Biarylmethoxy nicotinamides as novel and specific inhibitors of *Mycobacterium tuberculosis* (Mtu)

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Table 4: Ring B, linker modifications and SAR

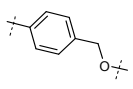
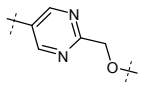
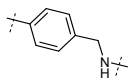
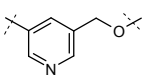
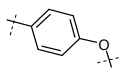
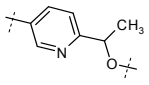
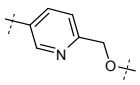
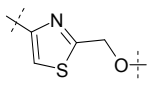
entry	Ring B & linker substitution	MIC (µg/mL)	entry	Ring B & linker substitution	MIC (µg/mL)
16		11.5	**19**		4.0
17		92.1	**20**		>100
18		>100	**21**		88.0
5b		22	**22**		>100

Table 5. In-vitro DMPK profiling

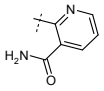
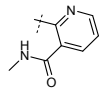
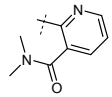
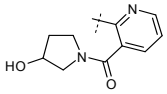
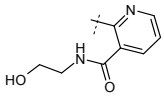
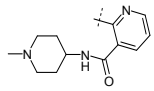
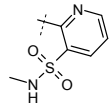
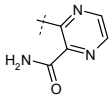
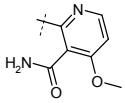
DMPK Properties	**9a**	**9f**	**9c**	**9j**	**9k**
LogD	3.0	3.4	3.1	2.8	3.0
$MuCL_{int}$ µL\min\mg)	26.0	ND	7.6	16	44
Hu PPB (% free)	4.2	<1	2.1	<1	1.8
CYP1A2 (µM)	>20	>20	>20	>20	>20
CYP3A4 (µM)	>20	>20	>20	>20	>20
CYP2D6 (µM)	>20	>20	>20	>20	>20
CYP2C9 (µM)	>20	12.4	10.7	>20	19
CYP2C19 (µM)	>20	9.1	>20	18	>20

Table 6. Studies on drug sensitive and single drug resistant clinical isolates

M.tu Strains: Name	*M.tu Strains: Type*							
	9a	**9j**	**9k**					
H37Rv ATCC 27294	0.63	0.39	0.39	**Sensitive, reference strains**				
Erdman	0.33	0.39	0.39					
ATCC 25618	0.15	0.39	0.39					
ATCC 35811	0.63	0.39	0.39					
Beijing	0.33	0.39	0.39					
Harlingen	0.15	0.39	0.39					
DKU211	0.15	0.39	0.39	**Drug sensitive clinical isolates**				
DKU220	0.15	0.39	0.39					
DKU 76	0.15	0.39	0.39					
97A	0.33	0.39	0.39					
JALMA	0.33	0.39	0.39					
Single Drug resistance strains (SDR)				**Reference drugs**				
				Rifampicin	**Streptomycin**	**Isoniazid**	**Ethambutol**	**Ofloxacin**
Rif^R-19000*	ND	0.39	0.39	**>1.2**	0.3	0.2	9.8	0.7
Str^R ATCC 35820†	2.5	0.78	0.78	0.04	**>10.9**	0.2	9.8	0.7
Inh^R ATCC 35822‡	0.33	0.78	0.78	0.04	0.3	**>29**	9.8	0.7
Etm ^{R}-17003*	0.33	0.39	0.39	0.04	0.3	0.2	**> 19.5**	0.7
$Oflx^R$-12119*	0.63	0.39	0.78	0.04	0.3	0.2	9.8	**>5.5**

*Uncharacterized clinical isolates, † Uncharacterized clinical isolate, refer to www.atcc.org, ‡Mutation mapped to alkyl hydroxyperoxide reductase subunit C (AhpC).

Table. 7. Solubility data for compounds*

entry	Ring C substitution	Solubility (μM)
9a		6
15a		234
15b		777
15c		983
15d		574
15e		>1000
15f		ND
15g		130
15h		52

*Throught the study, ring A was 4-(2-methoxyethoxy)-2-methylphenyl and ring B was pyridine.

Experimental Section: Chemistry

All anhydrous solvents, reagent grade solvents for chromatography and starting materials were purchased from either Sigma Aldrich Chemical Co. or Fisher Scientific. Water was distilled and purified through a Milli-Q water system (Millipore Corp., Bedford, MA). General methods of purification of compounds involved the use of preloaded silica cartridges purchased from Grace Purification systems and / or re-crystallized. The reactions were monitored by TLC on pre-coated Merck 60 F_{254} silica gel plates and visualized using UV light (254 nm). All compounds were analyzed for purity by LCMS, HPLC 1H NMR and HRMS. 1H NMR was done using Bruker 300MHz NMR and/or Bruker 400 MHz NMR spectrometers. Chemical shifts are reported in ppm (δ) relative to the residual solvent peak in the corresponding spectra; chloroform δ 7.26 and δ 77.23, methanol δ 3.31 and δ 49.00, DMSO-d6 δ 3.33 and coupling constants (*J*) are reported in hertz (Hz) (where, s = singlet, bs = broad singlet, d = doublet, dd = double doublet, bd = broad doublet, ddd = double doublet of doublet, t = triplet, tt – triple triplet, q = quartet, m = multiplet) and analyzed using ACD NMR data processing. Mass spectra values are reported as *m/z*. HPLC was carried out on Agilent 1200 series instrument using SUNFIRE C-18 4.6 x 50 mm column. Mobile phase: Solvent A: 10mM NH_4OAc at *p*H 4.0; Solvent B: Acetonitrile; Flow rate: 1.0 mL\min.

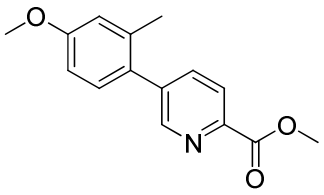
All reactions were conducted under Nitrogen unless otherwise noted. Solvents were removed *in vacuo* on a rotary evaporator.

Abbreviations: NMP = N-methyl Pyrrolidine; HCl = hydrochloric acid; DMF = dimethylformamide; NaH= sodium hydride; CsF= caesium fluoride; CsCO3= Caesium carbonate; LAH=Lithium aluminium hydride.

Preparation of Key Intermediates and Final Products

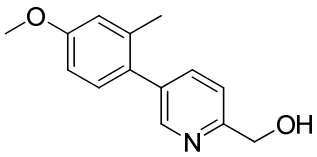
General procedure followed for the synthesis of title compounds **5a-g and 16-22** is demonstrated through the synthesis of a representative compound 2-((5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methoxy) nicotinamide **5b**

Step 1: Synthesis of 5-(4-methoxy-2-methylphenyl)picolinate intermediate (3).



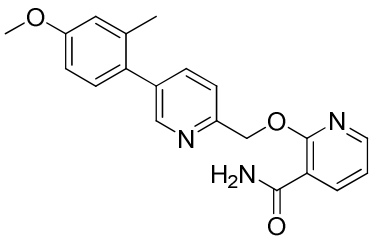
In a 10mL Biotage Microwave vial, a solution of 4-methoxy-2-methylphenylboronic acid (0.250 g, 1.51 mmol) and methyl 5-bromopicolinate (0.325 g, 1.51 mmol) dissolved in methanol (10mL) was placed. To this solution, CsF (0.686g, 4.52mmol) and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.062 g, 0.08 mmol) was added. The resulting suspension was purged with N_2 gas for 5 minutes and then irradiated with microwave at 120^oC for 30min. The completion of the reaction was monitored by LCMS. After completion of the reaction, the crude mixture was filtered through celite bed and the filterate was evaporated under reduced pressure. The resulting residue was re-dissolved in ethylacetate (20mL) and the organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give a crude mass. The crude mass was purified by flash chromatography through pre-loaded silica gel columns using 0-5% methanol-dichloromethane gradient to give 0.220g of methyl 5-(4-methoxy-2-methylphenyl)picolinate (**3**), in 56.8% yield. ^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 2.26 (s, 3 H), 3.80 (s, 3 H), 3.91 (s, 3 H), 6.88 - 6.98 (m, 2 H), 7.25 (d, *J*=8.29 Hz, 1 H), 7.97 (dd, *J*=8.10, 2.26Hz, 1 H), 8.08 - 8.14 (m, 1 H), 8.68 (d, *J*=1.51 Hz, 1 H); ESMS calcd. 257.2; Found: 258.0 $(M+H)^+$

Step 2. Synthesis of 5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methanol intermediate (4).



In a 100 mL RB flask, methyl 5-(4-methoxy-2-methylphenyl)picolinate (0.2 g, 0.78 mmol) dissolved in THF (10 mL) was taken. The resulting solution was then cooled to 0°C on an ice bath. Lithium aluminium hydride (0.057 g, 1.56 mmol) was slowly added onto the reaction mixture under N_2 atmosphere. With stirring, the reaction mixture was allowed to warm to room temperature over a period of 1 hr. After completion of the reaction, the reaction mass was re-cooled to 0 ^{O}C and quenched slowly by addition of saturated solution of NH_4Cl. The crude mass was extracted with ethylacetate (3 x 20mL) and the organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to give crude product. The crude mass was purified by flash chromatography through pre-loaded silica gel columns using 0-10% methanol-dichloromethane gradient to give 0.120g of (5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methanol (**4**), in 67.3% yield. ^{1}H NMR (300 MHz, CHLOROFORM-d) δ ppm 2.15 (s, 3 H), 3.74 (s, 3 H), 4.73 (s, 2 H), 6.65 - 6.84 (m, 2 H), 7.02 (d, *J*=8.53 Hz, 1 H), 7.27 (d, *J*=8.03 Hz, 1 H), 7.54 (dd, J=8.03, 2.01Hz, 1 H), 8.38 (s, 1 H); ESMS calcd. 229.2; Found: 230.0 $(M+H)^+$

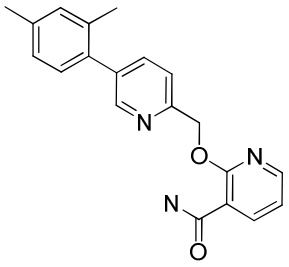
Step 3. Synthesis of 2-((5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotin amide (5b).



In a 25 mL RB flask, sodium hydride 60% in paraffin oil (0.031 g, 0.79 mmol) was suspended in DMF (10 mL) at 0 °C. To the above suspension, (5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methanol (0.12 g, 0.52 mmol) was added slowly at 0 °C and the temperature was allowed

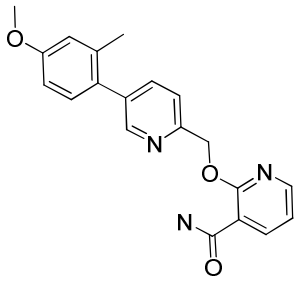
to warm to room temperature over a period of 10 min. and stirred for 30 min. The above reaction mixture was re-cooled to 0 °C and 2-chloronicotinamide (0.082 g, 0.52 mmol) was added slowly over a period of 10min.The resulting solution was then heated to 100 ° C for 2 hours. The reaction was monitored by LCMS. After complétion of the reaction, the reaction mixture was quenched with water and the preciptated solid was filtered, washed with water and dried. The crude material was purified on reverse phase preparative HPLC system to give 0.12 g of 2-((5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (**5b**) in 60% yield. ^{1}H NMR (400 MHz, CHLOROFORM-*d*) δ ppm 2.20 (s, 3 H) 3.77 (s, 3 H) 5.67 (s, 2 H) 5.95 (br. s., 1 H) 6.72 - 6.84 (m, 2 H) 6.98 - 7.12 (m, 2 H) 7.37 (d, *J*=8.03 Hz, 1 H) 7.60 (dd, *J*=8.03, 2.01 Hz, 1 H) 8.24 (dd, J=4.77, 1.76 Hz, 1 H) 8.31 (br. s., 1 H) 8.43 - 8.56 (m, 2 H). ESMS Found: 350.0 $(M+H)^+$ HRMS calcd. For (M+1) $C_{20}H_{19}N_3O_3$, 350.1505; found 350.1508; HPLC t_R = 5.934 min, purity 99%.

2-((5-(2,4-dimethylphenyl)pyridin-2-yl)methoxy)nicotinamide (5a)



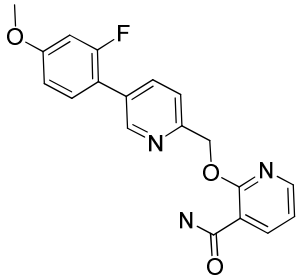
^{1}H NMR (300 MHz, DMSO-*d*$_6$) δ ppm 2.21 (s, 3 H) 2.32 (s, 3 H) 5.65 (s, 2 H) 7.07 - 7.21 (m, 4 H) 7.54 (d, *J*=7.91 Hz, 1 H) 7.74 - 7.85 (m, 2 H) 8.02 (br. s., 1 H) 8.21 (dd, *J*=7.35, 1.70 Hz, 1 H) 8.31 (dd, *J*=4.80, 1.79 Hz, 1 H) 8.48 - 8.57 (m, 1 H); ESMS Found: 333.9 $(M+H)^+$ HRMS calcd. For (M+1) $C_{21}H_{20}N_2O_2$,333.1603; found: 333.1601; HPLC t_R = 6.313 min, purity 99%.

2-((5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotin amide (5b).



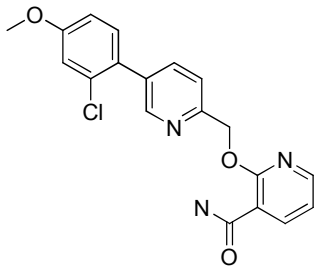
Data already given as a part of general procedure towards the synthesis of compound **5b**

2-((5-(2-fluoro-4-methoxyphenyl)pyridin-2-yl)methoxy)nicotinamide (5c).



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.83 (s, 3 H) 5.64 (s, 2 H) 6.89 - 7.06 (m, 2 H) 7.16 (dd, *J*=7.35, 4.90 Hz, 1 H) 7.50 - 7.60 (m, 2 H) 7.79 (br. s., 1 H) 7.92 - 8.06 (m, 2 H) 8.20 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.29 (dd, *J*=4.80, 1.98 Hz, 1 H) 8.70 (s, 1 H); ESMS Found: 353.9 $(M+H)^+$ HRMS calcd. For $C_{19}H_{16}FN_3O_3$,354.1248; found(M+1) 354.1249; HPLC t_R = 5.882 min, purity 99%.

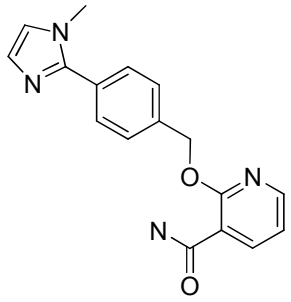
2-((5-(2-chloro-4-methoxyphenyl)pyridin-2-yl)methoxy)nicotinamide (5d).



^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 3.84 (s, 3 H) 5.66 (s, 2 H) 7.05 (dd, *J*=8.57, 2.54 Hz, 1 H) 7.13 - 7.22 (m, 2 H) 7.42 (d, *J*=8.48 Hz, 1 H) 7.56 (d, *J*=8.10 Hz, 1 H) 7.76 (br. s., 1 H) 7.88 (dd, *J*=8.10, 2.26 Hz, 1 H) 8.01 (br. s., 1 H) 8.21 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.30 (dd,

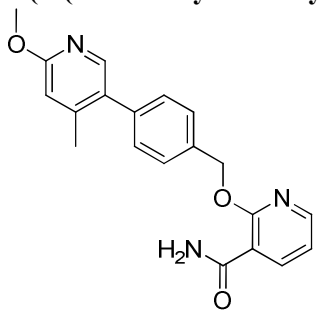
J=4.71, 1.88 Hz, 1H) 8.59 (d, *J*=2.07 Hz, 1 H); ESMS Found: 369.8 (M+); HRMS calcd. For (M+H) $C_{19}H_{16}ClN_3O_3$,370.0952; found: 370.0963; HPLC t_R = 6.078 min, purity 99%.

2-(4-(1-methyl-1H-imidazol-2-yl)benzyloxy)nicotinamide (5e).



1H NMR (300 MHz, DMSO-*d*6) δ ppm 3.75 (s, 3 H) 5.57 (s, 2 H) 6.98 (s, 1 H) 7.15 (dd, *J*=7.54, 4.90 Hz, 1 H) 7.25 (s, 1 H) 7.55 - 7.63 (m, 2 H) 7.71 (d, *J*=8.10 Hz, 4 H) 8.18 (dd, *J*=7.54, 1.88Hz, 1 H) 8.32 (dd, *J*=4.71, 1.88 Hz, 1 H); ESMS found: 309.3 (M+); HRMS calcd. For (M+1) $C_{17}H_{16}N_4O_2$,; 309.1352 found: 309.1353; HPLC t_R = 4.254, purity 99%

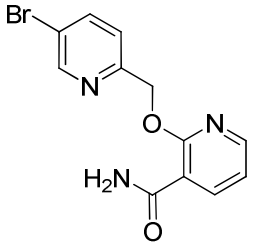
2-(4-(6-methoxy-4-methylpyridin-3-yl)benzyloxy)nicotinamide (5f).



1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.22 (s, 3 H) 3.87 (s, 3 H) 5.56 (s, 2 H) 6.79 (s, 1 H) 7.16 (dd, *J*=7.53, 5.02 Hz, 1 H) 7.39 (m, *J*=8.53 Hz, 2H) 7.58 (m, *J*=8.03 Hz, 2 H) 7.74 (br. s., 2 H) 7.98 (s, 1 H) 8.17 (dd, *J*=7.53, 2.01 Hz, 1 H) 8.33 (dd, *J*=5.02, 2.01 Hz, 1 H); ESMS found: 350.0 (M+); HRMS calcd. For (M+1) $C_{20}H_{19}N_3O_3$,; 350.1498; found: 350.1502; HPLC t_R = 5.95 min, Purity 97 %.

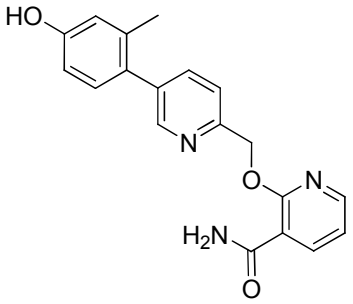
General procedure followed for the synthesis of title compounds **9a-k** is demonstrated through the synthesis of a representative compound 2-((5-(4-methoxy-2-methylphenyl)pyridin-2-yl)methoxy) nicotinamide **9a**

Step 1: 2-((5-bromopyridin-2-yl)methoxy)nicotinamide (7).



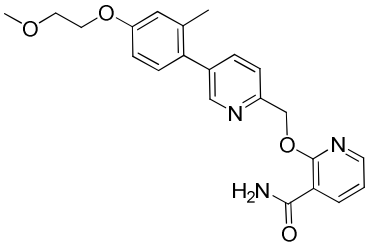
In a 50 mL round-bottomed flask, sodium hydride 60% in paraffin oil (0.585 g, 14.63 mmol) was suspended in DMF (10 mL) at 0 °C. To the above suspension, (5-bromopyridin-2-yl)methanol (2.5 g, 13.30 mmol) was added slowly at 0 °C and the temperature was allowed to warm to room temperature over a period of 20 min. and stirred for additional 30 min. The above reaction mixture was re-cooled to 0 °C and 2-chloronicotinamide (2.290 g, 14.63 mmol) was added slowly over a period of 10min.The resulting solution was then heated to 110 °C for 2 hours and the reaction was monitored by LCMS. After completion of the reaction, the reaction mixture was quenched with water (50mL) and the resulting residue was extracted into ethylacetate (50mL x 2). The combined organic layer was washed with 10% aqueous solution of Na_2CO_3 (30mL x 2), water (30mL x 2) and dried over Na_2SO_4. Evaporation of solvent resulted in brown solid. The crude product was purified by flash chromatography through pre-loaded silica gel columns using 0-10% methanol-dichloromethane gradient to give 3.5 g of 2-((5-bromopyridin-2-yl)methoxy)nicotinamide (7) in 85% yield. ESMS calcd. 308.1; found: 309.5

Step2. 2-((5-(4-hydroxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (8)



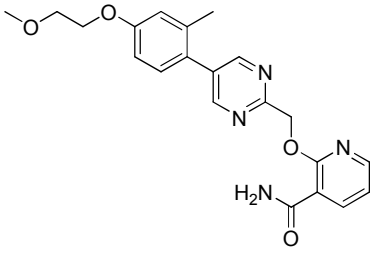
In a 10mL Biotage Microwave vial, a solution of 2-((5-bromopyridin-2-yl)methoxy) nicotinamide (2g, 6.5mmol), 4-hydroxy-2-methylphenylboronic acid (0.986 g, 6.49 mmol), PdCl2(dppf)-CH2Cl2 adduct (0.265 g, 0.32 mmol) and CsF (2.96 g, 19.47 mmol) dissolved in methanol (10 mL) was placed. The resulting brown coloured solution was purged with N_2 gas for 5 minutes and then irradiated with microwave at 120^{o}C for 30min. The completion of the reaction was monitored by LCMS. After completion of the reaction, the crude mixture was filtered through celite bed and the filterate was evaporated under reduced pressure. The resulting residue was re-dissolved in ethylacetate (100mL) and the organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give a crude solid. The crude solid was purified by flash chromatography through pre-loaded silica gel columns using 0-5% methanol-dichloromethane gradient to give 1.31 g of 2-((5-(4-hydroxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (8) in 60.3% yield. ^{1}H NMR (300 MHz, DMSO-*d*6 δ ppm 2.17 (s, 3 H) 5.64 (s, 2 H) 6.62 - 6.78 (m, 2 H) 7.06 (d, *J*=8.10 Hz, 1 H) 7.16 (dd, *J*=7.44, 4.99 Hz, 1 H) 7.51 (d, *J*=7.91Hz, 1 H) 7.76 (dd, *J*=8.19, 1.98 Hz, 2 H) 8.00 (br. s., 1 H) 8.21 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.30 (dd, *J*=4.90, 1.88 Hz, 1 H) 8.48 (d, *J*=2.07 Hz, 1 H) 9.46 (s, 1H); ESMS calcd. 335.3 Found: 335.6 (M+).

2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (9a)



In a 25 mL RB flask, 2-((5-(4-hydroxy-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (0.434 g, 1.29 mmol) and potassium carbonate (0.447 g, 3.24 mmol) was suspended in DMF(5mL). After stirring for 5min at room temperature, 1-bromo-2-methoxyethane (0.146 mL, 1.55 mmol) was added at once. The resulting suspension was heated to 110oC for 2hr and the reaction was monitored by LCMS. After complétion of the reaction, the reaction mixture was quenched with water (50mL) and the resulting residue was extracted into ethylacetate (25mL x 2). The organic layer was washed with 10% Na_2CO_3 solution (20mL x 2), water (20mL x 2) and dried over Na_2SO_4. Evoparation of solvent resulted in crude product which was purified on reverse phase preparative HPLC system to give 0.4g of 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (9a) in 79% yield. 1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.22 (s, 3 H) 3.32 (s, 3 H) 3.67 (dd, *J*=5.27, 3.77 Hz, 2 H) 3.99 - 4.18 (m, 2 H) 5.64 (s, 2 H) 6.87 (dd, *J*=8.29, 2.64 Hz,1 H) 6.93 (d, *J*=2.45 Hz, 1 H) 7.10 - 7.22 (m, 2 H) 7.53 (d, *J*=8.29 Hz, 1 H) 7.74 - 7.83 (m, 2 H) 8.02 (br. s., 1 H) 8.20 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.31 (dd, *J*=4.90, 2.07 Hz, 1 H) 8.51 (d, *J*=1.70 Hz, 1 H); ESMS found: 393.7 (M+); HRMS calcd. For $C_{22}H_{23}N_3O_4$,; 394.1761; found (M+1) 394.1760; HPLC t_R = 5.536 min., Purity = 99 %.

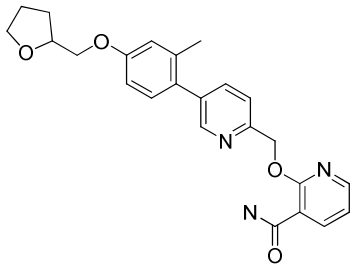
2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyrimidin-2-yl)methoxy)nicotinamide (9b).



1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.24 (s, 3 H) 3.31 (s, 3 H) 3.65 - 3.68 (m, 2 H) 4.11 - 4.15 (m, 2 H) 5.78 (s, 2 H) 6.90 (d, *J*=8.53 Hz, 1 H) 6.95 (s, 1 H) 7.17 (dd, *J*=7.53, 5.02 Hz, 1 H) 7.24 (d, *J*=8.03 Hz, 1 H) 7.82 - 7.88 (m, 1 H) 8.21 - 8.25 (m, 1 H) 8.26 - 8.32 (m, 2 H)

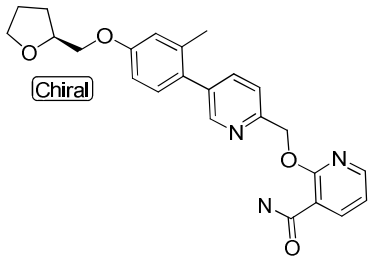
8.80 (s, 2 H); ESMS found: 395.2 (M+1); HRMS calcd. For (M+1) $C_{21}H_{22}N_4O_4$, 395.1713 found 395.1714; HPLC t_R = 5.367 min purity 97%.

2-((5-(2-methyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)pyridin-2-yl)methoxy) nicotinamide (9c).



^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 1.64 - 1.78 (m, 1 H) 1.83 - 1.96 (m, 2 H) 1.96 - 2.10 (m, 1 H) 2.18 (s, 3 H) 3.71 - 3.82 (m, 1 H) 3.82- 3.96 (m, 3 H) 4.14 - 4.29 (m, 1 H) 5.70 (s, 2 H) 6.04 (br. s., 1 H) 6.72 - 6.84 (m, 2 H) 6.94 - 7.11 (m, 2 H) 7.43 (d, *J*=8.10 Hz, 1 H) 7.67 (dd, *J*=8.01, 2.17 Hz, 1 H) 8.21 (dd, *J*=4.80, 1.98 Hz, 1 H) 8.29 (br. s., 1 H) 8.43 - 8.57 (m, 2 H).; ESMS found: 420.44 (M+1); HRMS calcd. For $C_{24}H_{25}N_3O_4$, 420.1917; found(M+1) 420.1918; HPLC t_R = 6.026 min purity 99%.

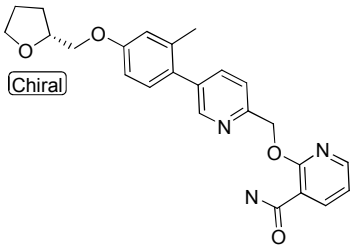
(S)-2-((5-(2-methyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)pyridin-2-yl)methoxy) nicotinamide (9d)



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.60 - 1.73 (m, 1 H) 1.79 - 1.92 (m, 2 H) 1.95 - 2.05 (m, 1 H) 2.22 (s, 3 H) 3.62 - 3.73 (m, 1 H) 3.74 - 3.84 (m, 1 H) 3.90 - 4.01 (m, 2 H) 4.10 - 4.21 (m, 1 H) 5.64 (s, 2 H) 6.87 (dd, *J*=8.53, 2.51 Hz, 1 H) 6.93 (d, *J*=2.01 Hz, 1 H) 7.13 -

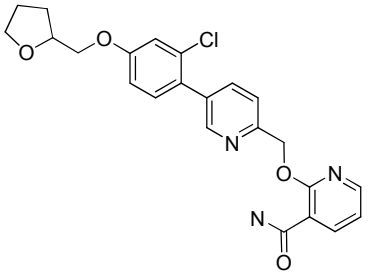
7.19 (m, 2 H) 7.53 (d, *J*=8.03 Hz, 1 H) 7.74 - 7.83 (m, 2 H) 8.02 (br. s., 1 H) 8.20 (dd, *J*=7.53, 2.01 Hz, 1 H) 8.30 (dd, *J*=5.02, 2.01 Hz, 1 H) 8.50 (d, *J*=2.01 Hz, 1 H); ESMS found: 419.6 (M+1); HRMS calcd. For $C_{24}H_{25}N_3O_4$,; 420.1917 found(M+1) 420.1920; HPLC t_R = 6.038 min. Purity = 99 %

(R)-2-((5-(2-methyl-4-((tetrahydrofuran-2-yl)methoxy)phenyl)pyridin-2-yl)methoxy) nicotinamide (9e)



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.61 - 1.74 (m, 1 H) 1.81 - 1.94 (m, 2 H) 1.97 - 2.07 (m, 1 H) 2.22 (s, 3 H) 3.63 - 3.72 (m, 1 H) 3.74 - 3.84 (m, 1 H) 3.90 - 4.02 (m, 2 H) 4.10 - 4.23 (m, 1 H) 5.64 (s, 2 H) 6.87 (dd, *J*=8.57, 2.54 Hz, 1 H) 6.93 (d, *J*=2.26 Hz, 1 H) 7.13 - 7.20 (m, 2 H) 7.53 (d, *J*=8.10 Hz, 1 H) 7.71 - 7.83 (m, 2 H) 8.02 (br. s., 1 H) 8.20 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.31 (dd, *J*=4.90, 2.07 Hz, 1 H) 8.50 (d, *J*=2.07 Hz, 1 H); ESMS found: 419.6 (M+1); HRMS calcd. For $C_{24}H_{25}N_3O_4$,; 420.1917 found(M+1) 420.1915; HPLC t_R = 6.044min. Purity = 99 %.

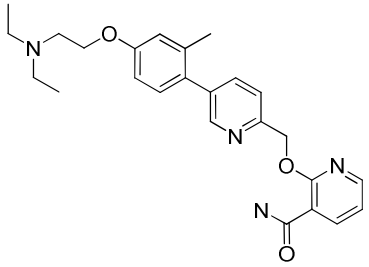
2-((5-(2-chloro-4-((tetrahydrofuran-2-yl)methoxy)phenyl)pyridin-2-yl)methoxy) nicotinamide (9f)



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.60 - 1.75 (m, 1 H) 1.77 - 1.94 (m, 2 H) 1.94 - 2.08 (m, 1 H) 3.63 - 3.74 (m, 1 H) 3.74 - 3.85 (m, 1 H) 3.94 - 4.11 (m, 2 H) 4.11 - 4.22 (m, 1 H)

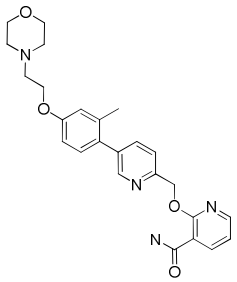
5.65 (s, 2 H) 7.06 (dd, *J*=8.67, 2.45 Hz, 1 H) 7.13 - 7.24 (m, 2 H) 7.40 (d, *J*=8.48 Hz, 1 H) 7.55 (d, *J*=8.10 Hz, 1 H) 7.79 (br. s., 1 H) 7.88 (dd, *J*=8.01, 2.17 Hz, 1 H) 8.03 (br. s., 1 H) 8.20 (dd, *J*=7.54, 1.88 Hz, 1 H) 8.30 (dd, *J*=4.71, 1.88 Hz, 1 H) 8.58 (d, *J*=1.88 Hz, 1 H); ESMS found: 440.1 (M+1); HRMS calcd. For $C_{23}H_{22}ClN_3O_4$; 440.1371 found (M+1) 440.1364; HPLC t_R =6.117, Purity 99 %.

2-((5-(4-(2-(diethylamino)ethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinamide (9g).



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 0.98 (t, *J*=7.06 Hz, 6 H) 2.22 (s, 3 H) 2.53 - 2.60 (m, 4 H) 2.78 (t, *J*=6.03 Hz, 2 H) 4.04 (t, *J*=6.12 Hz, 2 H) 5.64 (s, 2 H) 6.86 (d, *J*=8.29 Hz, 1 H) 6.91 (s, 1 H) 7.12 - 7.21 (m, 2 H) 7.53 (d, *J*=7.91 Hz, 1 H) 7.75 - 7.84 (m, 2 H) 8.03 (br. s., 1 H) 8.20 (dd, *J*=7.35, 2.07 Hz, 1 H) 8.28 - 8.34 (m, 1 H) 8.51 (s, 1 H); ESMS found: 435.3.3 (M+1); HRMS calcd. For $C_{25}H_{30}N_4O_3$; 434.2317 found(M+1) 434.2418; HPLC t_R =6.078, Purity 99.8 %.

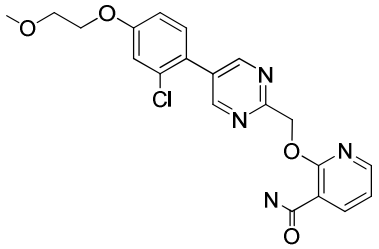
2-((5-(2-methyl-4-(2-morpholinoethoxy)phenyl)pyridin-2-yl)methoxy)nicotinamide (9h).



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.22 (s, 3 H) 2.43-2.49(m, 4H) 2.70 (t, *J*=5.65 Hz, 2 H) 3.58 (t, *J*=4.43 Hz, 4 H) 4.12 (t, *J*=5.56 Hz, 2 H) 5.64 (s, 2 H) 6.87 (d, *J*=8.48 Hz, 1 H) 6.93 (s, 1 H) 7.14 - 7.21 (m, 2 H) 7.53 (d, *J*=7.91 Hz, 1 H) 7.76 - 7.83 (m, 2 H) 8.02 (br, s, 1

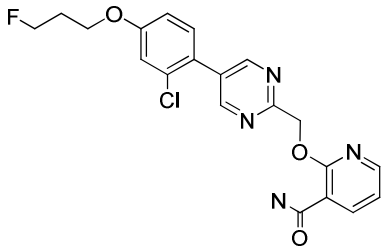
H) 8.20 (d, *J*=7.54 Hz, 1 H) 8.31 (d, *J*=3.01 Hz, 1 H) 8.51 (s, 1 H); ESMS found: 449.1 (M+1); HRMS calcd. For $C_{25}H_{28}N_4O_4$,; 449.2183 found (M+1) 449.2183; HPLC t_R =5.263, Purity 98 %.

2-((5-(2-chloro-4-(2-methoxyethoxy)phenyl)pyrimidin-2-yl)methoxy)nicotinamide (9i)



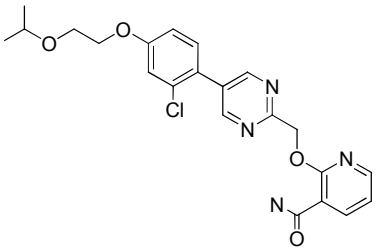
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 3.31 (s, 3 H) 3.81 - 3.90 (m, 14 H) 4.19 (t, J=6.0 Hz, 2H) 4.78 (7, *J*=6.22 Hz, 2 H) 5.79 (s, 2 H) 7.09 (dd, *J*=8.57, 2.54 Hz, 1 H) 7.18 (dd, *J*=7.35, 4.90 Hz, 1 H) 7.25 (d, *J*=2.64 Hz, 1 H) 7.49 (d, *J*=8.48 Hz, 1 H) 7.85 (br. s., 1 H) 8.24 - 8.33 (m, 3 H) 8.88 (s, 2 H); ESMS found: 415.2 (M+1); HRMS calcd. For $C_{20}H_{19}ClN_4O_4$, 415.1167 found (M+1) 415.1170; HPLC t_R =5.33, Purity 97 %.

2-((5-(2-chloro-4-(3-fluoropropoxy)phenyl)pyrimidin-2-yl)methoxy)nicotinamide (9j).



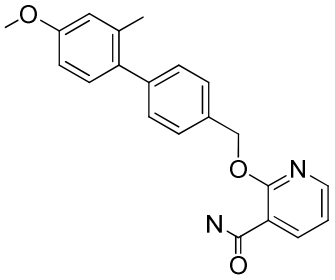
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.06 - 2.29 (m, 2 H) 4.17 (t, *J*=6.31 Hz, 2 H) 4.54 (t, *J*=5.93 Hz, 1 H) 4.70 (t, *J*=5.84 Hz, 1 H) 5.79 (s, 2 H) 7.10 (dd, *J*=8.67, 2.64 Hz, 1 H) 7.18 (dd, *J*=7.35, 4.90 Hz, 1 H) 7.26 (d, *J*=2.45 Hz, 1 H) 7.50 (d, *J*=8.67 Hz, 1 H) 7.85 (br. s., 1 H) 8.22 - 8.34 (m, 3 H) 8.88 (s, 2 H); ESMS found: 417.2 (M+1); HRMS calcd. For $C_{20}H_{18}ClFN_4O_3$, 417.1123 found (M+1) 417.1119; HPLC t_R =5.80, Purity 99 %.

2-((5-(2-chloro-4-(2-isopropoxyethoxy)phenyl)pyrimidin-2-yl)methoxy)nicotinamide (9k)



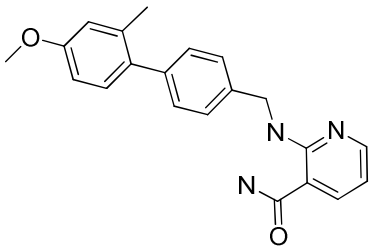
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 1.10 - 1.12 (d, J= 6.0Hz, 6 H) 3.61 - 3.66 (m, 1 H) 3.68 - 3.73 (m, 2 H) 4.14 - 4.18 (m, 2 H) 5.79 (s, 2 H) 7.09 (dd, *J*=8.67, 2.64 Hz, 1 H) 7.18 (dd, *J*=7.35, 4.90 Hz, 1 H) 7.25 (d, *J*=2.45 Hz, 1 H) 7.49 (d, *J*=8.67 Hz, 1 H) 7.85 (br. s., 1 H) 8.22 - 8.34 (m, 3 H) 8.88 (s, 2 H); ESMS found: 443.2; HRMS calcd for (M+1) $C_{22}H_{23}ClN_4O_4$, 443.1480 found: 443.1474; HPLC t_R = 5.99, purity 99%.

2-((4'-methoxy-2'-methylbiphenyl-4-yl)methoxy)nicotinamide (16).



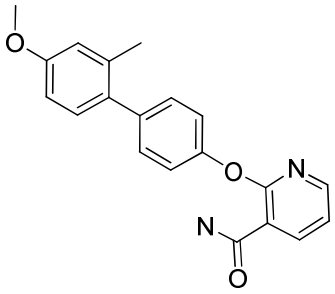
1H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.20 (s, 3 H) 3.77 (s, 3 H)5.52 (s, 2 H) 5.65 (br. s., 1 H) 6.75 (d, *J*=2.26 Hz, 2 H) 7.03 (dd, *J*=7.63,4.80 Hz, 1 H) 7.09 (d, *J*=8.29 Hz, 1 H) 7.27 (m, *J*=8.10 Hz, 2 H) 7.41 (m, *J*=8.10 Hz, 2 H) 7.72 (br. s., 1 H) 8.27 (dd, *J*=4.80, 1.98 Hz, 1 H) 8.49(dd, *J*=7.54, 2.07 Hz, 1 H); ESMS found: 349.4 (M+1); HRMS calcd. For $C_{21}H_{20}N_2O_{3,}$; 349.1552 found(M+1) 349.1549; HPLC t_R = 8.589, Purity 97 %.

2-((4'-methoxy-2'-methylbiphenyl-4-yl)methylamino)nicotinamide (17)



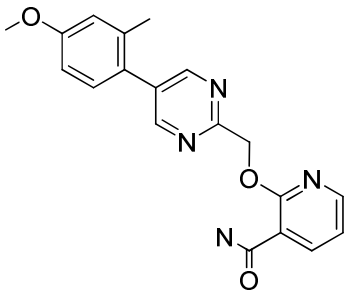
^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.21 (s, 3 H) 3.76 (s, 3 H) 4.68 (d, *J*=5.84 Hz, 2 H) 6.59 (dd, *J*=7.63, 4.80 Hz, 1 H) 6.78 - 6.84 (m, 1 H) 6.86 (d, *J*=2.45 Hz, 1 H) 7.11 (d, *J*=8.29 Hz, 1 H) 7.25 (m, *J*=8.10 Hz, 2 H) 7.35 (m, *J*=8.10 Hz, 2 H) 7.42 (br. s., 1 H) 7.99 (dd, *J*=7.72, 1.70 Hz, 1 H) 8.05 (br. s., 1 H) 8.17 (dd, *J*=4.90, 1.70 Hz, 1 H) 9.02 (t, *J*=5.75 Hz, 1 H); ESMS found: 350.0 (M+1); HRMS calcd. For $C_{21}H_{21}N_3O_2$,; 348.1706 found(M+1) 348.1705; HPLC t_R = 5.717 min. Purity = 99 %.

2-(4'-methoxy-2'-methylbiphenyl-4-yloxy)nicotinamide (18).



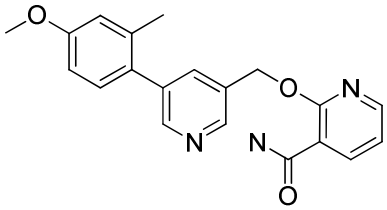
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.24 (s, 3 H) 3.77 (s, 3 H) 6.02 (br. s., 1 H) 6.70 - 6.80 (m, 2 H) 7.09 - 7.20 (m, 5 H) 7.28 - 7.35 (m, 2 H) 7.73 (br. s., 1 H) 8.22 (dd, *J*=4.80, 1.98 Hz, 1 H) 8.57 (dd, *J*=7.63, 1.98 Hz, 1 H); ESMS found: 335.0 (M+1); HRMS calcd. For $C_{18}H_{16}N_4O_3$, 336.1348, found (M+1): 336.1355; HPLC t_R = 6.264 min. Purity = 99 %.

2-((5-(4-methoxy-2-methylphenyl)pyrimidin-2-yl)methoxy)nicotinamide (19)



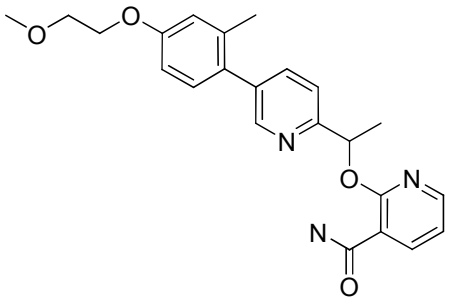
1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.26 (s, 3 H) 3.79 (s, 3 H) 5.79 (s, 2 H) 6.90 (d, *J*=8.53 Hz, 1 H) 6.95 (d, *J*=2.51 Hz, 1 H) 7.18 (dd, *J*=7.28,4.77 Hz, 1 H) 7.26 (d, *J*=8.53 Hz, 1 H) 7.86 (br. s., 1 H) 8.24 (br. s., 1 H) 8.27 - 8.33 (m, 2 H) 8.81 (s, 2 H); ESMS found 350.8; HRMS calcd for C19H18N4O3 (M+1) 351.1144 found: 351.1150; HPLC t_R = 5.493 min. Purity = 99.9 %.

2-((5-(4-methoxy-2-methylphenyl)pyridin-3-yl)methoxy)nicotinamide (20).



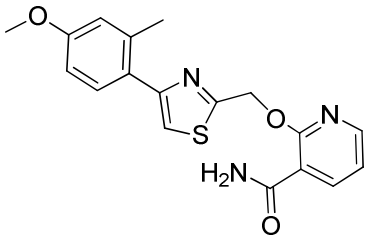
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.18 (s, 3 H) 3.78 (s, 3 H) 5.32 (s, 2 H) 6.57 (t, *J*=6.78 Hz, 1 H) 6.80 - 6.99 (m, 2 H) 7.16 (d, *J*=8.53 Hz, 1 H) 7.55 - 7.67 (m, 1 H) 7.67 - 7.74 (m, 1 H) 8.22 - 8.40 (m, 2 H) 8.48 (d, J=2.01 Hz, 1 H) 8.57 (d, J=2.01 Hz, 1 H) 8.96 (d, J=3.01 Hz, 1 H); ESMS found: 350.0 (M+1); HRMS calcd. For $C_{20}H_{19}N_3O_3$,; 350.1498 found (M+1) 350.1501; HPLC t_R = 5.717 min. Purity = 99 %.

2-(1-(5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)ethoxy)nicotinamide (21)



^{1}H NMR (300 MHz, DMSO-*d*6) δ ppm 1.71 (d, *J*=6.59 Hz, 3 H) 2.21 (s, 3 H) 3.32 (s, 3 H) 3.64 - 3.70 (m, 2 H) 4.04 - 4.16 (m, 2 H) 6.43 (q, *J*=6.53Hz, 1 H) 6.82 - 6.90 (m, 1 H) 6.92 (d, *J*=2.07 Hz, 1 H) 7.07 - 7.21 (m, 2 H) 7.54 (d, *J*=8.10 Hz, 1 H) 7.77 (dd, *J*=8.10, 2.26 Hz, 1 H) 7.81 (br. s., 1H) 8.04 (br. s., 1 H) 8.19 (dd, *J*=7.44, 1.98 Hz, 1 H) 8.25 (dd, *J*=4.80, 1.98 Hz, 1 H) 8.49 (d, *J*=1.70 Hz, 1 H); ESMS found: 407.7 (M+1); HRMS calcd. For $C_{23}H_{25}N_3O_4$,; 408.1917 found(M+1) 408.1910; HPLC t_R = 5.993 min. Purity = 99 %.

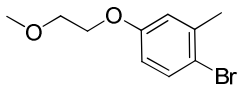
2-((4-(4-methoxy-2-methylphenyl)thiazol-2-yl)methoxy)nicotinamide (22).



^{1}H NMR (300 MHz, DMSO-d_6) δ ppm 2.39 (s, 3 H) 3.78 (s, 3 H) 5.83 (s, 2 H) 6.80 - 6.90 (m, 2 H) 7.21 (dd, *J*=7.44, 4.99 Hz, 1 H) 7.55 (d, *J*=8.48 Hz, 1 H) 7.68 (s, 1 H) 7.83 (d, *J*=6.03 Hz, 2 H) 8.21 (dd, *J*=7.35, 1.88 Hz, 1 H) 8.35 (dd, *J*=4.90, 1.88 Hz, 1 H); ESMS found: 350.0 (M+1); HRMS calcd. For $C_{18}H_{17}N_3O_3S$,; 356.1063 found (M+1) 356.1058; HPLC t_R = 5.717 min. Purity = 99 %.

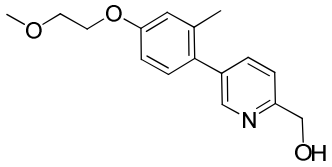
General procedure followed for the synthesis of title compounds **15a-h** is demonstrated through the synthesis of a representative compound 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N-methyl nicotinamide **15a**

Step 1. 1-bromo-4-(2-methoxyethoxy)2-methylbenzene (11)



Synthesis of In a 10mL RB flask, 4-bromo-3-methyl phenol (700mg, 3.74mmol) dissolved in DMF(5mL) was taken. K2CO3 (672mg, 4.87 mmol) was added and the reaction mixture was heated to 50oC for 30min. At that temperature, 1-bromo-2-methoxyethane (422 uM, 4.49mmol) was added in one lot. The temperature of the reaction mixture was raised to 100oC and heated for 4 h. The reaction was monitored by LCMS. After complétion of the reaction, the reaction mixture was diluted with water (50mL) and the resulting residue was extracted kinto ethylacetate (35mL x 2). The organic layer was washed with water (20mL x 2) and dried over Na_2SO_4. Evoparation of solvent resulted in crude product which was purified on a preloaded silica column using 0-40% EtOAC-Hexane gradient to give 850mg of 1-bromo-4-(2-methoxyethoxy)2-methylbenzene (**11**) in 92% yield. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.30 (s, 3 H) 3.34 (s, 3 H) 3.60-3.66 (m, 2 H) 4.04-4.09 (m 2 H) 6.73 (dd, J= 8.53, 3.01 Hz, 1 H) 6.97 (d, J= 3.01Hz, 1 H) 7.43 (d, J= 8.53 Hz, 1 H); ESMS found: 263.7, 265.7 (M+).

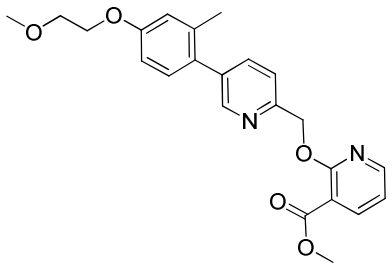
Step 2. (5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methanol (12).



In a 10mL Biotage Microwave vial, a solution of was 1-bromo-4-(2-methoxyethoxy)-2-methylbenzene (0.6 g, 2.44 mmol), 6-(hydroxymethyl)pyridin-3-ylboronic acid (0.374 g, 2.44 mmol), $CsCO_3$ (1.196 g, 3.67 mmol), and $PdCl_2$(dppf)-CH_2Cl_2 adduct (0.10 g, 0.12 mmol) in methanol (8 mL) was placed. The resulting brown coloured solution was purged with N_2 gas

for 5 minutes and then irradiated with microwave at 120°C for 45 min. The completion of the reaction was monitored by LCMS. After completion of the reaction, the crude mixture was filtered through celite bed and the filterate was evaporated under reduced pressure. The resulting residue was re-dissolved in ethylacetate (50mL) and the organic layer was washed with water, dried over Na_2SO_4 and evaporated under reduced pressure to give a crude solid. The crude solid was purified by flash chromatography through pre-loaded silica gel columns using 0-100% EtOAc-Hexane gradient to give 0.244 g of (5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methanol in 36.5% yield. ESMS calcd. 273.3; found: 274.2 (M+H).

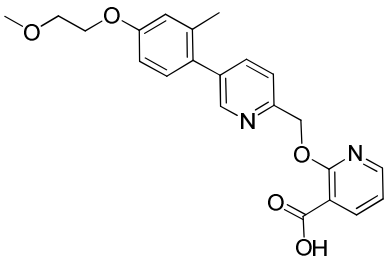
Step 3. methyl 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy) nicotinate (13).



In a 50 mL RB flask, sodium hydride 60% in paraffin oil (0.643 g, 13.40 mmol) was suspended in DMF (25 mL) at 0 °C. To the above suspension, (5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methanol (3.33 g, 12.18 mmol) was added slowly at 0 °C and the temperature was allowed to warm to room temperature over a period of 10 min. and stirred for 30 min. The above reaction mixture was re-cooled to 0 °C and methyl 2-chloronicotinate (2.299 g, 13.40 mmol) was added slowly over a period of 10min.The resulting solution was then heated to 120 ° C for 2 hours. The reaction was monitored by LCMS. After complétion of the reaction, the reaction mixture was quenched with water and the preciptate was extracted into EtOAc (100mL), washed with water and dried over Na2SO4. Evaporation of solvent resulted in curde product as oil which was purified on flash chromatography over preloaded silica gel column using 0-100% EtOAc-Hexane gradient. This resulted in 2.70 g of oily 2-

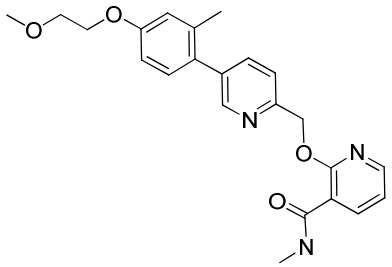
((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinate (**13**) in 54% yield. ESMS calcd. 408.4.4; found: 409.2 (M+H).

Step 4. Synthesis of 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy) nicotinic acid (14).



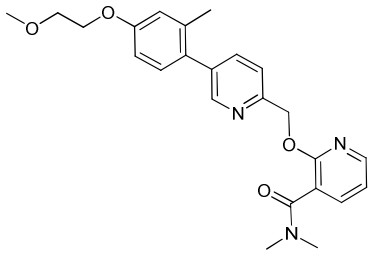
In a 25 mL RB flask, methyl 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinate (1.031 g, 2.52 mmol) dissolved in dioxane (10 mL) was placed. LiOH (0.073 g, 3.03 mmol) was added slowly and the resulting reaction mixture was stirred at room temperature for 18 hrs. The reaction was monitered by LCMS. After completion of the reaction, the reaction mixture was diluted with water (50mL) and back washed with EtOAc (25mL x 2). The combined aqueous layer was acidified with slow addition of 1NHCl to pH6.5, extracted into EtOAc (30mL x 2) washed with water, dried over Na2SO4 and evoparated. This resulted in 0.95g of 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)nicotinic acid as pure white solid in 94% yield. ESMS calcd. 394.4; found: 394.6 (M+).

Step 5. 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N-methyl nicotin amide (15a)



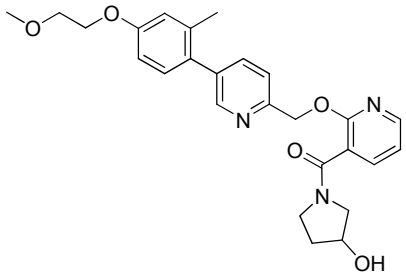
In a 10 mL RB flask, 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy) nicotinic acid (0.2 g, 0.51 mmol) dissolved in DMF (2mL) was taken. To this solution, HATU (0.212 g, 0.56 mmol) and DIEA (0.195 mL, 1.12 mmol) was added. The resulting brown coloured solution was stirred at room temperature for 10min and 2M methanamine solution in methanol (0.254 mL, 0.51 mmol) was added once and the reaction mixture was stirred for 2 hr at room temperature. The reaction was monitored by LCMS. After complétion of the reaction, the reaction mixture was diluted with water (50mL) and the resulting residue was extracted into ethylacetate (25mL x 2). The organic layer was washed with 10% Na_2CO_3 solution (20mL x 2), water (20mL x 2) and dried over Na_2SO_4. Evoparation of solvent resulted in crude product which was purified on reverse phase preparative HPLC system to give 0.11g of 2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N-methylnicotinamide (16a) in 53% yield. 1H NMR (400 MHz, DMSO-*d*6) δ ppm 2.23 (s, 3 H) 2.86 (d, *J*=4.52 Hz, 3 H) 3.64 - 3.71 (m, 2 H) 4.08 - 4.15 (m, 2 H) 5.65 (s, 2 H) 6.87 (dd,*J*=8.28, 2.76 Hz, 1 H) 6.93 (d, *J*=2.51 Hz, 1 H) 7.12 - 7.21 (m, 2 H) 7.50 (d, *J*=8.03 Hz, 1 H) 7.80 (dd, *J*=8.03, 2.01 Hz, 1 H) 8.18 (dd, *J*=7.53, 2.01 Hz, 1 H) 8.29 (dd, *J*=5.02, 2.01 Hz, 1 H) 8.54 (d, *J*=1.51 Hz, 1 H) 8.70 (d, *J*=4.02 Hz, 1 H); ESMS found: 407.7 (M+1); HRMS calcd. For $C_{23}H_{25}N_3O_4$,; 408.1917 found(M+1) 408.1912; HPLC t_R = 6.071 min. Purity = 99 %.

2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N,N-dimethyl nicotinamide (15b).



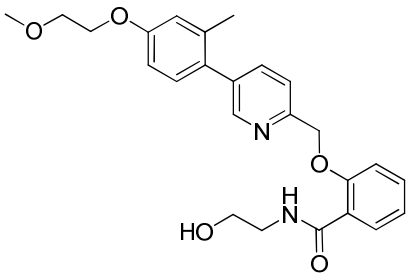
1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.22 (s, 3 H) 2.85 (s, 3 H) 3.01 (s, 3 H) 3.32 (s, 3 H) 3.63 - 3.71 (m, 2 H) 4.12 (dd, *J*=5.46, 3.77 Hz, 2 H) 5.55 (s, 2 H) 6.87 (dd, *J*=8.38, 2.54 Hz, 1 H) 6.93 (d, *J*=2.45 Hz, 1 H) 7.11 (dd, *J*=7.35, 5.09 Hz, 1 H) 7.17 (d, *J*=8.48 Hz, 1 H) 7.42 (d, *J*=8.10 Hz,1 H) 7.73 (dd, *J*=7.16, 1.88 Hz, 1 H) 7.79 (dd, *J*=8.10, 2.26 Hz, 1 H) 8.24 (dd, *J*=5.09, 1.88 Hz, 1 H) 8.50 (d, *J*=1.70 Hz, 1 H); ESMS found: 421.7 (M+1); HRMS calcd. For $C_{24}H_{27}N_3O_4$,; 422.2074 found (M+1) 422.2072; HPLC t_R = 5.854 min. Purity = 99 %.

(3-hydroxypyrrolidin-1-yl)(2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl) methoxy)pyridin-3-yl)methanone (15c)



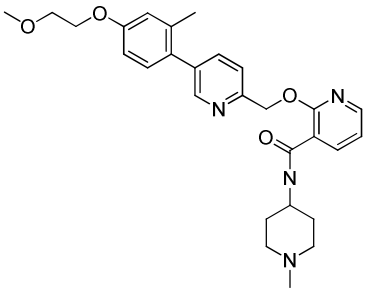
1H NMR (300 MHz, DMSO-*d*6) δ ppm 1.70 - 1.97 (m, 2 H) 2.22 (s, 3 H) 3.32 (s, 3 H) 3.37 - 3.47 (m, 2 H) 3.48 - 3.60 (m, 2 H) 3.67 (dd, *J*=5.46,3.77 Hz, 2 H) 4.07 - 4.15 (m, 2 H) 4.24 (br. s., 1 H) 4.33 (br. s., 1 H) 5.00 (dd, *J*=11.68, 3.20 Hz, 1 H) 5.54 (s, 2 H) 6.87 (dd, *J*=8.57, 2.54 Hz, 1 H)6.93 (d, *J*=2.45 Hz, 1 H) 7.11 (dd, *J*=6.88, 5.37 Hz, 1 H) 7.17 (d, *J*=8.48 Hz, 1 H) 7.48 (dd, *J*=10.74, 8.10 Hz, 1 H) 7.69 - 7.83 (m, 2 H) 8.25 (dt,*J*=4.99, 1.84 Hz, 1 H) 8.49 (s, 1 H); ESMS found: 463.7 (M+1); HRMS calcd. For (M+1) $C_{26}H_{29}N_3O_5$, 464.2179, found: 464.2176; HPLC: t_R = 5.15, purity 99 %

N-(2-hydroxyethyl)-2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy) nicotinamide (15d)



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 2.23 (s, 3 H) 3.32 (br. s., 3 H) 3.38 - 3.45 (m, 2 H) 3.54 (q, *J*=5.69 Hz, 2 H) 3.64 - 3.70 (m, 2 H) 4.10 - 4.16 (m, 2 H) 4.77 (t, *J*=5.52 Hz, 1 H) 5.66 (s, 2 H) 6.88 (dd, *J*=8.78, 2.26 Hz, 1 H) 6.94 (s, 1 H) 7.14 - 7.22 (m, 2 H) 7.58 (d, *J*=8.03 Hz, 1 H) 7.81 (dd, *J*=8.03, 2.01 Hz, 1 H) 8.23 (dd, *J*=7.53, 1.51 Hz, 1 H) 8.28 - 8.35 (m, 1 H) 8.54 (s, 1 H) 8.74 (t, *J*=5.77 Hz, 1 H); ESMS found: 438 (M+1); HRMS calcd. For (M+1) $C_{24}H_{27}N_3O_5$, 438.2023 found: 438.2017; HPLC: t_R = 5.416, purity 98%.

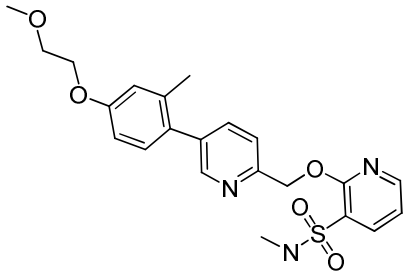
2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N-(1-methyl piperidin-4-yl)nicotinamide (15e)



^{1}H NMR (400 MHz, DMSO-d_6) δ ppm 1.41 - 1.55 (m, 2 H) 1.73 - 1.84 (m, 2 H) 1.98 (t, *J*=10.54 Hz, 2 H) 2.13 (s, 3 H) 2.24 (s, 3 H) 2.58 - 2.67 (m, 2 H) 3.33 (br. s., 3 H) 3.68 (dd, *J*=5.27, 3.76 Hz, 2 H) 3.71 - 3.83 (m, 1 H) 4.13 (dd, *J*=5.77, 3.76 Hz, 2 H) 5.61 (s, 2 H) 6.89 (dd, *J*=8.28, 2.76 Hz, 1 H) 6.95 (d, *J*=2.51 Hz, 1 H) 7.19 (dt, *J*=7.78, 2.38 Hz, 2 H) 7.62 (d, *J*=8.03 Hz, 1 H) 7.85 (dd, *J*=8.03, 2.51 Hz, 1 H) 8.19 (dd, *J*=7.53, 2.01 Hz, 1 H) 8.34 (dd, *J*=5.02, 2.01 Hz, 1 H) 8.52 (d, *J*=7.53 Hz, 1 H) 8.55 (d, *J*=1.51 Hz, 1 H); ESMS found: 490.7

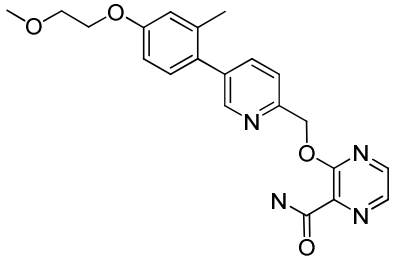
(M+); HRMS calcd. For $C_{28}H_{34}N_4O_4$; 491.2652 found (M+1) 491.2659; HPLC tR = 5.779, Purity 98 %.

2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)-N-methylpyridine-3-sulfonamide (15f).



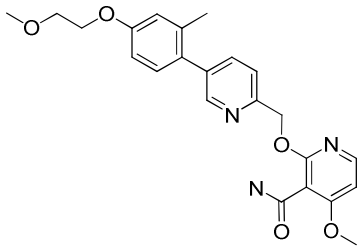
^{1}H NMR (300 MHz, CHLOROFORM-*d*) δ ppm 2.19 (s, 3 H) 2.49 - 2.57 (m, 3 H) 3.40 (s, 3 H) 3.66 - 3.75 (m, 2 H) 4.06 - 4.13 (m, 2 H) 5.68 (s, 2 H) 6.74 - 6.85 (m, 2 H) 7.00 - 7.10 (m, 2 H) 7.41 (d, *J*=8.10 Hz, 1 H) 7.66 (d, *J*=6.41 Hz, 1 H) 8.17 (dd, *J*=7.54, 1.88 Hz, 1 H) 8.29 (dd, *J*=4.99, 1.79 Hz, 1 H) 8.48 (s, 1 H); ESMS found: 444.1 (M+1); HRMS calcd. For $C_{22}H_{25}N_3O_5S$; 444.1587 found (M+1) 444.1579; HPLC t_R =6.281, Purity 99 %.

3-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy)pyrazine-2-carboxamide (15g).



1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.23 (s, 3 H) 3.32 (s, 3 H) 3.63 - 3.70 (m, 2 H) 4.08 - 4.15 (m, 2 H) 5.57 (s, 2 H) 6.87 (dd, *J*=8.48, 2.26 Hz, 1H) 6.93 (d, *J*=2.26 Hz, 1 H) 7.18 (d, *J*=8.48 Hz, 1 H) 7.59 (d, *J*=8.10 Hz, 1 H) 7.73 (br. s., 1 H) 7.81 (dd, *J*=8.10, 2.26 Hz, 1 H) 8.07 (br. s., 1 H)8.28 (d, *J*=2.64 Hz, 1 H) 8.36 (d, *J*=2.64 Hz, 1 H) 8.51 (d, *J*=1.70 Hz, 1 H); ESMS found: 395.4 (M+1); HRMS calcd. For $C_{20}H_{19}ClN_4O_4$; 395.1713 found (M+1) 395.1720; HPLC t_R =5.169, Purity 98 %.

4-methoxy-2-((5-(4-(2-methoxyethoxy)-2-methylphenyl)pyridin-2-yl)methoxy) nicotinamide (15h).



1H NMR (300 MHz, DMSO-*d*6) δ ppm 2.20 - 2.24 (m, 3 H) 3.32 (s, 3 H) 3.64 - 3.70 (m, 2 H) 3.85 (s, 3 H) 4.07 - 4.16 (m, 2 H) 5.48 (s, 2 H) 6.82 -6.90 (m, 2 H) 6.92 (s, 1 H) 7.17 (d, *J*=8.29 Hz, 1 H) 7.48 (d, *J*=8.67 Hz, 2 H) 7.72 - 7.82 (m, 2 H) 8.07 (d, *J*=6.03 Hz, 1 H) 8.48 (s, 1 H); ESMS found: 424.2 (M+1); HRMS calcd. For $C_{23}H_{25}N_3O_{5,}$; 424.1866 found(M+1) 424.1865; HPLC t_R = 5.340 min., Purity 99 %.

Materials and Methods :

Determination of Minimal inhibitory concentration (MIC) of APCs against *M.tuberculosis*

Mycobacterium tuberculosis (Mtu) H37Rv ATCC 27294 used for MIC determination was grown as reported earlier.[1] All test compound stocks and dilutions were prepared in DMSO.

Mtb MICs of test compounds were determined by the standard microdilution method [2] in 7H9 broth containing 0.2% glycerol, 0.05% Tween 80 and 10% v/v ADC with some modifications in a total volume of 40µl. Briefly, 1µl of serial two-fold dilutions of test compound was dispensed in a 384 well microtitre plate (Corning 3702), at final concentrations ranging from 100µM- 0.19µM. Control wells included media and culture controls. 40 µl (3-7 x 10^5 CFU/ml) of the bacterial culture was added to all the wells except the media control wells. The plates were packed in gas permeable polythene bags and incubated at 37°C for 5 days. Following this incubation period, 8 µl of a freshly prepared 1:1 mixture of Resazurin (0.02%

in water), and 10% Tween 80 was added to all the wells. The plates were re-incubated for an additional 24 hours at 37°C and the colour conversion of all wells recorded. Absorbance at 575nm & 610nm was monitored and their ratio calculated. The media control and the no inhibitor / culture controls were considered equivalent to 100% and 0% inhibition respectively. The least concentration which yielded 80% inhibition was considered as MIC. In all the assays Isoniazid MIC values was generated in parallel to ensure the validity of the assay conditions.

Determination of MICs against various *M.tuberculosis* isolates (sensitive and single drug resistant-SDR)

This assay is set up using the same protocol as above, however the incubation period is extended to 2-3 weeks. The duration is dependent on the growth rate of the clinical isolate and the incubation period is continued until the no compound control show growth/turbidity. Growth is monitored visually or turbidometrically and the least concentration which shows no growth was identified as MIC. With the single drug resistant strains, the respective resistance marker drug is also included as an additional reference.

Method for MIC determination for other bacteria (Gram positives & Gram negatives)

Minimum inhibitory concentration (MIC) values for different bacterial strains (*Staphylococcus aureus* ARC517, *Streptococcus pneumoniae* ARC548, *Haemophilus influenzae* ARC446, *H. influenzae* ARC158, *Escherichia coli* ARC523, *E. coli* ARC524, *Pseudomonas aeruginosa* ARC545, *Peudomonas aeruginosa* ARC546, *Klebsiella pneumoniae* ARC1865, *Mycobacterium smegmatis* ATCC607, *M. smegmatis* mc^2 155 and *Candida albicans* ARC526 were determined according to Clinical Laboratory Standards Institute (CLSI) guidelines (3) using 384 well format in cation adjusted Muller Hinton broth media. Media control, culture control and appropriate reference drug controls were included.

Growth is monitored by checking absorbance at 600nm. Minimum inhibitory concentration (MIC) was taken as the concentration that resulted in growth inhibition of ≥ 80%.

Reference:

1. R. Jayaram, S. Gaonkar, P. Kaur, B.L. Suresh, B.N. Mahesh, R. Jayashree, V. Nandi, S. Bharat, R.K. Shandil, E. Kantharaj, V. Balasubramanian, *Antimicrob. Agents Chemother*. **2003**, 47: 2118-2124.
2. Balganesh M, Kuruppath S,Marcel N,Sharma S, Nair A, Sharma U *Antimicrob. Agents Chemother*. **2010**, 54: 5167-5172.
3. National Committee for Clinical Laboratory Standards. 2009. Volume 29, Number 2. National Committee for Clinical Laboratory Standards, Wayne, PA.

Method for determination of Cytotoxicity on THP-1 cell lines.

THP-1 cells were cultured in RPMI growth medium supplemented with 1% (v/v) 2mM Glutamine and 10% (v/v) heat inactivated foetal bovine serum. Cultures were maintained at 37^{o}C in a 95% humidified atmosphere of 5% (v/v) CO2 /95% (v/v) air [standard cell culture conditions). Fresh THP-1 cells were centrifuged at 300g for 5 minutes and re-suspended into growth medium at the required cell density (4.0 x 105/ml). Cell should not be grown at a density above 1x10^{6} cells/ml. THP-1 cells were seeded at 40,000/well in growth medium (95µl) and 5µl compound added immediately at the indicated concentrations (see Plate format below). 5µl of solvent (5% (v/v) DMSO in growth medium) was used in the control wells giving a final 0.5% v/v DMSO. All stock compounds in 50mM neat DMSO were diluted in growth medium to 10% (v/v) DMSO and 5µl used in the assay, giving a final 0.5% v/v DMSO (final assay volume 100µl). Menadione, the standard cytotoxic agent, was used in each experiment for quality control at a top test concentration of 125µM. 96 well plates containing THP-1 cells with compounds or solvent were incubated for 24hr under standard

cell culture conditions. 11µl of stock resazurin solution (450µM, dissolve 11.3mg in 100ml PBS) was added to all wells, mixed and incubated under standard cell culture conditions for a further 2 hr. Plates were read on the Envision reader using an excitation λ of 560nm and emission λ of 590nm.

Method for identification of CYP inhibition:

This study was conducted using specific substrates for 5 major human CYP isozymes. These substrates were used as a cocktail (phenacetin, diclofenac, S-mephenytoin, bufuralol and midazolam which are predominantly metabolised by CYP 1A2, 2C9, 2C19, 2D6 and 3A4/5, respectively) at concentrations equivalent to their respective Km values. LC-MS-MS (MRM mode) was used to follow the formation of the CYP specific metabolites. A decrease in the formation of the metabolites in peak area to vehicle control was used to calculate the IC50 value. In addition, as a positive control, a cocktail of five standard inhibitors, specific for an individual CYP (α-naphthoflavone, sulphaphenazole, N-3-benzylnirvanol, quinidine and ketoconazole, which specifically inhibit CYP 1A2, 2C9, 2C19, 2D6 and 3A4/5, respectively) was incubated. Test compound was used at 6 different concentrations (20, 10, 3, 1, 0.3, 0.1 µM) to estimate IC50.

The incubation was carried out in 96 deep well plates. Mixture of 180 µL of 20 mg/mL HLM and 90 µL of substrates cocktail solution was added to 15840 µL of phosphate buffer and 179 µLof this mixture was mixed with 1 µL of the test compound, inhibitor cocktail solution or vehicle in each well. The final concentration of DMSO: ACN in the assaymix was 0.3:0.7 % v/v. The incubation plate was placed into the water bath and pre-warmed at 37^{o}C for 5 minutes before the reactions were started by the addition of 20 µL of 10 mmol/L NADPH

solution in phosphate buffer. After the addition of NADPH, the incubation plate was incubated at 37^{o}C for a further 5 minutes. The reaction was quenched by the addition of 1

volume (200 μL) of cold ACN containing 3% formic acid and 40 nmol/L verapamil. The plates were kept on ice for 20 minutes and then centrifuged at 4000 rpm for 30 minutes to precipitate protein. The supernatant 180 μL was transferred to the analysis plate for LC/MS/MS analysis.

Materials used for CYP assay:

Phenacetin is purchased from Jince Analysis Technology Co. Ltd. Tianjin, China. The diclofenac sodium and bufuralol hydrochloride are purchased from Sigma Aldrich, Shanghai, China. S-Mephenytoin is purchased from Toronto Research Chemicals, Tornto, Canada. Midazolam is purchased from International Laboratory USA, South San Francisco, USA. Human liver microsomes (HLM) were obtained from BD Gentest UltraPool 150 donor (Lot no. 38289) at a concentration of 20 mg/mL protein. HLMs were stored in a -80^{o}C. Prior to use, the pooled HLM were allowed to thaw in a 37^{o}C water bath and then stored on wet ice.

Solubility, Human Plasma Protein Binding, Mouse Clearance and LogD

For a detailed experimental procedure please refer to the supporting information part of

1. J Med. Chem. 2013, 56(23) 9701-9708.