Supporting Information

Easy-to-Synthesize Spirocyclic Compounds Possess Remarkable *In Vivo* Activity Against *Mycobacterium Tuberculosis*

Ana Guardia,[†] Jessica Baiget,[‡] Mónica Cacho,[†] Arancha Pérez,[†] Montserrat Ortega-Guerra,[†] Winston Nxumalo,[†] Setshaba D. Khanye,[†] Joaquín Rullas,[†] Fátima Ortega,[†] Elena Jiménez,[†] Esther Pérez-Herrán,[†] María Teresa Fraile-Gabaldón,[†] Jorge Esquivias,[†] Raquel Fernández,[†] Esther Porras-De Francisco,[†] Lourdes Encinas,[†] Marta Alonso,[†] Ilaria Giordano,[†] Cristina Rivero,[†] Juan Miguel-Siles,[†] Javier G. Osende,[‡] Katrina A. Badiola,[‡] Peter J. Rutledge,[‡] Matthew H. Todd,*[‡§] Modesto Remuiñán,[†] and Carlos Alemparte*[†]

[†]*GlaxoSmithKline, Tres Cantos Medicines Development Campus, Severo Ochoa 2, 28760 Tres Cantos, Madrid, Spain*

[‡]*School of Chemistry, The University of Sydney, NSW 2006, Australia*

[§]*School of Pharmacy, University College London, 29-39 Brunswick Square, London WC1N 1AX, UK*

TABLE OF CONTENTS

Synthetic Procedures

General Procedure A. Reductive amination

A solution of secondary amine (1 equiv) and the appropriate aldehyde (1–1.1 equiv) in CH_2Cl_2 or DCE (molarity 0.05–0.14 M) was stirred at rt for 1–4 h. Sodium triacetoxyborohydride or solid-supported Amberlite® IRA-900 cyanoborohydride (1–6 equiv) was added and the reaction was stirred at room temperature or 40–100 ºC for 1.5–48 h. After allowing to cool, the reaction was quenched by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, the organic layer was dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by column chromatography and/or preparative HPLC to give the corresponding tertiary amine.

General Procedure B. Reductive amination

A solution of secondary amine (1 equiv), the appropriate aldehyde (1–1.1 equiv), Biotage® MP-Cyanoborohydride (1.7 equiv) or solid-supported Amberlite® IRA-900 cyanoborohydride (1–1.7 equiv) and acetic acid (4 equiv) in CH_2Cl_2 (molarity 0.06–0.16 M) was subjected to MW irradiation for 40–180 min at 100 ºC. The reaction was filtered, quenched by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2. The organic layer was dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by column chromatography or preparative HPLC to give the corresponding tertiary amine.

General Procedure C. Reductive amination

A solution of primary or secondary amine (1 equiv), tetraisopropoxytitanium oxide (1.6–2 equiv) and the appropriate aldehyde or ketone (1–1.1 equiv), under nitrogen atmosphere, in THF or CH_2Cl_2 (molarity 0.1–0.4 M), was stirred at rt for 1 h. Sodium borohydride (1.6–3 equiv) and EtOH or MeOH (0.2–3.6 M) were added and the reaction was stirred at room temperature for 12–36 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution and extracted with CH_2Cl_2, the organic layer was dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by flash column chromatography to give the corresponding tertiary amine.

General Procedure D. Paal Knorr reaction.

A mixture of the corresponding aniline (1.1 equiv), 2,5-hexanedione (1 equiv) and *p*-toluenesulfonic acid monohydrate (0.1 equiv) in toluene (0.25 M) was heated in a Dean-Stark apparatus at 110 ˚C for 12–20 h. After allowing to cool, the solvent was evaporated, the crude material was dissolved in hot EtOH (5.3 M), and a mixture of EtOH (1.1 M) and aqueous solution of 10 % citric acid (5.3 M) was added. The mixture was cooled to 10 ˚C with periodic manual shaking, and the resulting powder was filtered and washed with water to obtain the desired product. In some cases, when no solid appeared, the solution was extracted with EtOAc, the organic layer was dried ($MgSO_4$), filtered and concentrated to afford a crude mixture which was purified by flash column chromatography.

General Procedure E. Pyrrole formylation

Phosphoryl chloride (11.2 equiv) was added to DMF (1.2 M) at 0˚C under an argon atmosphere. After 30 min, a solution of the corresponding pyrrole (1 equiv) in DMF (1 M) was added dropwise over 10 min. The reaction was allowed to warm to room temperature and stirred for 1 h. The reaction mixture was poured onto ice and the pH adjusted to 7 with 20% NaOH solution and stirred at room temperature overnight. The pH was raised again until pH 11 and the reaction mixture was stirred for 30 min. The solid that precipitated was filtered, washed with water and purified by recrystallization with a mixture of acetonitrile/water (1/1) to obtain the desired product. In some cases, when no solid precipitated, the solution was extracted with EtOAc, the organic layer was dried ($MgSO_4$), filtered and concentrated to afford the desired product.

General Procedure F. Formation of amine precursor: Oxa–Pictet–Spengler reaction and Cbz-deprotection

This procedure was adapted from the literature.[1] To a vigorously stirred solution of the alcohol (1 equiv), the appropriate aldehyde or ketone (1–1.3 equiv), sodium sulfate (1.3–1.7 equiv) in acetonitrile (0.1 M of the alcohol) was added *p*-toluenesulfonic acid monohydrate (2.3 equiv) dropwise. The reaction mixture was refluxed overnight. The reaction was filtered and concentrated. The crude was dissolved in CH_2Cl_2 (50 mL) and washed with 2 M aqueous NaOH (50 mL). The organic layer was separated, dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that

was purified by flash chromatography or preparative HPLC to give to the corresponding *N*-Cbz cyclized product.

TMSI (2–3 equiv) was added to a solution of *N*-Cbz cyclized product. (1 equiv) in CH_2Cl_2 (0.07–0.17 M) under argon atmosphere. The reaction was stirred at rt for 1–1.5 h, the volatiles were evaporated under reduced pressure, and the crude was purified using an ion exchange column (SCX-2) and/or preparative HPLC to obtain the corresponding amine.

1-(Benzofuran-2-ylmethyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (2)

The title compound was prepared using General Procedure A. Yield 88% (28.6 mg, 0.084 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.59 (bd, 1H, *J*=7.3), 7.54 (bd, 1H, *J*=7.6), 7.26 (dt, 1H, *J*=7.3, *J*=1.3), 7.25 (d, 1H, *J*=5.3), 7.21 (dt, 1H, *J*=7.6, *J*=1.3), 6.94 (d, 1H, *J*=5.1), 6.78 (s, 1H), 3.82 (t, 2H, *J*=5.3), 3.68 (s, 2H), 2.74–2.66 (m, 4H), 2.44–2.37 (m, 2H), 1.94–1.86 (m, 2H), 1.75–1.70 (m, 2H). [ES+ MS] m/z 340 $(M+H)^+$.

1-(Benzofuran-2-ylmethyl)-4',5'-dihydrospiro[piperidine-4,7'-thieno[2,3-c]pyran] (3)

The title compound was prepared using General Procedure A. Yield 72% (23.4 mg, 0.069 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.59 (bd, 1H, *J*=7.3), 7.54 (bd, 1H, *J*=7.6), 7.34 (d, 1H, *J*=4.8), 7.27 (dt, 1H, *J*=7.3, *J*=1.3), 7.21 (dt, 1H, *J*=7.6, *J*=1.3), 6.81 (d, 1H, *J*=5.1), 6.78 (s, 1H), 3.82 (t, 2H, *J*=5.6), 3.70 (s, 2H), 2.73–2.67 (m, 2H), 2.59 (t, 2H, *J*=5.6), 2.46–2.39 (m, 2H), 1.96–1.90 (m, 2H), 1.83–1.75 (m, 2H). [ES+ MS] m/z 340 $(M+H)^+$.

1'-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)spiro[isochroman-1,4'-piperidine], trifluoroacetic acid salt (4)

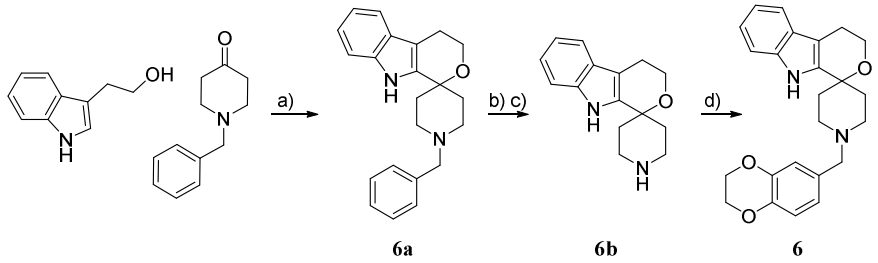
The title compound was prepared using General Procedure A. HPLC purification under acidic conditions afforded the compound as the TFA salt. White solid, yield 19% (35 mg, 0.075 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.24–7.08 (m, 4H), 7.05 (bd, 1H, *J*=1.8), 7.00–6.90 (m, 2H), 4.26 (s,

4H), 4.24 (s, 2H), 3.92 (t_{app}, 2H, *J*=5.6), 3.37 (bd, 4H), 2.82 (t_{app}, 2H, *J*=5.6), 2.28–2.16 (m, 2H), 2.15–2.06 (m, 2H). [ES+ MS] m/z 352 $(M+H)^+$.

1'-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-6-methoxyspiro[isochroman-1,4'-piperidine (5)

The title compound was prepared using General Procedure A. Yield 66% (21.5 mg, 0.056 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.12 (d, 1H, *J*=8.6), 6.80–6.72 (m, 4H), 6.64 (d, 1H, *J*=2.8), 4.21 (s, 4H), 3.78 (t, 2H, *J*=5.6), 3.70 (s, 3H), 3.37 (s, 2H), 2.69 (t, 2H, *J*=5.3), 2.59–2.57 (m, 2H), 2.30–2.24 (m, 2H), 1.89-1.81 (m, 2H), 1.73–1.69 (m, 2H). [ES+ MS] m/z 382 $(M+H)^+$.

Synthesis of compound 6[2, 3]



Reagents and Conditions: a) MsOH, toluene, 80°C, 3 h; b) 1-chloroethyl chloroformate, THF, –78°C, 90 min; c) MeOH, 65°C, 1 h; d) General Procedure A.

1-Benzyl-4',9'dihydro-3'H-spiro[piperidine-4,1'-pyrano[3,4-b]indole] (6a)

A mixture of 1-benzyl-4-piperidone (0.230 mL, 1.30 mmol), 3-(2-hydroxyethyl)indole (0.210 g, 1.30 mmol), methanesulfonic acid (86 µL, 1.32 mmol) in toluene (15 mL) was heated at 80 ºC for 3 h. After allowing to cool, EtOAc (15 mL), saturated $NaHCO_3$ solution (10 mL) and potassium hydroxide (1 g) were added. The phases were separated and the aqueous fraction was extracted with EtOAc (3 × 30 mL). The combined organic layer was dried (Na_2SO_4), filtered and concentrated to afford a crude mixture which was purified by flash chromatography to obtain the title compound. Foamy yellow powder, yield 43% (186 mg, 0.559 mmol). ^{1}H NMR (500 MHz, $CDCl_3$) δ ppm 7.88 (br s, 1H), 7.48

(br d, 1H, *J*=7.7), 7.37–7.27 (m, 6H), 7.15 (t_{app}, 1H, *J*=7.0), 7.10 (t_{app}, 1H, *J*=7.1), 3.99 (t, 2H, *J*=5.4) , 3.60 (s, 2H), 2.81–2.79 (m, 4H), 2.52–2.47 (m, 2H), 2.12–1.96 (m, 4H).

4',9'-Dihydro-3'H-spiro[piperidine-4,1'-pyrano[3,4-b]indole] (6b)

1-Chloroethyl chloroformate (0.460 mL, 4.33 mmol) was added to a stirred solution of **6a** (0.575 g, 1.73 mmol) in anhydrous THF (45 mL) under argon at –78 ºC. The reaction mixture was stirred for 90 min at –78 ºC and allowed to warm to rt. After 2 h, the solvent was evaporated, the residue suspended in methanol (40 mL) and the mixture heated at reflux for 1 h. The solution was concentrated to give the crude product which was purified by flash chromatography to obtain the title compound. White solid, yield 49% (203 mg, 0.841 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm 8.90 (br s, 1H), 7.50 (d, 1H, *J*=7.7), 7.38 (d, 1H, *J*=7.9), 7.21–7.09 (m, 2H), 3.99 (t, 2H, *J*=5.2), 3.47–3.43 (m, 5H), 2.83 (t, 2H, *J*=5.2), 2.66–2.55 (m, 2H), 2.17–2.12 (m, 2H).

1-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)methyl)-4',9'-dihydro-3'H-spiro[piperidine-4,1'-pyrano[3,4-b]indole] (6)

The title compound was prepared using the General Procedure A with **6b**. Yellow powder, yield 25% (53 mg, 0.136 mmol)**.** ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.15 (br s, 1H), 7.48 (d, 1H, *J*=7.5), 7.32 (d, 1H, *J*=7.7), 7.18–7.07 (m, 2H), 6.91–6.80 (m, 3H), 4.25 (s, 4H), 3.98 (t, 2H, *J*=5.3), 3.54 (s, 2H), 2.85–2.78 (m, 4H), 2.56–2.49 (m, 2H), 2.20–2.09 (m, 2H) 1.99–1.94 (m, 2H). [ES+ MS] m/z 391 $(M+H)^+$.

1-(2,3-Dihydro-1,4-benzodioxin-6-ylcarbonyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (8)

EDCI (41.6 mg, 0.217 mmol) was added to a solution of amine **7**[4] (43.3 mg, 0.207 mmol), 1,4-benzodioxane-6-carboxylic acid (39.1 mg, 0.217 mmol) and 1-hydroxy-1H-benzotriazol hydrate (33.3 mg, 0.217 mmol) in CH_2Cl_2 (20 mL). The resulting mixture was stirred at room temperature for 6 h. The reaction was quenched by addition of saturated $NaHCO_3$ solution (20 mL) and extracted with

CH_2Cl_2 (3 × 20 mL), the combined organic layer was dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by flash column chromatography to obtain the title compound. White solid, yield 66% (53.1 mg, 0.137 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (d, 1H, *J*=4.0), 7.00 (s, 1H), 6.96–6.94 (m, 1H), 6.88 (d, 1H, *J*=8.0), 6.75 (d, 1H, *J*=4.0), 4.57 (bs, 1H), 4.27 (s, 4H), 3.95 (t, 2H, *J*=4.0), 3.76 (bs, 1H), 3.40–3.24 (m, 2H), 2.84 (t, 2H, *J*=4.0), 1.86 (bs, 4H). [ES+ MS] m/z 372 $(M+H)^+$.

1-((2,3-Dihydrobenzo[b][1,4]dioxin-6-yl)sulfonyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (**9**)

2,3-Dihydrobenzo[b][1,4]dioxine-6-sulfonyl chloride (22.5 mg, 0.096 mmol) was added to a solution of 6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (20 mg, 0.096 mmol) and triethylamine (27 µL, 0.19 mmol) in CH_2Cl_2 (2 mL) at 0 ºC. The resulting mixture was stirred at room temperature for 2 h. The reaction was quenched with aqueous citric acid and the organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by flash column chromatography to obtain the title compound. Yield 40%. (15.6 mg, 0.038 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.29 (d, 1H, *J*=5.1), 7.24–7.20 (m, 2H), 7.12 (d, 1H, *J*=8.3), 6.97 (d, 1H, *J*=5.3), 4.38–4.32 (m, 4H), 3.75 (t, 2H, *J*=5.6), 3.54–3.48 (m, 2H), 2.70 (t, 2H, *J*=5.3), 2.47–2.44 (m, 2H), 2.00–1.92 (m, 2H), 1.82–1.79 (m, 2H). [ES+ MS] m/z 408 $(M+H)^+$.

***N*-(2,3-Dihydrobenzo[*b*][1,4]dioxin-6-yl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-*c*]pyran]-1-carboxamide (10)**

6-Isocyanato-2,3-dihydrobenzo[*b*][1,4]dioxine (19.7 µL, 0.143 mmol) was added to a solution of 6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (30 mg, 0.143 mmol), diisopropylethylamine (one drop) in THF (1 mL) at 0 ºC under argon atmosphere. The reaction mixture was stirred for 2 h at 0 ºC. The reaction was quenched with aqueous citric acid and the organic phase was washed with saturated $NaHCO_3$ solution, dried (Na_2SO_4), filtered and concentrated to afford a crude mixture that was purified by flash column chromatography to obtain the title compound. Yield 19% (10.5 mg, 0.027 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 8.30 (s, 1H), 7.28 (d, 1H, *J*=5.3), 7.07 (d, 1H, *J*=2.3),

6.96 (d, 1H, *J*=5.3), 6.89 (dd, 1H, *J*=2.3 and 8.6), 6.70 (d, 1H, *J*=8.8), 4.21–4.15 (m, 4H), 4.03–3.97 (m, 2H), 3.91 (t, 2H, *J*=5.3), 3.08–3.01 (m, 2H), 2.78 (t, 2H, *J*=5.3), 1.86–1.74 (m, 4H). [ES+ MS] m/z 387 $(M+H)^+$.

6',7'-Dihydrospiro[pyrrolidine-3,4'-thieno[3,2-c]pyran] (11)

The title compound was prepared using General Procedure F. Yellow oil, yield 77% (0.07 g, 0.3 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.30 (d, 1H, *J*=5.3), 6.93 (d, 1H, *J*=5.3), 3.84–3.81 (m, 2H), 3.01–2.74 (m, 6H), 2.02–1.82 (m, 2H). [ES+ MS] m/z 196 $(M+H)^+$.

1-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)-6',7'-dihydrospiro[pyrrolidine-3,4'-thieno[3,2-c]pyran] (12)

The title compound was prepared using General Procedure B with compound **11**. Pale yellow solid, yield 37% (47.6 mg, 0.134 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.31 (d, 1H, *J*=5.3), 6.93 (d, 1H, *J*=5.3), 6.79–6.74 (m, 3H), 4.20 (s, 4H), 3.84–3.78 (m, 2H), 3.55–3.43 (m, 2H), 2.74–2.61 (m, 6H), 2.09–1.95 (m, 2H). [ES+ MS] m/z 344 $(M+H)^+$.

2-(6,7-Dihydro-4H-thieno[3,2-c]pyran-4-yl)ethanamine (13)

The title compound was prepared using General Procedure F. Pale yellow oil. Yield 25% (120 mg, 0.655 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.11 (d, 1H, *J*=5.3), 6.77 (d, 1H, *J*=5.1), 4.81–4.78 (m, 1H), 4.22–4.18 (m, 1H), 3.79–3.74 (m, 1H), 3.02–2.72 (m, 4H), 2.04–1.84 (m, 2H).

***N*-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)-2-(6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl)ethanamine (14)**

The title compound was prepared using General Procedure C with compound **13**. Yield 4% (8.4 mg, 0.023 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.10 (d, 1H, *J*=5.3), 6.86–6.82 (m, 3H), 6.72 (d, 1H, *J*=5.3), 4.83–4.76 (m, 1H), 4.24 (s, 4H), 4.22–4.18 (m, 1H), 3.79–3.70 (m, 3H), 3.00–1.98 (m, 7H). [ES+ MS] m/z 332 $(M+H)^+$.

_N_-(2,3-Dihydro-1,4-benzodioxin-6-ylmethyl)-2-(4-methyl-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl)ethanamine (15)

Triethylamine (0.185 mL, 1.324 mmol) and methanesulfonyl chloride (0.061 mL, 0.794 mmol) were added to a solution of 2-(4-methyl-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl)ethanol (0.105 g, 0.530 mmol) in CH_2Cl_2 (2 mL) at 0 ºC under nitrogen. The reaction was allowed to warm to rt and stirred overnight. The reaction mixture was concentrated and the residue was dissolved in CH_2Cl_2 (30 mL) and washed with saturated $NaHCO_3$ solution (25 mL). The organic layer was dried (Na_2SO_4), filtered and concentrated to provide the crude 2-(4-methyl-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl)ethyl methanesulfonate as a yellow oil which was used in the next step without further purification.

To a solution of the crude 2-(4-methyl-6,7-dihydro-4H-thieno[3,2-c]pyran-4-yl)ethyl methanesulfonate (0.150 g) and 2,3-dihydro-1,4-benzodioxin-6-ylmethylamine (0.179 g, 1.085 mmol) in acetonitrile (2 mL) was added triethylamine (0.151 mL, 1.085 mmol) and the reaction was heated at 75 °C under nitrogen overnight. After allowing to cool, the reaction was filtered and concentrated to obtain a reaction crude that was purified using an ion exchange SCX Column (SCX-2) and preparative HPLC to obtain the title compound. Colorless oil, yield 15% (27.1 mg, 0.079 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.26 (d, 1H, *J*=5.3), 6.86 (d, 1H, *J*=5.1), 6.75–6.67 (m, 3H), 4.19 (s, 4H), 3.90–3.73 (m, 2H), 3.51–3.44 (m, 2 H), 2.75–2.63 (m, 2H), 2.50–2.46 (m, 1H), 2.30–2.24 (m, 1H), 1.98–1.80 (m, 2H), 1.34 (s, 3H). [ES+ MS] m/z 346 $(M+H)^+$.

1-(Chroman-6-ylmethyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (16)

The title compound was prepared using General Procedure A. Colorless oil, yield 37% (32 mg, 0.090 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.16–7.11 (m, 3H), 6.90 (d, 1H, *J*=5.3), 6.83 (d, 1H, *J*=8.1), 4.28–4.25 (m, 2H), 4.03–4.00 (m, 2H), 3.55 (s, 2H), 2.92–2.81 (m, 6H), 2.48–2.42 (m, 2H), 2.12–2.04 (m, 4H), 1.95–1.92 (m, 2H). [ES+ MS] m/z 356 $(M+H)^+$.

1-((5,6,7,8-Tetrahydronaphthalen-2-yl)methyl)-6',7'-dihydrospiro[piperidine-

4,4'-thieno[3,2-c]pyran] (17)

The title compound was prepared using General Procedure B. Colorless oil, yield 37% (33.5 mg, 0.090 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.09–7.02 (m, 4H), 6.83 (d, 1H, *J*=5.3), 3.94 (t, 2H, *J*=5.3), 3.51 (bs, 2H), 2.83 (t, 2H, *J*=5.3), 2.78–2.77 (m, 6H), 2.42–2.36 (m, 2H), 2.04–1.96 (m, 2H), 1.88–1.79 (m, 6H). [ES+ MS] m/z 354 $(M+H)^+$.

1-(2,3-Dihydro[1,4]dioxino[2,3-c]pyridin-7-ylmethyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (18)

The title compound was prepared using General Procedure B. Pale solid, yield 2% (3.7 mg, 0.009 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.15 (s, 1H), 7.08 (d, 1H, *J*=4.0), 6.93 (s, 1H), 6.82 (d, 1H, *J*=4.0), 4.35–4.33 (m, 2H), 4.30–4.28 (m, 2H), 3.93 (t, 2H, *J*=4.0), 3.59 (s, 2H), 2.83 (t, 2H, *J*=4.0), 2.76–2.73 (m, 2H), 2.51–2.45 (m, 2H), 2.07–1.99 (m, 2H), 1.87–1.83 (m, 2H). [ES+ MS] m/z 359 $(M+H)^+$.

1-[(4-Methylphenyl)methyl]-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (20)

The title compound was prepared using General Procedure B. Colorless oil, yield 35% (28 mg, 0.085 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.26 (d, 2H, *J*=8.1), 7.16 (d, 2H, *J*=7.8), 7.08 (d, 1H, *J*=5.3), 6.83 (d, 1H, *J*=5.1), 3.93 (t, 2H, *J*=5.3), 3.54 (bs, 2H), 2.83 (t, 2H, *J*=5.3), 2.75–2.72 (m, 2H), 2.42–2.36 (m, 2H), 2.35 (s, 3H), 2.04–1.93 (m, 2H), 1.89–1.81 (m, 2H). [ES+ MS] m/z 314 (M+H)+.

1-(3-Methylbenzyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (**21**)

The title compound was prepared using General Procedure B. Colorless oil, yield 54% (55 mg, 0.167 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.24–7.14 (m, 3H), 7.09–7.07 (m, 2H), 6.83 (d, 1H, *J*=5.3), 3.95–3.93 (m, 2H), 3.54 (s, 2H), 2.85–2.82 (m, 2H), 2.76–2.73 (m, 2H), 2.43–2.38 (m, 2H), 2.37 (s, 3H), 2.03–1.95 (m, 2H), 1.89–1.84 (m, 2H). [ES+ MS] m/z 314 $(M+H)^+$.

1-[(2-Methylphenyl)methyl]-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (**22**)

The title compound was prepared using General Procedure B. Colorless oil, yield 40% (41 mg, 0.131 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.34–7.32 (m, 1H), 7.18–7.15 (m, 3H), 7.09 (d, 1H,

J=5.3), 6.81 (d, 1H, *J*=5.3), 3.96–3.94 (m, 2H), 3.52 (s, 2H), 2.85–2.82 (m, 2H), 2.74–2.70 (m, 2H), 2.43–2.46 (m, 2H), 2.40 (s, 3H), 1.99–1.91 (m, 2H), 1.87–1.82 (m, 2H). [ES+ MS] m/z 314 $(M+H)^+$.

1-[(3,4-Dimethylphenyl)methyl]-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (23)

The title compound was prepared using General Procedure B. Colorless oil, yield 35% (30 mg, 0.082 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.25 (d, 1H, *J*=5.1), 7.08–7.05 (m, 2H), 7.01–7.00 (m, 1H), 6.93 (d, 1H, *J*=5.3), 3.83 (t, 2H, *J*=5.3), 3.40 (br s, 2H), 2.73 (t, 2H, *J*=5.3), 2.59–2.56 (m, 2H), 2.28–2.22 (m, 2H), 2.20–2.18 (m, 6H), 1.88–1.81 (m, 2H), 1.71–1.68 (m, 2H). [ES+ MS] m/z 328 $(M+H)^+$.

1-(4-(*tert*-Butyl)benzyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran], hydrochloride (24)

The title compound was obtained as a free base colorless oil using General Procedure B**.** The compound as a free amine (75 mg, 0.211 mmol) was dissolved in CH_2Cl_2 (3 mL) and 2 M HCl in Et_2O (111 µl, 0.222 mmol) was added. After stirring at rt for 6 h, the solvent was evaporated to obtain hydrochloride salt of the compound. White solid, yield 55% (75.8 mg, 0.184 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm: 7.56 (d, 2H, *J*=8.3), 7.48 (d, 2H, *J*=8.3), 7.24 (d, 1H, *J*=5.3), 6.81 (d, 1H, *J*=5.1), 4.35 (br s, 2H), 3.97 (t, 2H, *J*=5.4), 3.39–3.37 (m, 4H), 2.85 (t, 2H, *J*=5.4), 2.21–2.09 (m, 4H), 1.36 (s, 9H). [ES+ MS] m/z 356 $(M+H)^+$.

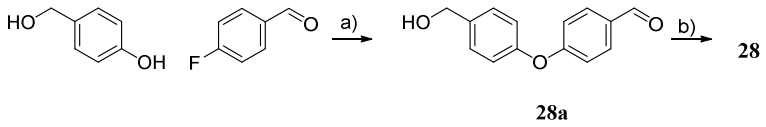
1-{[4-(Pentafluoro-λ^6-sulfanyl)phenyl]methyl}-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (**25**)

The title compound was prepared using General Procedure B. Colorless oil, yield 58% (62 mg, 0.138 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.73–7.71 (m, 2H), 7.48–7.46 (m, 2H), 7.09 (d, 1H, *J*=5.3), 6.83 (d, 1H, *J*=5.3), 3.94 (t, 2H, *J*=5.4), 3.60 (br s, 2H), 2.84 (t, 2H, *J*=5.4), 2.70–2.68 (m, 2H), 2.48–2.41 (m, 2H), 2.02–1.91 (m, 2H), 1.89–1.85 (m, 2H). [ES+ MS] m/z 426 $(M+H)^+$.

1-(1-(4-(Trifluoromethyl)phenyl)ethyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (26)

The title compound was prepared using General Procedure C. Colorless oil, yield 26% (24 mg, 0.063 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.60–7.58 (m, 2H), 7.50–7.48 (m, 2H), 7.09 (d, 1H, *J*=5.1), 6.84 (d, 1H, *J*=5.1), 3.95–3.86 (m, 2H), 3.52 (q, 1H, *J*=6.6), 2.95–2.88 (m, 1H), 2.85–2.79 (m, 2H), 2.59–2.52 (m, 1H), 2.45–2.36 (m, 1H), 2.35–2.27 (m, 1H), 2.06–1.96 (m, 1H), 1.95–1.84 (m, 2H), 1.82–1.75 (m, 1H), 1.40 (d, 3H, *J*=6.6). [ES+ MS] m/z 382 $(M+H)^+$.

Synthesis of compound 28



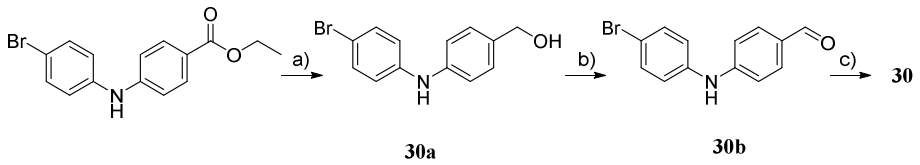
28a

Reagents and Conditions: a) K_2CO_3, DMF, reflux, on; b) General Procedure A.

4-(4-(Hydroxymethyl)phenoxy)benzaldehyde (28a)

A mixture of 4-(hydroxymethyl)phenol (500 mg, 4.03 mmol), 4-fluorobenzaldehyde (500 mg, 4.03 mmol) and potassium carbonate (668 mg, 4.83 mmol) in DMF (5 mL) was heated under reflux overnight. After allowing to cool, the reaction was diluted with water, extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with water, dried (Na_2SO_4), filtered and concentrated to obtain the reaction crude which was purified by flash chromatography to afford the title compound. White solid, yield 15% (138 mg, 0.605 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.93 (s, 1H), 7.84–7.87 (m, 2H), 7.42–7.44 (m, 2H), 7.05–7.11 (m, 4H), 4.74 (d, 2H, *J*=5.1), 1.74 (bt, 1H, *J*=5.6). [ES+ MS] m/z 229 $(M+H)^+$.

Synthesis of compound 30



Reagents and Conditions: a) DIBALH, CH_2Cl_2, −78 ºC, on; b) MnO_2, CH_2Cl_2, 40 ºC, on; c) General Procedure B.

(4-((4-Bromophenyl)amino)phenyl)methanol (30a)

A mixture of ethyl 4-((4-bromophenyl)amino)benzoate (500 mg, 1.562 mmol) in CH_2Cl_2 (50 mL) under nitrogen was cooled to –78 °C. DIBALH (1 M in hexane, 3.28 mL, 3.28 mmol) was added and the mixture was stirred at –78 °C. After 1 h, more DIBALH (0.5 eq, 0.78 mL) was added and the solution was stirred at –78 °C for 2 h. Saturated Na-K tartrate aqueous solution (30 mL) was added and the reaction was allowed to warm at room temperature. Ethyl acetate (30 mL) was added and the phases were separated, the aqueous layer was extracted with ethyl acetate (2 × 25 mL). The combined organic layers were dried (Na_2SO_4), filtered and evaporated to afford the title compound. Orange solid, yield 93% (404 mg, 1.452 mmol). 1H NMR (400 MHz, CDCl3) δ ppm: 7.37–7.35 (m, 2H), 7.31–7.28 (m, 2H), 7.06–7.04 (m, 2H), 6.95–6.93 (m, 2H), 5.71 (bs, 1H), 4.65–4.63 (d, 2H, *J*=5.8).

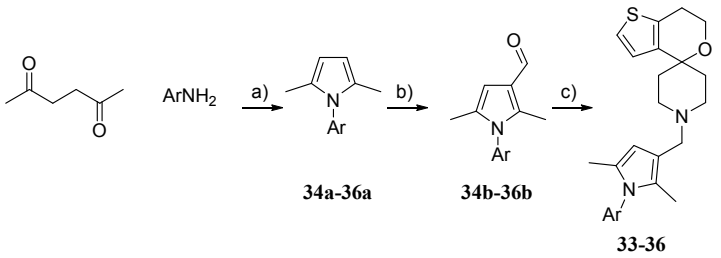
4-((4-Bromophenyl)amino)benzaldehyde (30b)

Compound 30a (404 mg, 1.452 mmol) was placed in a sealed tube and dissolved in CH_2Cl_2 (20 mL), then manganese(IV) oxide (379 mg, 4.36 mmol) was added and the reaction was stirred at 40 ºC overnight. More manganese (IV) oxide (126 mg, 1.452 mmol) was added and the mixture was stirred at reflux for 3 h. The mixture was filtered through Celite® and the filtrates were concentrated to afford the title compound (425 mg) as a brown oil that was used in the next step without further purification. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 9.82 (s, 1H), 7.78–7.76 (m, 2H), 7.48–7.46 (m, 2H), 7.08–7.01 (m, 2H), 7.04–7.02 (m, 2H), 6.14 (bs, 1H). [ES+ MS] m/z 469 $(M+H)^+$

1-((5-Methyl-1H-pyrrol-2-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran], hydrochloride (31)

The compound as a free amine was obtained using General Procedure A. The compound as a free amine (78 mg, 0.258 mmol,) was dissolved in CH_2Cl_2 (2 mL) and treated with 1 M HCl in Et_2O (258 µL, 0.258 mmol). After stirring at rt for 20 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield: 33% (80 mg, 0.236 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.80 (bs, 1H), 10.43 (bs, 1H), 7.12 (d, 1H, *J*=5.1), 6.91 (d, 1H, *J*=5.3), 6.09–6.08 (m, 1H), 5.77–5.78 (m, 1H), 4.09 (d, 2H, *J*=5.6), 3.92 (t, 2H, *J*=5.3), 3.33–3.30 (m, 2H), 3.11–3.01 (m, 2H), 2.86 (t, 2H, *J*=5.3), 2.31 (s, 3H), 2.61–2.53 (m, 2H), 2.05–2.01 (m, 2H). [ES+ MS] m/z 303 $(M+H)^+$.

Synthesis of compounds 33–36[3, 5]



Reagents and Conditions: a) General procedure D, Paal Knorr reaction; b) General procedure E, Pyrrole formylation; c) General procedure A or B, Reductive amination.

1-((2,5-Dimethyl-1-phenyl-1H-pyrrol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (33)

The title compound was prepared using General Procedure A with 2,5-dimethyl-1-phenyl-1H-pyrrole-3-carbaldehyde.[5] Orange solid, yield 30% (56 mg, 0.143 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.50–7.35 (m, 3H), 7.20 (d, 2H, *J*=7.1), 7.06 (d, 1H, *J*=5.1), 6.83 (d, 1H, *J*=5.1), 5.98 (s, 1H), 3.94 (t_{app}, 2H, *J*=5.3), 3.45 (s, 2H), 2.89–2.81 (m, 4H), 2.41 (t_{app}, 2H, *J*=11.2), 2.10–2.02 (m, 2H), 2.02 (s, 3H), 1.99 (s, 3H), 1.87 (d, 2H, *J*=13.1). [ES+ MS] m/z 392.80 $(M+H)^+$

2-(2,5-Dimethyl-1H-pyrrol-1-yl)pyridine (34a)

Prepared according to General Procedure D. Yellow oil, yield 63% (1.85 g, 10.76 mmol).). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 8.62 (dd, *J* = 4.8, *J* = 2.0 Hz, 1H), 7.85 (td, *J* = 7.6, *J* = 2.0 Hz, 1H), 7.31 (dd, *J* = 7.6, *J* = 4.8 Hz, 1H), 7.24 (d, *J* = 7.6, 1H), 5.91 (s, 2H), 2.14 (s, 6H). [ES+ MS] m/z 173.11 $(M+H)^+$.

2,5-Dimethyl-1-(pyridin-2-yl)-1H-pyrrole-3-carbaldehyde (34b)

Prepared according to General Procedure E with **34a**. Brown solid, yield 48% (833 mg, 4.16 mmol).). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 9.90 (s, 1H), 8.67 (d, *J* = 4.8, 1H), 7.93 (td, *J* = 7.7, *J* = 1.8 Hz, 1H), 7.44 (dd, *J* = 7.7, *J* = 4.8 Hz, 1H), 7.26 (d, *J* = 7.7, 1H), 6.39 (s, 1H), 2.37 (s, 3H), 2.07 (s, 3H). [ES+ MS] m/z 201.10 $(M+H)^+$.

1-((2,5-Dimethyl-1-(pyridin-2-yl)-1H-pyrrol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (34)

The title compound was prepared using General Procedure A with **34b**. Orange solid, yield 33% (62 mg, 0.158 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.62 (dd, 1H, *J*=4.8), 7.85 (dd, 1H, *J*=8.1, *J*=7.3), 7.33 (dd, 1H, *J*=7.3, *J*=4.8), 7.23 (d, 1H, *J* = 8.1), 7.07 (d, 1H, *J*=5.3), 6.87 (d, 1H, *J*=5.3), 6.03 (s, 1H), 3.94–3.91 (m, 2H), 3.72 (s, 2H), 3.12–3.09 (m, 2H), 2.84–2.81 (m, 2H), 2.74–2.61 (m, 2H), 2.34–2.26 (m, 2H), 2.11–2.10 (m, 6H), 1.91 (d, 2H, *J*=13.1). [ES+ MS] m/z 393.73 $(M+H)^+$.

3-(2,5-Dimethyl-1H-pyrrol-1-yl)pyridine (35a)

Prepared according to General Procedure D. Yellow oil, yield 73% (2.15 g, 12.46 mmol).). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 8.67 (dd, 1H, *J*=5.1, *J*=2.0), 8.55 (d, 1H, *J*=2.0), 7.62 (d, 1H, *J*=8.1), 7.31 (dd, 1H, *J*=8.1, *J*=5.1), 5.95 (s, 2H), 2.05 (s, 6H). [ES+ MS] m/z 173.00 $(M+H)^+$.

2,5-Dimethyl-1-(pyridin-3-yl)-1H-pyrrole-3-carbaldehyde (35b)

Prepared according to General Procedure E with **35a**. Beige solid, yield 46% (807 mg, 4.03 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 9.91 (s, 1H), 8.77 (dd, 1H, *J*=4.6, *J*=2.1), 8.56 (d, 1H, *J*=2.1), 7.67–7.61 (m, 1H), 7.54 (dd, 1H, *J*=7.6, *J*=4.6), 6.44 (s, 1H), 2.31 (s, 3H), 2.02 (s, 3H). [ES+ MS] m/z 200.87 $(M+H)^+$.

1-((2,5-Dimethyl-1-(pyridin-3-yl)-1H-pyrrol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (35)

The title compound was prepared using General Procedure A with **35b**. Yellow oil, yield 54% (101 mg, 0.258 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 8.66 (d, 1H, *J*=4.8), 8.52 (d, 1H, *J*=2.2), 7.57 (d, 1H, *J*=8.1), 7.44 (dd, 1H, *J*=8.1, *J*=4.8), 7.07 (d, 1H, *J*=5.1), 6.84 (d, 1H, *J*=5.1), 6.03 (s, 1H), 3.95–3.91 (m, 2H), 3.58 (s, 2H), 3.0 (d, 2H, *J*=11.3), 2.85–2.81 (m, 2H), 2.59–2.52 (m, 2H), 2.22–2.12 (m, 2H), 2.03–2.00 (br s, 6H), 1.99 (d, 2H, *J*=3.1). [ES+ MS] m/z 393.80 $(M+H)^+$.

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole (36a)

Prepared according to General Procedure D to give a brown solid, yield 87% (8.75 g, 43.45 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 7.15 (d, *J* = 8.8 Hz, 2H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.90 (s, 2H), 3.88 (s, 3H), 2.03 (s, 6H). [ES+ MS] m/z 202.00 $(M+H)^+$.

1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrole-3-carbaldehyde (36b)

Prepared according to General Procedure E with **36a**. Beige solid, yield 89% (2.03 g, 8.84 mmol). ^{1}H NMR (200 MHz, $CDCl_3$) δ ppm: 9.86 (s, 1H), 7.13 (d, 2H, *J*=8.8), 7.01 (d, 2H, *J*=8.8), 6.37 (s, 1H), 3.88 (s, 3H), 2.27 (s, 3H), 1.98 (s, 3H). [ES+ MS] m/z 230.12 $(M+H)^+$.

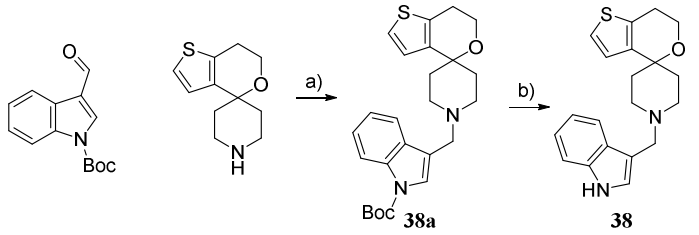
1-((1-(4-Methoxyphenyl)-2,5-dimethyl-1H-pyrrol-3-yl)methyl)-6',7'- dihydrospiro[piperidine-4,4'- thieno[3,2-c]pyran] (36)

The title compound was prepared using General Procedure A with **36b**. Beige solid, yield 21% (42 mg, 0.099 mmol). ^{1}H NMR (300 MHz, $CDCl_3$) δ ppm: 7.13 (d, 2H, *J*=8.8), 7.07 (d, 1H, *J*=5.1), 6.97 (d, 2H, *J*=8.8), 6.83 (d, 1H, *J*=5.1), 5.96 (s, 1H), 3.97–3.93 (m, 2H), 3.86 (s, 3H), 3.44 (s, 2H), 2.88–2.82 (m, 4H), 2.44–2.36 (m, 2H), 2.10–2.04 (m, 2H), 2.01 (s, 3H), 1.98 (s, 3H), 1.90–1.85 (m, 2H). [ES+ MS] m/z 422.73 $(M+H)^+$.

1-((1-Methyl-1H-indol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran (37)

The title compound was prepared using General Procedure B. White solid, yield: 55% (58 mg, 0.156 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.76 (d, 1H, *J*=7.8), 7.32 (d, 1H, *J*=8.1), 7.25 (dt, 1H, *J*=7.1, 1.0), 7.14 (dt, 1H, *J*=7.8, 1.0), 7.07–7.06 (m, 2H), 6.81 (d, 1H, *J*=5.3), 3.93 (t, 2H, *J*=5.3), 3.79, (s, 3H), 3.78 (s, 2H), 2.86–2.81 (m, 4H), 2.49–2.42 (m, 2H), 2.02–1.96 (m, 2H), 1.88–1.84 (m, 2H). [ES+ MS] m/z 353 $(M+H)^+$.

Synthesis of compound 38



Reagents and Conditions: a) General Procedure B; b) TFA, DCM, MW, 75 °C, 2 h.

***tert*-Butyl 3-((6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran]-1-yl)methyl)-1H-indole-1-carboxylate (38a)**

The title compound was prepared using General Procedure B. White solid, yield: 71% (234 mg, 0.534 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 8.15 (d, 1H, *J*=7.1), 7.75 (d, 1H, *J*=7.8), 7.56 (s, 1H), 7.35–7.30 (m, 1H), 7.29–7.23 (m, 1H), 7.07 (d, 1H, *J*=5.1), 6.81 (d, 1H, *J*=5.3), 3.93 (t, 2H, *J*=5.4),

3.71 (s, 2H), 2.85–2.78 (m, 4H), 2.46 (t, 2H, *J*=10.7), 2.03–1.93 (m, 2H), 1.90–1.82 (m, 2H), 1.68 (s, 9H). [ES+ MS] m/z 439 $(M+H)^+$.

1-((1H-Indol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] (38)

Trifluoroacetic acid (0.641 mL, 8.32 mmol) was added to a mixture of **38a** (730 mg, 1.664 mmol) in CH_2Cl_2 (15 mL), and the mixture was heated under microwave irradiation at 75 ºC for 2 h. The reaction was washed with saturated Na_2CO_3 solution and brine, the organic layer was separated, dried (Na_2SO_4), filtered and concentrated to afford the title compound. Brown solid, yield 71% **(**420 mg, 1.241 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.91 (bs, 1H), 7.64 (d, 1H, *J*=7.8), 7.35 (d, 1H, *J*=8.1), 7.26–7.22 (m, 2H), 7.07 (t_{app}, 1H, *J*=7.1), 6.99 (t_{app}, 1H, *J*=7.3), 6.91 (d, 1H, *J*=5.4), 3.82 (t, 2H, *J*=5.4), 3.66 (s, 2H), 2.75–2.65 (m, 4H), 2.31 (m, 2H), 1.89–1.79 (m, 2H), 1.75–1.65 (m, 2H). [ES+ MS] m/z 339 $(M+H)^+$.

1-((6-Chloro-1H-indol-3-yl)methyl)-6',7'-dihydrospiro[piperidine-4,4'-thieno[3,2-c]pyran] trifluoroacetic acid salt (39)

The title compound was prepared using General Procedure A. HPLC purification under acidic conditions afforded the compound as TFA salt. White solid, yield 29% (80.4 mg, 0.165 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 11.64 (s, 1H), 9.44 (bs, 1H), 7.87 (d, 1H, *J*=8.6), 7.66 (d, 1H, *J*=2.8), 7.52 (d, 1H, *J*=1.8), 7.36 (d, 1H, *J*=5.1), 7.17 (dd, 1H, *J*=2.0), 6.74 (d, 1H, *J*=5.3), 4.54 (bd, 2H, *J*=4.3), 3.87 (t, 2H *J*=5.3), 3.42–3.34 (m, 2H), 3.25–3.12 (m, 2H), 2.77 (t, 2H *J*=5.1), 2.16–2.05 (m, 2H), 2.02–1.93 (m, 2H). [ES+ MS] m/z 373 $(M+H)^+$.

1-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)piperidine 2,2,2-trifluoroacetate], trifluoroacetic acid salt (40)

The title compound was prepared using General Procedure B. HPLC purification under acidic conditions afforded the compound as TFA salt. Colorless oil, yield 58% (120 mg, 0.245 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 11.68 (bs, 1H), 7.38 (d, 2H, *J*=8.6), 7.23 (d, 2H, *J*=8.3), 6.99–7.08

(m, 4H), 4.16 (d, 2H, *J*=3.3), 3.60 (d, 2H, *J*=11.6), 2.53–2.68 (m, 2H), 1.82–2.05 (m, 5H), 1.31–1.45 (m, 1H). [ES+ MS] m/z 352 $(M+H)^+$.

3-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-3-azaspiro[5.5]undecane, hydrochloride (41)

The compound as a free amine was obtained as a colorless oil using General Procedure B. The compound as a free amine (38 mg, 0.09 mmol) was dissolved in CH_2Cl_2 (1 mL), 2 M HCl in Et_2O (45 µL, 0.09 mmol) was added and the mixture was stirred at room temperature for 1 h. The reaction was concentrated to afford the title compound. Yellow solid, yield 28% (40 mg, 0.088 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.83 (bs, 1H), 7.58 (d, 2H, *J*=8.6), 7.42 (d, 2H, *J*=8.3), 7.18–7.10 (m, 4H), 4.27 (d, 2H, *J*=5.6), 3.15–3.08 (m, 2H), 3.07–2.95 (m, 2H), 1.78–1.70 (m, 2H), 1.55–1.44 (m, 4H), 1.38 (bs, 6H), 1.23 (bs, 2H). [ES+ MS] m/z 420 $(M+H)^+$.

9-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-1,5-dioxa-9-azaspiro[5.5]undecane, hydrochloride (43)

The compound as a free amine was obtained using General Procedure A. The compound as a free amine (155 mg, 0.366 mmol) was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (366 µL, 0.366 mmol). After stirring at rt for 30 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 54% (142 mg, 0.198 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.31 (bs, 1H), 7.61 (d, 2H, *J*=8.0), 7.42 (d, 2H, *J*=8.0), 7.17–7.11 (m, 4H), 4.31–4.30 (m, 2H), 3.84–3.83 (m, 4H), 3.26–3.23 (m, 2H), 2.97–2.89 (m, 2H), 2.39–2.35 (m, 2H), 1.85–1.78 (m, 2H), 1.63–1.61 (m, 2H). [ES+ MS] m/z 424 $(M+H)^+$.

8-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-1,4-dioxa-8-azaspiro[4.5]decane, hydrochloride (44)

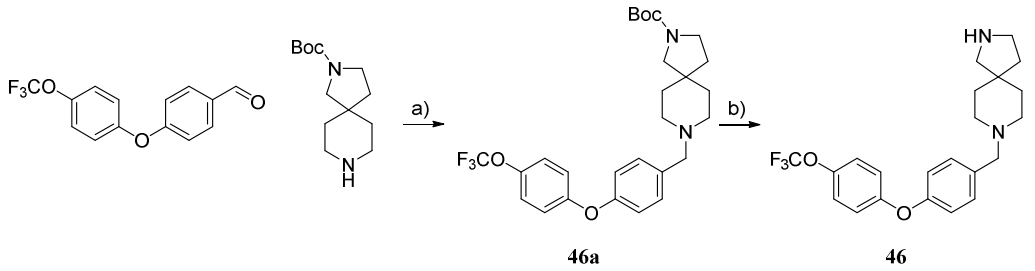
The compound as a free amine was obtained using General Procedure A. The compound as a free amine (201.7 mg, 0.493 mmol) was dissolved in CH_2Cl_2 (3 mL) and 1 M HCl in Et2O (591 µL, 0.591 mmol)). After stirring at rt for 90 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 70% (218 mg, 0.489 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm:

7.55 (d, 2H, *J*=8.6), 7.33 (d, 2H, *J*=8.3), 7.14–7.10 (m, 4H), 4.34 (s, 2H), 4.01 (s, 4H), 3.56–3.44 (m, 2H), 3.28–3.16 (m, 2H), 2.04–1.94 (m, 4H). [ES+ MS] m/z 410 $(M+H)^+$.

8-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-1-oxa-8-azaspiro[4.5]decane, hydrochloride (45)

The compound as a free amine was obtained using General Procedure A. The compound as a free amine (45.3 mg, 0.111 mmol) was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (338 µL, 0.338 mmol). After stirring at rt for 30 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 30% (45 mg, 0.101 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 12.25 (bs, 1H), 7.66 (bs, 2H), 7.24–7.22 (m, 2H), 7.06–7.04 (m, 4H), 4.07 (bs, 2H), 3.81 (t, 2H, *J*=4.0), 3.31 (bs, 2H), 3.01 (bs, 2H), 2.47 (bs, 2H), 1.98–1.94 (m, 2H), 1.82–1.80 (m, 2H), 1.74–1.72 (m, 2H). [ES+ MS] m/z 408 $(M+H)^+$.

Synthesis of compound 46



46a **46**

Reagents and Conditions: a) General Procedure A; b) TFA, DCM, rt, 4h.

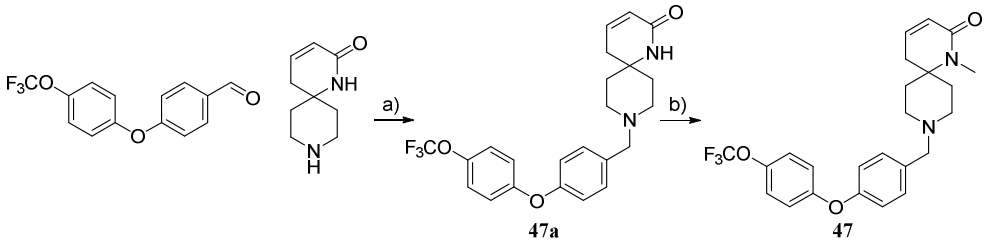
***tert*-Butyl-8-(4-(4-(trifluoromethoxy)phenoxy)benzyl)-2,8-diazaspiro[4.5]decane-2-carboxylate (46a)**

The title compound was prepared using General Procedure A. Colorless oil, yield 62% (245 mg, 0.484 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.38 (d, 2H, *J*=8.3), 7.32 (d, 2H, *J*=8.3), 7.08 (d, 2H, *J*=9.0), 7.00 (d, 2H, *J*=9.0), 3.44 (s, 2H), 3.29–3.22 (m, 2H), 3.04 (bs, 2H), 2.44–2.33 (m, 2H), 2.29–2.20 (m, 2H), 1.68–1.62 (m, 2H), 1.47–1.43 (m, 4H), 1.39 (s, 9H). [ES+ MS] m/z 507 $(M+H)^+$.

8-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-2,8-diazaspiro[4.5]decane, hydrochloride (46)

Trifluoroacetic acid (3 mL) was added to a solution of **46a** (237.5 mg, 0.469 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred at rt for 4 h. The reaction was concentrated to dryness and the residue was purified by using an ion exchange column (SCX-2) to obtain the compound as a free amine. The compound as a free amine (150 mg, 0.369 mmol) was dissolved in CH_2Cl_2 (2 mL) and 2 M HCl in Et_2O (222 μL, 444 mmol). After stirring at rt for 20 min, the solvent was evaporated to obtain the title compound. White solid, yield 75%. (156 mg, 0.38 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.54 (d, 2H, *J*=8.3), 7.31 (d, 2H, *J*=8.3), 7.12–7.08 (m, 4H), 4.20 (bs, 2H), 3.44–3.41 (m, 2H), 2.29–2.20 (m, 2H), 3.24–3.13 (m, 5H), 2.03–1.88 (m, 6H). [ES+ MS] m/z 407 $(M+H)^+$.

Synthesis of compound 47



Reagents and Conditions: a) General Procedure A; b) NaH, THF, rt, 20 min. Then, MeI, 30 min.

9-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-1,9-diazaspiro[5.5]undec-3-en-2-one, hydrochloride (47a)

The compound was obtained using General Procedure A. The compound as a free amine (84.7 mg, 0.196 mmol) was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (215 μL, 0.215 mmol). After stirring at rt for 30 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 27% (92 mg, 0.196 mmol). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.57 (d, 2H, *J*=8.3 Hz), 7.34 (d, 2H, *J*=8.3 Hz), 7.17–7.10 (m, 4H), 6.71 (br dd, 1H, *J*=9.3, *J*=4.3 Hz), 5.91 (br d, 1H, *J*=9.9 Hz), 4.35 (br d, 2H, *J*=4.8 Hz), 3.51–3.41 (m, 2H), 3.29–3.19 (m, 2H), 2.68 (br s, 1H), 2.51–2.41 (m, 1H), 2.21 (br d, 2H, *J*=14.4 Hz), 2.07–1.86 (m, 2 H) [ES+ MS] m/z 433 $(M+H)^+$.

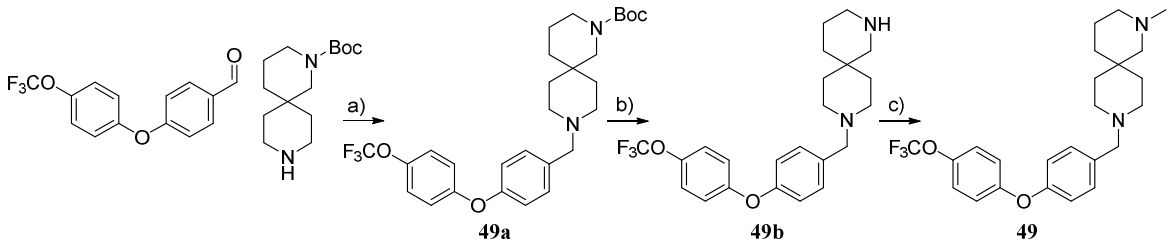
1-Methyl-9-(4-(4-(trifluoromethoxy)phenoxy)benzyl)-1,9-diazaspiro[5.5]undec-3-en-2-one, hydrochloride (47)

A mixture of **47a** (62 mg, 0.132 mmol) and sodium hydride (12.69 mg, 0.317 mmol) in THF (5 mL) was stirred at room temperature for 20 min. Methyl iodide (0.082 mL, 1.322 mmol) was added and reaction mixture was stirred at room temperature for 30 min. The solvent was evaporated and the residue was purified by flash column chromatography to obtain the compound as a free amine (24.1 mg, 0.054 mmol) which was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (60 µL, 0.060 mmol). After stirring at rt for 30 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. Yield: 41% (26 mg, 0.054 mmol). ^{1}H NMR (400 MHz, CD_3OD) δ ppm 7.54 (d, 2H, *J*=8.3 Hz), 7.33 (dd, 2H, *J*=9.2, *J*=0.9 Hz), 7.15–7.10 (m, 4H), 6.67–6.61 (m, 1H), 5.97 (d, 1H, *J*=9.9 Hz), 4.34 (s, 2H), 3.49–3.36 (m, 2H), 3.29–3.21 (m, 2H), 3.02–2.96 (m, 3H), 2.75 (br d, 2H, *J*=2.8 Hz), 2.34–2.34 (m, 2H), 2.13–2.03 (m, 2H). [ES+ MS] m/z 447 $(M+H)^+$.

8-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-2-oxa-8-azaspiro[4.5]decan-1-one, hydrochloride. (48)

The compound as a free amine (48 mg, 0.114 mmol) was obtained using General Procedure A. ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.39 (d, 2H, *J*=8.3 Hz), 7.26 (d, 2H, *J*=9.1 Hz), 7.08 (d, 2H, *J*=9.1 Hz), 7.05 (d, 2H, *J*=8.6 Hz), 4.37 (t, *J*=7.1, 2H), 3.59 (s, 2H), 2.95–2.90 (m, 2H), 2.29–2.23 (m, 2H), 2.25 (t, *J*=7.1 Hz, 2H), 2.13–2.06 (m, 2H), 1.70–1.62 (m, 2H). The compound was dissolved in CH_2Cl_2 (2 mL) and 2 M HCl in Et_2O (60 µL, 0.12 mmol). After stirring at rt overnight, the solvent was evaporated to obtain the title compound. White solid, yield 12% (52 mg, 0.114 mmol). [ES+ MS] m/z 422 $(M+H)^+$.

Synthesis of compound 49



Reagents and Conditions: a) General Procedure A; b) TFA, DCM, rt, 4 h; c) General procedure A with HCHO.

***tert*-Butyl-9-(4-(4-(trifluoromethoxy)phenoxy)benzyl)-2,9-diazaspiro[5.5]undecane-2-carboxylate (49a)**

The title compound was prepared using General Procedure A. Pale yellow oil, yield 63% (236 mg, 0.454 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 7.38 (d, 2H, *J*=7.4), 7.31 (d, 2H, *J*=7.4), 7.08 (d, 2H, *J*=6.8), 6.99 (d, 2H, *J*=6.8), 3.43 (s, 2H), 3.29–3.22 (m, 2H), 3.18 (bs, 2H), 2.46–2.38 (m, 2H), 2.27–2.14 (m, 2H), 1.46–1.38 (m, 4H), 1.37 (s, 9H), 1.34–1.25 (m, 4H). [ES+ MS] m/z 521 $(M+H)^+$.

9-(4-(4-(Trifluoromethoxy)phenoxy)benzyl)-2,9-diazaspiro[5.5]undecane, hydrochloride (49b)

Trifluoroacetic acid (3 mL) was added to a solution of **49a** (238 mg, 0.457 mmol) in CH_2Cl_2 (4 mL). The resulting mixture was stirred at rt for for 4 h. The reaction was concentrated to dryness and the residue was purified by using an ion exchange column (SCX-2) to obtain the compound as a free amine (183 mg, 0.436 mmol). Some of the compound as a free amine (52.3 mg, 0.124 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and 2 M HCl in Et_2O (75 µL, 0.150 mmol). After stirring at rt for 20 min, the solvent was evaporated to obtain hydrochloride salt of the compound. White solid, yield: 27% (56 mg, 0.13 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.44 (d, 2H, *J*=7.4), 7.28 (d, 2H, *J*=7.4), 7.10–7.00 (m, 4H), 3.88 (bs, 2H), 3.11(bt, 2H), 3.04 (s, 2H), 2.83 (bs, 4H), 1.86–1.63 (m, 8H). [ES+ MS] m/z 421 $(M+H)^+$.

2-Methyl-9-(4-(4-(trifluoromethoxy)phenoxy)benzyl)-2,9-diazaspiro[5.5]undecane, hydrochloride (49)

The compound as a free amine was obtained using General Procedure A with **49b** and formaldehyde. The compound as a free amine (110 mg, 0.253 mmol) was dissolved in CH_2Cl_2 (1.5 mL) and 2 M HCl in Et_2O (153 µL, 0.306 mmol). After stirring at rt for 20 min, the solvent was evaporated to obtain the hydrochloride salt of the compound. Beige solid, yield 84% (119 mg, 0.273 mmol). ^{1}H NMR (400 MHz, MeOD) δ ppm 7.53 (d, 2H, *J*=8.3), 7.31 (d, 2H, *J*=8.3), 7.12–7.08 (m, 4H), 3.41 (s, 2H), 2.32–2.27 (m, 4H), 2.18–2.19 (m, 2H), 2.09–2.03 (m, 5H), 1.48–1.38 (m, 6H), 1.24–1.21 (m, 2H). [ES+ MS] m/z 435 $(M+H)^+$.

9-(4-(*tert*-Butyl)benzyl)-2-oxa-9-azaspiro[5.5]undecane, hydrochloride (51)

The compound as a free amine (142.6 mg, 0.470 mmol) was obtained using General Procedure A as a pale yellow oil. The compound was dissolved in CH_2Cl_2 (5 mL) and 1 M HCl in Et_2O (470 µL, 0.470 mmol). The solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 74% (160 mg, 0.47 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.30 (bs, 1H), 7.59–7.53 (m, 4H), 4.29 (dd, 2H, *J*=11.4, 5.5), 3.60–3.59 (m, 3H), 3.28–3.25 (m, 1H), 3.21–3.05 (m, 4H), 1.90–1.52 (m, 7H), 1.46–1.40 (m, 1H), 1.36 (s, 9H). [ES+ MS] m/z 302 $(M+H)^+$.

9-(4-(*tert*-Butyl)benzyl)-3-oxa-9-azaspiro[5.5]undecane, hydrochloride (52)

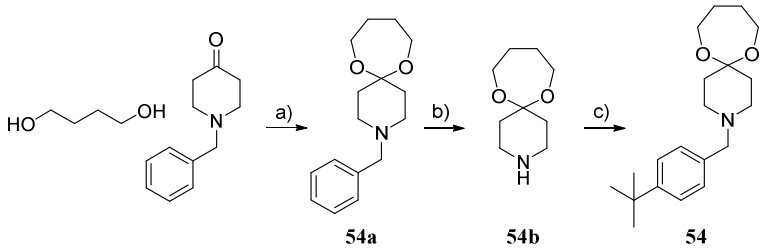
The compound as a free amine was obtained using General Procedure A. The compound (54.6 mg, 0.18 mmol) was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (220 µL, 0.222 mmol). The mixture was stirred at rt for 10 min. The solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield: 60% (60.8 mg, 0.180 mmol) ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 12.15 (bs, 1H), 7.63 (d, 2H, *J*=7.8), 7.46 (d, 2H, *J*=7.1), 4.30–4.15 (m, 2H), 3.70–3.60 (m, 2H), 3.42–3.22 (m, 2H), 3.04–2.79 (m, 2H), 2.34–2.15 (m, 4H), 1.95–1.80 (m, 2H), 1.70–1.50 (m, 4H), 1.37 (s, 9H). [ES+ MS] m/z 302 $(M+H)^+$.

9-(4-(*tert*-Butyl)benzyl)-1,5-dioxa-9-azaspiro[5.5]undecane, hydrochloride (53)

The compound as a free amine was obtained using General Procedure B. The compound (114.8 mg, 0.378 mmol) was dissolved in CH_2Cl_2 (2 mL) and 1 M HCl in Et_2O (378 µL, 0.378 mmol). The

mixture was stirred at rt for 30 min. The solvent was evaporated to obtain the hydrochloride salt of the compound. Pale solid, yield: 57% (117 mg, 0.334 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.52 (bs, 1H), 7.69–7.41 (m, 4H), 4.34 (d, 2H, *J*=5.3), 3.97–3.82 (m, 4H), 3.33–3.25 (m, 2H), 3.09–2.89 (m, 2H), 2.47–2.37 (m, 2H), 1.98–1.85 (m, 2H), 1.73–1.63 (m, 2H), 1.36 (bs, 9H). [ES+ MS] m/z 304 $(M+H)^+$.

Synthesis of compound 54



Reagents and Conditions: a) pTsOH, $CH(OCH_3)_3$, DCM, 48h; b) Pd/C, H_2, 55 °C; c) General Procedure A.

3-Benzyl-7,12-dioxa-3-azaspiro[5.6]dodecane (54a)

A mixture of 1-benzyl-4-piperidone (1.469 mL, 7.93 mmol), 1,4-butanediol (7.02 mL, 79 mmol), *p*-toluenesulfonic acid monohydrate (0.151 g, 0.793 mmol), trimethyl orthoformate (4.34 mL, 39.6 mmol), and CH_2Cl_2 (150 mL) was stirred at rt for 48 h. Volatiles were removed. 2 M NaOH and TBME were added. The organic layer was separated, dried ($MgSO_4$), filtered, and concentrated to afford a residue that was purified by flash column chromatography and preparative HPLC. White solid, yield 33% (0.68 g, 2.60 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.36–7.25 (m, 5H), 3.69 (bs, 4H), 3.56 (s, 2H), 2.50 (bs, 4H), 1.79 (bs, 4H), 1.61 (bs, 4H). [ES+ MS] m/z 261 $(M+H)^+$.

7,12-Dioxa-3-azaspiro[5.6]dodecane, hydrochloride (54b)

Compound **54a** (0.67 g, 2.56 mmol) was dissolved in methanol and hydrogenated using a 10% Pd/C cartridge in H-Cube (full H_2, 55 °C) for 2 h. 3 M HCl (1.282 mL, 3.85 mmol) was added and after stirring 10 min at rt, volatiles were removed to afford the title compound. Off-white solid, yield: 94%

(501 mg, 2.412 mmol). ^{1}H NMR (400 MHz, $CDCl_3$) δ ppm: 7.31 (bs, 1H), 3.66 (bs, 4H), 3.17 (s, 4H), 1.95 (bs, 4H), 1.60 (bs, 4H). [ES+ MS] m/z 172 $(M+H)^+$.

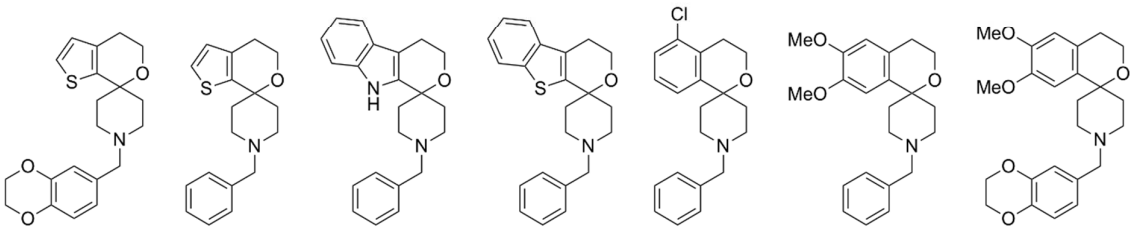
3-(4-(*tert*-Butyl)benzyl)-7,12-dioxa-3-azaspiro[5.6]dodecane, hydrochloride (54)

The compound as a free amine (35.9 mg, 0.113 mmol) was obtained using General Procedure A with **54b**. The compound was dissolved in CH_2Cl_2 (5 mL) and 1 M HCl in Et_2O (113 μL, 0.113 mmol). The solvent was evaporated to obtain the hydrochloride salt of the compound. White solid, yield 27% (40 mg, 0.113 mmol). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 10.48 (bs, 1H), 7.59 (d, 2H, *J*=8.6), 7.54 (d, 2H, *J*=8.6), 4.33 (d, 2H, *J*=5.3), 3.69–3.64 (m, 4H), 3.32–3.29 (m, 2H), 3.05–2.97 (m, 2H), 2.14–2.11 (m, 2H), 1.95–1.87 (m, 2H), 1.65–1.55 (m, 4H), 1.36 (s, 9H). [ES+ MS] m/z 318 $(M+H)^+$.

Supplementary Compounds Already in the Public Domain as Part of the Open Source TB (OSTB) Project

These compounds may be found on the OSTB infrastructure.[3]

OSTB Compounds With Variation in North



S1
OSTBS79
Thesis: #62E
MIC90 >100 μM

S2
OSTBS14
Thesis: #23
MIC >125 μM

S3
OSTBS15
Thesis: #19
MIC 125 μM

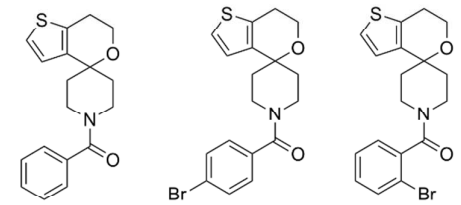
S4
OSTBS18
Thesis: #22
MIC 93 μM

S5
OSTBS19
Thesis: #20
MIC 125 μM

S6
OSTBS20
Thesis: #21
MIC >125 μM

S7
OSTBS80
Thesis: #62B
MIC 100 μM

OSTB Compounds With Variation in Center

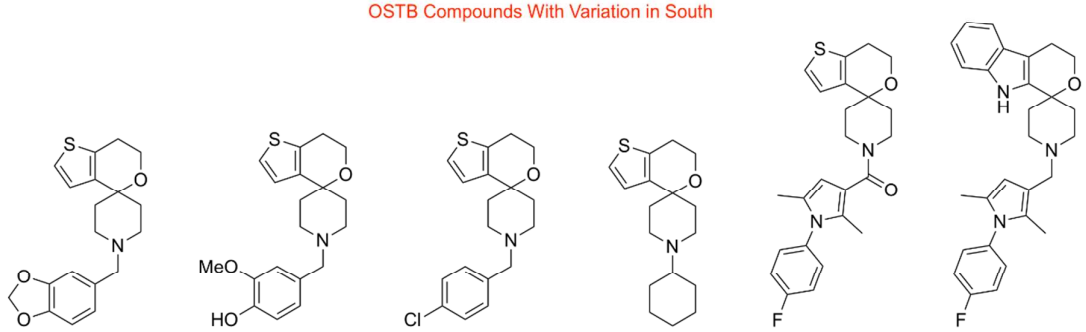


S8
OSTBS11
Previously: #16
IC_{50} >100 μM

S9
OSTBS12
Previously: #17
IC_{50} >100 μM

S10
OSTBS13
Previously: #18
IC_{50} >100 μM

OSTB Compounds With Variation in South



S11
OSTBS5
Previously: #11
IC_{50} 10 μM

S12
OSTBS6
Previously: #12
IC_{50} >100 μM

S13
OSTBS7
Previously: #13
IC50 1.25 μM

S14
OSTBS10
Previously: #15
IC_{50} 100 μM

S15
OSTBS25
Batch JBG16-1
IC_{50} >125 μM

S16
OSTBS26
Batch JBG20-1
IC_{50} 32 μM

The compounds with variation in the *North* (**S1**–**S7**) are described in the thesis entitled "Diversification and Development of Spiros Compounds for the Treatment of Tuberculosis" by Javier González Osende, The University of Sydney, June 2014. The thesis may be found on the online OSTB infrastructure or downloaded directly from the University of Sydney Electronic Repository.[3,2]

The compounds with variation in the *Center* (**S8**–**S10**) were previously published;[4] the compound numbers used in that paper are given.

The compounds with variation in the *South* (**S11**–**S16**) were either previously published (**S11**–**S14**)[4] or described in the OSTB online infrastructure (**S15**–**S16**).[3]

Possible PAINS Compounds

All structures in this paper have been evaluated as PAINS as per the *Journal of Medicinal Chemistry* guidelines. The only compounds flagged were compounds **32**–**36** and **S16**. There is a risk that these compounds (specifically *via* the *N*-aryl pyrrole motif) are susceptible to chemical degradation to reactive moieties. These compounds were all prepared and chromatographically purified to >90% purity as judged by ^{1}H NMR and/or LCMS spectra before biological evaluation, and related compounds have previously not shown chemical instability when handled in isolation.[5] Nevertheless, care should be taken with the associated biological data since PAINS behaviour is a possibility. Due to the relatively low activity of these compounds, this possibility was not examined further in this work.

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2. Osende, J. G. Diversification and Development of Spiros Compounds for the Treatment of Tuberculosis, http://hdl.handle.net/2123/18355, accessed Jul 02, 2018.

3. OpenSourceTB: OSTB Series 1. https://github.com/OpenSourceTB/OSTB_Series_1, accessed Jul 02, 2018..

4. Badiola, K. A.; Quan, D. H.; Triccas, J. A.; Todd, M. H. Efficient Synthesis and Anti-Tubercular Activity of a Series of Spirocycles: An Exercise in Open Science. *PLoS One,* **2014**, 9, e111782.

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