz), 4.90 (m, 1H), 3.86-4.04 (m, 4H), 3.98 (s, 2H), 3.92 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H), 2.11-2.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.0, 153.6, 152.8, 152.4, 151.4, 147.6, 141.9, 125.7, 122.2, 118.1, 116.9, 115.3, 113.1, 113.0, 111.4, 79.1, 73.0, 67.4, 56.6, 56.3, 56.1, 33.2, 23.1. LC/MS: RT (min) = 5.05; (MH^+) 469.1. HRMS: (CI+, *m/z*), calcd for $C_{23}H_{25}N_4O_5S$ (MH^+), 469.1540; found, 469.1543.



6-(3,4-dimethoxyphenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (21). cream solid. Mp 155-156 °C. ^{1}H NMR (d_6-DMSO, 400 MHz) δ 7.55-7.61 (m, 2H), 7.50 (dd, 1H, *J* = 2.0, 8.4 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 7.24 (d, 1H, *J* = 8.0 Hz), 7.07-7.15 (m, 2H), 4.22 (s, 2H), 3.80 (s, 3H), 3.77 (s, 3H), 3.73 (s, 3H). ^{13}C NMR (d_6-DMSO, 100 MHz) δ 158.3, 156.3, 152.9, 150.5, 149.5, 142.9, 6, 132.2, 125.9, 122.4, 121.0, 114.3, 112.6, 112.2, 110.6, 56.5, 56.4, 56.2, 23.5. HRMS: (CI+, *m/z*), calcd for $C_{19}H_{19}N_4O_3S$ (MH^+), 383.1100; found, 383.1181.

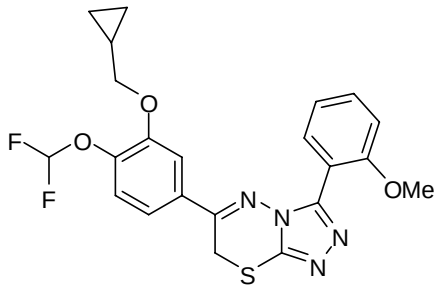


6-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (22). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.47-7.52 (m, 1H), 7.43 (d, 1H, *J* = 2.0 Hz), 7.30 (dd, 1H, *J* = 2.2, 8.4 Hz), 7.06-7.10 (m, 1H), 7.01 (d, 1H, *J* = 8.2 Hz), 6.89 (d, 1H, *J* = 8.6 Hz), 4.65-4.70 (m, 1H), 3.97 (s, 2H), 3.89 (s, 3H), 3.76 (s, 3H), 1.80-1.88 (m, 6H), 1.57-1.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.0, 153.5, 152.4, 151.5, 148.2, 141.3, 132.1, 131.8, 125.7, 120.9, 120.5, 115.1, 112.5, 111.2, 110.9, 80.7, 56.1, 55.7, 32.7, 24.1, 23.0. LC/MS: RT (min) = 5.92; (MH^+) 437.1. HRMS: (CI+, *m/z*), calcd for $C_{23}H_{25}N_4O_3S$ (MH^+), 437.1569; found, 437.1649.

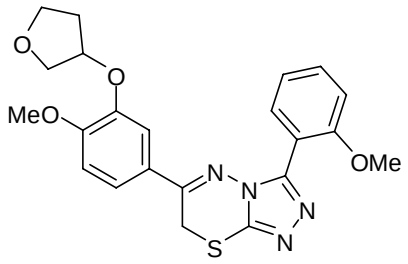


6-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (23). pale yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, 1H, *J* = 2.0, 7.4 Hz), 7.48-7.52 (m, 1H), 7.41 (d, 1H, *J* = 2.0 Hz), 7.34 (dd, 1H, *J* = 2.2, 8.1 Hz), 7.08 (td, 1H, *J* = 1.0, 7.5 Hz), 7.00 (d, 1H, *J* = 8.2 Hz), 6.91 (d, 1H, *J* = 8.6 Hz), 3.96 (s, 2H), 3.93 (s, 3H), 3.81 (d, 2H, *J* = 7.0 Hz), 3.76 (s, 3H), 1.25-1.29 (m, 1H), 0.60-0.65 (m, 2H), 0.29-0.33 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 154.4, 149.5, 149.0, 147.9, 145.3, 137.8, 128.6, 128.3, 122.3,

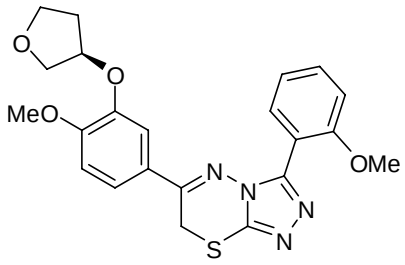
117.7, 117.0, 111.5, 107.9, 107.7, 107.4, 101.2, 70.6, 52.6, 52.2, 19.6, 6.6. LC/MS: RT (min) = 5.60; (MH^+) 423.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{23}N_4O_3S$ (MH^+), 423.1413; found, 423.1488.



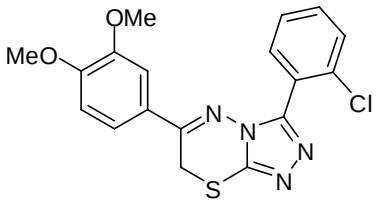
6-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (24). white solid. Mp 163 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.61 (dd, 1H, *J* = 1.8, 7.6 Hz), 7.48-7.53 (m, 1H), 7.44 (d, 1H, *J* = 2.4 Hz), 7.31-7.34 (m, 1H), 7.22-7.25 (m, 1H), 7.09 (td, 1H, *J* = 1.0, 7.5 Hz), 7.01 (d, 1H, *J* = 8.2 Hz), 6.69 (t, 1H, *J* = 74.7 Hz), 3.97 (s, 2H), 3.85 (d, 2H, *J* = 7.0 Hz), 3.76 (s, 3H), 1.21-1.27 (m, 1H), 0.61-0.67 (m, 2H), 0.31-0.35 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 157.8, 151.9, 151.5, 150.7, 143.1, 140.9, 132.0, 131.8, 131.7, 122.3, 120.5, 120.3, 115.6, 115.4, 113.0, 112.7, 111.2, 74.1, 55.7, 23.4, 9.9, 3.2. LC/MS: RT (min) = 6.07; (MH^+) 459.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{21}F_2N_4O_3S$ (MH^+), 459.1224; found, 459.1304.



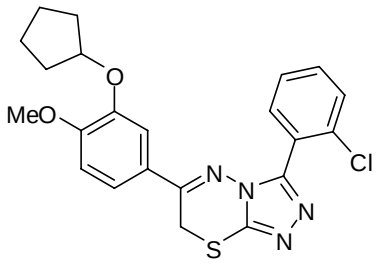
6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (25). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.63 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.52-7.57 (m, 1H), 7.38-7.42 (m, 2H), 7.10 (td, 1H, *J* = 1.0, 7.5 Hz), 7.04 (d, 1H, *J* = 7.8 Hz), 6.94 (d, 1H, *J* = 8.2 Hz), 4.87 (tt, 1H, *J* = 2.5, 5.1 Hz), 3.87-4.04 (m, 4H), 4.02 (s, 2H), 3.92 (s, 3H), 3.78 (s, 3H), 2.10-2.16 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.3, 154.2, 153.6, 151.0, 147.6, 142.2, 133.2, 132.0, 125.5, 122.4, 120.8, 113.8, 113.1, 111.6, 111.5, 79.1, 73.0, 67.4, 56.3, 56.0, 33.1, 23.0. LC/MS: RT (min) = 4.99; (MH^+) 439.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{23}N_4O_4S$ (MH^+), 439.1362; found, 439.1439.



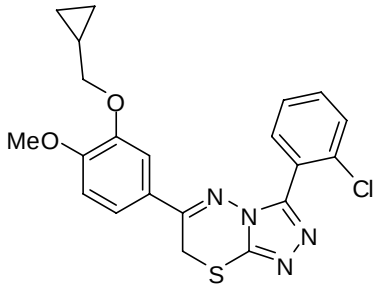
(*R*)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-3-(2-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (26). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.62 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.50-7.55 (m, 1H), 7.37-7.40 (m, 2H), 7.09 (td, 1H, *J* = 1.0, 7.5 Hz), 7.03 (d, 1H, *J* = 7.8 Hz), 6.92-6.95 (m, 1H), 4.87 (tt, 1H, *J* = 2.5, 5.1 Hz), 3.86-4.04 (m, 4H), 3.99 (s, 2H), 3.92 (s, 3H), 3.76 (s, 3H), 2.09-2.15 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 158.2, 154.0, 152.9, 151.4, 147.6, 141.9, 132.8, 132.0, 125.7, 122.2, 120.8, 114.6, 113.1, 111.6, 111.5, 79.1, 73.0, 67.4, 56.3, 56.0, 33.1, 23.1. LC/MS: RT (min) = 4.99; (MH^+) 439.1.



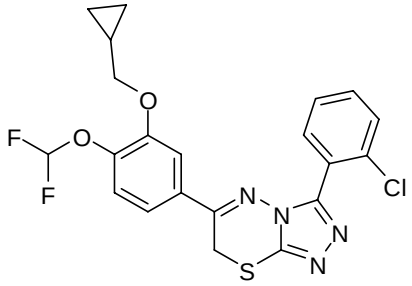
3-(2-chlorophenyl)-6-(3,4-dimethoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (27). off-white needles. Mp 225-226 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.71 (dd, 1H, *J* = 2.0, 7.4 Hz), 7.41-7.54 (m, 4H), 7.34 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.91 (d, 1H, *J* = 8.6 Hz), 3.98 (s, 2H), 3.94 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.5, 149.4, 141.6, 132.6, 131.6, 131.5, 129.8, 127.1, 126.8, 125.9, 125.8, 121.2, 110.5, 109.5, 56.0, 55.8, 23.5. LC/MS: RT (min) = 5.29; (MH^+), . HRMS: (CI+, *m/z*), calcd for $C_{18}H_{16}ClN_4O_2S$ (MH^+), 387.0604; found, 387.0675.



3-(2-chlorophenyl)-6-(3-(cyclopentyloxy)-4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (28). pale yellow solid. Mp 168 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, 1H, *J* = 2.0, 7.4 Hz), 7.39-7.52 (m, 4H), 7.29 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.88 (d, 1H, *J* = 6.8 Hz), 4.66-4.72 (m, 1H), 3.97 (s, 2H), 3.90 (s, 3H), 1.81-1.89 (m, 6H), 1.59-1.61 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.7, 153.1, 151.9, 148.4, 141.7, 134.6, 132.8, 131.7, 129.9, 127.0, 126.2, 125.8, 121.1, 112.7, 111.1, 80.8, 56.3, 32.8, 24.3, 23.5. LC/MS: RT (min) = 6.24; (MH^+) 441.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{22}ClN_4O_2S$ (MH^+) 441.1074; found, 425.1455.

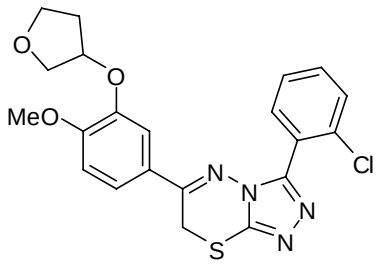


3-(2-chlorophenyl)-6-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (29). glossy cream needles. Mp 173 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.69 (dd, 1H, *J* = 1.8, 7.2 Hz), 7.40-7.52 (m, 4H), 7.33 (dd, 1H, *J* = 2.2, 8.1 Hz), 6.90 (d, 1H, *J* = 8.6 Hz), 3.97 (s, 2H), 3.93 (s, 3H), 3.83 (d, 2H, *J* = 7.0 Hz), 1.25-1.30 (m, 1H), 0.60-0.65 (m, 2H), 0.30-0.34 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 149.5, 149.4, 145.2, 130.8, 129.1, 128.1, 126.3, 123.2, 122.3, 122.1, 117.7, 107.9, 107.3, 70.4, 52.5, 27.0, 19.9, 6.5. LC/MS: RT (min) = 5.88; (MH^+) 427.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{20}ClN_4O_2S$ (MH^+), 427.0917; found, 427.0989.

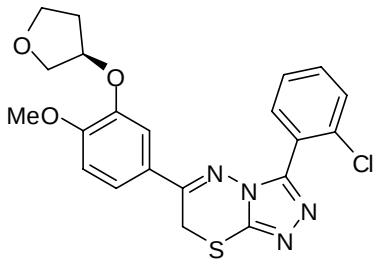


3-(2-chlorophenyl)-6-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (30). white needles. Mp 193 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.68-7.72 (m, 1H), 7.41-7.54 (m, 4H), 7.32 (dd, 1H, *J* = 2.0, 8.2 Hz), 7.24 (d, 1H, *J* = 8.2 Hz), 6.70 (t, 1H, *J* = 75.1 Hz), 3.99 (s, 2H), 3.87 (d, 2H, *J* = 7.0 Hz), 1.21-1.32 (m, 1H), 0.62-0.68 (m, 2H), 0.31-0.36 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.7, 152.2, 151.0, 141.8, 134.5, 132.9, 132.0, 131.8, 130.1, 127.2, 126.0, 122.6, 120.7, 118.5, 115.9, 113.1, 74.3, 24.0,

10.2, 3.6. LC/MS: RT (min) = 6.32; (MH^+) 463.0. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{18}ClF_2N_4O_2S$ (MH^+), 463.0729; found, 463.0798.

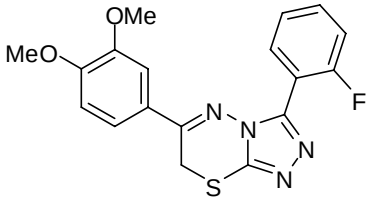


3-(2-chlorophenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (31). colorless needles. Mp 212 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 1H, *J* = 2.0, 7.4 Hz), 7.47-7.54 (m, 2H), 7.44 (dd, 1H, *J* = 1.8, 7.2 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 7.35 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.92 (d, 1H, *J* = 8.6 Hz), 4.86-4.90 (m, 1H), 3.87-4.05 (m, 4H), 3.98 (s, 2H), 3.92 (s, 3H), 2.13-2.18 (m, 2H). LC/MS: RT (min) = 5.24; (MH^+) 443.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{20}ClN_4O_3S$ (MH^+), 443.0866; found, 443.0955.

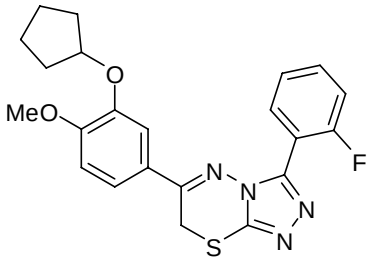


(*R*)-3-(2-chlorophenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (32). off-white powder. Mp 218 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.70 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.47-7.54 (m, 2H), 7.44 (dd, 1H, *J* = 1.6, 7.4 Hz), 7.41 (d, 1H, *J* = 2.0 Hz), 7.35 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.92 (d, 1H, *J* = 8.6 Hz), 4.86-4.90

(m, 1H), 3.87-4.04 (m, 4H), 3.97 (s, 2H), 3.91 (s, 3H), 2.12-2.18 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.8, 152.8, 152.1, 147.7, 141.8, 134.6, 132.9, 132.0, 130.0, 127.1, 126.2, 125.9, 122.0, 112.9, 111.4, 79.0, 73.0, 67.4, 56.3, 33.2, 23.6. LC/MS: RT (min) = 5.25; (MH^+) 443.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{20}ClN_4O_3S$ (MH^+), 443.0866; found, 443.0942.

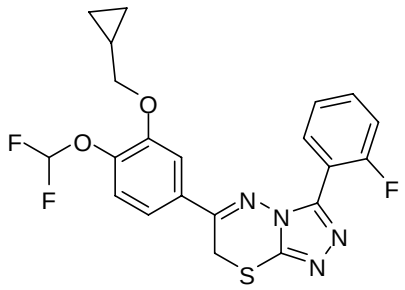


6-(3,4-dimethoxyphenyl)-3-(2-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (33). cream solid. Mp 222 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (td, 1H, *J* = 1.8, 7.3 Hz), 7.48-7.54 (m, 1H), 7.45 (d, 1H, *J* = 2.0 Hz), 7.34 (dd, 1H, *J* = 2.2, 8.4), 7.29 (td, 1H, *J* = 1.0, 7.5 Hz), 7.16-7.21 (m, 1H), 6.91 (d, 1H, *J* = 8.2 Hz), 3.98 (s, 2H), 3.93 (s, 3H), 3.86 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 152.9, 152.5, 149.3, 132.5, 132.4, 131.6, 125.8, 124.3, 124.2, 121.2, 116.0, 115.8, 114.5, 110.5, 109.3, 56.0, 55.8, 23.3. LC/MS: RT (min) = 5.15; (MH^+) 371.1. HRMS: (CI+, *m/z*), calcd for $C_{18}H_{16}FN_4O_2S$ (MH^+) 371.0900; found, 371.0979.

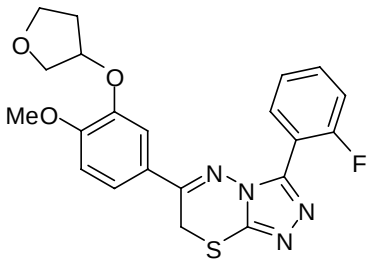


6-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(2-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (34). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79-7.82 (m, 1H), 7.63-7.69 (m, 3H), 7.32 (d, 1H, *J* = 2.0 Hz), 7.24 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.84 (d, 1H, *J* = 8.6 Hz),

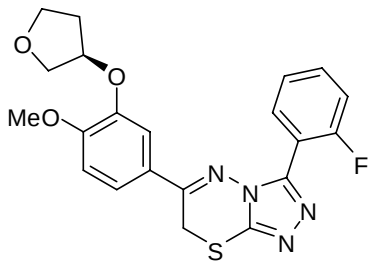
4.58-4.63 (m, 1H), 3.94 (s, 2H), 3.86 (s, 3H), 1.75-1.80 (m, 6H), 1.52-1.58 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 153.3, 148.0, 141.2, 132.7, 131.5, 130.7, 130.6, 130.3, 126.8, 126.7, 126.6, 125.3, 122.1, 120.9, 112.4, 110.8, 80.6, 56.0, 32.5, 23.9, 23.2. LC/MS: RT (min) = 6.12; (MH^+) 425.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{22}FN_4O_2S$ (MH^+), 425.1369; found, 425.1455.



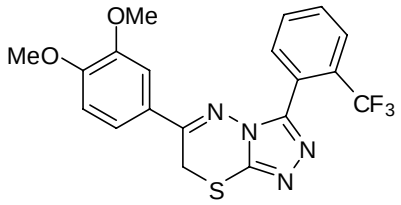
6-(3-(cyclopropylmethoxy)-4-(difluoromethoxy)phenyl)-3-(2-fluorophenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (35). white powder. Mp 183 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (td, 1H, *J* = 1.8, 7.3 Hz), 7.51-7.57 (m, 1H), 7.50 (d, 1H, *J* = 2.0 Hz), 7.30-7.36 (m, 2H), 7.26 (app. d, 1H, *J* = 8.0 Hz), 7.18-7.23 (m, 1H), 6.70 (t, 1H, *J* = 74.7 Hz), 4.01 (s, 2H), 3.88 (d, 2H, *J* = 7.0 Hz), 1.24-1.33 (m, 1H), 0.63-0.68 (m, 2H), 0.33-0.37 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 159.1, 152.7, 150.3, 142.2, 132.9, 132.8, 131.0, 131.8, 122.7, 120.7, 116.3, 116.1, 115.9, 113.3, 113.0, 74.3, 23.8, 10.2, 3.6. LC/MS: RT (min) = 6.21; (MH^+) 447.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{18}F_3N_4O_2S$ (MH^+), 447.1024; found, 447.1103.



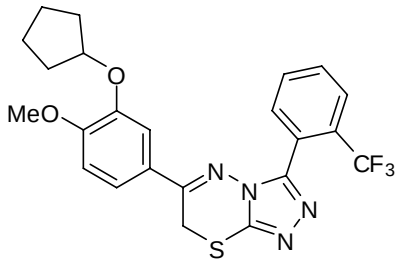
3-(2-fluorophenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (36). white solid. Mp 198-199 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.78 (td, 1H, *J* = 1.8, 7.3 Hz), 7.49-7.55 (m, 1H), 7.43 (d, 1H, *J* = 2.0 Hz, 1H), 7.37 (dd, 1H, *J* = 2.2, 8.4 Hz), 7.31 (td, 1H, *J* = 1.2, 7.6 Hz), 7.19 (ddd, 1H, *J* = 1.0, 8.6, 10.0 Hz), 6.92 (d, 1H, *J* = 8.6 Hz), 4.88-4.92 (m, 1H), 3.85-4.02 (m, 4H), 4.00 (s, 2H), 3.90 (s, 3H), 2.11-2.17 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 159.1, 153.8, 152.9, 150.0, 147.6, 142.2, 132.7, 132.6, 131.9, 129.9, 124.6, 124.5, 122.1, 116.3, 116.1, 114.9, 114.8, 113.1, 111.5, 79.0, 73.0, 67.4, 56.3, 33.1, 23.4. LC/MS: RT (min) = 5.12; (MH^+) 427.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{20}FN_4O_3S$ (MH^+), 427.1162; found, 427.1245.



(*R*)-3-(2-fluorophenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (37). off-white solid. Mp 196-197 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81 (td, 1H, *J* = 1.8, 7.3 Hz), 7.51-7.57 (m, 1H), 7.44 (d, 1H, *J* = 2.0 Hz), 7.37 (dd, 1H, *J* = 2.2, 8.4 Hz), 7.31 (td, 1H, *J* = 1.2, 7.6 Hz), 7.20 (ddd, 1H, *J* = 1.2, 8.4, 10.0 Hz), 6.93 (d, 1H, *J* = 8.6 Hz), 4.89-4.93 (m, 1H), 3.87-4.04 (m, 4H), 3.99 (s, 2H), 3.91 (s, 3H), 2.13-2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 161.6, 159.1, 153.8, 152.9, 150.1, 147.6, 142.3, 132.8, 132.7, 132.0, 125.9, 124.7, 124.6, 122.1, 116.3, 116.1, 114.9, 114.8, 112.9, 111.4, 79.02, 73.0, 67.4, 56.3, 33.1, 23.4. LC/MS: RT (min) = 5.13; (MH^+) 427.1. HRMS: (CI+, *m/z*), calcd for $C_{21}H_{20}FN_4O_3S$ (MH^+), 427.1162; found, 427.1240.

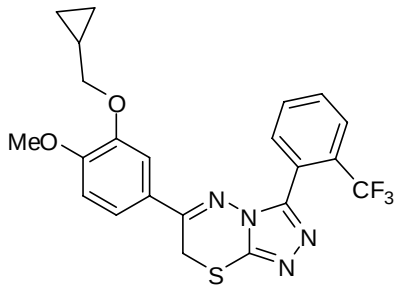


6-(3,4-dimethoxyphenyl)-3-(2-(trifluoromethyl)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (38). white solid. Mp 204-205 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.79-7.82 (m, 1H), 7.65-7.68 (m, 3H), 7.33 (d, 1H, *J* = 2.4 Hz), 7.28 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.87 (d, 1H, *J* = 8.2 Hz), 3.96 (s, 2H), 3.91 (s, 3H), 3.79 (s, 3H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.3, 152.6, 151.4, 149.3, 141.3, 132.8, 131.5, 130.7, 130.2, 126.9, 126.8, 125.7, 122.2, 121.2, 110.5, 109.4, 56.0, 55.8, 23.4. LC/MS: RT (min) = 5.43; (MH^+) 421.1. HRMS: (CI+, *m/z*), calcd for $C_{19}H_{16}F_3N_4O_2S$ (MH^+) 421.0868; found, 421.0948.

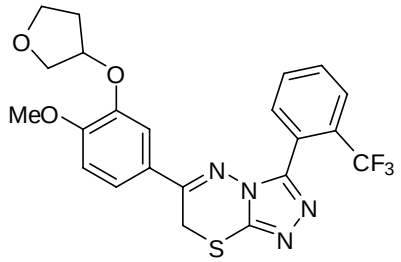


6-(3-(cyclopentyloxy)-4-methoxyphenyl)-3-(2-(trifluoromethyl)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (39). yellow oil. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.80 (dd, 1H, *J* = 2.7, 7.0 Hz), 7.64-7.68 (m, 3H), 7.32 (d, 1H, *J* = 2.4 Hz), 7.23 (dd, 1H, *J* = 2.2, 8.4 Hz), 6.84 (d, 1H, *J* = 8.6 Hz), 4.59-4.64 (m, 1H), 3.94 (s, 2H), 3.86 (s, 3H), 1.75-1.80 (m, 6H), 1.53-1.59 (m, 2H). ^{13}C NMR ($CDCl_3$, 100 MHz) δ 153.5, 153.2, 151.3, 148.0, 141.1, 132.7, 131.5, 130.5, 126.8, 126.7, 126.6, 125.4, 120.8, 112.4, 110.8, 80.6, 56.0, 32.5, 23.9, 23.2.

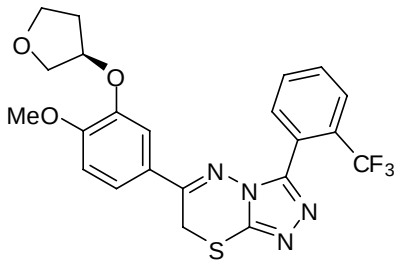
LC/MS: RT (min) = 6.30; (MH^+) 475.1. HRMS: (CI+, *m/z*), calcd for $C_{23}H_{22}F_3N_4O_2S$ (MH^+), 475.1337; found, 475.1416.



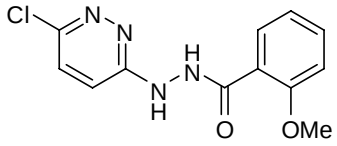
6-(3-(cyclopropylmethoxy)-4-methoxyphenyl)-3-(2-(trifluoromethyl)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (40). white solid. Mp 166 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.81-7.84 (m, 1H), 7.66-7.71 (m, 3H), 7.35 (d, 1H, *J* = 2.4 Hz), 7.29 (dd, 1H, *J* = 2.4, 8.6 Hz), 6.88 (d, 1H, *J* = 8.2 Hz), 3.96 (s, 2H), 3.92 (s, 3H), 3.78 (d, 2H, *J* = 7.0 Hz), 1.21-1.29 (m, 1H), 0.58-0.64 (m, 2H), 0.27-0.31 (m, 2H). LC/MS: RT (min) = 5.97; (MH^+) 461.1.



6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-3-(2-(trifluoromethyl)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (41). white solid. Mp 186 °C (dec.). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.85 (m, 1H), 7.66-7.73 (m, 3H), 7.33 (d, 1H, *J* = 2.0 Hz), 7.29-7.31 (m, 1H), 6.90 (d, 1H, *J* = 8.2 Hz), 4.82 (tt, 1H, *J* = 2.4, 5.4 Hz), 3.84-4.05 (m, 4H), 3.97 (s, 2H), 3.90 (s, 3H), 2.03-2.12 (m, 2H). LC/MS: RT (min) = 5.38; (MH^+) 477.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{20}F_3N_4O_3S$ (MH^+), 477.1130; found, 477.1205.

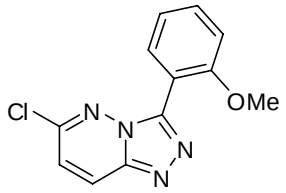


(*R*)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-3-(2-(trifluoromethyl)phenyl)-7*H*-[1,2,4]triazolo[3,4-*b*][1,3,4]thiadiazine (42). off-white needles. Mp 199-200 °C. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 7.82-7.85 (m, 1H), 7.65-7.73 (m, 3H), 7.27-7.33 (m, 2H), 6.92 (d, 1H, *J* = 8.2 Hz), 4.79-4.84 (m, 1H), 3.84-3.99 (m, 4H), 3.96 (s, 2H), 3.90 (s, 3H), 2.04-2.11 (m, 2H). LC/MS: RT (min) = 5.38; (MH^+) 477.1. HRMS: (CI+, *m/z*), calcd for $C_{22}H_{20}F_3N_4O_3S$ (MH^+), 477.1130; found, 477.1203.



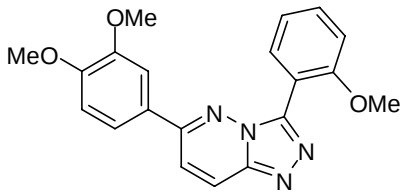
***N′*-(6-chloropyridazin-3-yl)-2-methoxybenzohydrazide (43).** ***Method A*:** To a stirred solution of *o*-anisic acid (2.07 g, 13.59 mmol, 1.0 eq) in DMF (54 mL, 0.25M) under N_2 at rt was added 1,1′-carbonyldiimidazole (2.43 g, 14.95 mmol, 1.1 eq). After stirring for 30 min, 3-chloro-6-hydrazinopyridazine (1.97 g, 13.59 mmol, 1.0 eq) was added and the solution was stirred at rt for an additional 1 h. The reaction mixture was poured into H_2O and the resultant precipitate was filtered, washed with H_2O then hexane, and dried under reduced pressure to provide hydrazide **1** (2.08 g, 55%) as a white solid. ***Method B*:** To a stirred solution of 3-chloro-6-hydrazinylpyridazine (1.03 g, 7.14 mmol, 1.0 eq) in Et_2O (29 mL, 0.25M) under N_2 at rt was added triethylamine (1.0 mL, 0.72 g, 7.14 mmol, 1.0 eq) followed by 2-methoxybenzoyl chloride

(1.1 mL, 1.22 g, 7.14 mmol, 1.0 eq) dropwise slowly. After stirring at rt for 1 h, the precipitate was filtered, washed with H_2O then hexane, and dried under reduced pressure to provide hydrazide **43** (1.99 g, quant.) as a white solid. R_f = 0.49 (CH_2Cl_2/MeOH 95:5). Mp 211 °C (dec.). IR (neat, diamond/ZnSe) 3313, 3204, 3113, 3070, 3026, 1659, 1637, 1592, 1523, 1484, 1470, 1460, 1431, 1292, 1243, 1182, 1166, 1148, 1109, 1078, 1040, 1008, 951, 906, 851, 832, 798, 786, 753, 693, 667 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 10.18 (d, 1H, *J* = 1.3 Hz, NH), 9.41 (d, 1H, *J* = 1.3 Hz, NH), 7.70 (dd, 1H, *J* = 1.8, 7.6 Hz, aryl), 7.59 (d, 1H, *J* = 9.3 Hz, aryl), 7.52 (ddd, 1H, *J* = 1.8, 7.5, and 8.2 Hz, aryl), 7.18 (d, 1H, *J* = 8.3 Hz, aryl), 7.08 (d, 1H, *J* = 9.4 Hz, aryl), 7.07 (dt, 1H, *J* = 0.6, 7.5 Hz, aryl), 3.92 (s, 3H, Me). ^{13}C NMR (100 MHz, d_6-DMSO) δ 165.3, 160.2, 157.0, 147.4, 132.6, 130.1, 129.5, 121.9, 120.5, 116.2, 112.0, 55.9. LC/MS: RT (min) = 4.02; (MH^+) 279.1. HRMS: (CI+, *m/z*), calcd for $C_{12}H_{12}ClN_4O_2$ (MH^+), 279.0649; found, 279.0648.



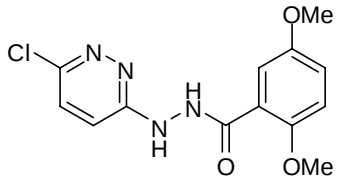
6-chloro-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (44). ***Method A*:** To a stirred suspension of *N*′-(4-chlorophenyl)-2-methoxybenzohydrazide (**43**) (1.02 g, 3.65 mmol, 1.0 eq) in *o*-xylene under N_2 at rt was added triethylamine hydrochloride (251 mg, 1.83 mmol, 0.5 eq). After refluxing for 16 h, the reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The crude material was diluted with CH_2Cl_2, washed with brine (2x), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a crude solid which was recrystallized from Et_2O to give [1,2,4]triazolo[4,3-*b*]pyridazine **44** (115 mg,

12%) as a white solid.; ***Method B*:** A solution of *N*′-(4-chlorophenyl)-2-methoxybenzohydrazide (**1**) (524 mg, 1.88 mmol, 1.0 eq) in phosphorus oxychloride (9.4 mL, 0.2M) under N_2 was heated at 105 °C for 2 h. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The crude material was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ was added dropwise until pH 8 was obtained. The biphasic solution was separated and the aqueous layer was extracted with CH_2Cl_2 (1x). The organic layers were combined, washed with brine (1x), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave an oil which was recrystallized from Et_2O to give [1,2,4]triazolo[4,3-*b*]pyridazine **44** (458 mg, 94%) as a white solid. R_f = 0.60 (CH_2Cl_2/MeOH 95:5). Mp 140-141 °C. IR (neat, diamond/ZnSe) 3081, 3048, 3019, 2934, 2836, 1609, 1585, 1532, 1519, 1480, 1461, 1444, 1431, 1383, 1351, 1327, 1277, 1257, 1181, 1159, 1149, 1124, 1101, 1050, 1037, 1028, 984, 938, 827, 800, 779, 741, 710, 666 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 8.52 (d, 1H, *J* = 9.7 Hz, aryl), 7.62 (ddd, 1H, *J* = 1.8, 7.5, and 8.5 Hz, aryl), 7.54 (dd, 1H, *J* = 1.7, 7.5 Hz, aryl), 7.54 (d, 1H, *J* = 9.6 Hz, aryl), 7.28 (d, 1H, *J* = 8.0 Hz, aryl), 7.16 (dt, 1H, *J* = 0.9, 7.5 Hz, aryl), 3.77 (s, 3H, Me). ^{13}C NMR (100 MHz, d_6-DMSO) δ 158.0, 148.9, 146.6, 143.1, 132.6, 131.7, 127.0, 122.9, 120.6, 114.3, 112.3, 55.8. LC/MS: RT (min) = 4.58; (MH^+) 261.0. HRMS: (CI+, *m/z*), calcd for $C_{12}H_{10}ClN_4O$ (MH^+), 261.0543; found, 261.0551.



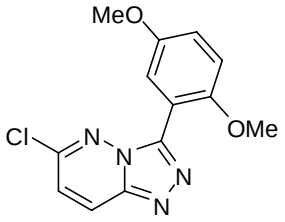
6-(3,4-dimethoxyphenyl)-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (45). To a suspension of 6-chloro-3-(2-methoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (**44**) (50 mg, 0.19

mmol, 1.0 eq) in DME (1.9 mL, 0.1M) in a microwave tube was added 3,4-dimethoxyphenylboronic acid (105 mg, 0.57 mmol, 3.0 eq), $Pd(PPh_3)_4$ (11 mg, 9.57 μmol, 5 mol %), and 2.0M aq. Na_2CO_3 soln. (0.19 mL, 0.38 mmol, 2.0 eq). The solution was sparged with Ar for 5 min and then heated at 150 °C in a microwave for 30 min. After cooling to rt, the reaction mixture was diluted with EtOAc and filtered through a silica gel plug. The filtrate was washed with brine (1x), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a residue, which was purified by semi-preparative HPLC to give [1,2,4]triazolo[4,3-*b*]pyridazine **45** (31 mg, 44%) as a white solid. R_f = 0.46 (CH_2Cl_2/MeOH 95:5). Mp 95-97 °C. IR (neat, diamond/ZnSe) 3100, 2941, 2847, 1740, 1610, 1597, 1585, 1514, 1493, 1465, 1440, 1417, 1358, 1340, 1284, 1257, 1225, 1194, 1176, 1155, 1130, 1097, 1065, 1017, 997, 895, 880, 814, 774, 760, 714 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 8.46 (d, 1H, *J* = 9.8 Hz, aryl), 8.03 (d, 1H, *J* = 9.8 Hz, aryl), 7.60-7.65 (m, 3H, aryl), 7.55 (d, 1H, *J* = 2.1 Hz, aryl), 7.31 (dd, 1H, *J* = 0.9, 9.0 Hz, aryl), 7.17 (dt, 1H, *J* = 0.9, 7.5 Hz, aryl), 7.11 (d, 1H, *J* = 8.6 Hz, aryl), 3.82 (s, 3H, Me), 3.82 (s, 3H, Me), 3.81 (s, 3H, Me). ^{13}C NMR (100 MHz, d_6-DMSO) δ 157.9, 152.6, 151.3, 149.1, 147.1, 143.5, 132.3, 131.8, 126.4, 124.7, 120.6, 120.5, 120.1, 115.0, 111.9 (2C), 109.9, 55.8, 55.7, 55.5. LC/MS: RT (min) = 5.03; (MH^+) 363.2. HRMS: (CI+, *m/z*), calcd for $C_{20}H_{19}N_4O_3$ (MH^+), 363.1457; found, 363.1463.

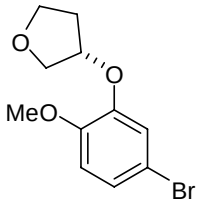


***N′*-(6-chloropyridazin-3-yl)-2,5-dimethoxybenzohydrazide (13).** ***Method A*:** To a stirred solution of 2,5-dimethoxybenzoic acid (**11**) (2.01 g, 11.02 mmol, 1.0 eq) in DMF (44.0 mL,

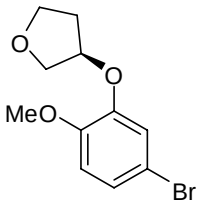
0.25M) under N_2 at rt was added 1,1′-carbonyldiimidazole (1.97 g, 14.95 mmol, 1.1 eq). After stirring for 30 min, 3-chloro-6-hydrazinopyridazine (**12**) (1.97 g, 12.12 mmol, 1.1 eq) was added and the solution was stirred at rt for an additional 1 h. The reaction mixture was poured into H_2O and the resultant precipitate was filtered, washed with H_2O then hexane, and dried under reduced pressure to provide hydrazide **13** (1.78 g, 52%) as a white solid. ***Method B*:** To a stirred solution of 2,5-dimethoxybenzoic acid (**11**) (2.10 g, 11.51 mmol, 1.0 eq) in Et_2O (46.0 mL, 0.25M) under N_2 at 0 °C was added DMF (45 μL, 42 mg, 0.58 mmol, 5 mol %) followed by oxalyl chloride (5.0 mL, 7.30 g, 57.50 mmol, 5.0 eq) slowly dropwise then warmed to rt and stirred for 1 h. The solution was concentrated under reduced pressure to give a viscous oil which was added slowly dropwise to a stirred solution of 3-chloro-6-hydrazinylpyridazine (**12**) (1.66 g, 11.51 mmol, 1.0 eq) and triethylamine (1.60 mL, 1.17 g, 11.51 mmol, 1.0 eq) in Et_2O (46.0 mL, 0.25M) under N_2 at rt. After stirring at rt for 1 h, the precipitate was filtered, washed with H_2O then hexane, and dried under reduced pressure to provide hydrazide **13** (3.40 g, 96%) as a white solid. R_f = 0.41 (CH_2Cl_2/MeOH 95:5); 0.58 (EtOAc). Mp 189 °C (dec.). IR (neat, diamond/ZnSe) 3309, 3210, 3185, 3069, 3039, 3002, 2966, 2943, 2837, 1665, 1641, 1595, 1579, 1526, 1492, 1453, 1408, 1313, 1283, 1261, 1215, 1176, 1160, 1135, 1081, 1064, 1040, 1020, 958, 931, 891, 875, 839, 805, 782, 765, 733, 712 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 10.21 (s, 1H, NH), 9.43 (s, 1H, NH), 7.58 (d, 1H, J = 9.0 Hz, aryl), 7.26 (d, 1H, J = 2.7 Hz, aryl), 7.07-7.14 (m, 3H, aryl), 3.88 (s, 3H, Me), 3.75 (s, 3H, Me). ^{13}C NMR (100 MHz, d_6-DMSO) δ 164.7, 160.0, 153.0, 151.1, 147.4, 129.5, 122.2, 117.9, 116.3, 114.9, 113.5, 56.4, 55.6. LC/MS: RT (min) = 4.20; (MH^+) 309.1. HRMS: (CI+, *m/z*), calcd for $C_{13}H_{14}ClN_4O_3$ (MH^+), 309.0754; found, 309.0754.



6-chloro-3-(2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (14). A solution of *N*′-(6-chloropyridazin-3-yl)-2,5-dimethoxybenzohydrazide (**13**) (569 mg, 1.84 mmol, 1.0 eq) in phosphorus oxychloride (9.2 mL, 0.2M) under N_2 was heated at 105 °C for 2 h. The reaction mixture was cooled to rt and concentrated under reduced pressure to give a residue. The crude material was diluted with CH_2Cl_2 and sat. aq. $NaHCO_3$ was added dropwise until pH 8 was obtained. The biphasic solution was separated and the aqueous layer was extracted with CH_2Cl_2 (1x). The organic layers were combined, washed with brine (1x), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave an oil, which was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as the eluent to give [1,2,4]triazolo[4,3-*b*]pyridazine **14** (457 mg, 85%) as a white solid. R_f = 0.43 (CH_2Cl_2/MeOH 95:5); 0.33 (EtOAc). Mp 111-112 °C. IR (neat, diamond/ZnSe) 3093, 2943, 2845, 1757, 1628, 1591, 1524, 1489, 1471, 1438, 1343, 1291, 1275, 1187, 1130, 1069, 1050, 1025, 971, 876, 862, 810, 782, 759, 735, 719, 709 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 8.52 (d, 1H, J = 9.4 Hz, aryl), 7.53 (d, 1H, J = 9.8 Hz, aryl), 7.17-7.23 (m, 2H, aryl), 7.12 (d, 1H, J = 2.4 Hz, aryl), 3.77 (s, 3H, Me), 3.72 (s, 3H, Me). ^{13}C NMR (100 MHz, d_6-DMSO) δ 153.0, 152.1, 148.9, 146.5, 143.1, 127.0, 122.8, 117.6, 116.8, 115.0, 113.7, 56.3, 55.7. LC/MS: RT (min) = 4.69; (MH^+) 291.0. HRMS: (CI+, *m/z*), calcd for $C_{13}H_{12}ClN_4O_2$ (MH^+), 291.0649; found, 291.0649.

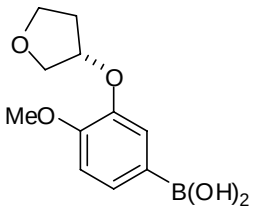


(*S*)-(+)-3-(5-bromo-2-methoxyphenoxy)tetrahydrofuran (46). To a stirred solution of 5-bromo-2-methoxyphenol (2.51 g, 12.36 mmol, 1.0 eq) in THF (124 mL, 0.1M) under N_2 at rt was sequentially added (*R*)-(-)-tetrahydrofuran-3-ol (1.19 mL, 1.30 g, 14.83 mmol, 1.2 eq), PPh_3 (5.19 g, 19.78 mmol, 1.6 eq), and DEAD (40 wt % in toluene) (9.0 mL, 8.61 g, 19.78 mmol, 1.6 eq). After stirring at rt for 16 h, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel using hexanes/EtOAc (3:1) as the eluent to give (*S*)-(2-methoxyphenoxy)THF **46** (2.59 g, 78%) as a white solid. R_f = 0.36 (hexane/EtOAc 3:1); R_f = 0.56 (hexane/EtOAc 1:1). Mp 66-68 °C. $[\alpha]_D^{23}$ 9.8 (c 2.44, MeOH). IR (neat, diamond/ZnSe) 3017, 2977, 2949, 2915, 2855, 1587, 1498, 1467, 1436, 1399, 1349, 1322, 1251, 1218, 1182, 1132, 1094, 1065, 1021, 991, 968, 911, 892, 844, 796 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 7.07-7.09 (m, 2H, aryl), 6.93 (d, 1H, *J* = 8.2 Hz, aryl), 5.02 (m, 1H), 3.71-3.86 (m, 4H), 3.74 (s, 3H, Me), 2.13-2.22 (m, 1H), 1.91-1.99 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 149.1, 147.5, 123.7, 117.3, 113.9, 111.6, 78.3, 72.1, 66.4, 55.7, 32.3. LC/MS: RT (min) = 5.51; (MH^+) 273.0. HRMS: (CI+, *m/z*), calcd for $C_{11}H_{14}BrO_3$ (MH^+), 273.0126; found, 273.0127.



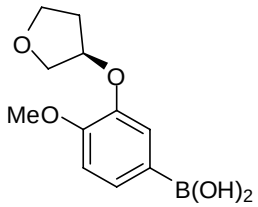
(*R*)-(-)-3-(5-bromo-2-methoxyphenoxy)tetrahydrofuran (47). To a stirred solution of 5-bromo-2-methoxyphenol (2.50 g, 12.33 mmol, 1.0 eq) in THF (123 mL, 0.1M) under N_2 at rt

was sequentially added (*S*)-(+)-tetrahydrofuran-3-ol (1.19 mL, 1.30 g, 14.80 mmol, 1.2 eq), PPh_3 (5.18 g, 19.73 mmol, 1.6 eq), and DEAD (40 wt % in toluene) (9.0 mL, 8.59 g, 19.73 mmol, 1.6 eq). After stirring at rt for 16 h, the reaction mixture was concentrated under reduced pressure and purified by column chromatography on silica gel using hexanes/EtOAc (3:1) as the eluent to give (*R*)-(2-methoxyphenoxy)THF **47** (2.61 g, 78%) as a white solid. R_f = 0.36 (hexane/EtOAc 3:1); R_f = 0.56 (hexane/EtOAc 1:1). Mp 66-68 °C. $[\alpha]_D^{23}$ -10.3 (c 2.42, MeOH). IR (neat, diamond/ZnSe) 3017, 2977, 2949, 2915, 2855, 1587, 1498, 1468, 1435, 1399, 1349, 1323, 1252, 1218, 1182, 1132, 1095, 1065, 1021, 992, 968, 912, 892, 844, 796 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 7.07-7.09 (m, 2H, aryl), 6.93 (d, 1H, *J* = 8.2 Hz, aryl), 5.02 (m, 1H), 3.69-3.86 (m, 4H), 3.74 (s, 3H, Me), 2.13-2.22 (m, 1H), 1.91-1.99 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 149.1, 147.5, 123.7, 117.3, 113.9, 111.6, 78.3, 72.1, 66.4, 55.7, 32.3. LC/MS: RT (min) = 5.51; (MH^+) 273.0. HRMS: (CI+, *m/z*), calcd for $C_{11}H_{14}BrO_3$ (MH^+), 273.0126; found, 273.0127.



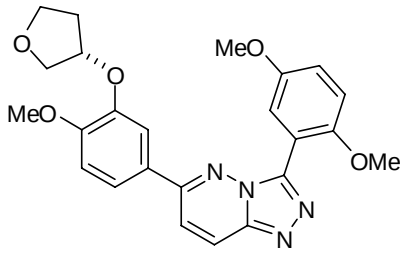
(*S*)-(+)-4-methoxy-3-(tetrahydrofuran-3-yloxy)phenylboronic acid (15). To a stirred of (*S*)-(+)-3-(5-bromo-2-methoxyphenoxy)tetrahydrofuran (**46**) (405 mg, 1.48 mmol, 1.0 eq) in THF (7.4 mL, 0.2M) under N_2 at -78 °C was added *n*-butyllithium (1.6M in hexane) (1.0 mL, 1.63 mmol, 1.1 eq) dropwise. After stirring at -78 °C for 1 h, trimethylborate (0.25 mL, 231 mg, 2.23 mmol, 1.5 eq) was added dropwise to the solution which was stirred an additional 1 h at -78 °C then warmed to rt. After stirring at rt for 16 h, the reaction mixture was quenched with sat. aq. NH_4Cl and concentrated under reduced pressure. The residue was adjusted to pH 3 by addition

of aq. 10% HCl soln. and extracted with CH_2Cl_2 (3x). The combined organic layers were diluted with brine and the biphasic solution was stirred at rt for 20 min. Subsequently, the organic layer was separated, dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a pasty, yellowish-white solid, which was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as the eluent to give the (*S*)-phenylboronic acid **15** (315 mg, 89%) as a white solid. R_f = 0.40 (CH_2Cl_2/MeOH 95:5). Mp 198-200 °C. $[\alpha]_D^{23}$ 8.0 (c 1.18, MeOH). IR (neat, diamond/ZnSe) 3360, 2954, 2941, 2866, 2837, 1595, 1517, 1412, 1348, 1319, 1252, 1213, 1179, 1136, 1110, 1077, 1019, 970, 909, 878, 814, 774, 743, 714, 674 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 7.47 (dd, 1H, *J* = 1.2, 7.8 Hz, aryl), 7.35 (d, 1H, *J* = 1.2 Hz, aryl), 7.00 (d, 1H, *J* = 8.2 Hz, aryl), 5.01 (m, 1H), 3.73-3.90 (m, 4H), 3.78 (s, 3H, Me), 2.12-2.21 (m, 1H), 1.99-2.05 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 151.2, 145.7, 127.5, 120.0, 111.8, 78.1, 72.4, 66.4, 55.4, 32.6. LC/MS: RT (min) = 3.53; (MH^+) 239.1. HRMS: (CI+, *m/z*), calcd for $C_{11}H_{16}BO_5$ (MH^+), 239.1091; found, 239.1092.



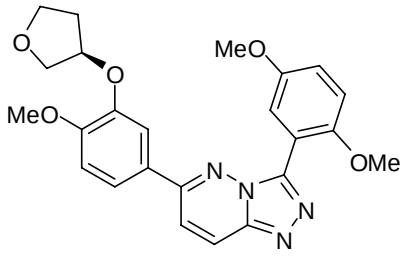
(*R*)-(-)-4-methoxy-3-(tetrahydrofuran-3-yloxy)phenylboronic acid (16). To a stirred of (*R*)-(-)-3-(5-bromo-2-methoxyphenoxy)tetrahydrofuran (**47**) (405 mg, 1.48 mmol, 1.0 eq) in THF (7.4 mL, 0.2M) under N_2 at -78 °C was added *n*-butyllithium (1.6M in hexane) (1.0 mL, 1.63 mmol, 1.1 eq) dropwise. After stirring at -78 °C for 1 h, trimethylborate (0.25 mL, 231 mg, 2.22 mmol, 1.5 eq) was added dropwise to the solution which was stirred an additional 1 h at -78 °C then warmed to rt. After stirring at rt for 16 h, the reaction mixture was quenched with sat. aq. NH_4Cl

and concentrated under reduced pressure. The residue was adjusted to pH 3 by addition of aq. 10% HCl soln. and extracted with CH_2Cl_2 (3x). The combined organic layers were diluted with brine and the biphasic solution was stirred at rt for 20 min. Subsequently, the organic layer was separated, dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a pasty, yellowish-white solid, which was purified by column chromatography on silica gel using CH_2Cl_2/MeOH (95:5) as the eluent to give the (*R*)-phenylboronic acid **16** (309 mg, 87%) as a white solid. R_f = 0.40 (CH_2Cl_2/MeOH 95:5). Mp 198-200 °C. $[\alpha]_D^{23}$ -8.6 (c 1.16, MeOH). IR (neat, diamond/ZnSe) 3358, 2954, 2941, 2865, 2838, 1595, 1517, 1413, 1348, 1319, 1251, 1213, 1179, 1136, 1110, 1077, 1019, 970, 909, 878, 814, 774, 743, 714, 674 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 7.47 (dd, 1H, *J* = 1.2, 7.8 Hz, aryl), 7.35 (d, 1H, *J* = 1.2 Hz, aryl), 7.00 (d, 1H, *J* = 8.2 Hz, aryl), 5.01 (m, 1H), 3.73-3.90 (m, 4H), 3.78 (s, 3H, Me), 2.11-2.21 (m, 1H), 1.99-2.05 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 151.1, 145.7, 127.4, 120.0, 111.8, 78.1, 72.4, 66.4, 55.4, 32.6. LC/MS: RT (min) = 3.54; (MH^+) 239.1. HRMS: (CI+, *m/z*), calcd for $C_{11}H_{16}BO_5$ (MH^+), 239.1091; found, 239.1091.



(*S*)-(+)-3-(2,5-dimethoxyphenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (17). To a suspension of 6-chloro-3-(2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (**14**) (115 mg, 0.39 mmol, 1.0 eq) in DME (3.9 mL, 0.1M) in a microwave tube was added (*S*)-(+)-4-methoxy-3-(tetrahydrofuran-3-yloxy)phenylboronic acid

(**15**) (282 mg, 1.18 mmol, 3.0 eq), $Pd(PPh_3)_4$ (23 mg, 20.00 μmol, 5 mol %), and 2.0M aq. Na_2CO_3 soln. (0.39 mL, 0.79 mmol, 2.0 eq). The solution was sparged with Ar for 5 min and then heated at 90 °C in a microwave for 30 min. After cooling to rt, the reaction mixture was diluted with EtOAc and filtered through a silica gel plug. The filtrate was washed with brine (1x), dried over $MgSO_4$, and filtered. Removal of the solvent under reduced pressure gave a residue, which was purified by semi-preparative HPLC to give [1,2,4]triazolo[4,3-*b*]pyridazine **17** (63 mg, 35%) as a white solid. R_f = 0.40 (CH_2Cl_2/MeOH 95:5); 0.06 (EtOAc). Mp 120-121 °C. $[\alpha]_D^{23}$ 17.3 (c 1.04, CH_2Cl_2). IR (neat, diamond/ZnSe) 3083, 2939, 2838, 1601, 1586, 1514, 1485, 1465, 1427, 1383, 1356, 1329, 1303, 1276, 1256, 1217, 1179, 1153, 1112, 1070, 1042, 1019, 1001, 976, 902, 870, 804, 779, 758, 745, 706, 678, 659 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 8.45 (d, 1H, *J* = 9.8 Hz, aryl), 8.01 (d, 1H, *J* = 9.8 Hz, aryl), 7.66 (dd, 1H, *J* = 2.2, 8.4 Hz, aryl), 7.53 (d, 1H, *J* = 2.0 Hz, aryl), 7.18-7.25 (m, 3H, aryl), 7.15 (d, 1H, *J* = 8.6 Hz, aryl), 5.02 (m, 1H), 3.75-3.88 (m, 4H), 3.83 (s, 3H, Me), 3.78 (s, 3H, Me), 3.74 (s, 3H, Me), 2.11-2.20 (m, 1H), 1.95-2.01 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 152.9, 152.2, 152.0 (2C), 146.7 (2C), 143.5, 126.4, 124.6, 121.1, 119.8, 117.1, 116.9, 115.7, 113.2, 112.9, 112.4, 78.2, 72.2, 66.4, 56.2, 55.7, 55.6, 32.4. LC/MS: RT (min) = 4.99; (MH^+) 449.1. HRMS: (CI+, *m/z*), calcd for $C_{24}H_{25}N_4O_5$ (MH^+), 449.1825; found, 449.1829.



(*R*)-(-)-3-(2,5-dimethoxyphenyl)-6-(4-methoxy-3-(tetrahydrofuran-3-yloxy)phenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (18). To a suspension of 6-chloro-3-(2,5-dimethoxyphenyl)-[1,2,4]triazolo[4,3-*b*]pyridazine (**14**) (529 mg, 1.82 mmol, 1.0 eq) in THF (9.1 mL, 0.2M) in a microwave tube was added (*R*)-(-)-4-methoxy-3-(tetrahydrofuran-3-yloxy)phenylboronic acid (**16**) (1.30 g, 5.46 mmol, 3.0 eq), $Pd(OAc)_2$ (20 mg, 91.0 μmol, 5 mol %), and KF (317 mg, 5.46 mmol, 3.0 eq). The solution was sparged with Ar for 5 min and then heated at 90 °C in a microwave for 45 min. After cooling to rt, the reaction mixture was filtered through an SPE column which was then flushed with MeOH. The combined filtrate was concentrated under reduced pressure to give a residue, which was purified by semi-preparative HPLC to give [1,2,4]triazolo[4,3-*b*]pyridazine **18** (692 mg, 85%) as a white solid. R_f = 0.40 (CH_2Cl_2/MeOH 95:5); 0.06 (EtOAc). Mp 120-121 °C. $[\alpha]_D^{23}$ -19.2 (c 1.04, CH_2Cl_2). IR (neat, diamond/ZnSe) 3082, 2935, 2838, 1599, 1584, 1515, 1486, 1468, 1428, 1386, 1355, 1331, 1304, 1274, 1256, 1217, 1183, 1148, 1140, 1114, 1090, 1072, 1040, 1018, 1000, 979, 909, 864, 834, 804, 784, 761, 750, 733, 704, 678, 660 cm^{-1}. ^1H NMR (400 MHz, d_6-DMSO) δ 8.45 (d, 1H, *J* = 9.8 Hz, aryl), 8.01 (d, 1H, *J* = 9.8 Hz, aryl), 7.66 (dd, 1H, *J* = 2.2, 8.4 Hz, aryl), 7.53 (d, 1H, *J* = 2.0 Hz, aryl), 7.18-7.25 (m, 3H, aryl), 7.14 (d, 1H, *J* = 8.6 Hz, aryl), 5.02 (m, 1H), 3.75-3.88 (m, 4H), 3.83 (s, 3H, Me), 3.78 (s, 3H, Me), 3.74 (s, 3H, Me), 2.11-2.20 (m, 1H), 1.95-2.01 (m, 1H). ^{13}C NMR (100 MHz, d_6-DMSO) δ 152.9, 152.2, 152.0 (2C), 146.7 (2C), 143.5, 126.4, 124.7, 121.1, 119.8, 117.1, 116.9, 115.7, 113.2, 112.9, 112.4, 78.2, 72.2, 66.4, 56.2, 55.7, 55.6, 32.4. LC/MS: RT (min) = 4.99; (MH^+) 449.1. HRMS: (CI+, *m/z*), calcd for $C_{24}H_{25}N_4O_5$ (MH^+), 449.1825; found, 449.1823.