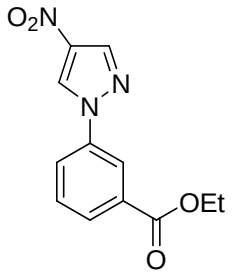
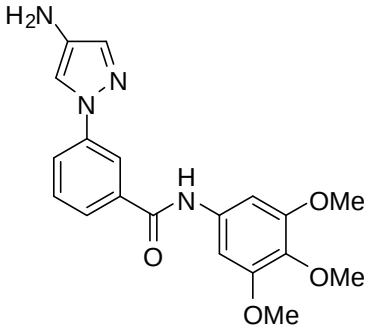
Ethyl 3-(4-nitro-1*H*-pyrazol-1-yl)benzoate



A mixture of 4-nitro-1H-pyrazole (1.13 g, 10 mmol), ethyl 3-bromobenzoate (6.84 g, 30 mmol), CuI (0.57 g, 3 mmol), *trans*-*N*,*N*-dimethylcyclohexane-1,2-diamine (0.85 g, 6 mmol) and Cs_2CO_3 (9.78 g, 30 mmol) in dioxane (20 mL) was purged with argon and stirred for 16 h at 110 °C in a sealed tube. The reaction mixture was cooled, and filtered through a pad of silica gel and rinsed with EtOAc. The resulting solution was concentrated *in vacuo* to yield a crude residue which was purified by chromatography on silica gel (EtOAc/hexane) to provide ethyl 3-(4-nitro-1H-pyrazol-1-yl)benzoate. ^{1}H NMR ($CDCl_3$) δ 8.89 (s, 1H), 8.47 (s, 1H), 8.37 (s, 1H), 8.15–8.13 (m, 1H), 8.06–8.00 (m, 1H), 7.64 (t, *J* = 8.0 Hz, 1H), 4.41 (q, *J* = 7.2 Hz, 2H), 1.46 (t, *J* = 7.2 Hz, 3H).

3-(4-amino-1H-pyrazol-1-yl)-N-(3,4,5-trimethoxyphenyl)benzamide

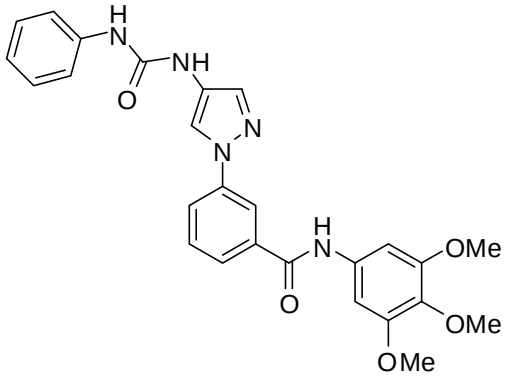


A mixture of ethyl 3-(4-nitro-1H-pyrazol-1-yl)benzoate (560mg, 2.14 mmol) and lithium hydroxide monohydrate (1.05 g) was stirred in THF (20 mL)/ water (40 mL) at RT for 90 min. The resulting homogenous reaction was acidified with 2M HCl (13 mL) and extracted with chloroform (2x100mL). The combined organic extracts were washed with water (100mL), dried ($MgSO_4$) and evaporated. The crude residue was dried under vacuum and used without further purification.

To a mixture of this crude solid and anhydrous chloroform (40 mL) was added oxalyl chloride (0.90 mL,10.3 mmol) followed by 3 drops of DMF. The mixture was gently refluxed for 10 min and then stirred at RT for 20 min. The mixture was evaporated and the residue was dried under vacuum. The crude acid chloride (a pale yellow solid) was dissolved in anhydrous chloroform (40 mL) and treated with 3,4,5-trimethoxyaniline (405mg, 2.2mmol) followed by diisopropylethylamine (0.70 mL, 4mmol). The mixture was stirred for 2 hours and then directly applied onto a column of silica (120g) in dichloromethane. Elution with ethyl acetate gradient (0 to 30%) in dichloromethane provided pure nitro-intermediate. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.66 (s, 1H), 8.22 (s, 1H), 8.19 (t, 1H), 7.94 (s, 1H), 7.86 (d, 1H), 7.84(m, 1H), 7.59 (t, 1H), 6.90 (s, 2H), 3.79 (s, 6H), 3.77 (s, 3H)

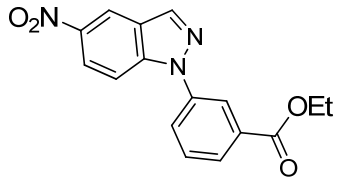
This intermediate was hydrogenated in anhydrous ethanol (100 mL) in the presence of 5% Pt-C (1.0 g) under a balloon of hydrogen for 1 hour. The mixture was filtered through a Celite pad and evaporated. The residue was purified by chromatography on silica gel (dichloromethane / ethyl acetate) to give the title compound (496 mg, 63% overall) as a white foamy glass.

3-(4-(3-phenylureido)-1H-pyrazol-1-yl)-N-(3,4,5-trimethoxyphenyl)benzamide (SR-3451)



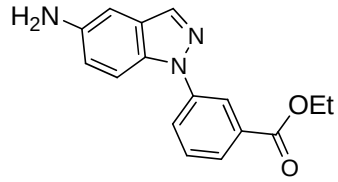
Phenylisocyanate (0.103 mL, 0.12 mmol) was added to 3-(4-amino-1H-pyrazol-1-yl)-N-(3,4,5-trimethoxyphenyl)benzamide (0.030 g, 0.08 mmol) in CH_2Cl_2 (1 mL) at RT and stirred for 30 min. The solvent was evaporated and the residue was purified by silica gel column chromatography (EtOAc/hex) to give the title compound (0.019 g) in 50 % yield. LC-MS 488 (M + H). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.81 (s, 1H), 7.71 (s, 2H), 7.51-7.46 (m, 3H), 7.37 (m, 2H), 7.19 (s, 1H), 7.15(t, 1H), 7.06–6.96 (m, 3H), 6.93 (s, 2H), 6.77 (d, 1H), 3.76 (s, 3H), 3.69 (s, 6H).

Ethyl 3-(5-nitro-1*H*-indazol-1-yl)benzoate



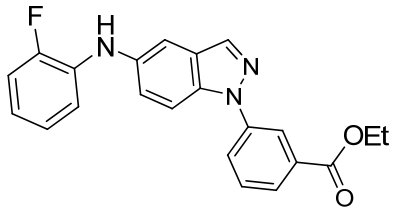
A solution of 5-nitroindazole (1.26 g, 7.7 mmol), ethyl 3-bromobenzoate (4.95 g, 23.1 mmol) and K_2CO_3 (4.3 g, 30.8 mmol) in anhydrous dioxane (100 mL) was charged with CuI (0.44g, 2.31 mmol) and *trans*-*N*,*N*-dimethylcyclohexane-1,2-diamine (0.73 mL, 4.6 mmol). The resulting solution was degassed and heated under argon to 100 °C for 16 h. The reaction mixture was cooled, filtered through a pad of silica gel (EtOAc) and concentrated *in vacuo.* The resulting residue was purified by chromatography on silica gel to give ethyl 3-(5-nitro-1*H*-indazol-1-yl)benzoate.

Ethyl 3-(5-amino-1*H*-indazol-1-yl)benzoate



To a mixture of ethyl 3-(5-nitro-1*H*-indazol-1-yl)benzoate (1.0 g, 3.4 mmol) in MeOH (20 mL) and EtOAc (20 mL) was added Pd/C (10%). The flask was evaporated/H_2 purged (3x) and then stirred under a hydrogen balloon for 18h. The resulting mixture was filtered through a pad of celite and concentrated *in vacuo* to give ethyl 3-(5-amino-1*H*-indazol-1-yl)benzoate in quantitative yield.

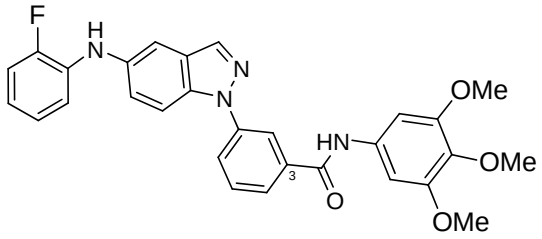
Ethyl 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)benzoate



A mixture of ethyl 3-(5-amino-1*H*-indazol-1-yl)benzoate (0.46 g, 1.72 mmol), 1-fluoro-2-iodobenzene (0.20 mL, 1.72 mmol), $Pd_2(dba)_3$ (0.16 g, 0.17 mmol), Xantphos (0.30 g, 0.52 mmol), Cs_2CO_3 (1.69 g, 5.20 mmol) and dioxane (6 mL) was degassed and heated to 110 °C under argon for 16 h. The reaction mixture was diluted with ethyl acetate and washed with waster (2x) and brine (1x). The organic layer was dried (Na_2SO_4) and concentrated to give a

crude residue which was purified by chromatography on silica gel to give ethyl 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)benzoate in 93% yield. ^{1}H NMR ($CDCl_3$, 400 MHz) δ 8.45 (t, 1H), 8.14 (d, 1H), 8.07–8.04 (m, 1H), 7.98–7.95 (m, 1H), 7.75 (d, 1H), 7.64 (t, 1H), 7.55 (d, 1H), 7.32–7.29 (m, 1H), 7.24–7.20 (m, 1H), 7.15–7.09 (m, 1H), 7.03 (t, 1H), 6.87–6.82 (m, 1H), 5.92 (d, 1H), 4.48–4.41 (m, 2H), 1.45 (t, 3H).

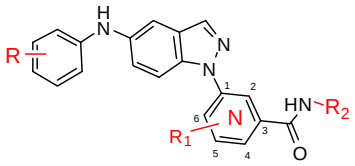
3-(5-(2-Fluorophenylamino)-1*H*-indazol-1-yl)-*N*-(3,4,5-trimethoxyphenyl)benzamide (SR-3737)

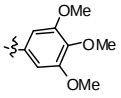
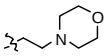
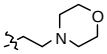
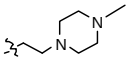
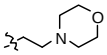
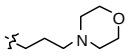


A mixture of ethyl 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)benzoate (0.40 g, 1.1 mmol) in THF (5 mL) and 1N LiOH (5 mL) was stirred at room temperature for 14 h and then concentrated. The residue was diluted with water and acidified with 1N HCl. The resulting aqueous solution was extracted with EtOAc and the organic layer was separated, dried ($MgSO_4$) and concentrated to give 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)benzoic acid.

A solution of 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)benzoic acid (0.07g, 0.2 mmol) and 3,4,5-trimethoxyaniline (0.044 g, 0.34 mmol) in DMF (1.0 mL) was charged with HATU (0.15 g, 0.4 mmol) and diisopropyl ethyl amine (0.10 g, 0.8 mmol). The resulting mixture was stirred at room temperature overnight and subjected to reverse-phase preparative HPLC purification to give 3-(5-(2-fluorophenylamino)-1*H*-indazol-1-yl)-*N*-(3,4,5-trimethoxyphenyl)benzamide in 70% yield. ^{1}H NMR (DMSO-d_6, 400 MHz) 10.32 (s, 1H), 8.32 (t, 1H), 8.30 (d, 1H), 8.02–7.99 (m, 2H), 7.97–7.95 (m, 1H), 7.88 (d, 1H), 7.75 (t, 1H), 7.46 (d, 1H), 7.38–7.32 (m, 1H), 7.32–7.20 (m, 4H), 7.11–7.07 (m, 1H), 6.92–6.89 (m, 1H), 3.84 (s, 6H), 3.66 (s, 3H).

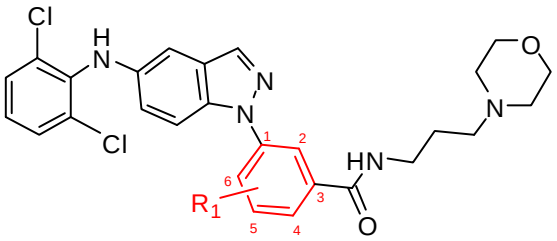
Supplemental Table 1. Structure Activity Relationship (SAR) For Indazole Inhibitors



SR#	R	R_1	R_2	JNK3 IC_{50} (μM)	JNK1 IC_{50} (μM)	p38 IC_{50} (μM)	p38/JNK3
3737	2-F	2-C, H		0.012	0.073	0.003	0.25
4131	2-F	2-N, H		0.76	8.2	0.82	1.1
4245	2-Cl	4-N, H		0.65	NT	0.48	0.73
4228	2-Cl,6-Cl	5-N, H		0.11	NT	0.34	3.1
4004	2-Cl	6-N, H		0.12	2.5	1.44	12
4315	2-Cl	6-N, 5-Me		0.14	2.9	1.5	10.7

$n \geq 4$ for JNK3 and $n \geq 2$ for p38 and JNK1. All standard deviation $\leq 20\%$.

Supplemental Table 2. Structure Activity Relationship (SAR) For Indazole Inhibitors



SR#	R_1	JNK3 IC_{50} (μM)	JNK1 IC_{50} (μM)	p38 IC_{50} (μM)	p38/JNK3
4184	H	0.06	1.3	0.04	0.67
4182	2-Me	3.6	>20	0.06	0.02
4180	4-Cl	0.05	1.1	0.04	0.8
4187	5-F	0.07	1.8	0.22	3.1
4227	5-Cl	0.19	NT	0.59	3.1
4186	5-CF_3	1.0	>20	>20	>20
4183	6-F	0.06	2.8	0.01	0.17
4185	6-Cl	0.42	7.5	0.001	0.002
4181	6-Me	1.7	>20	0.002	0.001

$n \geq 4$ for JNK3 and $n \geq 2$ for p38 and JNK1. All standard deviation $\leq 20\%$.