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Novel potent neuropeptide Y Y5 receptor antagonists: Synthesis and structure–activity relationships of phenylpiperazine derivatives

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Abstract—A series of phenylpiperazine derivatives were synthesized and evaluated for their neuropeptide Y (NPY) Y5 receptor antagonistic activities. The benzindane portion of **2** was replaced by 1-phenylpiperazine, resulting in novel urea derivative **3f**. Subsequent optimization of the phenylpiperazine template by substitution of the phenyl moiety resulted in a series of (2-methanesulfonamidephenyl)piperazine derivatives that showed potent binding affinity and antagonistic activity for the Y5 receptor.

1. Introduction

Neuropeptide Y (NPY) is a 36-amino-acid polypeptide which is amidated on the C-terminus. NPY was isolated in 1982 from porcine brain and was found to be a member of the pancreatic polypeptide family consisting of peptide YY and pancreatic polypeptide.[1] NPY is an abundant and widely distributed neuropeptide in both the central and peripheral nervous systems and has a diverse range of physiological functions. NPY is well known as a potent orexigenic peptide.[2,3] Intracerebroventricular (ICV) administration of NPY has been shown to elicit hyperphagia in satiated rats,[4] and chronic administration of NPY into the brain induces obesity.[5,6] Concentrations of NPY and its mRNA in the hypothalamus were found to increase markedly during food deprivation and in some models of obesity in rodents.[7–9] Furthermore, NPY-deficient *ob*/*ob* mice are less obese and have reduced food intake compared with *ob*/*ob* mice;[10] taken together, these data suggest that NPY is one of the major regulators of energy homeostasis. NPY elicits its physiological effects by interacting with G-protein coupled receptors (GPCRs). Five NPY receptor subtypes (Y1, Y2, Y4, Y5 and mouse Y6) have been cloned to date.[11] Recently, attention has focused on the role of each subtype of NPY receptor in the regulation of energy homeostasis. Synaptic reported that the Y5 receptor is the primary mediator of NPY-induced food intake in rodents.[12] A number of structural classes that target the Y5 receptor have been reported in the literature, including the following derivatives: hydrazide,[13] tricyclic thiazole,[14] guanidine,[15] carbazole,[16] sulfonamide,[17] oxobenzothiazolin,[18] tetrahydrodiazabenzazulene,[19] benzo[*a*]cycloheptene,[20] and tetraline.[21] We previously reported the preliminary structure–activity relationship (SAR) of arylpyrazole derivative **1** and the identification of compound **2**, which showed potent binding affinity and antagonistic activity for the Y5 receptor (Fig. 1).[22] The search for more potent Y5 antagonists involved exploring structurally diverse surrogates for the benzindane portion of **2**, resulting in the identification of **3f**. The phenylpiperazine structure of **3f** appeared to be a structurally diverse template ideal

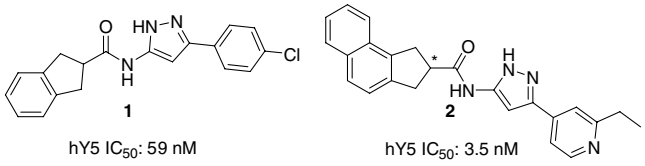

Figure 1. Structures of Y5 antagonist **1** and **2**.

Keywords: Neuropeptide Y Y5 receptor; Anti-obesity; Y5 antagonist; (2-Methanesulfonamidephenyl)piperazine derivatives.
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for further optimization. The present paper describes a SAR study of **3f** and reports the identification of a novel (2-methanesulfonamidephenyl)piperazine class of Y5 antagonists.

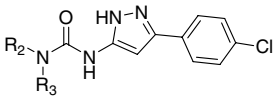
2. Chemistry

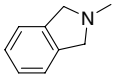
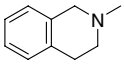
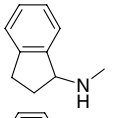
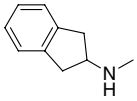
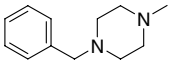
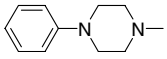
The synthetic route for the derivatives reported herein is described in Scheme 1. The 3-amino-5-arylpyrazoles **7a**–**j** were prepared from substituted benzoic acid esters **6a**–**j** by treatment with acetonitrile anions, followed by cyclization with hydrazine.[22] Compounds **7a**–**j** were converted to the corresponding phenyl carbamate **8a**–**j**, which were reacted with the desired amine to provide the target compounds **3**, **4**, and **5**.[23] With the exception of phenylpiperazines **20**, **23**, and **27**, the secondary amines used to prepare the derivatives in Tables 1–3 were either commercially available or reported in the literature. Methanesulfonamide-substituted phenylpiperazines (**13** and**18**) were prepared by modified literature procedures (Schemes 2 and 3).[24] After the coupling of **9** and **10**, the nitro group of **11** was reduced, and the resulting aniline was mesylated to give **12**. Deprotection of the formyl group of **12** under acidic conditions furnished **13a** and **13b**. *meta*-Methanesulfonamide-substituted phenylpiperazine (**18**) was obtained via Buchwald amination of 3-bromonitrobenzene (**15**) with 1-benzylpiperazine (**14**) (Scheme 3).[25] The nitro group of phenylpiperazine **16** was reduced, and the resulting aniline was mesylated, followed by deprotection of the benzyl group to yield **18**. N-Methylated sulfonamide **20** was obtained by methylation of **12a** followed by deprotection of the formyl group (Scheme 4). *ortho*-Dimethylamino-substituted phenylpiperazine **23** was prepared in good yield by dimethylation of the amino group of **21**[26] followed by deprotection of the formyl group (Scheme 5). *ortho*-Methanesulfonyl-substituted phenylpiperazine **27** was derived from commercially available 2-fluorothioanisole (**24**) in good overall yield, as illustrated in Scheme 6. Oxidation of **24** with hydrogen peroxide in acetic acid provided sulfone **25**, and subsequent nucleophilic substitution by 1-formylpiperazine gave **26**. Deprotection of the formyl group provided **27** in good yield.

3. Results and discussion

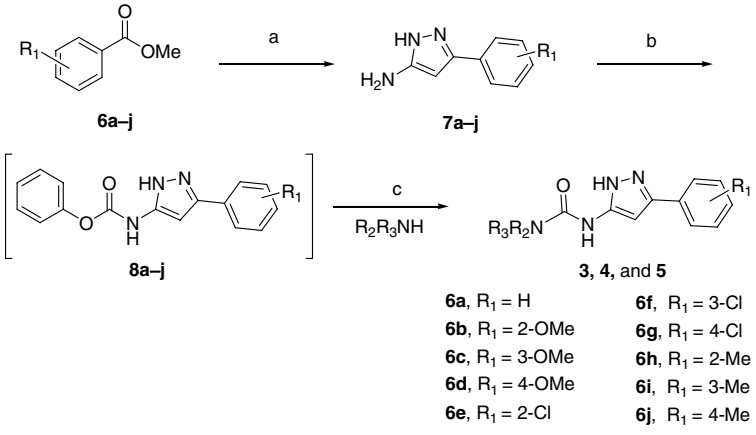
Structurally diverse surrogates for the benzindane portion of **2** were explored by screening substituted amines

Table 1. Y5 Binding affinities of **3a**–**f**[a]



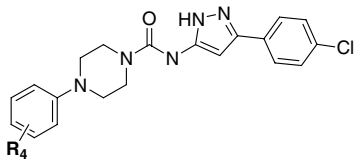
Compound	R_2, R_3	Binding affinity[b] (IC_{50}, nM)
3a		>10000
3b		280 ± 63
3c		4800 ± 1800
3d		2800 ± 590
3e		6700 ± 2700
3f		35 ± 3

[a] The values represent means ± SE for $n = 3$.
[b] Human recombinant Y5 receptors in LMtk$^-$ cell membranes, [^{125}I]PYY; see Ref. 27.



Scheme 1. Reagents and conditions: (a) i—LDA, CH_3CN, THF, −78 °C, 2 h; ii—hydrazine, EtOH, reflux, 5 h; (b) chlorophenylformate, pyridine, rt, 2 h; (c) R_2R_3NH, $CHCl_3$, reflux, 1 h.

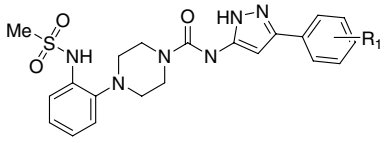
Table 2. Y5 Binding affinities of **3f** and **4a**–**m**[a]



Compound	R_4	Binding affinity[b](IC_{50}, nM)
3f	H	35 ± 3
4a	2-OMe	220 ± 28
4b	3-OMe	91 ± 30
4c	4-OMe	46 ± 4
4d	2-Cl	45 ± 13
4e	3-Cl	56 ± 16
4f	4-Cl	51 ± 5
4g	2-Me	23 ± 6
4h	3-Me	33 ± 7
4i	4-Me	28 ± 7
4j	2-$NHSO_2Me$	1.4 ± 0.2
4k	3-$NHSO_2Me$	180 ± 64
4l	4-$NHSO_2Me$	>1000
4m	2-NHCOMe	44 ± 6
4n	2-NHMe	4.9 ± 0.3
4o	2-$NMeSO_2Me$	14 ± 3
4p	2-NMe_2	623 ± 101
4q	2-SO_2Me	62 ± 5
4r	2-CO_2Me	1100 ± 58
4s	2-NO_2	13 ± 3
4t	2-CN	24 ± 3

[a] The values represent means ± SE for $n = 3$.
[b] Human recombinant Y5 receptors in LMtk$^-$ cell membranes, [^{125}I]PYY; see Ref. 27.

Table 3. Y5 Binding affinities and antagonistic activities of **4j** and **5a**–**i**[a]

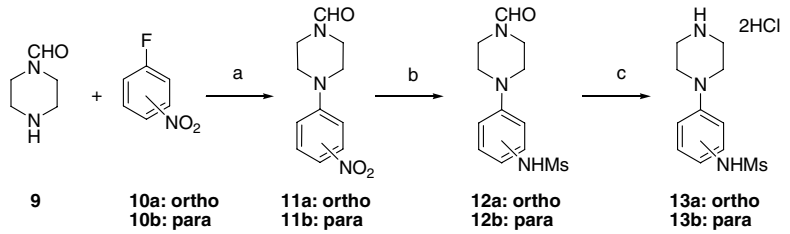


Compound	R_1	hY5 Binding affinity[b] (IC_{50}, nM)	$[Ca^{2+}]_i$ response[c] (IC_{50}, nM)
5a	H	2.0 ± 0.3	nd[d]
5b	2-OMe	4.0 ± 0.5	nd[d]
5c	3-OMe	1.8 ± 0.4	1.6 ± 0.1
5d	4-OMe	7.6 ± 2.2	nd[d]
5e	2-Cl	4.1 ± 1.0	nd[d]
5f	3-Cl	1.9 ± 0.6	2.7 ± 0.3
4j	4-Cl	1.4 ± 0.2	3.7 ± 0.1
5g	2-Me	2.9 ± 0.6	nd[d]
5h	3-Me	1.4 ± 0.2	2.6 ± 0.2
5i	4-Me	1.7 ± 0.03	2.7 ± 0.2

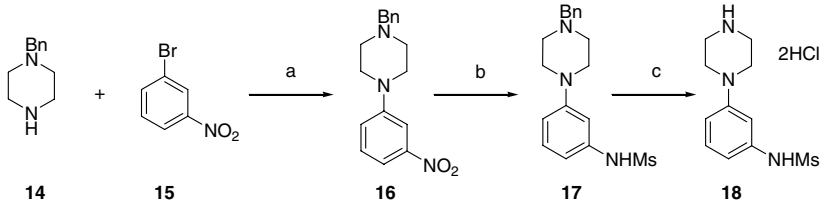
[a] The values represent means ± SE for $n = 3$.
[b] Human recombinant Y5 receptors in LMtk$^-$ cell membranes, [^{125}I]PYY; see Ref. 27 for details.
[c] Antagonistic activities (human recombinant Y5 receptors/Gqi5 in CHO cells) at 100 nM NPY stimulation.
[d] Not determined.

(R_2R_3NH) (Table 1). The SAR for this site was found to be very specific; substantial loss of potency was observed for isoindoline **3a**, 1,2,3,4-tetrahydroisoquinoline **3b**, 1-aminoindane **3c**, 2-aminoindane **3d**, and benzylpiperazine **3e**. The novel urea derivative **3f** exhibited moderate binding affinity; nevertheless, the phenylpiperazine structure was considered to be an excellent structurally diverse template ideal for further optimization. The effects of substituents (R_4) on the phenyl ring of the phenylpiperazine template were subsequently examined (Table 2). The 2-methoxy derivative **4a** displayed a substantial decrease in potency, and the 3-methoxy derivative **4b** was three times less potent than **3f**. Chloro derivatives **4d**–**f** were slightly less potent and methyl derivatives **4g**–**i** were slightly more potent than **3f**. A dramatic enhancement in binding affinity was achieved by ortho-substitution with a methanesulfonamide group, resulting in the 2-methanesulfonamide derivative **4j**. The IC_{50} of this compound was 1.4 nM, a 25-fold improvement over **3f**. In contrast, the 3- and 4-methanesulfonamide derivatives **4k** and **4l** showed significant decreases in potency. Inspired by the ortho-substitution effect demonstrated by **4j**, we examined additional 2-substituted derivatives (**4m**–**t**). The acetamide derivative **4m** was significantly less potent (IC_{50} = 44 nM) than **4j**, while the methylamino derivative **4n** showed potent binding affinity (IC_{50} = 4.9 nM). N-Methylation of the potent 2-amino derivatives **4j** and **4n** resulted in substantially less potent derivatives **4o** and **4p**. This decrease in potency is presumably due to loss of hydrogen-bonding interactions of the N–H of the sulfonamide and methylamino groups with the receptor (e.g., to His387 of the Y5 receptor.) [17a] It is intriguing that the extent of potency decrease caused by N-methylation in **4p** is more than 100-fold, while that in **4o** is 10-fold. This observation suggests that the methanesulfonyl portion of the sulfonamide group is very important for the strong binding affinity of **4j**, in addition to the hydrogen-bonding interaction of the N–H portion. Direct *ortho*-methanesulfonyl substitution, as in **4q**, did not improve binding affinity, and the methoxycarbonyl derivative **4r** displayed a marked decrease in binding affinity. The nitro and cyano derivatives (**4s** and **4t**) were slightly more potent than **3f**.

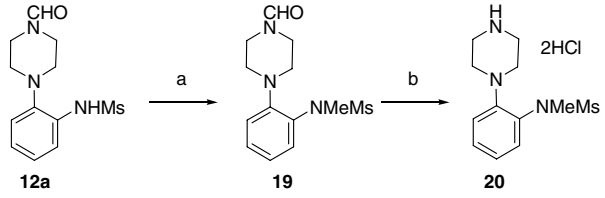
Using the potent (2-methanesulfonamidephenyl)piperazine structure as a base, optimization of the arylpyrazole moiety by substitution of the phenyl ring was attempted (Table 3). Removal of the 4-chloro group, as in **5a**, resulted in retention of binding affinity, whereas the ortho-substituted derivatives (2-methoxy, **5b**; 2-chloro, **5e**; and 2-methyl, **5g**) were generally less potent. Meta- and para-substituted derivatives displayed high binding affinity, except for the 4-methoxy derivative **5d**. Selected potent compounds were tested for their antagonistic activity and selectivity over the NPY receptor subtypes. Compounds **4j**, **5c**, **5f**, **5h**, and **5i** showed good selectivity for the Y5 receptor compared to the other subtypes (IC_{50} > 10 μM for human Y1, Y2, and Y4 receptors). Antagonistic activity was determined by measuring the ability of the antagonists to inhibit NPY-induced $[Ca^{2+}]_i$ increase in LMtk$^-$ cells expressing the recombinant human Y5 receptor. In this $[Ca^{2+}]_i$ functional assay, all the tested compounds showed potent antagonistic activities (Table 3).



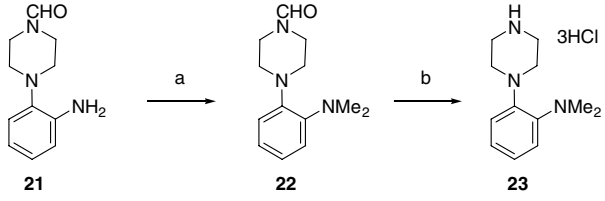
Scheme 2. Reagents and conditions: (a) K_2CO_3, DMSO, 50 °C, 1 h, 88% for **11a**, 89% for **11b**; (b) i—H_2, 10% Pd/C, EtOH, THF, rt, 14 h; ii—MsCl, Et_3N, THF, 0 °C, 1 h, 73% for **12a**, 80% for **12b**; (c) 2 N methanolic HCl, 50 °C, 1 h, 76% for **13a**, 92% for **13b**.



Scheme 3. Reagents and conditions: (a) $Pd_2(dba)_3$, BINAP, *t*-BuONa, toluene, 90 °C, 5 h, 36%; (b) i—Fe, NH_4Cl, H_2O, MeOH, 100 °C, 3 h, ii—MsCl, Et_3N, THF, 0 °C, 1 h, 91% over 2 steps; (c) H_2, 20% $Pd(OH)_2$/C, 2 N methanolic HCl, rt, 14 h, 63%.



Scheme 4. Reagents and conditions: (a) NaH, CH_3I, DMF, rt, 3 h, 78%; (b) 2 N methanolic HCl, 50 °C, 1 h, 97%.



Scheme 5. Reagents and conditions: (a) $NaBH_3CN$, HCHO, $ZnCl_2$, MeOH, rt, 14 h, 82%; (b) 2 N methanolic HCl, 50 °C, 1 h, 86%.

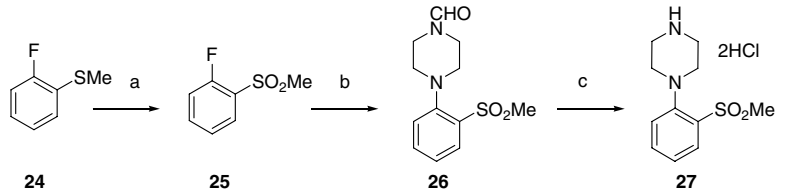
4. Conclusion

In summary, a series of phenylpiperazine derivatives were synthesized and evaluated as NPY Y5 receptor antagonists. The initial modification of the benzindane portion of **2** resulted in the identification of a structurally distinct phenylpiperazine surrogate. Further optimization of the phenylpiperazine moiety led to a series of extremely potent (2-methanesulfonamidephenyl)piperazine derivatives. Selected compounds showed potent antagonistic activity for the Y5 receptor and good selectivity over other NPY receptor subtypes. In vivo activities of this series of compounds will be reported elsewhere.

5. Experimental

5.1. Materials and methods

All reagents were obtained from commercial suppliers and used without further purification or drying. TLC was performed with Merck silica gel 60 F_{254} pre-coated plates. Silica gel column chromatography was carried out on Wakogel® C-300 (mesh 45–75 μm) or an appropriately sized pre-packed silica cartridge with KP-Sil™ (mesh 40–63 μm) from Biotage. ^{1}H NMR spectra were recorded on a Varian MERCURYvx 400 spectrometer at 400 MHz and are referenced to residual solvent peaks (DMSO-d_6, δ 2.49 ppm; CD_3OD, δ 3.30 ppm) or to an internal standard of tetramethylsilane (TMS, δ 0.00 ppm). Mass spectra were recorded with electron-spray ionization (ESI) or atmospheric pressure chemical ionization (APCI) on a Waters micromass ZQ,



Scheme 6. Reagents and conditions: (a) H_2O_2, AcOH, $Na_2WO_4 \cdot 2H_2O$, 80 °C, 5 h, 60%; (b) 1-formylpiperazine, K_2CO_3, DMSO, 100 °C, 15 h, 88%; (c) 2 N methanolic HCl, 50 °C, 1 h, 61%.

micromass Quattro II or micromass Q-Tof-2 instrument. Analytical HPLC analyses were performed under the following conditions: Wakopak combi ODS fast (30 × 2.0 mm ID), liner gradient system of H_2O/CH_3CN/TFA 95:5:0.1 to 5:95:0.1 over 6 min, flow rate of 0.8 mL/min, detection with UV 210 nm.

5.2. Chemistry

5.2.1. 4-(2-Nitrophenyl)piperazine-1-carbaldehyde (11a). To a stirred suspension of **10a** (50.0 g, 354 mmol) and K_2CO_3 (53.9 g, 390 mmol) in DMSO (200 mL) was added **9** (44.5 g, 389.80 mmol) at room temperature, and the mixture was stirred at 50 °C for 1 h. After addition of water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The solid product obtained was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 73.0 g (88%) of **11a** as an orange solid: mp 48–50 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.83 (1H, dd, J = 8.4, 1.8 Hz), 7.57–7.52 (1H, m), 7.20–7.16 (2H, m), 3.74 (2H, t, J = 5.1 Hz), 3.56 (2H, t, J = 5.1 Hz), 3.08 (4H, dt, J = 9.5, 4.1 Hz); MS(ESI) 236.1 $[M+H]^+$.

5.2.2. *N*-[2-(4-Formylpiperazin-1-yl)phenyl]methanesulfonamide (12a). **11a** (20.0 g, 85.0 mmol) in EtOH (200 mL) and THF (200 mL) was hydrogenated over 10% Pd/C (5.0 g) under an atmospheric pressure of H_2 for 14 h at room temperature. The mixture was filtered, and the filtrate was concentrated to give 13.8 g of 4-(2-aminophenyl) piperazine-1-carbaldehyde as a colorless oil, which was used in the next reaction without further purification. To a stirred solution of 13.8 g of 4-(2-aminophenyl) piperazine-1-carbaldehyde and triethylamine (9.40 mL, 67.2 mmol) in THF (200 mL) was added methanesulfonyl chloride (5.20 mL, 67.2 mmol) at 0 °C. After being stirred at 0 °C for 1 h, the mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel with 50% EtOAc in hexanes to afford 17.7 g (73%) of **12a** as a yellow solid: mp 125–127 °C; ^{1}H NMR ($CDCl_3$) δ 8.11 (1H, s), 7.72 (1H, s), 7.51 (2H, d, J = 8.0 Hz), 7.17 (2H, d, J = 8.0 Hz), 3.58–3.55 (4H, m), 3.11 (3H, s), 2.90–2.82 (4H, m); MS(ESI) 284.2 $[M+H]^+$.

5.2.3. *N*-(2-Piperazin-1-ylphenyl)methanesulfonamide dihydrochloride (13a). To a stirred solution of **12a** (17.7 g, 62.5 mmol) in MeOH (30 mL) was added a 2 N solution of HCl in MeOH (10 mL), and the mixture was stirred at 50 °C for 1 h and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 15.5 g (76%) of **13a** as a colorless solid: mp 255–260 °C (dec); ^{1}H NMR (CD_3OD) δ 7.50–7.47 (1H, m), 7.28–7.14 (4H, m), 3.44–3.40 (4H, m), 3.25–3.12 (4H, m), 3.12(3H, s); MS(ESI) 256.1 $[M+H]^+$.

5.2.4. 4-(4-Nitrophenyl)piperazine-1-carbaldehyde (11b). The title compound was prepared from **10b** (5.87 g, 42 mmol) and **9** (5.59 g, 49 mmol), following the procedure for **11a**, to give a yellow solid (8.75 g, 89%): mp 126–128 °C; ^{1}H NMR ($CDCl_3$) δ 8.19–8.14 (3H, m), 6.88 (2H, d, J = 9.0 Hz), 3.72 (2H, m), 3.57 (2H, m), 3.50–3.40 (4H, m); MS(ESI) 236.1 $[M+H]^+$.

5.2.5. *N*-[4-(4-Formylpiperazin-1-yl)phenyl]methanesulfonamide (12b). The title compound was prepared from **11b** (3.0 g, 12.8 mmol), following the procedure for **12a**, to give a yellow solid (2.92 g, 80%): mp 162–164 °C; ^{1}H NMR (CD_3OD) δ 8.00 (1H, s), 7.26 (2H, d, J = 8.0 Hz), 7.08 (2H, d, J = 8.0 Hz), 3.77–3.64 (4H, m), 3.40–3.24 (4H, m), 3.03 (3H, s); MS(ESI) 284.2 $[M+H]^+$.

5.2.6. *N*-(4-Piperazin-1-ylphenyl)methanesulfonamide dihydrochloride (13b). The title compound was prepared from **12b** (2.92 g, 10.3 mmol), following the procedure for **13a**, to give a white solid (3.12 g, 92%): mp 152–155 °C; ^{1}H NMR (CD_3OD) δ 7.35 (1H, d, J = 9.0 Hz), 7.25 (1H, d, J = 9.0 Hz), 7.11 (2H, d, J = 9.0 Hz), 3.60–3.40 (8H, m), 2.92 (3H, s); MS(ESI) 256.1 $[M+H]^+$.

5.2.7. 1-Benzyl-4-(3-nitrophenyl)piperazine (16). To a solution of **14** (0.97 g, 5.5 mmol), **15** (1.01 g, 5.0 mmol), tris(dibenzylideneacetone)dipalladium(0) (23 mg, 0.025 mmol), and *rac*-2,2-bis(diphenylphosphino)-1,1-binaphthyl (34 mg, 0.05 mmol) in toluene (20 mL) was added sodium *tert*-butoxide (708 mg, 7.0 mmol) at room temperature. The mixture was heated to 90 °C for 5 h and concentrated. The residue was purified by flash chromatography on silica gel with 80% EtOAc in hexanes to afford 540 mg (36%) of **16** as a yellow oil: ^{1}H NMR ($CDCl_3$) δ 7.69 (1H, s), 7.63 (1H, d, J = 8.0 Hz), 7.40–7.22 (6H, m), 7.17 (1H, d, J = 8.0 Hz), 3.58 (2H, s), 3.29 (4H, t, J = 5.2 Hz), 2.63 (4H, t, J = 5.2 Hz); MS(ESI) 298.2 $[M+H]^+$.

5.2.8. *N*-[3-(4-Benzyl-1-piperazinyl)phenyl]methanesulfonamide (17). To a vigorously stirred suspension of **16** (540 mg, 1.82 mmol) and NH_4Cl (876 mg, 16.4 mmol) in MeOH (10 mL) and H_2O (10 mL) was added iron powder (609 mg, 10.9 mmol) at room temperature, and the mixture was heated to 100 °C for 3 h. The resulting mixture was filtered, and the filtrate was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated to give 442 mg of 3-(4-benzyl-1-piperazinyl)aniline as a yellow oil, which was used in the next reaction without further purification. To a stirred solution of 442 mg of crude 3-(4-benzyl-1-piperazinyl)aniline and triethylamine (346 μL, 2.48 mmol) in THF (10 mL) was added methanesulfonyl chloride (192 μL, 2.48 mmol) dropwise at 0 °C. After being stirred at 0 °C for 1 h, the mixture was diluted with EtOAc, washed with saturated aqueous NH_4Cl and brine, dried over Na_2SO_4, and concentrated. The residue was purified by flash chromatography on silica gel with 50% EtOAc in hexanes to afford 570 mg (91%) of **17** as a brown oil: ^{1}H NMR ($CDCl_3$) δ 7.60–7.40 (5H, m), 7.19 (1H, t, J = 8.0 Hz), 6.90 (1H, s), 6.81 (1H, d, J = 8.0 Hz), 6.53 (1H, d, J = 8.0 Hz), 4.03 (2H, s), 3.50–3.40 (4H, m), 3.10–2.90 (4H, m), 3.00 (3H, s); MS(ESI) 346.2 $[M+H]^+$.

5.2.9. *N*-[3-(1-Piperazinyl)phenyl]methanesulfonamide dihydrochloride (18). **17** (570 mg, 1.65 mmol) in a 4 N solution of HCl in MeOH (10 mL) was hydrogenated over 20% palladium hydroxide on carbon (250 mg) under an atmospheric pressure of H_2 for 14 h at room temperature. The mixture was filtered, and the filtrate was concentrated to give **18** (340 mg, 63%) as a brown solid: mp 52–55 °C; ^{1}H NMR (CD_3OD) δ 7.29 (1H, t, J = 8.0 Hz), 6.97 (1H, s), 6.84 (2H, m), 3.42 (4H, m), 3.35 (4H, m), 3.34 (3H, s); MS(ESI) 256.1 $[M+H]^+$.

5.2.10. *N*-[2-(4-Formyl-1-piperazinyl)phenyl]-*N*-methylmethanesulfonamide (19). To a stirred solution of **12a** (1.84 g, 6.5 mmol) in DMF (20 mL) was added sodium hydride (60% dispersion in mineral oil, 286 mg, 7.2 mmol) at 0 °C. After 15 min, iodomethane (2.0 mL, 32.5 mmol) was added, and the mixture was stirred at room temperature for 15 h. After addition of water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 1.51 g (78%) of **19** as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 8.08 (1H, s), 7.30 (1H, dt, J = 7.7, 1.7 Hz), 7.23 (1H, dd, J = 7.6, 1.6 Hz), 7.13–7.06 (2H, m), 3.71 (2H, br s), 3.53 (2H, t, J = 4.9 Hz), 3.28 (3H, s), 3.09 (2H, br s), 3.08 (3H, s), 3.01 (2H, t, J = 5.1 Hz); MS(ESI) 298.1 $[M+H]^+$.

5.2.11. *N*-Methyl-*N*-(2-piperazinylphenyl)methanesulfonamide dihydrochloride (20). To a solution of **19** (1.51 g, 5.1 mmol) in MeOH (10 mL) was added a 2 N solution of HCl in MeOH (10 mL), and the mixture was stirred at 50 °C for 1 h and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 1.70 g (97%) of **20** as a colorless solid: mp 262–270 °C (dec); ^{1}H NMR (CD_3OD) δ 7.44–7.36 (2H, m), 7.28–7.22 (2H, m), 3.43–3.40 (4H, m), 3.38–3.33 (4H, m), 3.29 (3H, s), 3.14 (3H, s); MS(ESI) 270.2 $[M+H]^+$.

5.2.12. 4-(2-Dimethylaminophenyl) piperazine-1-carbaldehyde (22). To a stirred solution of **21**[26] (1.32 g, 6.43 mmol), zinc chloride (0.44 g, 3.20 mmol), and 37% aqueous formaldehyde (2.14 mL, 28.7 mmol) in MeOH (20 mL) was added sodium cyanoborohydride (485 mg, 7.71 mmol) at 0 °C, and the mixture was stirred at room temperature for 14 h. The reaction was quenched by addition of 1 N NaOH. The resultant mixture was extracted with ethyl acetate three times. The combined organic layers were dried over Na_2SO_4 and concentrated. The residue was purified by flash chromatography on silica gel with 50% EtOAc in hexanes to afford 1.23 g (82%) of **22**: ^{1}H NMR ($CDCl_3$) δ 8.09 (1H, s), 7.01 (1H, dt, J = 7.4, 1.8 Hz), 6.96–6.92 (2H, m), 6.86 (1H, dd, J = 8.0, 1.8 Hz), 3.72 (2H, t, J = 5.1 Hz), 3.54 (2H, t, J = 5.1 Hz), 3.15 (2H, t, J = 4.9 Hz), 3.10 (2H, t, J = 5.1 Hz), 2.84 (6H, s); MS(ESI) 234.3 $[M+H]^+$.

5.2.13. 1-(2-Dimethylaminophenyl)piperazine trihydrochloride (23). To a solution of **22** (1.23 g, 5.27 mmol) in MeOH (10 mL) was added a 2 N solution of HCl in MeOH (10 mL), and the mixture was stirred at 50 °C for 1 h and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 1.42 g (86%) of **23** as a colorless solid: ^{1}H NMR (CD_3OD) δ 7.93 (1H, dd, J = 8.2, 1.2 Hz), 7.76 (1H, dd, J = 8.0, 1.4 Hz), 7.68 (1H, dt, J = 7.7, 1.3 Hz), 7.61 (1H, dt, J = 7.7, 1.4 Hz), 3.90–3.81 (2H, m), 3.60–3.40 (2H, m), 3.40–3.30 (2H, m), 3.38 (6H, s), 3.30–3.20 (2H, m); MS(ESI) 206.4 $[M+H]^+$.

5.2.14. 1-Fluoro-2-(methylsulfonyl)benzene (25). To a stirred solution of **24** (14.22 g, 100.0 mmol) and sodium tungstate dihydrate (660 mg, 2.0 mmol) in acetic acid (50 mL) was added 30% hydrogen peroxide in water (200 mL) at room temperature, and the mixture was stirred at 80 °C for 5 h. The reaction was quenched by addition of saturated aqueous Na_2SO_3, and the resultant mixture was extracted with EtOAc. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated to give 10.40 g (60%) of **25** as a colorless solid: mp 46–48 °C; ^{1}H NMR ($CDCl_3$) δ 7.98 (1H, dt, J = 7.3, 1.6 Hz), 7.69–7.64 (1H, m), 7.36 (1H, dt, J = 7.8, 1.0 Hz), 7.29–7.24 (1H, m), 3.24 (3H, s); MS(ESI) 175.0 $[M+H]^+$.

5.2.15. 4-(2-Methylsulfonylphenyl)piperazine-1-carbaldehyde (26). To a stirred suspension of **25** (6.30 g, 36.0 mmol) and K_2CO_3, 7.46 g 54.0 mmol) in DMSO (20 mL) was added **9** (6.27 g, 55.0 mmol) at room temperature, and the mixture was stirred at 110 °C for 15 h. After addition of water, the mixture was extracted with EtOAc. The organic layer was washed with brine, dried over Na_2SO_4, and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 8.50 g (88%) of **26** as a white solid: mp 205–207 °C; ^{1}H NMR ($CDCl_3$) δ 8.10 (2H, d, J = 8.0 Hz), 7.65 (1H, t, J = 7.8 Hz), 7.35 (2H, m), 3.58 (2H, t, J = 4.8 Hz), 3.32 (3H, s), 3.06 (6H, br); MS(ESI) 269.0 $[M+H]^+$.

5.2.16. 1-(2-Methanesulfonylphenyl)piperazine dihydrochloride (27). To a solution of **26** (2.1 g, 7.83 mmol) in MeOH (30 mL) was added a 2 N solution of HCl in MeOH (10 mL), and the mixture was stirred at 50 °C for 1 h, cooled to room temperature, and concentrated. The residual solid was suspended in diethyl ether, collected by filtration, and vacuum-dried to give 1.50 g (61%) of **27** as a colorless solid: mp 285–289 °C (dec); ^{1}H NMR (CD_3OD) δ 8.02 (1H, dd, J = 8.0, 1.5 Hz), 7.74 (1H, dt, J = 7.7, 1.6 Hz), 7.56 (1H, d, J = 8.3 Hz), 7.47 (1H, t, J = 7.8 Hz), 3.48–3.40 (2H, m), 3.30 (3H, s), 3.38–3.26 (6H, m); MS(ESI) 241.1 $[M+H]^+$.

5.2.17. 5-(4-Chlorophenyl)-2*H*-pyrazol-3-yl-amine (7g). To a 2.0 M solution of lithium diisopropylamide (30.9 mL, 61.7 mmol, 2.0 M in heptane/THF/ethylbenzene) in THF (200 mL) was added acetonitrile (3.33 mL, 63.8 mmol) dropwise at −78 °C. After the solution was stirred at −78 °C for 1 h, methyl 4-chlorobenzoate (10.0 g, 58.8 mmol) in THF (20 mL) was added dropwise at −78 °C. The reaction mixture was kept at −78 °C for 1 h and allowed to warm to room temperature. After being stirred for an additional 2 h, the

reaction was quenched by addition of H_2O. The aqueous layer was acidified to pH 5 with 1 N hydrochloric acid and extracted three times with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated to give 7.85 g (74%) of the ketonitrile as a white solid. The crude product was dissolved in EtOH (50 mL) and treated with hydrazine monohydrate (2.2 mL, 44.0 mmol) at room temperature. The mixture was heated to 80 °C for 3 h and concentrated. The crude solid product obtained was suspended in EtOAc, filtered, and vacuum-dried to give 7.08 g (84%) of **7g** as a white solid: mp 173–175 °C; ^{1}H NMR ($CDCl_3$) δ 7.47 (2H, d, J = 8.7 Hz), 7.37 (2H, d, J = 8.7 Hz), 5.90 (1H, s), 3.70 (2H, br); MS(ESI) 194.0 $[M+H]^+$.

5.2.18. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-phenylpiperazine-1-carboxamide (3f). To a stirred solution of **7g** (53 mg, 0.27 mmol) in pyridine (1 mL) was added phenyl chloroformate (56 mg, 0.36 mmol) at room temperature, and the mixture was stirred at room temperature for 1 h. The resultant reaction mixture was diluted with chloroform and washed with H_2O and brine. The organic phase was dried over Na_2SO_4 and concentrated to give **8g** as a white solid, which was used in the next reaction without further purification. To a stirred solution of 1-phenylpiperazine (58 mg, 0.36 mmol) and triethylamine (91 mg, 0.90 mmol) in chloroform (5 mL) was added crude **8g** at room temperature, and the mixture was stirred at 80 °C for 1 h. The resulting mixture was cooled to room temperature, diluted with chloroform, and washed with saturated aqueous $NaHCO_3$ and brine. The organic phase was dried over Na_2SO_4 and concentrated. The residual solid was suspended in EtOAc and stirred at room temperature for 30 min. The precipitates were collected by filtration and vacuum-dried to give 83 mg (81%) of **3f** as a white solid: mp 245–247 °C; ^{1}H NMR ($CDCl_3$) δ 9.13 (1H, br s), 7.72 (2H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.4 Hz), 7.22 (2H, t, J = 8.0 Hz), 6.98 (2H, d, J = 8.0 Hz), 6.83–6.72 (2H, m), 3.62 (4H, m), 3.15 (4H, m); HRMS (ESI+) m/z $[M+H]^+$ 382.1434 ($C_{20}H_{21}ClN_5O_2$ requires: 382.1435). Analytical HPLC 99.9% pure, t_R = 3.5 min.

5.2.19. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-1,3-dihydro-2*H*-isoindole-2-carboxa mide (3a). The title compound was prepared from **7g** (19 mg, 0.10 mmol) and isoindoline (15 mg, 0.12 mmol) in a manner similar to that described for **3f**. The residual solid was suspended in EtOAc, filtered, and vacuum-dried to give 33 mg (97%) of **3a** as a white solid: mp 223–225 °C; ^{1}H NMR (DMSO-d_6) δ 7.76 (2H, d, J = 7.8 Hz), 7.49 (2H, d, J = 7.8 Hz), 7.36–7.30 (5H, m), 4.76 (4H, s); HRMS (ESI+) m/z $[M+H]^+$ 339.1012 ($C_{18}H_{16}ClN_4O$ requires: 339.1013). Analytical HPLC 99.4% pure, t_R = 4.0 min.

5.2.20. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-3,4-dihydroisoquinoline-2(1*H*)-carboxamide (3b). The title compound was prepared from **7g** (58 mg, 0.30 mmol) and 1,2,3,4-tetrahydroisoquinoline (44 mg, 0.33 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to give 20 mg (19%) of **3b** as a white solid: mp 188–191 °C; ^{1}H NMR ($CDCl_3$) δ 7.59 (2H, d, J = 8.6 Hz), 7.38 (2H, d, J = 8.8 Hz), 7.25–7.15 (4H, m), 7.07 (1H, s), 6.51 (1H, s), 4.68 (2H, s), 3.74 (2H, d, J = 5.8 Hz), 2.96 (2H, d, J = 6.0 Hz); HRMS (ESI+) m/z $[M+H]^+$ 353.1168 ($C_{19}H_{18}ClN_4O$ requires: 353.1169). Analytical HPLC 99.5% pure, t_R = 4.1 min.

5.2.21. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-*N*′-(2,3-dihydro-1*H*-inden-1-yl)urea (3c). The title compound was prepared from **7g** (58 mg, 0.30 mmol) and 1-aminoindane (44 mg, 0.33 mmol) in a manner similar to that described for **3f**. The solid product obtained was suspended in EtOAc, filtered, and vacuum-dried to give 59 mg (56%) of **3c** as a white solid: mp 192–195 °C; ^{1}H NMR (DMSO-d_6) δ 12.66 (1H, s), 8.81 (1H, s), 7.70 (2H, d, J = 8.2 Hz), 7.50 (2H, d, J = 8.2 Hz), 7.30–7.18 (3H, m), 6.56 (1H, s), 5.20 (1H, q, J = 8.0 Hz), 2.94–2.78 (2H, m), 2.50–2.44 (1H, m), 1.79–1.72 (1H, m); HRMS (ESI+) m/z $[M+H]^+$ 353.1167 ($C_{19}H_{18}ClN_4O$ requires: 353.1169). Analytical HPLC 98.0% pure, t_R = 4.3 min.

5.2.22. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-*N*′-(2,3-dihydro-1*H*-inden-2-yl)urea (3d). The title compound was prepared from **7g** (58 mg, 0.30 mmol) and 2-aminoindane (44 mg, 0.33 mmol) in a manner similar to that described for **3f**. The solid product obtained was suspended in EtOAc, filtered, and vacuum-dried to give 94 mg (89%) of **3d** as a white solid: mp 203–205 °C; ^{1}H NMR (DMSO-d_6) δ 12.64 (1H, s), 8.69 (1H, s), 7.69 (2H, d, J = 8.4 Hz), 7.49 (2H, d, J = 8.4 Hz), 7.27–7.23 (1H, m), 7.18–7.14 (1H, m), 7.06 (1H, br s), 6.52 (1H, s), 4.48–4.41 (1H, m), 3.30–3.18 (2H, m), 2.77 (2H, dd, J = 15.6, 5.0 Hz); HRMS (ESI+) m/z $[M+H]^+$ 353.1165 ($C_{19}H_{18}ClN_4O$ requires: 353.1169). Analytical HPLC 99.1% pure, t_R = 4.2 min.

5.2.23. 4-Benzyl-*N*-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]piperazine-1-carboxamide (3e). The title compound was prepared from **7g** (58 mg, 0.30 mmol) and **14** (58 mg, 0.33 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to give 25 mg (21%) of **3e** as a white solid: mp 174–177 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (2H, d, J = 8.4 Hz), 7.40–7.24 (6H, m), 7.02 (1H, s), 6.45 (1H, s), 3.55 (2H, s), 3.51 (4H, t, J = 4.8 Hz), 2.50 (4H, t, J = 5.1 Hz); HRMS (ESI+) m/z $[M+H]^+$ 396.1591 ($C_{21}H_{23}ClN_5O$ requires: 396.1591). Analytical HPLC 99.9% pure, t_R = 4.3 min.

5.2.24. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(2-methoxyphenyl)piperazine-1-carboxamide (4a). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(2-methoxyphenyl)piperazine (29 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 25 mg (51%) of **4a** as a white solid: mp 219–221 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.25 (1H, m), 7.06–7.02 (1H, m), 6.95–6.86 (3H, m), 6.51 (1H, s), 3.87 (3H, s), 3.67 (4H, t, J = 4.9 Hz), 3.08 (4H, t, J = 5.1 Hz); HRMS (ESI+) m/z $[M+H]^+$ 412.1535

($C_{21}H_{23}ClN_5O_2$ requires: 412.1535). Analytical HPLC 99.9% pure, t_R = 3.2 min.

5.2.25. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(3-methoxyphenyl)piperazine-1-carboxamide (4b). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(3-methoxyphenyl)piperazine dihydrochloride (40 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 28 mg (57%) of **4b** as a white solid: mp 214–216 °C; ^{1}H NMR (CD_3OD) δ 7.89 (1H, s), 7.69 (2H, d, J = 7.4 Hz), 7.44 (2H, d, J = 8.6 Hz), 7.18 (1H, t, J = 8.2 Hz), 6.62–6.47 (3H, m), 3.79 (3H, s), 3.71 (4H, t, J = 4.7 Hz), 3.23 (4H, t, J = 4.9 Hz); HRMS (ESI+) m/z $[M+H]^+$ 412.1535 ($C_{21}H_{23}Cl_2N_5O$ requires: 412.1535). Analytical HPLC 99.3% pure, t_R = 3.7 min.

5.2.26. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(4-methoxyphenyl)piperazine-1-carboxamide (4c). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(4-methoxyphenyl)piperazine dihydrochloride (40 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 20 mg (40%) of **4c** as a white solid: mp 255–257 °C; ^{1}H NMR (CD_3OD) δ 7.87 (3H, m), 7.65 (2H, m), 7.41 (2H, m), 7.00 (1H, d, J = 9.0 Hz), 6.88 (1H, d, J = 8.6 Hz), 3.77 (3H, s), 3.71 (4H, t, J = 4.3 Hz), 3.11 (4H, t, J = 4.3 Hz); HRMS (ESI+) m/z $[M+H]^+$ 412.1534 ($C_{21}H_{23}ClN_5O_2$ requires: 412.1535). Analytical HPLC 99.7% pure, t_R = 3.2 min.

5.2.27. 4-(2-Chlorophenyl)-*N*-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]piperazine-1-carboxamide (4d). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(2-chlorophenyl)piperazine hydrochloride (32 mg, 0.14 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 39 mg (78%) of **4d** as a white solid: mp 238–240 °C; ^{1}H NMR (CD_3OD) δ 7.90 (1H, d, J = 2.0 Hz), 7.71–7.67 (2H, m), 7.46–7.40 (3H, m), 7.30 (1H, t, J = 7.8 Hz), 7.18 (1H, t, J = 4.5 Hz), 7.06 (1H, t, J = 7.6 Hz), 3.74 (4H, t, J = 4.4 Hz), 3.11 (4H, t, J = 4.3 Hz); HRMS (ESI+) m/z $[M+H]^+$ 416.1046 ($C_{20}H_{20}Cl_2N_5O$ requires: 416.1045). Analytical HPLC 99.6% pure, t_R = 4.6 min.

5.2.28. 4-(3-Chlorophenyl)-*N*-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]piperazine-1-carboxamide (4e). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(3-chlorophenyl)piperazine hydrochloride (35 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 42 mg (84%) of **4e** as a white solid: mp 222–224 °C; ^{1}H NMR (CD_3OD) δ 7.69 (2H, d, J = 7.4 Hz), 7.43 (2H, t, J = 8.6 Hz), 7.25–7.15 (2H, m), 7.01 (1H, d, J = 8.2 Hz), 6.94 (1H, t, J = 6.1 Hz), 6.81–6.75 (2H, m), 3.72 (4H, t, J = 5.1 Hz), 3.26 (4H, t, J = 5.3 Hz); HRMS (ESI+) m/z $[M+H]^+$ 416.1049 ($C_{20}H_{20}Cl_2N_5O$ requires: 416.1045). Analytical HPLC 99.8% pure, t_R = 4.6. min.

5.2.29. 4-(4-Chlorophenyl)-*N*-[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]piperazine-1-carboxamide (4f). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(4-chlorophenyl)piperazine (32 mg, 0.16 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 38 mg (76%) of **4f** as a white solid: mp 266–268 °C; ^{1}H NMR ($CDCl_3$) δ 7.54 (2H, d, J = 8.7 Hz), 7.30 (3H, m), 7.25 (4H, m), 6.80 (1H, d, J = 8.4 Hz), 3.71 (4H, m), 3.20 (4H, m); HRMS (ESI+) m/z $[M+H]^+$ 416.1051 ($C_{20}H_{20}Cl_2N_5O$ requires: 416.1045). Analytical HPLC 99.5% pure, t_R = 4.4 min.

5.2.30. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(2-methylphenyl)piperazine-1-carboxamide (4g). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(2-methylphenyl)piperazine dihydrochloride (38 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 38 mg (80%) of **4g** as a white solid: mp 239–241 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 9.6 Hz), 7.19 (2H, t, J = 6.3 Hz), 7.00–7.04 (2H, m), 6.51 (1H, s), 3.65 (4H, m), 2.95 (4H, m), 2.33 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 396.1583 ($C_{21}H_{23}ClN_5O$ requires: 396.1591). Analytical HPLC 98.2% pure, t_R = 4.2 min.

5.2.31. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(3-methylphenyl)piperazine-1-carboxamide (4h). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(3-methylphenyl)piperazine dihydrochloride (38 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 40 mg (84%) of **4h** as a white solid: mp 215–218 °C; ^{1}H NMR (CD_3OD) δ 7.85 (1H, s), 7.69 (2H, m), 7.43 (2H, m), 7.15 (2H, m), 6.84 (2H, m), 3.71 (4H, m), 3.21 (4H, m), 2.32 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 396.1597 ($C_{21}H_{23}ClN_5O$ requires: 396.1591). Analytical HPLC 98.8% pure, t_R = 3.6 min.

5.2.32. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(4-methylphenyl)piperazine-1-carboxamide (4i). The title compound was prepared from **7g** (23 mg, 0.12 mmol) and 1-(4-methylphenyl)piperazine dihydrochloride (38 mg, 0.15 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 45 mg (95%) of **4i** as a white solid: mp 263–265 °C; ^{1}H NMR ($CDCl_3$) δ 7.57 (1H, d, J = 8.2 Hz), 7.37 (2H, d, J = 8.2 Hz), 7.09–7.07 (3H, m), 6.88–6.84 (3H, m), 3.65 (4H, t, J = 4.9 Hz), 3.17 (4H, t, J = 4.9 Hz), 2.28 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 396.1586 ($C_{21}H_{23}ClN_5O$ requires: 396.1591). Analytical HPLC 99.8% pure, t_R = 3.5 min.

5.2.33. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (4j). The title compound was prepared from **7g** (19 mg, 0.10 mmol) and **13a** (39 mg, 0.12 mmol) in a manner

similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 47 mg (99%) of **4j** as a white solid: mp 241–243 °C; ^{1}H NMR (DMSO-d_6) δ 7.76 (1H, br s), 7.50–7.40 (3H, m), 7.22 (1H, m), 7.20–7.10 (3H, m), 6.72 (1H, br s), 3.67 (4H, m), 3.13 (3H, s), 2.85 (4H, m); HRMS (ESI+) *m/z* $[M+H]^+$ 475.1321 ($C_{21}H_{24}ClN_6O_3S$ requires: 475.1319). Analytical HPLC 99.9% pure, t_R = 4.0 min.

5.2.34. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{3-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (4k). The title compound was prepared from **7g** (19 mg, 0.10 mmol) and **18** (39 mg, 0.12 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 30 mg (63%) of **4k** as a white solid: mp 211–214 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (2H, d, J = 7.6 Hz), 7.37 (3H, m), 7.25–7.20 (2H, m), 6.80 (1H, s), 6.75–6.65 (2H, m), 3.66 (4H, br s), 3.25 (4H, br s), 3.01 (3H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 475.1328 ($C_{21}H_{24}ClN_6O_3S$ requires: 475.1319). Analytical HPLC 99.1% pure, t_R = 3.5 min.

5.2.35. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{4-[(methylsulfonyl)amino]phenyl}piperazine-1- carboxamide (4l). The title compound was prepared from **7g** (19 mg, 0.10 mmol) and **13b** (39 mg, 0.12 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 43 mg (91%) of **4l** as a white solid: mp 226–229 °C; ^{1}H NMR ($CDCl_3$) δ 9.26 (1H, br s), 7.72 (1H, d, J = 7.2 Hz), 7.47 (2H, d, J = 8.1 Hz), 7.09 (2H, d, J = 7.5 Hz), 6.95 (2H, d, J = 8.7 Hz), 6.66 (1H, br s), 3.59 (4H, br s), 3.26 (4H, br s), 2.85 (3H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 475.1312 ($C_{21}H_{24}ClN_6O_3S$ requires: 475.1319). Analytical HPLC 99.9% pure, t_R = 3.3 min.

5.2.36. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(2-acetylaminophenyl) piperazine-1-carboxamide (4m). The title compound was prepared from **7g** (29 mg, 0.15 mmol) and *N*-(2-piperazin-1-ylphenyl)acetamide[26] (50 mg, 0.23 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 28 mg (43%) of **4m** as a white solid: mp 239–241 °C; ^{1}H NMR ($CDCl_3$) δ 8.32 (2H, m), 7.54 (3H, m), 7.35 (2H, d, J = 8.6 Hz), 7.18–7.13 (1H, m), 7.08–7.04 (2H, m), 6.57 (1H, br s), 3.64 (4H, br s), 2.85 (4H, t, J = 4.9 Hz), 2.19 (3H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 439.1656 ($C_{22}H_{24}ClN_6O_2$ requires: 439.1649). Analytical HPLC 95.8% pure, t_R = 3.7 min.

5.2.37. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-[2-(methylamino)phenyl]piperazine-1-carboxamide (4n). The title compound was prepared from **7g** (29 mg, 0.15 mmol) and *N*-methyl-2-piperazin-1-ylaniline (61 mg, 0.32 mmol) in a manner similar to that described for **3f** and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 60 mg (97%) of **4n** as a white solid: mp 210–213 °C; ^{1}H NMR ($CDCl_3$) δ 7.55 (2H, d, J = 8.2 Hz), 7.42 (1H, s), 7.34 (2H, d, J = 8.6 Hz), 7.10–7.05 (1H, m), 6.94 (1H, d, J = 7.6 Hz), 6.70–6.62 (2H, m), 6.53 (1H, s), 2.95–2.86 (8H, m), 2.85 (3H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 411.1709 ($C_{21}H_{24}ClN_6O$ requires: 411.1709). Analytical HPLC 99.6% pure, t_R = 3.8 min.

5.2.38. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{2-[methyl(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (4o). The title compound was prepared from **7g** (29 mg, 0.15 mmol) and **20** (79 mg, 0.23 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 33 mg (45%) of **4o** as a white solid: mp 186–190 °C; ^{1}H NMR ($CDCl_3$) δ 9.91 (1H, s), 7.77 (2H, d, J = 8.8 Hz), 7.50–7.60 (2H, m), 7.38–7.20 (2H, m), 7.12 (1H, d, J =8.6 Hz), 6.99 (1H, s), 6.52 (1H, s), 3.72–3.60 (4H, m), 3.29 (3H, s), 3.23–3.21 (2H, m), 3.20–3.10 (1H, m), 3.13–3.02 (1H, m), 3.11 (3H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 489.1476 ($C_{22}H_{26}ClN_6O_3S$ requires: 489.1476). Analytical HPLC 97.0% pure, t_R = 3.8 min.

5.2.39. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-[2-(dimethylamino)phenyl]piperazine-1-carboxamide (4p). The title compound was prepared from **7g** (45 mg, 0.23 mmol) and **23** (78 mg, 0.25 mmol) in a manner similar to that described for **3f** and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 62 mg (63%) of **4p** as a white solid: mp 201–205 °C; ^{1}H NMR ($CDCl_3$) δ 7.56 (2H, d, J = 8.6 Hz), 7.36 (2H, d, J = 8.6 Hz), 7.31 (1H, s), 7.02–6.96 (1H, m), 6.95–6.91 (2H, m), 6.85 (1H, d, J = 7.0 Hz), 6.51 (1H, s), 3.64 (4H, t, J = 5.1 Hz), 3.15 (4H, t, J = 4.9 Hz), 2.83 (6H, s); HRMS (ESI+) *m/z* $[M+H]^+$ 425.1866 ($C_{22}H_{26}ClN_6O$ requires: 425.1857). Analytical HPLC 99.8% pure, t_R = 3.7 min.

5.2.40. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-[2-(methylsulfonyl)phenyl]piperazine-1-carboxamide (4q). The title compound was prepared from **7g** (19 mg, 0.10 mmol) and **27** (38 mg, 0.12 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 44 mg (96%) of **4q** as a white solid: mp 210–213 °C; ^{1}H NMR (DMSO-d_6) δ 8.29(1H, s), 7.94 (2H, d, J = 7.8 Hz), 7.75–7.70 (3H, m), 7.50–7.40 (2H, m), 7.12 (1H, m), 6.75 (1H, s), 3.65 (4H, br s), 3.41(3H, s), 2.99 (4H, br s); HRMS (ESI+) *m/z* $[M+H]^+$ 460.1209 ($C_{21}H_{23}ClN_5O_3S$ requires: 460.1210). Analytical HPLC 98.9% pure, t_R = 3.9 min.

5.2.41. Methyl 2-[4-({[3-(4-chlorophenyl)-1*H*-pyrazol-5-yl]amino}carbonyl)piperazin-1-yl]benzoate (4r). The title compound was prepared from **7g** (29 mg, 0.15 mmol) and methyl 2-piperazin-1-ylbenzoate (51 mg, 0.23 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 52 mg (79%) of **4r** as a white solid: mp 206–209 °C; ^{1}H NMR ($CDCl_3$) δ 7.79 (1H, dd, J = 7.6, 1.8 Hz), 7.57–7.54 (2H, m), 7.44 (1H, dt, J = 9.2, 3.3 Hz), 7.38 (1H, d, J = 8.6 Hz), 7.34 (2H, d, J = 8.6 Hz), 7.07 (1H, dt, J = 7.5, 0.9 Hz), 7.00 (1H, d, J = 7.8 Hz), 6.58 (1H, s), 3.88 (3H, s), 3.65 (4H, t, J = 4.9 Hz), 3.06 (4H, t,

J = 4.9 Hz); HRMS (ESI+) m/z $[M+H]^+$ 440.1491 ($C_{22}H_{23}ClN_5O_3$ requires: 440.1489). Analytical HPLC 98.5% pure, t_R = 3.7 min.

5.2.42. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(2-nitrophenyl) piperazine-1-carboxamide (4s). The title compound was prepared from **7g** (29 mg, 0.15 mmol) and 1-(2-nitrophenyl)piperazine (48 mg, 0.23 mmol) in a manner similar to that described for **3f** and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 45 mg (70%) of **4s** as a white solid: mp 202–205 °C; ^{1}H NMR ($CDCl_3$) δ 7.82 (1H, dd, J = 8.2, 1.6 Hz), 7.57 (2H, d, J = 8.6 Hz), 7.53 (1H, m), 7.39 (2H, d, J = 8.6 Hz), 7.22 (1H, s), 7.18–7.12 (2H, m), 6.55 (1H, s), 3.68 (4H, t, J = 4.9 Hz), 3.12 (4H, t, J = 5.1 Hz); HRMS (ESI+) m/z $[M+H]^+$ 427.1286 ($C_{20}H_{20}ClN_6O_3$ requires: 427.1285). Analytical HPLC 99.8% pure, t_R = 4.3 min.

5.2.43. *N*-[3-(4-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-(2-cyanophenyl) piperazine-1-carboxamide (4t). The title compound was prepared from **7g** (35 mg, 0.18 mmol) and 1-(2-cyanophenyl)piperazine (43 mg, 0.23 mmol) in a manner similar to that described for **3f** and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 59 mg (81%) of **4t** as a white solid: mp 182–185 °C; ^{1}H NMR ($CDCl_3$) δ 7.63 (2H, m), 7.60 (1H, d, J = 8.4 Hz), 7.55 (2H, m), 7.39 (2H, m), 7.10 (1H, t, J = 7.5 Hz), 7.05 (1H, d, J = 8.2 Hz), 6.57 (1H, s), 3.76 (4H, t, J = 5.1 Hz), 3.28 (4H, t, J = 5.1 Hz); HRMS (ESI+) m/z $[M+H]^+$ 407.1388 ($C_{21}H_{20}ClN_6O$ requires: 407.1387). Analytical HPLC 99.9% pure, t_R = 4.2 min.

5.2.44. 4-{2-[(Methylsulfonyl)amino]phenyl}-*N*-(3-phenyl-1*H*-pyrazol-5-yl)piperazine-1-carboxamide (5a). The title compound was prepared from **7a** (70 mg, 0.25 mmol) and **13a** (82 mg, 0.25 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 68 mg (62%) of **5a** as a white solid: mp 172–174 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, s), 7.61 (2H, d, J = 7.4 Hz), 7.51 (1H, d, J = 7.8 Hz), 7.39–7.37 (3H, m), 7.18 (1H, m), 7.08 (1H, t, J = 7.2 Hz), 6.72 (1H, s), 3.66 (4H, br s), 3.09 (3H, s), 2.86 (4H, br s); HRMS (ESI+) m/z $[M+H]^+$ 441.1713 ($C_{21}H_{25}N_6O_3S$ requires: 441.1709). Analytical HPLC 99.7% pure, t_R = 3.5 min.

5.2.45. *N*-[3-(2-Methoxyphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5b). The title compound was prepared from **7b** (34 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 54 mg (64%) of **5b** as a white solid: mp 149–151 °C; ^{1}H NMR ($CDCl_3$) δ 7.78 (1H, s), 7.70 (1H, dd, J = 7.8, 1.6 Hz), 7.51 (2H, d, J = 7.0 Hz), 7.29 (1H, t, J = 7.2 Hz), 7.18 (2H, d, J = 7.6 Hz), 7.10–7.00 (4H, m), 3.98 (3H, s), 3.67 (4H, br s), 3.07 (3H, s), 2.87 (4H, t, J = 4.7 Hz); HRMS (ESI+) m/z $[M+H]^+$ 471.1812 ($C_{22}H_{27}N_6O_4S$ requires: 471.1815). Analytical HPLC 98.2% pure, t_R = 3.6 min.

5.2.46. *N*-[3-(3-Methoxyphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5c). The title compound was prepared from **7c** (34 mg, 0.18 mmol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 33 mg (39%) of **5c** as a white solid: mp 162–165 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, s), 7.50 (1H, dd, J = 8.0, 1.4 Hz), 7.42 (1H, s), 7.31 (1H, t, J = 8.0 Hz), 7.22–7.18 (4H, m), 7.08 (1H, t, J = 8.0 Hz), 6.88 (1H, dd, J = 7.8, 2.0 Hz), 6.70 (1H, s), 3.82 (3H, s), 3.65 (3H, br s), 3.09 (3H, s), 2.86 (4H, t, J = 4.9 Hz); HRMS (ESI+) m/z $[M+H]^+$ 471.1811 ($C_{22}H_{27}N_6O_4S$ requires: 471.1815). Analytical HPLC 99.9% pure, t_R = 3.6 min.

5.2.47. *N*-[3-(4-Methoxyphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5d). The title compound was prepared from **7d** (34 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 50 mg (59%) of **5d** as a white solid: mp 242–244 °C; ^{1}H NMR ($CDCl_3$) δ 7.76 (1H, d, J = 8.6 Hz), 7.52 (2H, m), 7.25–7.15 (3H, m), 6.95 (3H, m), 3.83 (3H, s), 3.66 (4H, br s), 3.10 (3H, s), 2.86 (4H, br s); HRMS (ESI+) m/z $[M+H]^+$ 471.1806 ($C_{22}H_{27}N_6O_4S$ requires: 471.1815). Analytical HPLC 98.4% pure, t_R = 3.5 min.

5.2.48. *N*-[3-(2-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5e). The title compound was prepared from **7e**[22] (35 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 71 mg (83%) of **5e** as a white solid: mp 145–147 °C; ^{1}H NMR ($CDCl_3$) δ 7.52 (1H, d, J = 7.2 Hz), 7.48 (1H, d, J = 7.2 Hz), 7.32–7.17 (6H, m), 7.08 (1H, t, J = 7.0 Hz), 3.67 (4H, br s), 3.09 (3H, s), 2.90 (4H, br s); HRMS (ESI+) m/z $[M+H]^+$ 475.1318 ($C_{21}H_{24}ClN_6O_3S$ requires: 475.1319). Analytical HPLC 99.4% pure, t_R = 3.9 min.

5.2.49. *N*-[3-(3-Chlorophenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5f). The title compound was prepared from **7f** (35 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 30 mg (35%) of **5f** as a white solid: mp 164–167 °C; ^{1}H NMR ($CDCl_3$) δ 7.72 (1H, s), 7.63 (1H, s), 7.50 (2H, d, J = 7.8 Hz), 7.33 (2H, t, J = 7.8 Hz), 7.10 (2H, d, J = 7.6 Hz), 6.55 (1H, s), 3.66 (4H, br s), 3.11 (3H, s), 2.88 (4H, br s); HRMS (ESI+) m/z $[M+H]^+$ 475.1320 ($C_{21}H_{24}ClN_6O_3S$ requires: 475.1319). Analytical HPLC 99.3% pure, t_R = 4.1 min.

5.2.50. *N*-[3-(2-Methylphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5g). The title compound was prepared from **7h**[28] (31 mg, 0.18 mmol) and **13a** (59 mg, 0.18 mmol) in a

manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 64 mg (78%) of **5g** as a white solid: mp 152–155 °C; ^{1}H NMR ($CDCl_3$) δ 7.95 (1H, br s), 7.75 (1H, br s), 7.48 (1H, dd, J = 7.8, 1.2 Hz), 7.36 (1H, d, J = 7.4 Hz), 7.23–7.03 (4H, m), 6.64 (1H, br s), 3.62 (4H, br s), 3.04 (3H, s), 2.78 (4H, t, J = 4.7 Hz), 2.39 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 455.1866 ($C_{22}H_{27}N_6O_3S$ requires: 455.1865). Analytical HPLC 99.2% pure, t_R = 3.6 min.

5.2.51. *N*-[3-(3-Methylphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5h). The title compound was prepared from **7i** (31 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 22 mg (27%) of **5h** as a white solid: mp 146–148 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, br s), 7.50 (1H, d, J = 7.8 Hz), 7.45 (1H, d, J = 8.8 Hz), 7.40 (1H, d, J = 8.0 Hz), 7.27 (1H, m), 7.23–7.14 (3H, m), 7.07 (1H, t, J = 7.6 Hz), 6.73 (1H, br s), 3.64 (4H, br s), 3.08 (3H, s), 2.84 (4H, t, J = 4.7 Hz), 2.36 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 455.1867 ($C_{22}H_{27}N_6O_3S$ requires: 455.1865). Analytical HPLC 99.2% pure, t_R = 3.8 min.

5.2.52. *N*-[3-(4-Methylphenyl)-1*H*-pyrazol-5-yl]-4-{2-[(methylsulfonyl)amino]phenyl}piperazine-1-carboxamide (5i). The title compound was prepared from **7j** (31 mg, 0.18 mol) and **13a** (59 mg, 0.18 mmol) in a manner similar to that described for **3f**, and purified by flash chromatography on silica gel with 65% EtOAc in hexanes to afford 53 mg (65%) of **5i** as a white solid: mp 182–184 °C; ^{1}H NMR ($CDCl_3$) δ 7.74 (1H, s), 7.48 (3H, t, J = 8.0 Hz), 7.17 (2H, t, J = 6.8 Hz), 7.11–7.03 (2H, m), 6.72 (1H, s), 3.60 (4H, br s), 3.06 (3H, s), 2.78 (4H, br s), 2.34 (3H, s); HRMS (ESI+) m/z $[M+H]^+$ 455.1857 ($C_{22}H_{27}N_6O_3S$ requires: 455.1865). Analytical HPLC 99.2% pure, t_R = 3.7 min.

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