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Discovery of 1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (Nelotanserin) and Related 5-Hydroxytryptamine$_{2A}$ Inverse Agonists for the Treatment of Insomnia

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Insomnia affects a growing portion of the adult population in the U.S. Most current therapeutic approaches to insomnia primarily address sleep onset latency. Through the 5-hydroxytryptamine$_{2A}$ (5-HT$_{2A}$) receptor, serotonin (5-HT) plays a role in the regulation of sleep architecture, and antagonists/inverse-agonists of 5-HT$_{2A}$ have been shown to enhance slow wave sleep (SWS). We describe here a series of 5-HT$_{2A}$ inverse-agonists that when dosed in rats, both consolidate the stages of NREM sleep, resulting in fewer awakenings, and increase a physiological measure of sleep intensity. These studies resulted in the discovery of 1-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (Nelotanserin), a potent inverse-agonist of 5-HT$_{2A}$ that was advanced into clinical trials for the treatment of insomnia.

Introduction

Sleep is a physiological state that is crucial for the maintenance of physical, mental, and emotional health. For optimum well being, an adult will spend approximately one-third of his/her life asleep. Insomnia, the most common sleep disorder, significantly impairs the ability of an individual to function effectively.[1,2] An indication of the prevalence of insomnia comes from the results of a poll released by the National Sleep Foundation in 2005.[3] This poll suggested that approximately one-half of the adult population in the U.S. experienced at least one symptom of insomnia a few nights a week, with one-third experiencing at least one symptom every night or almost every night.

Therapeutically, acute insomnia may be treated with γ-aminobutyric acid (GABA[a]) agonists. GABA is a primary inhibitory neurotransmitter in the central nervous system (CNS), and such agonists bind to specific sites on postsynaptic GABA$_A$ receptors, potentiate GABA signaling, and thereby cause sedation and sleep.[4] Unfortunately, most GABA agonists are associated with several adverse effects including dizziness, hypotension, and respiratory depression.[5,6] Furthermore, longer acting compounds are associated with next-day hangover effects including sedation, psychomotor, and cognitive impairment,[7] while shorter acting compounds are associated with rebound insomnia and anterograde amnesia.[8]

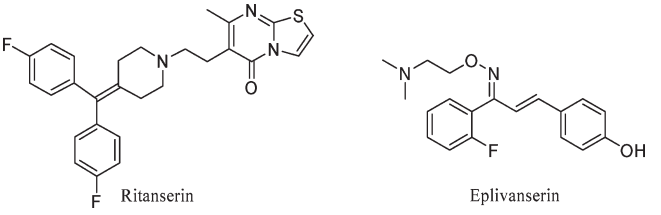

Figure 1. Some known 5-HT$_{2A}$ antagonists.

Serotonin (5-hydroxytryptamine, 5-HT) is an endogenous small molecule neuromodulator regulating diverse biological functions such as mood, aggression, cognition, satiety, sleep, locomotion, pain perception, sexual behavior, and body temperature and peripheral functions such as platelet aggregation and vascular tone.[9] The effects of 5-HT in the CNS are mediated by multiple receptor subtypes that have been classified into seven subfamilies (5-HT$_1$ to 5-HT$_7$).[10] The 5-HT$_2$ subfamily comprises three subtypes: 5-HT$_{2A}$, 5-HT$_{2B}$, and 5-HT$_{2C}$. Evidence from both clinical and preclinical studies suggests that 5-HT$_2$ receptors modulate slow wave sleep (SWS).[11−15] For example, the 5-HT$_2$ receptor antagonist, ritanserin (Figure 1), promotes sleep and enhances slow wave activity in humans and rats.[16,17] This activity is likely mediated through the 5-HT$_{2A}$ receptor,[18,19] as similar increases in SWS and slow wave activity are observed with more selective 5-HT$_{2A}$ receptor antagonists such as eplivanserin.[20,21]

Utilizing a 5-HT$_{2A}$ functional assay based on [^{3}H]inositol phosphate (IP) release, we identified a starting point for our structure−activity relationship (SAR), **1** (5-HT$_{2A}$ IC$_{50}$ = 120 nM), an inverse-agonist of 5-HT$_{2A}$ (Figure 2). The early SAR work was centered on improving potency at the 5-HT$_{2A}$ receptor and provided inverse-agonists with excellent low

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[a]Abbreviations: 5-HT, 5-hydroxytryptamine; SWS, slow wave sleep; NREM, nonrapid eye movement; GABA, γ-aminobutyric acid; CNS, central nervous system; IP, inositol phosphate; CYP, cytochome P450 enzyme; Bu, butyl; DMSO, dimethyl sulfoxide; DMF, dimethylformamide; THF, tetrahydrofuran; NBS, *n*-bromosuccinimide; DOI, 2,5-dimethoxy-4-iodoamphetamine

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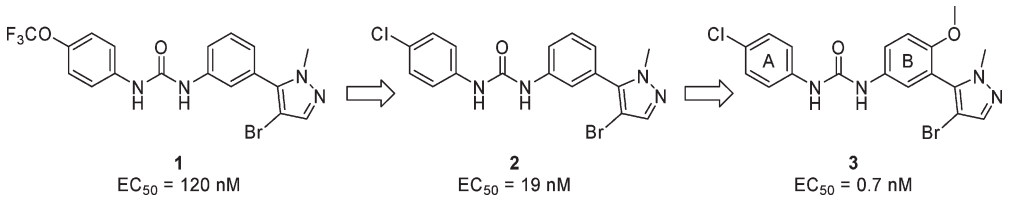
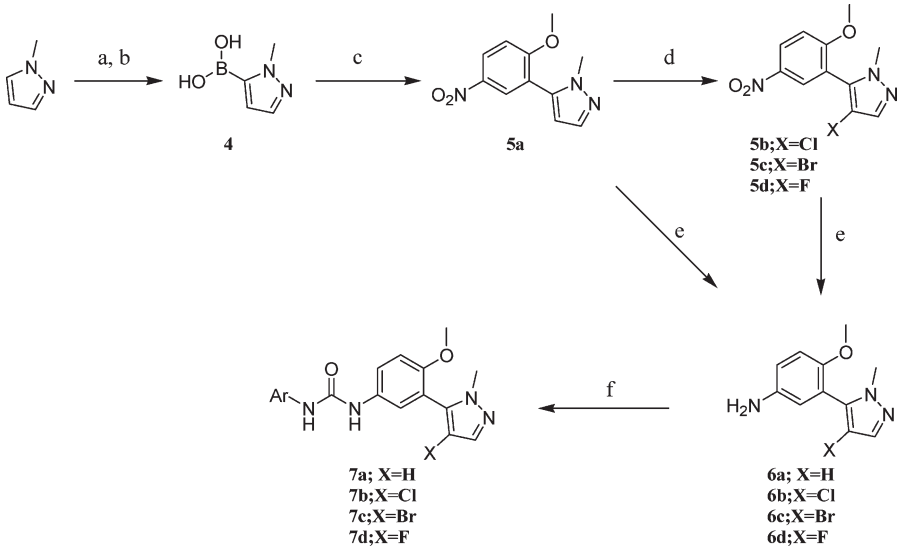


Figure 2. Early stage SAR development.

Scheme 1. Pyrazole Elaboration via Suzuki Coupling[a]



[a] Reagents: (a) *n*-BuLi, THF at −78°C; (b) $B(Oi\text{-}Pr)_3$; (c) 2-methoxy 5-nitrophenyltriflate, $Pd(PPh_3)_4$, various conditions; (d) (X = Br, NBS or X = Cl, NCS or X = F, Selectfluor), CH_2Cl_2; (e) iron dust, HOAc, CH_2Cl_2; (f) aryl isocyanate, CH_2Cl_2.

nanomolar functional activity such as **2** (5-HT_{2A} IC_{50} = 19 nM, 150-fold selective against 5-HT_{2C}).[22] These pyrazoles are unique 5-HT_{2A} compounds in that they contain no ionizable amine functionality. These early compounds, however, were associated with significant hepatotoxicity. Specifically, daily dosing of **2** in Sprague−Dawley rats at 100−250 mg/kg for 10 days showed a 15−30% increase in liver weight. In addition, inhibition of several human CYP subtypes was observed at low micromolar levels for **2**. This potential hepatotoxicity was seen with many closely related analogues in this series. Hence, an expansion of the SAR was undertaken in order to alleviate these significant issues. One of the areas of interest was the B phenyl ring (Figure 2). One of the B ring modifications prepared, containing a methoxy group ortho to the pyrazole, was found to be a highly potent 5-HT_{2A} inverse-agonist (**3**, 5-HT_{2A} IC_{50} = 0.7 nM). Furthermore, **3** showed no increase in liver weight in Sprague−Dawley rats at doses up to 500 mg/kg daily for 10 days. In that same study, **3** did not induce CYP enzyme production. Human CYP inhibition studies showed **3** did not inhibit these important liver enzymes. Further hepatic studies on compounds in this new class were devoid of liver weight increase and major CYP enzyme (1A2, 2D6, 3A4, 2C9, and 2C19) induction/inhibition. Herein, we describe the optimization of this series of phenylpyrazoleureas, leading to the identification of a clinical candidate for the treatment of insomnia, nelotanserin (APD125).

Chemistry

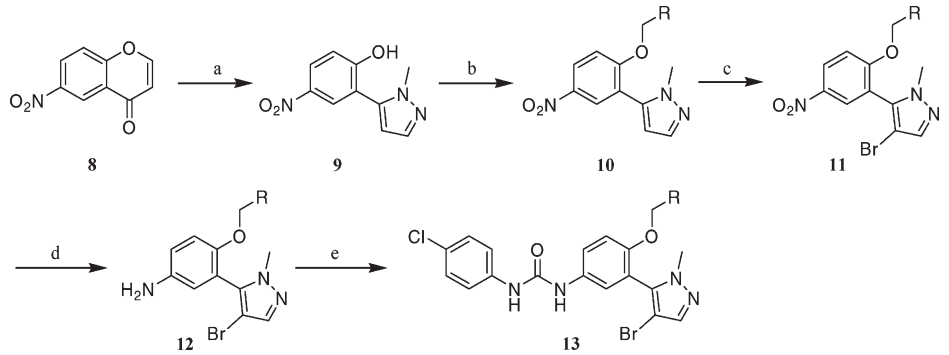
Preparation of the 1-*N*-alkyl-5-phenylpyrazole ring system proceeded through lithiation of *N*-methylpyrazole with *n*-BuLi, followed by quenching with triisopropoxyborane to form, after workup, the boronate **4** in 60% yield (Scheme 1).[23,24] Palladium mediated Suzuki coupling[25] with 2-methoxy 5-nitrophenyltriflate furnished intermediate **5a**. Selective halogenation of the pyrazole ring was achieved at the nitro stage using *N*-halosuccinimide in CH_2Cl_2 to form chloro- and bromopyrazoles **5b** and **5c**, respectively, in 89−93% yield. Fluoro substitution of the pyrazole ring was accomplished through selective fluorination of **5a**, which provided **5d** in 33% yield. Reduction of the nitro functionality of **5a**−**d** with elemental iron readily provided the anilines **6a**−**d** in 86−88% yield. Condensation of **6a**−**d** with a suitable aryl isocyanate provided the desired ureas **7a**−**d** in 50−92% yield.

In order to further investigate the ether moiety of the B ring (Figure 2), an alternative method was used to synthesize phenylpyrazoles (Scheme 2). Methylhydrazine was condensed with 6-nitrochromone (**8**) in DMSO at 70 °C, providing **9** in 44% yield. Treatment of **9** with NaH in DMF/THF, followed by the addition of an alkyl halide, furnished **10**, giving access to a wide range of ethers. Selective bromination of the pyrazole with NBS in CH_2Cl_2 provided **11**. Reduction of the nitro functionality with $SnCl_2$ in ethanol provided the penultimate aniline, **12**, in 40−80% yield over three steps. Finally, condensation with 4-chlorophenyl isocyanate furnished the target compounds, **13**, in 60−80% yield.

Primary Biological Evaluation

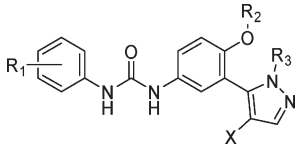
The relative affinity of the compounds for h5-HT_{2A} and h5-HT_{2C} receptors was determined in a competitive binding assay

Scheme 2. Generation of Phenyl Ethers[a]



[a] Reagents: (a) methylhydrazine, DMSO, 70°C; (b) RCH_2X, NaH, DMF/THF; (c) NBS, CH_2Cl_2; (d) $SnCl_2$, EtOH, reflux; (e) 4-chlorophenyl isocyanate, CH_2Cl_2.

Table 1. Functional Activity and Binding for 5-HT_{2A} and 5-HT_{2C} Receptors



						pK_i (n) binding		
compd	R_1	R_2	R_3	X	pIC_{50} (n) IP 5-HT_{2A}	5-HT_{2A}	5-HT_{2C}	selectivity[a]
3	4-Cl	CH_3	CH_3	Br	9.1 ± 0.3 (14)	9.3 ± 0.2 (3)	8.0 ± 0.1 (3)	1.3
14	3-Cl	CH_3	CH_3	Br	9.4 (1)	9.6 ± 0.2 (3)	7.8 ± 0.2 (3)	1.8
15	4-F	CH_3	CH_3	Br	9.6 ± 0.1 (6)	9.6 ± 0.1 (3)	7.5 ± 0.1 (3)	2.1
16	3-F	CH_3	CH_3	Br	9.1 (1)	9.5 ± 0.1 (3)	7.4 ± 0.2 (3)	2.1
17	2-F	CH_3	CH_3	Br	8.8 (1)	9.0 ± 0.1 (3)	6.4 ± 0.1 (3)	2.6
18	4-Br	CH_3	CH_3	Br	9.3 (1)	9.6 ± 0.2 (3)	8.4 ± 0.3 (3)	1.2
19	3-CF_3	CH_3	CH_3	Br	9.4 ± 0.7 (2)	9.4 ± 0.3 (3)	7.8 ± 0.2 (3)	1.6
20	4-CF_3	CH_3	CH_3	Br	8.8 ± 0.2 (2)	9.5 ± 0.2 (3)	8.4 ± 0.1 (3)	1.1
21	3-Ac	CH_3	CH_3	Br	8.4 ± 0.3 (4)	8.6 ± 0.1 (4)	6.6 ± 0.1 (3)	2.0
22	4-OMe	CH_3	CH_3	Br	9.4 (1)	9.3 ± 0.2 (3)	6.9 ± 0.2 (3)	2.4
23	4-NMe_2	CH_3	CH_3	Br	7.3 ± 0.3 (3)	8.8 ± 0.2 (4)	6.4 ± 0.1 (3)	2.4
24	4-*i*Pr	CH_3	CH_3	Br	8.6 (1)	9.5 ± 0.1 (3)	7.6 ± 0.3 (3)	1.9
25	3-CN	CH_3	CH_3	Br	8.2 (1)	9.3 ± 0.1 (3)	7.2 ± 0.2 (3)	2.1
26	4-Cl	CH_3	*i*-Pr	Br	8.9 ± 0.1 (2)	9.3 ± 0.1 (3)	8.6 ± 0.3 (3)	0.7
27	4-F	CH_3	*i*-Pr	Br	9.0 (1)	9.6 ± 0.1 (3)	8.4 ± 0.3 (3)	1.2
28	4-Cl	H	CH_3	Br	8.8 ± 0.2 (4)	9.4 ± 0.2 (3)	7.3 ± 0.3 (3)	2.1
29	4-Cl	CF_3	CH_3	Br	7.8 ± 0.1 (3)	9.1 ± 0.2 (3)	7.8 ± 0.3 (3)	1.3
30	4-Cl	CH_2CH_3	CH_3	Br	8.8 (1)	9.6 ± 0.1 (3)	8.7 ± 0.3 (3)	0.9
31	4-Cl	*i*-Pr	CH_3	Br	8.8 (1)	9.5 ± 0.2 (3)	8.0 ± 0.2 (3)	1.5
32	4-Cl	CH_2Ph	CH_3	Br	8.1 (1)	8.3 ± 0.3 (3)	6.8 ± 0.1 (3)	1.5
33	4-Cl	4-$ClPhCH_2$	CH_3	Br	7.9 (1)	7.7 ± 0.1 (3)	6.6 ± 0.2 (3)	1.1
34	4-Cl	CH_2CH_2Ph	CH_3	Br	7.3 (1)	8.2 ± 0.2 (3)	6.1 ± 0.1 (3)	2.1
35	4-Cl	CH_3	CH_3	Cl	9.3 ± 0.2 (3)	9.8 ± 0.1 (3)	8.0 ± 0.2 (3)	1.8
36	4-Cl	CH_3	CH_3	H	9.0 (1)	8.8 ± 0.1 (3)	6.8 ± 0.1 (3)	2.0
37	2,6-diCl	CH_3	CH_3	Br	8.9 (1)	9.7 ± 0.1 (3)	7.6 ± 0.1 (3)	2.1
38	3,5-diF	CH_3	CH_3	Br	8.9 (1)	9.5 ± 0.1 (3)	7.8 ± 0.2 (3)	1.7
39	2,4-diF	CH_3	CH_3	Br	9.2 ± 0.3 (8)	9.2 ± 0.3 (4)	6.8 ± 0.1 (4)	2.4
40	2,4-diF	CH_3	CH_3	Cl	9.0 ± 0.4 (3)	9.2 ± 0.1 (3)	6.5 ± 0.2 (3)	2.7
41	3,4-diF	CH_3	CH_3	Cl	9.3 ± 0.3 (2)	9.6 ± 0.1 (3)	7.6 ± 0.3 (3)	2.3
42	3,4-diF	CH_3	CH_3	F	8.6 (1)	8.9 ± 0.1 (3)	6.4 ± 0.1 (3)	2.5
43	3,5-diCF_3	CH_3	CH_3	Br	8.7 (1)	9.4 ± 0.3 (3)	7.5 ± 0.1 (3)	1.9
44	3,5-diCF_3	CH_3	CH_3	Cl	8.4 (1)	9.0 ± 0.3 (3)	7.2 ± 0.2 (3)	1.8
45	4-Cl-2-CF_3	CH_3	CH_3	Br	8.6 (1)	9.3 ± 0.2 (3)	6.9 ± 0.1 (3)	2.4
46	4-Cl-3-CF_3	CH_3	CH_3	Br	9.1 (1)	9.5 ± 0.2 (3)	8.5 ± 0.2 (3)	1.0

[a] Fold-selectivity (in log units) is expressed as the difference in 5-HT_{2A} and 5-HT_{2C} binding pK_i values.

using [^{125}I]DOI in stably transfected HEK-293 cells. Functional activity of the compounds was determined for h5-HT_{2A} and h5-HT_{2C} receptors by measuring [^{3}H] IP turnover in transiently transfected HEK-293 cells.[26]

Results

The in vitro screening results for the compounds, showing the inverse-agonist pIC_{50} and the binding pK_i on both

h5-HT_{2A} and h5-HT_{2C} receptors, are shown in Table 1. Structural modification of this series began through substitution on aryl ring A, and a wide range of monosubstitutions were evaluated (Figure 2). We observed excellent binding affinity with halo and $-CF_3$ substitutions with 5-HT_{2A} pK_i values ranging from 9.0 to 9.6. As illustrated with the monofluoro substitutions (**15**, **16**, and **17**), there was an observed rank order of activity against the 5-HT_{2A} receptor of para = meta > ortho. However, for chloro substitution, meta was marginally better than para (i.e., **14** vs **3**). The more hydrophobic CF_3 moiety was also equipotent for meta vs para substitution (i.e., **19** vs **20**). Overall, hydrophobic substitutions were more favorable for aryl ring A. The monosubstituted analogues were 10- to 150-fold more selective for the 5-HT_{2A} receptor verses the 5-HT_{2C} receptor, with the greatest selectivity being observed with 2-position substitutions (i.e., **17** was 400-fold more selective for 5-HT_{2A}). All compounds in this series maintained functional inverse-agonism pIC_{50} values similar to the binding pK_i values, as determined by the IP accumulation assay (Table 1).

Addressing the *N*-methylpyrazole moiety, we chose to look at *N*-isopropylpyrazole as a possible substitute. Direct comparison of two pairs of analogues (**3**, **26** and **15**, **27**) showed that the binding affinity for the 5-HT_{2A} receptor in each of these pairs was identical. The methyl substituted analogues, however, proved to be more selective over the 5-HT_{2C} receptor. It was for this reason that we concentrated our further efforts on *N*-methyl analogues.

Binding affinity for 5-HT_{2A} remained essentially constant when we addressed the halogen on the pyrazole ring. The selectivity over 5-HT_{2C}, however, was inversely proportional to the substituent size (**3** < **35** ≤ **36**).

We next addressed modifications of the B ring ether (Scheme 2). This series of compounds was tolerant of small alkyl substitutions (**3**, **30**, and **31**) but less tolerant of the larger hydrophobic groups (**32**, **34**, and **33**) or the electron withdrawing character of $-OCF_3$ (**29**).

During the fine-tuning stage of our SAR we were looking to maximize 5-HT_{2A} selectivity. As noted earlier, although 2-position substitutions on the A ring were not necessarily the most potent analogues against 5-HT_{2A}, these substitutions in combination with the two optimal substituents on the pyrazole as described above resulted in an improvement in 5-HT_{2A} selectivity. We therefore assessed a series of disubstituted analogues to look for the best combination of binding affinity and selectivity. Binding affinity was maximized for molecules having at least one of the substituents in the 3- or 4-position (e.g., **38**, **39**, and **41**). Although selectivity was very good when at least one substituent was in the ortho position (e.g., **39**, **40**, and **37**), a 3,4-substitution pattern also provided excellent selectivity (e.g., **41** and **42**).

In Vivo Experiments

DOI Screen. At this stage we needed to choose several compounds to assess for both pharmacokinetics (PK) and in vivo efficacy. Compounds of interest were identified using a preliminary assessment of in vivo activity in a 2,5-dimethoxy-4-iodoamphetamine (DOI) behavioral model in rats following oral administration of compound.[27] Attenuation of the DOI-induced inhibition of rearing with 5-HT_{2A} inverse-agonists is strongly suggestive of the compounds' ability to antagonize activity at 5-HT_{2A} receptors located in the CNS. Of the compounds that demonstrated activity in this screening model,[28] we chose four compounds (**3**, **15**, **35**, and **39**) that represented an adequate cross-section of activity, selectivity, and some structural diversity for further evaluation. Oral pharmacokinetics were assessed for these compounds in male Wistar rats (Table 2). All compounds had reasonable AUCs, with plasma half-lives of 2−5 h. However, **3** and **39** each had a shorter t_{max} of 3 h, which was thought to be of interest in the intended therapeutic area of sleep maintenance.

Table 2. Oral Pharmacokinetic Parameters in Male Wistar Rats

compd	*n*	dose (mg/kg)	t_{max} (h)[a]	C_{max} (ng/mL)[a]	$t_{1/2}$ (h)[a]	AUC_{0-inf} (h·ng/mL)[a]
3	2	1.0	3 ± 1	45 ± 19	3 ± 2	281 ± 10
15	2	1.4	4 ± 0	85 ± 57	2 ± 0	507 ± 356
35	2	1.5	6 ± 3	41 ± 11	5 ± 4	478 ± 282
39	2	1.4	3 ± 1	44 ± 5	3 ± 1	298 ± 95

[a] Mean ± SD.

Table 3. Rat Receptor in Vitro Binding and in Vivo Effect in the of DOI-Induced Behavior Model in Rats

	in vitro binding (^{125}I-DOI)		
compd	h5-HT_{2A} pK_i (*n*)	rHT_{2A} pK_i (*n*)	in vivo DOI ED_{50}[a]
3	9.3 ± 0.2 (3)	8.4 ± 0.3 (4)	0.5
15	9.6 ± 0.1 (3)	8.4 ± 0.3 (4)	0.7
35	9.8 ± 0.1 (3)	8.7 ± 0.5 (3)	0.7
39	9.2 ± 0.3 (4)	8.3 ± 0.3 (17)	0.7

[a] ED_{50} expressed in mg/kg.

Although the compounds evaluated showed somewhat lower affinity for the rat-5-HT_{2A} receptor than its human counterpart, we were able to determine an ED_{50} in our in vivo 5HT_2 antagonism model for each of the four compounds (Table 3). In this model, each of the selected compounds had an ED_{50} of less than 1 mg/kg when dosed orally.

Rat Sleep Studies. Individual doses were selected for each of the four compounds to measure their effects in rat sleep pharmacology studies that were 2-fold higher than the compound's ED_{50} in the DOI model. Each compound was tested in a minimum of five rats by oral gavage with administration occurring in the middle of the inactive period, 6 h after light onset. The delta power during non-REM sleep (NREMS) was significantly different between all the analogues tested and the vehicle control (Figure 3). Compounds **3** and **35** significantly increased delta power during the second hour following dosing. Compound **15** significantly increased delta power during the first and second hour following dosing. Compound **39** produced significant increases in delta power that persisted for the first 4 h following dosing.

No significant effects were found on either waking bout length or number of waking bouts. Significant differences were found, however, in NREMS bout length. Compound **39** significantly increased NREMS bout length during the first hour following dosing, and **3** did so during the second hour. In conjunction with this increased NREM bout duration, the number of NREM bouts decreased during the first hour for compound **39** ($p < 0.01$) as well as for compound **15** ($p < 0.05$).

Discussion

Several compounds of this series were very potent and selective for the 5-HT_{2A} receptor. Noted selectivity is for the 5-HT_{2A} receptor verses the 5-HT_{2C} receptor. The compounds

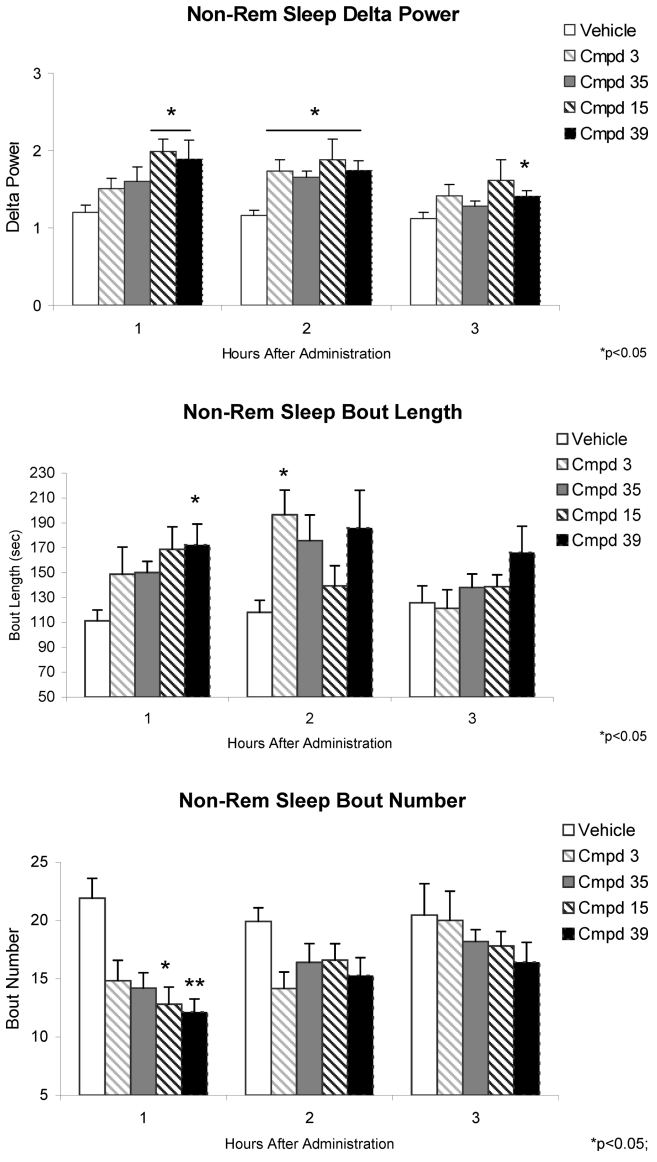


Figure 3. Effects on non-REM sleep parameters of male Wistar rats. Compounds were dosed 6 h after the beginning of the inactive period (lights on). All rats were dosed one time, po, with the following doses: **3**, 1 mg/kg; **15**, 1.4 mg/kg; **35**, 1.4 mg/kg; **39**, 1.4 mg/kg.

of this series generally showed poor affinity for the 5-HT_{2B} receptor. For instance, compounds **15** and **35** had 5-HT_{2B} $pK_i < 5$ on repeated measure. Compound **3** and **39** had a 5-HT_{2B} $pK_i = 6.1 \pm 0.2$ and 5.4 ± 0.3, respectively. These four compounds (**3**, **15**, **35**, and **39**) were chosen for evaluation in a sleep study in rats. Rat sleep is naturally fragmented and is ideal for the evaluation of compounds with the potential to induce sleep consolidation.[29] If sleep consolidation is increased while total sleep quantity remains the same, then an increase in sleep bout length would be accompanied by a corresponding decrease in bout number. Indeed, all four compounds tested in this assay showed a trend toward increasing NREMS bout length and decreasing NREMS bout number. This trend was statistically significant for **39**. These 5-HT_{2A} inverse-agonists also caused an increase in delta power during NREMS, suggesting that these compounds promote "deeper" sleep in addition to their effects on sleep consolidation. As a result of the positive sleep effects observed in rodents, compound **39** was advanced into clinical trials.[30]

Experimental Section

Biological Assays. [^{125}I]DOI Binding to Recombinant Human 5-HT_{2A} and 5-HT_{2C} Receptors. Radioligand binding assays for human 5-HT_{2A} and 5-HT_{2C} receptors were developed using crude plasma membranes prepared from HEK293 cells stably expressing these receptors (Thomsen et al.,[26] 2008). The 5-HT_2 agonist [^{125}I]DOI (0.5nM) was used as radioligand, and nonspecific radioligand binding was determined in the presence of 10 μM cold DOI. Competition experiments consisted of addition of 95 μL of assay buffer (20 mM HEPES, pH 7.4, 10 mM $MgCl_2$), 50 μL of membranes (5−25 μg of protein), 50 μL of [^{125}I]DOI (0.5 nM final assay concentration), and 5 μL of test compound diluted in assay buffer (final concentrations ranging from 1 pM to 10 μM) to 96-well Perkin-Elmer GF/C microtiter plates, and incubations were performed for 1 h at room temperature. Each radioligand competition study consisted of testing eight different concentrations in which triplicate determinations were performed for each test compound concentration. Assay incubations were terminated by rapid filtration of microtiter plates under vacuum pressure using a Brandell cell harvestor, followed by washing filter plates several times with ice-cold wash buffer (50 mM Tris-HCl, pH 7.4). Plates were then dried at 45 °C in an oven for a minimum of 2 h, 25 μL of BetaScint scintillation cocktail was added to each well, and microtiter plates were counted in a Packard TopCount scintillation counter.

Inositol Phosphate (IP3) Assay Protocol. A mutated constitutively active h5-HT_{2A} receptor was used for this assay. This constitutively active receptor was made by replacing the third intracellular loop and cytoplasmic tail of the wild type h5-HT_{2A} receptor with those same portions of the wild type h5-HT_{2C} receptor. The constitutive activity of this construct provides a sufficient window to measure 5-HT_{2A} inverse agonism in the IP3 assay. For this assay, HEK-293 cells, transiently transfected with mutated constitutively active h5-HT_{2A}, were added to 96-well microtiter plates and labeled with 0.4 mCi/mL [^{3}H]myoinositol in serum and myoinositol-free DMEM for 18 h. Unincorporated [^{3}H]myoinositol was removed and replaced with fresh myoinositol-free HBSS supplemented with LiCl (10 mM final), pargyline (10 mM final), and various concentrations of test compound. Plates were then incubated for 3 h at 37 °C. Incubations were terminated by lysing cells with ice-cold 0.1 M formic acid followed by freezing at −80 °C. After the samples were thawed, total [^{3}H]IP was resolved from unincorporated [^{3}H]myoinositol using AG1-X8 ion-exchange resin and [^{3}H]IP was measured by scintillation counting using a Wallac Microbeta scintillation counter.

Rat Pharmacokinetics. Male Wistar rats were dosed orally at 10 to 1.5 mg/kg, in 80% Tween-80/20% water. Animals were fasted overnight prior to oral dose administration. Whole blood samples were collected from the jugular vein over a 24 h period postdose. Plasma was prepared from sodium heparin-treated whole blood and separated by centrifugation. Plasma samples were frozen and stored at −70 °C until assayed using a specific and sensitive HPLC/MS/MS method. The method provided a lower limit of quantitation of 1 ng/mL and an upper limit of quantitation of 2000 ng/mL. Serial sampling [at 0.017 (iv only), 0.1 (iv only), 0.25, 0.5, 1, 2, 4, 6, 8, 12, 18 and 21hrs post dosing] was used to define the plasma concentration vs time profile (n = 2−3 animals/administration route). Noncompartmental pharmacokinetic analysis was performed with a commercial software package (WinNonlin Professional, version 4.1.b., Pharsight, Mountain View, CA).

DOI in Vivo Screen. 5-HT_{2A} inverse-agonism of the test compounds was evaluated in vivo in an acute DOI screen. In short, compounds were administered to adult, male Sprague−Dawley rats 45 min prior to administration of the 5-HT_{2A} agonist DOI (0.3 mg/kg; Sigma/Aldrich, St. Louis, MO), which decreases rearing behavior in rats. Fifteen minutes later the animals were placed in photocell monitored locomotor activity

cages. For each compound, a dose response curve was generated for reversal of DOI induced decreases in rearing and an ED_{50} calculated for later evaluation in sleep studies.

Rat Sleep Study. All experimental procedures complied with institutional animal care and use committee regulations at SRI International and National Institutes of Health guidelines for the care and use of experimental animals. To this end, eight male Wistar rats (300 ± 25 g; Charles River, Wilmington, MA) were prepared with chronic recording implants for continuous electroencephalograph (EEG) and electromyograph (EMG) recordings and allowed 1 week of recovery prior to treatment. The compounds were compared to vehicle treatment (80% Tween-80, Sigma, St. Louis, MO) and administered in a repeated measures design, wherein each rat received each treatment in random order via oral gavage. Rats were dosed during the middle of the normal inactive period (6 h following lights on).

For sleep recordings, animals were connected via a cable and a counter-balanced commutator to a Neurodata model 15 data collection system (Grass-Telefactor, West Warwick, RI). The animals were allowed an acclimation period of at least 48 h before the start of the experiment and were connected to the recording apparatus continuously throughout the experimental period except to replace damaged cables. The amplified EEG and EMG signals were digitized and stored on a computer using SleepSign software (Kissei Comtec, Irvine CA).

EEG and EMG data were scored visually in 10 s epochs for waking (W), REMS, and NREMS. Scored data were analyzed and expressed as time spent in each state per half hour. Sleep bout length and number of bouts for each state were calculated in hourly bins. A "bout" consisted of a minimum of two consecutive epochs of a given state. EEG delta power (0.5−3.5 Hz) within NREMS was also analyzed in hourly bins. The EEG spectra during NREMS were obtained offline with a fast Fourier transform algorithm on all epochs without artifact. The delta power was normalized to the average δ power in NREMS during the fifth and sixth hour following lights off, a time when delta power is low.

Data were analyzed using repeated measures ANOVA followed by post hoc analysis using *t* tests where appropriate. Light phase and dark phase data were analyzed separately. Since we predicted a treatment effect that changed (decreased) over time, we analyzed both the treatment effect within each rat and the time by treatment effect within each rat. Since two comparisons were made, a minimum value of $P < 0.025$ was used for post hoc analysis. When statistical significance was found from our ANOVAs, *t*-tests were performed comparing all compounds to vehicle.

Chemistry. All reagents were commercially available and used without further purification. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a Varian Mercury Vx-400 equipped with a four nucleus autoswitchable probe and *z*-gradient or a Bruker Avance-400 equipped with a QNP (quad nucleus probe) or a BBI (broad-band inverse) and *z*-gradient. Chemical shifts are given in parts per million (ppm) with the residual solvent signal used as reference. NMR abbreviations are used as follows: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. Microwave irradiations were carried out using the Emyrs synthesizer (Personal Chemistry). Thin-layer chromatography (TLC) was performed on silica gel 60 F_{254} (Merck), and column chromatography was carried out on silica gel columns using Kieselgel 60, 0.063−0.200 mm (Merck), and on prepacked silica gel columns using KP-Sil, supplied by Biotage. Evaporation was done under reduced pressure in a Buchi rotary evaporator. Celite 545 was used during palladium filtrations. Analytical HPLC/MS was conducted on an Applied Biosystem MDS Sciex API 150EX mass spectrometer with an atmospheric pressure ionization source and an APCI probe assembly, using a Shimadzu Inc. LC-10AD VP HPLC pump, Shimadzu Inc. SCL10A VP HPLC system controller, Shimadzu Inc. SPD-10A VP UV detector, monitoring at 214 and 280 nm, Leap Scientific CTC HTS, PAL autosampler, Analyst 1.2 software and either (a) Supelco Discovery C18 (5 cm × 2.1 mm), using a gradient of 5% v/v CH_3CN (containing 0.05% v/v TFA) in H_2O (containing 0.05% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 4.0 min), 0.6 mL/min or (b) Grace Prevail C18 column (5 μm, 5 cm × 4.6 mm), using a gradient of 5% v/v CH_3CN (containing 0.05% v/v TFA) in H_2O (containing 0.05% v/v TFA) (t = 0.0 min) gradient to 95% v/v CH_3CN in H_2O (t = 4.0 min), 3.5 mL/min. All final compounds were assessed via the above-described analytical method and found to be ≥95% in purity.

Preparative HPLC was conducted on a Varian Prostar reverse phase HPLC using a Phenomenex Luna C18 column (10 μm, 250 mm × 50 mm; and 10 μm, 250 mm × 21.2 mm), 5% (v/v) CH_3CN (containing 0.1% v/v TFA) in H_2O (containing 0.1% v/v TFA) gradient to 100% H_2O, 60 or 20 mL/min, λ = 220 nM. HRMS were analyzed using an Acquity BEH C18 2.1 mm × 50 mm, 1.7 microns column (Waters) on an UPLC (Waters) and QTOF micro (+ve mode) mass spectrometer. All chemicals and reagents were purchased from Aldrich or TCI America or Fluka.

Elemental analysis was conducted by West Coast Analytical Service Inc., 9240 Santa Fe Springs Road, Santa Fe Springs, CA 90670.

Preparation of Intermediates. 2-Methyl-2*H*-pyrazole-3-boronic Acid (4). *N*-Methylpyrazole (25 mL, 0.3 mol) was dissolved in 500 mL of tetrahydrofuran. The solution was cooled to −78 °C in a dry ice/isopropanol bath, and *n*-BuLi (140 mL of 2.5 M in hexanes, 0.35 mol) was added dropwise by cannula. The reaction mixture was stirred at −78 °C for 1.5 h. Then triisopropyl borate (280 mL, 1.2 mol) was added via cannula. While being stirred overnight, the reaction temperature was gradually increased from −78 to 0 °C. The pH of the mixture was adjusted to 6 with 1 N HCl. Tetrahydrofuran was removed under reduced pressure, and the resulting residue was triturated with ethyl acetate/dichloromethane (1:1). The solid suspension was then filtered and the solid was dried in vacuo to yield 60 g (60%) of 2-methyl-2*H*-pyrazole-3-boronic acid (**4**) as a light-yellow solid. LCMS m/z (%) = 127 M + H^+, (100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.24 (s, 2H), 7.2 (s, 1H), 6.5 (s, 1H), 3.75 (s, 3H).

Trifluoromethanesulfonic Acid 2-Methoxy-5-nitrophenyl Ester. To a stirred solution of 2-methoxy-5-nitrophenol (5.092 g, 30 mmol) in a mixture of methylene chloride (3 mL) and pyridine (20 mL) was added triflic anhydride (16.478 g, 9.8 mL) dropwise at 0 °C. The mixture was warmed to room temperature and stirred for 2 h. The pyridine was removed under vacuum. The residue was diluted with ethyl acetate, washed with 1 N HCl and water, and the aqueous phase was then extracted with ethyl acetate (3 × 100 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/3 then 1/2) to give trifluoromethanesulfonic acid 2-methoxy-5-nitrophenyl ester (8.943 g, 30 mmol, 100%) as a yellow solid. LCMS m/z (%) = 302 (M + H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.30 (dd, J = 4.0, 8.0 Hz, 1H), 8.16 (d, J = 4.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 4.06 (s, 3H).

5-(2-Methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (5a). Trifluoromethanesulfonic acid 2-methoxy-5-nitrophenyl ester (2.561 g, 8.50 mmol), 2-methyl-2*H*-pyrazole-3-boronic acid (**4**) (4.283 g, 34.01 mmol, 4.0 equiv), and sodium carbonate (10.816 g, 102.04 mmol, 12.0 equiv) were suspended in a mixture of tetrahydrofuran (200 mL) and water (100 mL). The resulting mixture was degassed with argon for 5 min, followed by the addition of $Pd(PPh_3)_4$ (0.486 g, 0.42 mmol, 0.05 equiv). After degassing for another 5 min, the reaction mixture was heated to 70 °C overnight. Once the reaction was complete, tetrahydrofuran was removed under reduced pressure and the aqueous phase was extracted with ethyl acetate (4 × 100 mL). The combined organic phase was dried over $MgSO_4$, filtered, and

evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/1) to afford 5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5a**) (1.799 g, 7.71 mmol, 91%) as a white solid. LCMS *m*/*z* (%) = 234 (M + H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.34 (dd, J = 2.8, 9.2 Hz, 1H), 8.19 (d, J = 2.8 Hz, 1H), 7.56 (d, J = 2.0 Hz, 1H), 7.08 (d, J = 9.2 Hz, 1H), 6.31 (d, J = 1.6 Hz, 1H), 3.96 (s, 3H), 3.74 (s, 3H).

4-Chloro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (5b). 5-(2-Methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5a**) (2.37 g, 10.17 mmol) was dissolved in DMF (100 mL). The solution was then heated to 80 °C. *N*-Chlorosuccinimide (1.49 g, 11.1 mmol) was added at 80 °C under argon gas. After 2 h of continuous stirring, the reaction was checked by TLC and LCMS and found to be incomplete. An additional aliquot of *N*-chlorosuccinimide (0.5 g, 3.7 mmol) was added, bringing the reaction to completion after 1.5 h. While the sample was being stirred, a portion of water (200 mL) was added to force the product to precipitate out of solution. After the precipitation was complete, the flask containing the solid was cooled in an ice−water bath for 10 min. The solid was then filtered under vacuum, rinsed with water, and dried to afford 2.4 g (89%) of 4-chloro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5b**) as a light-yellow solid. LCMS *m*/*z* (%) = 268 (M + H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.41 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 8.22 (d, J = 4 Hz, 1H), 7.53 (s, 1H), 7.14 (d, J = 12 Hz, 1H), 3.97 (s,3H), 3.72 (s, 3H).

4-Bromo-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (5c). To a stirred solution of 5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5a**) (1.787 g, 7.66 mmol) in DMF (20 mL) was added *N*-bromosuccinimide (1.515 g, 8.43 mmol) in DMF (5 mL) dropwise at 0 °C. After the mixture was stirred at 0 °C for 3 h, TLC showed completion of the reaction. The mixture was diluted with ethyl acetate (300 mL) and washed with water (3 × 100 mL) and brine. The ethyl acetate phase was dried with $MgSO_4$, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/3 and then 1/1) to give the product 4-bromo-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5c**) (2.214 g, 7.09 mmol, 93%) as a light-yellow solid. LCMS *m*/*z* (%) = 312 (M + H^{79}Br, 100), 314 (M + H^{81}Br, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.40 (dd, J = 2.4, 6.9 Hz, 1H), 8.22 (m, 1H), 7.57 (s, 1H), 7.14 (d, J = 9.2 Hz, 1H), 3.98 (s, 3H), 3.74 (s, 3H).

4-Fluoro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (5d). 5-(2-Methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5a**) (300.0 mg, 1.29 mmol) was dissolved in acetonitrile (15 mL) in a polypropylene 20 mL scintillation vial. To this solution, Selectfluor (913.9 mg, 2.58 mmol) was added, and the mixture was degassed with argon and heated to 80 °C for 6 h. The solvent was removed under reduced pressure, and the residue was dissolved in ethyl acetate (50 mL) and 3 N HCl (30 mL). The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (SiO_2, eluent hexanes (0.01% TEA)/ethyl acetate) to afford 108 mg (33%) of 4-fluoro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5d**) as a white solid. LCMS *m*/*z* (%) = 252 (M + H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.39 (d, J = 9.2 Hz, 1H), 8.22 (s, 1H), 7.44 (d, $J_{H,F}$ = 4.4 Hz, 1H), 7.12 (d, J = 9.2 Hz, 1H) 3.98 (s, 3H), 3.77 (s, 3H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −175.50 (d, $J_{H,F}$ = 5.3 Hz, 1F).

3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (6b). 4-Chloro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5b**) (2.27 g, 8.5 mmol) was dissolved in dry ethanol (150 mL) and heated to 75 °C. The heated solution was then treated with tin(II) chloride dihydrate (9.6 g, 42.5 mmol) and stirred at 75 °C. After 3 h, the reaction was found to be complete by TLC and LCMS. The solvent was removed under reduced pressure. The residue was subsequently diluted with ethyl acetate (100 mL) and 1 N sodium hydroxide, neutralizing the reaction to a pH of approximately 7. The mixture was then filtered through Celite. The organic layer was separated, and the aqueous layer was extracted with ethyl acetate (2 × 50 mL). The organic layers were combined, dried over sodium sulfate, filtered, and the solvent was removed under reduced pressure. The residue was then purified by flash chromatography (SiO_2, hexanes/ethyl acetate) to afford 1.73 g (86%) of 3-(4-chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (**6b**) as a light-brown solid. LCMS *m*/*z* (%) = 238 (M + H^{35}Cl, 100), 240 (M + H^{37}Cl, 37). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.48 (s, 1H), 6.87 (d, J = 8, 1H), 6.81 (dd, J_1 = 8, J_2 = 4, 1H), 6.63 (d, J = 4, 1H), 3.72 (s, 3H), 3.70 (s, 3H).

3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (6c). To a stirred solution of 4-bromo-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5c**) (1.799 g, 5.76 mmol) in ethanol (20 mL) was added tin(II) chloride dihydrate (5.306 g, 23.05 mmol). The mixture was stirred at reflux for 2 h, and then the solvent was removed under vacuum. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/3 and then 1/1) to give 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (**6c**) (1.430 g, 5.07 mmol, 88%) as a white solid. LCMS *m*/*z* (%) = 282 (M + H^{79}Br, 98), 284 (M + H^{81}Br, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.80 (dd, J = 2.8, 8.8 Hz, 1H), 6.22 (d, J = 2.4 Hz, 1H), 4.25 (broad s, 2H), 3.72 (s, 3H), 3.71 (s, 3H).

3-(4-Fluoro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (6d). 4-Fluoro-5-(2-methoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole (**5d**) (109 mg, 0.434 mmol) in ethanol (10 mL) was treated with Pd/C (10 wt %, Degussa), and H_2 was allowed to bubble through the slurry. The reaction mixture was filtered through Celite and the solvent was removed under reduced pressure to afford 93 mg (97%) of 3-(4-fluoro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (**6d**) as a light-brown oil. LCMS *m*/*z* (%) = 222 (M + H, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.38 (d, $J_{H,F}$ = 4.4 Hz, 1H), 6.86 (d, J = 8.8 Hz, 1H), 6.78 (dd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 6.63 (d, J = 2.8 Hz, 1H), 3.74 (s, 3H), 3.68 (s, 3H), 3.53 (s, 2H). ^{19}F NMR (376 MHz, $CDCl_3$) δ: −175.50 (d, $J_{H,F}$ = 5.3 Hz, 1F).

1-Isopropyl-1*H*-pyrazole. To a solution of pyrazole (50.0 g, 735.3 mmol) in aqueous sodium hydroxide (123.5 g of sodium hydroxide/200 mL of water) was added isopropyl bromide (180.0 g, 1470.1 mmol), and the mixture was then heated to reflux for 7 days. The reaction mixture was cooled and extracted with ethyl acetate (3 × 300 mL). The combined organic layers were dried over $MgSO_4$. Removal of the volatiles in vacuum provided a light-yellow oil, which was distilled via Kugelrohr at 140 °C and 10 Torr to provide 1-isopropyl-1*H*-pyrazole as a colorless oil (43 g, 53%). LCMS *m*/*z* (%) = 111 (M + H^+, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 7.72 (d, J = 2.3 Hz, 1H), 7.41 (t, 1H), 6.21 (t, 1H), 4.5 (q, 1H), 1.41−1.37 (d, J = 11.1 Hz).

2-Isopropyl-2*H*-pyrazole-3-boronic Acid. *n*-BuLi (110 mL, 275 mmol, 2.5 M in hexanes) was slowly added over 30 min at −78 °C to a tetrahydrofuran solution of 1-isopropyl-1*H*-pyrazole (25.0 g, 227 mmol). The reaction mixture was stirred at −78 °C for 2 h. A solution of cooled triisopropoxy boronate (170.0 g, 909 mmol) was added slowly via cannula over 45 min. The reaction mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was adjusted to pH 7 with HCl (1 M, 170 mL). The solvent was evaporated to dryness, and the resulting residue was triturated with 1:1 ethyl acetate/dichloromethane. The suspension was filtered and the solvent was evaporated in vacuum to yield 2-isopropyl-2*H*-pyrazole-3-boronic acid as a colorless solid (20.0 g, 58%).

LCMS m/z (%) = 155 ($M + H^+$, 100). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.14 (s, 2H), 7.2 (s, 1H), 6.5 (s, 1H), 5.05 (m, 1H), 1.2 (d, J = 9.0 Hz, 6H).

1-Isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole. To a mixture of trifluoromethanesulfonic acid 2-methoxy-5-nitrophenyl ester (4.1 g, 13.6 mmol), 2-isopropyl-2*H*-pyrazole-3-boronic acid (5.2 g, 34.1 mmol), and cesium carbonate (17.7 g, 54.4 mmol) in dimethoxyethane under argon was added Pd(PPh_3)$_4$ (0.79 g, 0.68 mmol), and the mixture was heated at 80 °C for 16 h. The reaction mixture was cooled, filtered through Celite, and evaporated to dryness. The residue was taken up in ethyl acetate, and the solution was washed with water. The organic layer was dried over $MgSO_4$ and evaporated to afford a crude product as a brown solid. The crude material was purified via flash chromatography (SiO_2, hexane/ethyl acetate, 3/1) to yield 1-isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole (1.88 g, 52%) as a colorless solid. LCMS m/z (%) = 262 ($M + H^+$, 100). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.36 (dd, J_1 = 9.09 Hz, J_2 = 2.5 Hz, 1H), 8.18 (d, J = 8.18 Hz, 1H), 7.65 (s, 1H), 7.09 (d, J = 8.08 Hz, 1H), 6.25 (s, 1H), 4.16 (dd, J_1 = 13.14 Hz, J_2 = 6.57 Hz, 1H), 3.95 (s, 3H), 1.45 (d, J = 6.82 Hz, 6H).

4-Bromo-1-isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole. To a stirred, ice-cooled solution of 1-isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole (1.0 g, 3.83 mmol) in DMF (10 mL) was added *N*-bromosuccinimide (0.75 g, 4.22 mmol) slowly over a period of 10 min. The reaction mixture was warmed to room temperature and stirred for 2 h. The reaction mixture was poured into an ice−water mixture with vigorous stirring to form a white solid, which was filtered and washed with cold water until free of DMF. The solid was dried in vacuum to give colorless solid 4-bromo-1-isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole (1.25 g, 96%). LCMS m/z (%) = 340 $M + H^+$ (^{79}Br, 100), 342 (^{81}Br, 96.5). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.4 (dd, J_1 = 9.09 Hz, J_2 = 2.78 Hz, 1H), 8.19 (d, J = 2.78), 7.6 (s, 1H), 7.14 (d, J = 9.35 Hz, 1H), 4.11 (m, 1H), 3.96 (s, 3H), 1.49 (d, J = 6.52 Hz, 3H), 1.36 (d, J = 6.52 Hz, 3H).

3-(4-Bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine. To a solution of 4-bromo-1-isopropyl-5-(2-methoxy-5-nitrophenyl)-1*H*-pyrazole (0.50 g, 1.47 mmol) in ethanol (5.0 mL) was added tin(II) chloride dihydrate (1.3 g, 5.88 mmol), and the mixture was heated at 55 °C overnight. The ethanol was evaporated, and the residue was taken up in ethyl acetate (50 mL) and washed with 10% sodium hydroxide (10 mL). The organic layer was dried over $MgSO_4$ and evaporated to yield a light-yellow solid. The crude material was purified via flash chromatography (SiO_2, hexane/ethyl acetate, 3/1) to yield of 3-(4-bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.38 g, 85%) as a pale-yellow solid. LCMS m/z (%) = 310 M + H^+, (^{79} Br, 100), 312 M + H^+ (^{81}Br, 96.5). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.47 (s, 1H), 6.78 (d, J = 8.08 Hz, 1H), 6.72 (dd, J_1 = 8.01 Hz, J_2 = 2.78 Hz, 1H), 6.54 (d, J = 2.78 Hz, 1H), 4.14 (m, 1H), 3.63 (s, 3H), 1.4 (d, J = 6.57 Hz, 3H), 1.23 (d, J = 6.57 Hz, 3H).

2-(2-Methyl-2*H*-pyrazol-3-yl)-4-nitrophenol. To methylhydrazine (1.106 g, 1.3 mL, 23.5 mmol) was added 6-nitrochromone (1.159 g, 5.88 mmol) in DMSO (40 mL) dropwise via syringe pump at 70 °C. The crude reaction mixture was purified by HPLC to afford 2-(2-methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.567 g, 2.59 mmol, 44%) as a white solid. LCMS m/z = 220 ($M + H$). ^1H NMR (400 MHz, acetone-d_6) δ: 8.24 (dd, J = 2.9, 9.0 Hz, 1H), 8.13 (d, J = 2.8 Hz, 1H), 7.46 (d, J = 1.8 Hz, 1H), 7.26 (d, J = 9.0 Hz, 1H), 6.36 (d, J = 1.8 Hz, 1H), 3.77 (s, 3H).

3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-ethoxyphenylamine. Step 1. To a stirred solution of 2-(2-methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.206 g, 0.94 mmol) in a mixture of dimethylformamide/tetrahydrofuran (1 mL/5 mL) was added sodium hydride (60%, 0.082 g, 1.88 mmol) at 0 °C. After the mixture was stirred for 30 min, iodoethane (0.444 g, 0.23 mL, 3.0 equiv) was added, and the mixture was warmed up to 70 °C and stirred until the starting material was completely consumed. The reaction was then quenched with saturated ammonium chloride, diluted with ethyl acetate, washed with water, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated, providing crude 5-(2-ethoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole. LCMS m/z = 248 ($M + H$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.33 (dd, J = 2.5, 9.1 Hz, 1H), 8.21 (d, J = 2.5 Hz, 1H), 7.57 (d, J = 1.3 Hz, 1H), 7.07 (d, J = 9.1 Hz, 1H), 6.34 (s, 1H), 4.22 (dd, J = 7.0, 13.9 Hz, 2H), 3.78 (s, 3H), 1.44 (t, J = 6.8 Hz, 3H).

Step 2. The crude mixture of 5-(2-ethoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole was treated dropwise at 0 °C with *N*-bromosuccinimide in dimethylformamide. After the mixture was stirred at 0 °C for 3 h, TLC showed completion of the reaction. The mixture was diluted with ethyl acetate (300 mL) and washed with water (3 × 100 mL) and brine. The ethyl acetate phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/3 and then 1/1), providing 4-bromo-5-(2-ethoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole as a colorless solid. LCMS m/z (%) = 326 ($M + H^{79}$Br, 88), 328 ($M + H^{81}$Br, 100). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.38 (dd, J = 2.7, 9.2 Hz, 1H), 8.22 (d, J = 2.7 Hz, 1H), 7.59 (s, 1H), 7.11 (d, J = 9.2 Hz, 1H), 4.14−4.32 (m, 2H), 3.76 (s, 3H), 1.43 (t, J = 6.8 Hz, 3H).

Step 3. To a stirred solution of 4-bromo-5-(2-ethoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole in ethanol was added tin(II) chloride dihydrate. After the mixture was stirred at reflux for 2 h, the solvent was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane) to afford (0.225 g, 0.76 mmol, 81% over three steps) 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-ethoxyphenylamine as a white solid. LCMS m/z (%) = 296 ($M + H^{79}$Br, 100), 298 ($M + H^{81}$Br, 98). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.52 (s, 1H), 6.86 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 2.2, 8.5 Hz, 1H), 6.62 (d, J = 2.3 Hz, 1H), 3.82−4.00 (m, 2H), 3.73 (s, 3H), 3.24−3.58 (broad s, 2H), 1.24 (t, J = 6.8 Hz, 3H).

4-Benzyloxy-3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)phenylamine. Step 1. 2-(2-Methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.124 g, 0.57 mmol) was treated with sodium hydride (60%, 0.049 g, 1.13 mmol) and benzyl bromide (0.21 mL, 1.70 mmol) in a mixture of DMF (2 mL) and THF (4 mL) at 0 °C. The mixture was warmed to 70 °C and stirred until the starting material was consumed. The reaction was quenched with saturated ammonium chloride, diluted with ethyl acetate, washed with water, and the aqueous phase was extracted with ethyl acetate (3× 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated, providing crude 5-(2-benzyloxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole. LCMS m/z = 310 ($M + H$). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.32 (dd, J = 2.8, 9.1 Hz, 1H), 8.24 (d, J = 2.8 Hz, 1H), 7.59 (d, J = 1.7 Hz, 1H), 7.22−7.45 (m, 5H), 7.16 (d, J = 9.1 Hz, 1H), 6.37 (d, J = 1.7 Hz, 1H), 5.25 (s, 2H), 3.77 (s, 3H).

Step 2. Crude 5-(2-benzyloxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole was treated dropwise at 0 °C with *N*-bromosuccinimide (0.113 g, 0.63 mmol) in DMF. After being stirred at 0 °C for 3 h, the mixture was cooled to room temperature, diluted with ethyl acetate (300 mL), and washed with water (3 × 100 mL) and brine. The ethyl acetate phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 5-(2-benzyloxy-5-nitrophenyl)-4-bromo-1-methyl-1*H*-pyrazole. LCMS m/z (%) = 388 ($M + H^{79}$Br, 100), 390 ($M + H^{81}$Br, 94). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.36

(dd, J = 2.8, 9.2 Hz, 1H), 8.23 (d, J = 2.8 Hz, 1H), 7.59 (s, 1H), 7.25−7.42 (m, 5H), 7.19 (d, J = 9.2 Hz, 1H), 5.24 (s, 2H), 3.73 (s, 3H).

Step 3. To a stirred solution of 5-(2-benzyloxy-5-nitrophenyl)-4-bromo-1-methyl-1*H*-pyrazole in ethanol was added tin(II) chloride dihydrate. After the mixture was stirred at reflux for 2 h, the solvent was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 4-benzyloxy-3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)phenylamine (0.079 g, 0.22 mmol, 39% over three steps). LCMS m/z (%) = 358 (M + $H^{79}Br$, 98), 360 (M + $H^{81}Br$, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.45 (s, 1H), 7.15−7.26 (m, 3H), 7.10 (d, J = 6.6 Hz, 2H), 6.83 (d, J = 8.7 Hz, 1H), 6.66 (dd, J = 2.8, 8.6 Hz, 1H), 6.55 (d, J = 2.8 Hz, 1H), 4.83 (AB quartet, J = 12.0, 17.2 Hz, 2H), 3.62 (s, 3H).

3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-(4-chlorobenzyloxy)-phenylamine. Step 1. 2-(2-Methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.143 g, 0.65 mmol) was treated with sodium hydride (0.057 g, 1.30 mmol) and 4-chlorobenzyl bromide (0.332 g, 1.96 mmol) in a mixture of DMF (0.9 mL) and THF (2.5 mL) (2.5 mL) at 0 °C. The mixture was warmed to 70 °C and stirred until the starting material was consumed. The reaction was quenched with saturated ammonium chloride, diluted with ethyl acetate, washed with water, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated, providing crude 5-[2-(4-chlorobenzyloxy)-5-nitrophenyl]-1-methyl-1*H*-pyrazole (0.142 g, 0.41 mmol, 63%) as an oil. LCMS m/z (%) = 344 (M + $H^{35}Cl$, 100), 346 (M + $H^{37}Cl$, 39). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.33 (dd, J = 2.8, 9.1 Hz, 1H), 8.23 (d, J = 9.1 Hz, 1H), 7.58 (d. J = 1.7 Hz, 1H), 7.36 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 1H), 7.13 (d, J = 9.1 Hz, 1H), 6.36 (d, J = 1.7 Hz, 1H), 5.20 (s, 2H), 3.75 (s, 3H).

Step 2. Crude 5-[2-(4-chlorobenzyloxy)-5-nitrophenyl]-1-methyl-1*H*-pyrazole was treated dropwise 0 °C with *N*-bromosuccinimide (0.082 g, 0.45 mmol, 1.05 equiv) in DMF. After being stirred at 0 °C for 3 h, the mixture was diluted with ethyl acetate (300 mL) and washed with water (3 × 100 mL) and then brine. The ethyl acetate phase was dried over anhydrous $MgSO_4$, filtered and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 4-bromo-5-[2-(4-chlorobenzyloxy)-5-nitrophenyl]-1-methyl-1*H*-pyrazole. LCMS m/z (%) = 422 (M + $H^{79}Br^{35}Cl$, 85), 424 (M + $H^{81}Br^{35}Cl$, 100), 426 (M + $H^{81}Br^{37}Cl$, 26). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.37 (dd, J = 2.7, 9.2 Hz, 1H), 8.22 (d, J = 2.7 Hz, 1H), 7.59 (s, 1H), 7.34 (d, J = 8.3 Hz, 2H), 7.21 (d, J = 8.3 Hz, 2H), 7.16 (d, J = 9.2 Hz, 1H), 5.20 (AB quartet, J = 12.1, 15.2 Hz, 2H), 3.72 (s, 3H).

Step 3. To a stirred solution of 4-bromo-5-[2-(4-chlorobenzyloxy)-5-nitrophenyl]-1-methyl-1*H*-pyrazole in ethanol was added tin(II) chloride dihydrate (0.378 g, 1.64 mmol) in ethanol (5 mL). After the mixture was stirred at reflux for 2 h the solvent was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-(4-chlorobenzyloxy)phenylamine (0.114 g, 0.29 mmol, 71% over the final two steps). LCMS m/z (%) = 393 (M + $H^{79}Br^{35}Cl$, 70), 395 (M + $H^{81}Br^{35}Cl$, 100), 397 (M + $H^{81}Br^{37}Cl$, 23). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.28 (d, J = 8.2 Hz, 2H), 7.11 (d, J = 8.2 Hz, 2H), 6.90 (d, J = 8.7 Hz, 1H), 6.76 (dd, J = 2.7, 8.7 Hz, 1H), 6.63 (d, J = 2.7 Hz, 1H), 4.86 (AB quartet, J = 12.1, 20.9 Hz, 2H), 3.71 (s, 3H).

3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-phenethyloxyphenylamine. Step 1. 2-(2-Methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.125 g, 0.57 mmol) was treated with sodium hydride (0.049 g, 1.14 mmol, 2.0 equiv) and (2-bromoethyl)benzene (0.323 g, 0.24 mL, 1.71 mmol, 3.0 equiv) in a mixture of DMF (0.9 mL) and THF (2.5 mL) at 0 °C. The mixture was warmed to 70 °C and stirred until the starting material was consumed. The reaction was quenched with saturated ammonium chloride, diluted with ethyl acetate, washed with water, and the aqueous phase was extracted with ethyl acetate (3 × 50 mL). The combined organic phase was washed with brine, dried over $MgSO_4$, filtered and the solvent evaporated, providing crude 1-methyl-5-(5-nitro-2-phenethyloxyphenyl)-1*H*-pyrazole (0.137 g, 0.42 mmol, 74%) as an oil. LCMS m/z (%) = 324 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (dd, J = 2.8, 9.1 Hz, 1H), 8.17 (d, J = 2.8 Hz, 1H), 7.59 (s, 1H), 7.20−7.36 (m, 3H), 7.09 (d, J = 7.1 Hz, 2H), 7.05 (d, J = 9.2 Hz, 1H), 6.26 (s, 1H), 4.33 (t, J = 6.6 Hz, 2H), 3.55 (s, 3H), 3.05 (t, J = 6.6 Hz, 2H).

Step 2. 1-Methyl-5-(5-nitro-2-phenethyloxyphenyl)-1*H*-pyrazole (0.137 g, 0.42 mmol) was treated with *N*-bromosuccinimide (0.084 g, 0.46 mmol, 1.05 equiv) in DMF (5 mL). After being stirred at 0 °C for 3 h, the mixture was diluted with ethyl acetate (300 mL) and washed with water (3 × 100 mL) and then brine. The ethyl acetate phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 4-bromo-1-methyl-5-(5-nitro-2-phenethyloxyphenyl)-1*H*-pyrazole. LCMS m/z (%) = 402 (M + $H^{79}Br$, 100), 404 (M + $H^{81}Br$, 97). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.27 (dd, J = 2.8, 9.2 Hz, 1H), 8.10 (d, J = 2.8 Hz, 1H), 7.52 (s, 1H), 7.16−7.24 (m, 3H), 6.94−7.03 (m, 3H), 4.18−4.28 (m, 2H), 3.37 (s, 3H), 2.88−3.02 (m, 2H).

Step 3. To a stirred solution of 4-bromo-1-methyl-5-(5-nitro-2-phenethyloxyphenyl)-1*H*-pyrazole in ethanol was added tin(II) chloride dihydrate (0.387 g, 1.68 mmol, 4.0 equiv) in ethanol. After the mixture was stirred at reflux for 2 h, the solvent was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-phenethyloxyphenylamine (0.124 g, 0.33 mmol, 80% over the final two steps) as an oil. LCMS m/z (%) = 372 (M + $H^{79}Br$, 94), 374 (M + $H^{81}Br$, 100). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 7.54 (s, 1H), 7.18−7.33 (m, 3H), 7.08 (d, J = 7.7 Hz, 2H), 6.85 (d, J = 8.7 Hz, 1H), 6.77 (dd, J = 2.7, 8.7 Hz, 1H), 6.61 (d, J = 2.6 Hz, 1H), 3.99−4.15 (m, 2H), 3.53 (s, 3H), 3.10−3.40 (broad s, 2H), 2.83−3.00 (m, 2H).

3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-isopropoxyphenylamine. Step 1. To a stirred solution of 2-(2-methyl-2*H*-pyrazol-3-yl)-4-nitrophenol (0.061 g, 0.28 mmol) in DMF (3 mL) was added potassium carbonate (0.077 g, 0.56 mmol) at room temperature. The reaction mixture was stirred for 30 min, and isopropyl bromide (110 μL, 1.16 mmol) was added. The mixture was heated to 50 °C until the consumption of starting material was complete. The reaction mixture was diluted with ethyl acetate, washed with water, and the aqueous phase was extracted with ethyl acetate. The combined organic phase was washed with brine, dried over $MgSO_4$, filtered, and evaporated to provide crude 5-(2-isopropoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole. LCMS m/z = 262 (M + H). ^{1}H NMR (400 MHz, $CDCl_3$) δ: 8.31 (dd, J = 2.8, 9.2 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.56 (s, 1H), 7.06 (d, J = 9.2 Hz, 1H), 6.3 (s, 1H), 4.74 (ddd, J = 6.1, 6.1, 12.1 Hz, 1H), 1.37 (s, 3H), 1.36 (s, 3H)

Step 2. Crude 5-(2-isopropoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole from step 1 was treated with *N*-bromosuccinimide in DMF (5 mL). After being stirred at 0 °C for 3 h, the mixture was diluted with ethyl acetate (300 mL) and washed with water (3 × 100 mL) and then brine. The organic phase was dried over $MgSO_4$, filtered and the solvent evaporated. The crude reaction mixture was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 4-bromo-5-(2-isopropoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole. LCMS *m*/*z* (%) = 340 (M + $H^{79}Br$, 85), 342 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.36 (dd, J = 2.8, 9.2 Hz, 1H), 8.20 (d, J = 2.8 Hz, 1H), 7.57 (s, 1H), 7.10 (d, J = 9.2 Hz, 1H), 4.73 (ddd, J = 6.1, 6.1, 12.1 Hz, 1H), 1.39 (d, J = 6.1 Hz, 3H), 1.32 (d, J = 6.0 Hz, 3H).

Step 3. To a stirred solution of 4-bromo-5-(2-isopropoxy-5-nitrophenyl)-1-methyl-1*H*-pyrazole in ethanol from step 2 was added tin(II) chloride dihydrate in ethanol. After the mixture was stirred at reflux for 2 h, the solvent was removed under reduced pressure. The resulting solid was dissolved in ethyl acetate, 1 N sodium hydroxide (30 mL) was added, and the mixture was stirred overnight. The white precipitate was filtered off through Celite, and the aqueous phase was extracted with ethyl acetate (3 × 80 mL). The combined organic phase was dried over anhydrous $MgSO_4$, filtered, and evaporated. The crude residue was purified by flash chromatography (SiO_2, eluent ethyl acetate/hexane), providing 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-isopropoxyphenylamine (0.043 g, 0.14 mmol, 50% over three steps). LCMS *m*/*z* (%) = 310 (M + $H^{79}Br$, 99), 312 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.51 (s, 1H), 6.89 (d, J = 8.8 Hz, 1H), 6.76 (dd, J = 2.7, 8.6 Hz, 1H), 6.62 (d, J = 2.7 Hz, 1H), 4.08 (ddd, J = 6.1, 6.1, 12,2 Hz, 1H), 3.74 (s, 3H), 1.21 (d, J = 6.1 Hz, 3H), 1.01 (d, J = 6.1 Hz, 3H).

(3-Bromo-4-trifluoromethoxyphenyl)carbamic Acid *tert*-Butyl Ester. A solution of 3-bromo-4-(trifluoromethoxy)aniline (3.84 g, 15 mmol) in dioxane (15 mL) was treated with di-*tert*-butyl dicarbonate (4.91 g, 22.5 mmol), and the reaction mixture was heated to 80 °C overnight. The solvent was removed under reduced pressure to give an oily residue that was triturated with hexanes. The resulting solid was collected by filtration to give (3-bromo-4-trifluoromethoxyphenyl)carbamic acid *tert*-butyl ester as a white solid (3.26 g, 9.2 mmol, 61.0% yield). ^1H NMR (400 MHz, DMSO-d_6) δ: 9.78 (bs, 1H), 7.87 (s, 1H), 7.54−7.43 (m, 2H),1.51 (s, 9H).

[3-(2-Methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic Acid *tert*-Butyl Ester. A 25-mL round-bottom flask was charged with (3-bromo-4-trifluoromethoxyphenyl)carbamic acid *tert*-butyl ester (230.0 mg, 0.65 mmol), 1-methylpyrazole-5-boronic acid (392.9 mg, 1.93 mmol), sodium carbonate (137.8 mg, 1.3 mmol), dimethoxyethane (5 mL), and water (0.5 mL) under argon atmosphere. $Pd(PPh_3)_4$ (75.1 mg, 0.065 mmol) was added and the reaction mixture again purged with argon. The mixture was heated to 80 °C overnight, then cooled to room temperature. Ethyl acetate (10 mL) was added and the mixture washed with brine and water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give a residue that was subjected to purification by flash chromatography (SiO_2, eluent hexanes/ethyl acetate) to afford [3-(2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic acid *tert*-butyl ester as an off-white solid (84 mg, 0.24 mmol, 37% yield). LCMS *m*/*z* (%) = 358 (M + H, 100). ^1H NMR (400 MHz, DMSO-d_6) δ: 9.83 (bs, 1H), 7.77 (d, J = 8.95 Hz, 1H), 7.69 (s, 1H), 7.63 (s, 1H), 7.57 (d, J = 8.84 Hz, 1H), 6.45 (s, 1H), 3.78 (s, 3H), 1.60 (s, 9H).

[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic Acid *tert*-Butyl Ester. To a solution of [3-(2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic acid *tert*-butyl ester (65 mg, 0.18 mmol) in DMF (1.5 mL) at 0 °C, *N*-bromosuccinimide (35.6 mg, 0.2 mmol) was added, and then the reaction mixture was stirred at room temperature overnight. The resulting mixture was diluted with ethyl acetate and washed with brine and water. The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give a yellow oily residue that was subjected to purification by flash chromatography (SiO_2, hexanes/ethyl acetate gradient elution) to afford [3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic acid *tert*-butyl ester as a white solid (70 mg, 0.16 mmol, 89% yield). LCMS *m*/*z* (%) = 436 (M + H ^{79}Br, 100), 438 (M + H ^{81}Br, 98). ^1H NMR (400 MHz, CD_3OD) δ: 7.79 (d, J = 8.90 Hz, 1H), 7.61 (s, 1H), 7.55 (s, 1H), 7.43 (d, J = 8.94 Hz, 1H), 3.73 (s, 3H), 1.55 (s, 9H).

***N*-[4-Hydroxy-3-(2-methyl-2*H*-pyrazol-3-yl)phenyl]acetamide.** A solution of *N*-[4-methoxy-3-(2-methyl-2*H*-pyrazol-3-yl)phenyl]acetamide (2.0 g, 8.65 mmol) in anhydrous 1,2-dichloroethane (60 mL) was cooled to 0 °C in an ice bath and stirred for 10 min. Anhydrous aluminum chloride (4.35 g, 32.6 mmol) was added and the reaction mixture stirred at 0 °C for 20 min, then stirred at 80 °C for 1 h. Ethyl acetate was added, and the organic was washed with 10% aqueous potassium sodium tartrate (2 × 50 mL). The organic layer was separated, dried over anhydrous sodium sulfate, filtered, and concentrated to give a crude product that was purified via preparative HPLC. The fractions containing product were collected and lyophilized to afford *N*-[4-hydroxy-3-(2-methyl-2*H*-pyrazol-3-yl)phenyl]-acetamide (1.5 g, 6.1 mmol, 70% yield) as a white solid. LCMS *m*/*z* (%) = 232 (M + H, 100). ^1H NMR (400 MHz, DMSO-d_6) δ: 7.39 (s,1H), 6.86 (d, J = 8.74 Hz, 1H), 6.62 (d, J = 8.70 Hz, 1H), 6.47 (s, 1H), 6.15 (s, 1H), 4.80 (bs, 2H), 3.87(t, J = 5.80 Hz, 2H), 3.63 (s, 3H), 2.44 (t, J = 5.80 Hz, 2H), 2.08 (s, 6H).

Preparation of Final Products. 1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chlorophenyl)urea (3). To a stirred solution of 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.260 g, 0.92 mmol) in methylene chloride (5 mL) was added 4-chlorophenyl isocyanate (0.144 g, 0.92 mmol). After the TLC showed the consumption of the starting material, the crude product was purified by preparative thin layer chromatography (TLC) (eluent ethyl acetate/hexane = 1/1) to afford 1-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chlorophenyl)urea, **3** (0.340 g, 0.78 mmol, 84%) as a white solid. LCMS *m*/*z* (%) = 435 (M + $H^{79}Br^{35}Cl$, 77), 437 (M + $H^{81}Br^{35}Cl$, 100), 439 (M + $H^{81}Br^{37}Cl$, 25). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.56 (s, 1H), 7.44 (dd, J = 2.7, 8.9 Hz, 1H), 7.34 (d, J = 9.0 Hz, 1H), 7.29 (d, J = 9.0 Hz, 1H), 7.19 (d, J = 2.7 Hz, 1H), 6.59 (s, 1H), 6.47 (s, 1H), 3.84 (s, 3H), 3.74 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3-chlorophenyl)urea (14). To a stirred solution of 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.015 g, 0.051 mmol) in methylene chloride (1 mL) was added 3-chlorophenyl isocyanate (7 μL, 0.054 mol). After TLC showed the consumption of the starting material, the crude material was purified by preparative thin layer chromatography (TLC) (eluent ethyl acetate/hexane = 1/1) to afford (**14**) (0.020 g, 0.047 mmol, 92%) as a colorless solid film. LCMS *m*/*z* (%) = 435 (M + $H^{79}Br$, 68), 437 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.29 (s, 1H), 8.19 (s, 1H), 7.80 (t, J = 1.9 Hz, 1H), 7.29 (dd, J = 2.7, 9.0 Hz, 1H), 7.49 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.34 (d, J = 8.4 Hz, 1H), 7.26 (t, J = 8.0 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 7.00 (d, J = 7.8 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-fluorophenyl)urea (15). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (2.965 g, 10.5 mmol) was treated with 4-fluorophenyl isocyanate (1.31 mL, 11.6 mmol) in methylene chloride (20 mL) in a similar manner as described for **3** to afford **15** (3.755 g, 8.94 mmol, 85%) as a white solid. LCMS *m*/*z* (%) = 419 (M + $H^{79}Br$, 99), 421 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.49 (broad s, 2H), 7.77 (d, J = 9.0 Hz, 1H), 7.50−7.58 (m, 2H), 7.50 (s, 1H), 7.43 (s, 1H), 7.12 (d, J = 8.9 Hz, 1H), 6.98−7.06 (m, 2H), 3.81 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3-fluorophenyl)urea (16). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.033 g, 0.12 mmol) was treated with 3-fluorophenyl isocyanate (0.017 g, 14.3 μL, 0.12 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **16** (0.040 g, 0.09 mmol, 82%) as a white solid. LCMS *m*/*z* (%) = 419 (M + $H^{79}Br$, 100), 421 (M + $H^{81}Br$, 91). ^1H NMR (400 MHz, acetone-d_6) δ: 8.31 (s, 1H), 8.17 (s, 1H), 7.69 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.59 (dt, *J* = 2.2, 12.0 Hz, 1H), 7.50 (s, 1H), 7.43 (d, *J* = 2.6 Hz, 1H), 7.27 (dd, *J* = 8.1, 15.0 Hz, 1H), 7.11−7.19 (m, 2H), 6.73 (ddd, *J* = 2.4, 8.4 Hz, 1H), 3.82 (s, 1H), 3.69 (s, 1H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2-fluorophenyl)urea (17). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.034 g, 0.12 mmol) was treated with 2-fluorophenyl isocyanate (0.018 g, 14.4 μL, 0.12 mmol, 1.05 equiv) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **17** (0.045 g, 0.11 mmol, 91%) as a solid film. LCMS *m*/*z* (%) = 419 (M + $H^{79}Br$, 99), 421 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, $CDCl_3$) δ: 8.08 (t, *J* = 8.1 Hz, 1H), 7.59 (s, 1H), 7.54 (s, 1H), 7.53−7.59 (m, 1H), 7.40 (s, 1H), 7.12 (d, *J* = 1.5 Hz, 1H), 6.95−7.12 (m, 3H), 6.94 (d, *J* = 5.7 Hz, 1H), 3.77 (s, 3H), 3.70 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-bromophenyl)urea (18). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.032 g, 0.11 mmol) was treated with 4-bromophenyl isocyanate (0.022 g, 0.11 mmol, 1.0 equiv) in methylene chloride (2 mL) in a similar manner as described for **3** to afford **18** (0.040 g, 0.08 mmol, 75%) as a white solid. LCMS *m*/*z* (%) = 479 (M + $H^{79}Br^{79}Br$, 51), 481 (M + $H^{79}Br^{81}Br$, 100), 483 (M + $H^{81}Br^{81}Br$, 50). ^1H NMR (400 MHz, acetone-d_6) δ: 8.22 (s, 1H), 8.14 (s, 1H), 7.68 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.48−7.54 (m, 3H), 7.39−7.46 (m, 3H), 7.14 (d, *J* = 9.0 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3-trifluoromethylphenyl)urea (19). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.035 g, 0.12 mmol) was treated with α,α,α-trifluoro-*m*-tolyl isocyanate (0.025 g, 18.0 μL, 0.13 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **19** (0.038 g, 0.080 mmol, 65%) as a white solid. LCMS *m*/*z* (%) = 469 (M + $H^{79}Br$, 91), 471 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.42 (s, 1H), 8.23 (s, 1H), 8.07 (s, 1H), 7.64−7.73 (m, 2H), 7.45−7.53 (m, 2H), 7.44 (s, 1H), 7.30 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 8.9 Hz, 1H), 3.82 (s, 3H), 3.69 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-trifluoromethylphenyl)urea (20). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.035 g, 0.12 mmol) was treated with α,α,α-trifluoro-*p*-tolyl isocyanate (0.024 g, 19.0 μL, 0.13 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **20** (0.048 g, 0.102 mmol, 83%) as a white solid. LCMS *m*/*z* (%) = 469 (M + $H^{79}Br$, 92), 471 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.51 (s, 1H), 8.27 (s, 1H), 7.76 (d, *J* = 8.3 Hz, 2H), 7.71 (dd, *J* = 2.3, 9.0 Hz, 1H), 7.62 (d, *J* = 8.4 Hz, 2H), 7.52 (s, 1H), 7.46 (d, *J* = 2.3 Hz, 1H), 7.16 (d, *J* = 8.9 Hz, 1H), 3.84 (s, 3H), 3.70 (s, 3H).

1-(3-Acetylphenyl)-3-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]urea (21). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.031 g, 0.11 mmol) was treated with 3-acetylphenyl isocyanate (0.019 g, 15.8 μL, 0.11 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **21** (0.038 g, 0.09 mmol, 79%) as a white solid. LCMS *m*/*z* (%) = 443 (M + $H^{79}Br$, 99), 445 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.30 (s, 1H), 8.19 (s, 1H), 8.13 (t, *J* = 1.8 Hz, 1H), 7.80 (dd, *J* = 1.4, 8.1 Hz, 1H), 7.70 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.62 (d, *J* = 7.7 Hz, 1H), 7.49 (s, 1H), 7.44 (d, *J* = 2.7 Hz, 1H), 7.41 (t, *J* = 7.9 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-methoxyphenyl)urea (22). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.031 g, 0.11 mmol) was treated with 4-methoxyphenyl isocyanate (0.016 g, 14.2 μL, 0.11 mmol, 1.0 equiv) in methylene chloride (2 mL) in a similar manner as described for **3** to afford **22** (0.037 g, 0.086 mmol, 78%) as a white solid. LCMS *m*/*z* (%) = 431 (M + $H^{79}Br$, 89), 433 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.02 (s, 1H), 7.89 (s, 1H), 7.67 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.42 (d, *J* = 9.0 Hz, 2H), 7.12 (d, *J* = 9.0 Hz, 1H), 6.85 (d, *J* = 9.0 Hz, 2H), 3.81 (s, 3H), 3.75 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-dimethylaminophenyl)urea (23). To 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (34.9 mg, 0.124 mmol) in methylene chloride (3 mL) was added 4-(dimethylamino)-phenyl isocyanate (21 mg, 0.129 mmol), and the mixture was stirred for 2 days. The resulting material was purified by HPLC. The product was dried in vacuum to afford **23** as a waxy solid (13.5 mg, 25%). LCMS *m*/*z* (%) = 444 (M + $H^{79}Br$, 100), 446 (M + $H^{81}Br$, 95). ^1H NMR (400 MHz, DMSO-d_6) δ: 8.51 (bs, 1H), 8.26 (bs, 1H), 7.61 (s, 1H), 7.53 (dd, *J* = 8.97, 2.71 Hz, 1H), 7.34 (d, *J* = 2.70 Hz, 1H), 7.24 (d, *J* = 9.03 Hz, 2H), 7.12 (d, *J* = 9.05 Hz, 1H), 6.68 (d, *J* = 9.07 Hz, 2H), 3.75 (s, 3H), 3.63 (s, 3H), 2.82 (s, 6H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-isopropylphenyl)urea (24). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.035 g, 0.12 mmol) was treated with 4-isopropylphenyl isocyanate (0.022 g, 21.0 μL, 0.13 mmol, 1.05 equiv) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **24** (0.028 g, 0.06 mmol, 50%) as a solid film. LCMS *m*/*z* (%) = 443 (M + $H^{79}Br$, 100), 445 (M + $H^{81}Br$, 99). ^1H NMR (400 MHz, acetone-d_6) δ: 8.08 (s, 1H), 8.00 (s, 1H), 7.68 (dd, *J* = 2.6, 8.9 Hz, 1H), 7.49 (s, 1H), 7.40−7.46 (m, 3H), 7.09−7.17 (m, 3H), 3.81 (s, 3H), 3.68 (s, 3H), 2.78−2.92 (m, 1H), 1.21 (s, 3H), 1.20 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3-cyanophenyl)urea (25). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.037 g, 0.13 mmol) was treated with 3-cyanophenyl isocyanate (0.020 g, 0.14 mol, 1.05 equiv) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **25** (0.032 g, 0.08 mmol, 58%) as a white powder. LCMS *m*/*z* (%) = 426 (M + $H^{79}Br$, 99), 428 (M + $H^{81}Br$, 100). ^1H NMR (400 MHz, acetone-d_6) δ: 8.45 (s, 1H), 8.26 (d, *J* = 9.6 Hz, 1H), 8.05 (t, *J* = 1.7 Hz, 1H), 7.74 (dd, *J* = 1.5, 8.2 Hz, 1H), 7.70 (dd, *J* = 2.7, 9.0 Hz, 1H), 7.50 (s, 1H), 7.48 (t, *J* = 8.1 Hz, 1H), 7.43 (d, *J* = 2.7 Hz, 1H), 7.36 (d, *J* = 7.6 Hz, 1H), 7.15 (d, *J* = 9.0 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H).

1-[3-(4-Bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chlorophenyl)urea (26). To a solution of 3-(4-bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.08 g, 0.258 mmol) in methylene chloride was added 4-chlorophenyl isocyanate (0.041 g, 0.263 mmol), and the mixture was stirred overnight. The resulting precipitate was filtered and washed with methylene chloride/hexane (1:1) and dried in vacuum to provide **26** as a colorless solid (0.052 g, 42%). LCMS *m*/*z* (%) = 463 (M + H + ^{79}Br, ^{35}Cl, 41), 465 M + H + (^{81}Br ^{35}Cl 88), 467 H+ (^{81}Br ^{37}Cl, 21). ^1H NMR (400 MHz, acetone-d_6) δ: 8.30 (bs, 1H), 8.24 (bs, 1H), 7.69 (d, *J* = 2.7 Hz, 1H), 7.58 (d, *J* = 1.9 Hz, 2H), 7.74 (d, *J* = 2.7, 1H), 7.29 (d, *J* = 1.9 Hz, 2H), 7.28 (d, *J* = 1.6 Hz, 1H), 7.135 (d, *J* = 9.0 Hz, 1H), 4.26 (m, 1H), 3.81 (s, 3H), 1.45 (d, *J* = 6.6 Hz, 3H), 1.29 (d, *J* = 6.6 Hz, 3H).

1-[3-(4-Bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-fluorophenyl)urea (27). To a solution of 3-(4-bromo-2-isopropyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.08 g, 0.258 mmol) in methylene chloride was added 4-fluorophenyl isocyanate (0.036 g, 0.263 mmol), and the mixture was stirred overnight. The resulting precipitate was filtered and washed with methylene chloride/hexane (1:1) and dried in vacuum to provide **27** as a colorless solid (0.037 g, 32%). LCMS *m*/*z* (%) = 447 M + H^+ (^{79}Br, 100), 449 M + H^+ (^{81}Br, 95). ^1H NMR (400 MHz, $CDCl_3$) δ: 7.5 (s, 1H), 7.35 (d, 2.0 Hz, 2H), 7.33 (9bs, 1H), 7.15 (d, *J* = 4.8 Hz, 1H), 7.12 (t, 1H), 7.00 (d, *J* = 1.9 Hz, 2H), 6.879 (d, *J* = 5.4 Hz, 1H), 6.85 (d, *J* = 4.7 Hz, 1H), 4.05

(m, 1H), 3.65 (s, 3H), 1.33 (d, J = 6.6 Hz, 3H), 1.16 (d, J = 6.6 Hz, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-hydroxyphenyl]-3-(4-chlorophenyl)urea (28). To **3** (1.170 g, 2.68 mmol) in methylene chloride was added anhydrous aluminum chloride (1.432 g, 10.74 mmol) slowly at 0 °C. The mixture was stirred under reflux overnight and then quenched with saturated sodium carbonate. The mixture was then extracted with ethyl acetate, and the combined organic phase was washed with water, 10% potassium sodium tartrate and brine, dried over $MgSO_4$, filtered and the solvent evaporated. The crude solid was first purified with flash chromatography (SiO_2, eluent ethyl acetate/hexane = 1/3 to 1/1), and the fractions containing **28** were then purified by HPLC. The pure fractions were neutralized with saturated sodium bicarbonate, extracted with ethyl acetate, dried with $MgSO_4$, filtered and the solvent was removed in vacuo to provide **28** as a white solid. LCMS m/z (%) = 421 (M + $H^{79}Br^{35}Cl$, 69), 423 (M + $H^{81}Br^{35}Cl$, 100), 425 (M + $H^{81}Br^{37}Cl$, 21). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.47 (s, 1H), 8.16 (s, 1H), 8.04 (s, 1H), 7.44 (d, J = 8.9 Hz, 2H), 7.38−7.43 (m, 1H), 7.35 (s, 1H), 7.26 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 8.9 Hz, 2H), 6.87 (d, J = 8.8 Hz, 1H), 3.62 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]-3-(4-chlorophenyl)urea (29). To a solution of [3-(2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenyl]carbamic acid *tert*-butyl ester (21.8 mg, 0.05 mmol) in methylene chloride (0.5 mL), trifluoroacetic acid (0.5 mL) was added. The reaction mixture stirred at room temperature for 20 min. The solvent was removed under reduced pressure to afford 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-trifluoromethoxyphenylamine trifluoroacetate as a colorless oil. LCMS m/z (%) = 336 (M + $H^{79}Br$, 100), 338 (M + $H^{81}Br$, 95). This intermediate was dissolved in methylene chloride (0.8 mL) and then treated with *N*,*N*-diisopropylethylamine until pH 7−8 was obtained. 4-Chlorophenyl isocyanate (8.5 mg, 0.055 mmol) was added and reaction mixture stirred at room temperature overnight and concentrated to give a residue that was subjected to a purification by flash chromatography (SiO_2, hexanes/ethyl acetate) to afford **29** as a white solid in 62.0% yield. LCMS m/z (%) = 489 (M + $H^{79}Br^{35}Cl$, 93), 491 (M + $H^{81}Br^{35}Cl$, 100), 493 (M + $H^{81}Br^{37}Cl$, 34). ^{1}H NMR (400 MHz, CD_3OD) δ: 7.71 (dd, J = 9.0 Hz, 2.7 Hz, 1H), 7.64−7.62 (m, 2H), 7.49−7.45 (m, 3H), 7.33−7.30 (m, 2H), 3.76 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-ethoxyphenyl]-3-(4-chlorophenyl)urea (30). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-ethoxyphenylamine (0.040 g, 0.13 mmol) was treated with 4-chlorophenyl isocyanate (0.023 g, 0.15 mmol, 1.1 equiv) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **30** (0.034 g, 0.08 mmol, 56%) as a white solid. LCMS m/z (%) = 449 (M + $H^{79}Br^{35}Cl$, 72), 451 (M + $H^{81}Br^{35}Cl$, 100), 453 (M + $H^{81}Br^{37}Cl$, 26). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.22 (s, 1H), 8.14 (s, 1H), 7.66 (dd, J = 2.7, 9.0 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.49 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.12 (d, J = 9.0 Hz, 1H), 3.98−4.18 (m, 2H), 3.71 (s, 3H), 1.28 (t, J = 7.1 Hz, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-isopropoxyphenyl]-3-(4-chlorophenyl)urea (31). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-isopropoxyphenylamine (0.024 g, 0.08 mmol) was treated with 4-chlorophenyl isocyanate (0.014 g, 0.09 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **31** (0.034 g, 0.07 mmol, 91%) as a white solid. LCMS m/z (%) = 463 (M + $H^{79}Br^{35}Cl$, 82), 465 (M + $H^{81}Br^{35}Cl$, 100), 467 (M + $H^{81}Br^{37}Cl$, 29). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.24 (s, 1H), 8.17 (s, 1H), 7.65 (dd, J = 2.5, 8.9 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.49 (s, 1H), 7.42 (d, J = 2.5 Hz, 1H), 7.28 (d, J = 8.6 Hz, 2H), 4.42−4.52 (m, 1H), 3.70 (s, 3H), 1.26 (d, J = 6.0 Hz, 3H), 1.11 (d, J = 6.0 Hz, 3H).

1-[4-Benzyloxy-3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)phenyl]-3-(4-chlorophenyl)urea (32). 4-Benzyloxy-3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-phenylamine (0.023 g, 0.09 mmol) was treated with 4-chlorophenyl isocyanate (0.016 g, 0.10 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **32** (0.019 g, 0.04 mmol, 42%) as a white solid. LCMS m/z (%) = 511 (M + $H^{79}Br^{35}Cl$, 82), 513 (M + $H^{81}Br^{35}Cl$, 100), 515 (M + $H^{81}Br^{37}Cl$, 33). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.22 (s, 1H), 8.16 (s, 1H), 7.66 (dd, J = 2.4, 8.9 Hz, 1H), 7.55 (d, J = 8.7 Hz, 2H), 7.50 (s, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.28−7.35 (m, 5H), 7.28 (d, J = 8.7 Hz, 2H), 7.22 (d, J = 8.9 Hz, 1H), 5.13 (AB quartet, J = 12.0, 24.3 Hz, 2H), 3.69 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-(4-chlorobenzyloxy)-phenyl]-3-(4-chlorophenyl)urea (33). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-(4-chlorobenzyloxy)phenylamine (0.029 g, 0.08 mmol) was treated with 4-chlorophenyl isocyanate (0.014 g, 0.09 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **33** (0.027 g, 0.05 mmol, 65%) as a white solid. LCMS m/z (%) = 545 (M + $H^{79}Br^{35}Cl^{35}Cl$, 65), 547 (M + $H^{79}Br^{35}Cl^{37}Cl$ $^{81}Br^{35}Cl^{35}Cl$, 100), 549 (M + $H^{81}Br^{35}Cl^{37}Cl^{79}Br^{37}Cl^{37}Cl$, 45), 551 (M + $H^{81}Br^{37}Cl^{37}Cl$, 6). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.23 (s, 1H), 8.17 (s, 1H), 7.66 (dd, J = 2.7, 9.0 Hz, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.50 (s, 1H), 7.46 (d, J = 2.7 Hz, 1H), 7.37 (d, J = 8.7 Hz, 2H), 7.33 (d, J = 8.7 Hz, 2H), 7.28 (d, J = 8.9 Hz, 2H), 7.22 (d, J = 9.0 Hz, 1H), 5.14 (AB quartet, J = 12.3, 24.8 Hz, 2H), 3.69 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-phenethyloxyphenyl]-3-(4-chlorophenyl)urea (34). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-phenethyloxyphenylamine (0.028 g, 0.07 mmol) was treated with 4-chlorophenyl isocyanate (0.014 g, 0.09 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **34** (0.025 g, 0.05 mmol, 66%) as a solid film. LCMS m/z (%) = 525 (M + $H^{79}Br^{35}Cl$, 85), 527 (M + $H^{81}Br^{35}Cl$, 100), 529 (M + $H^{81}Br^{37}Cl$, 31). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.34 (s, 1H), 8.26 (s, 1H), 7.65 (dd, J = 2.7, 8.9 Hz, 1H), 7.56 (d, J = 8.9 Hz, 2H), 7.53 (s, 1H), 7.43 (d, J = 2.7 Hz, 1H), 7.16−7.31 (m, 5 H), 7.09−7.16 (m, 3H), 4.11−4.30 (m, 2H), 3.51 (s, 3H), 2.86−3.06 (m, 2H).

1-[3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chlorophenyl)urea (35). 3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine was treated with 4-chlorophenyl isocyanate in methylene chloride in a similar manner as described for **3**, providing 12 mg (30%) of **35**. LCMS m/z (%) = 393 (M + $H^{37}Cl$, 60), 391 (M + $H^{35}Cl$, 100). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.80 (s, 1H), 8.71 (s, 1H), 7.62 (s, 1H), 7.57 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.49 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 2H), 7.39 (d, J = 4 Hz, 1H), 7.33 (dd, J_1 = 8 Hz, J_2 = 2 Hz, 2H), 7.17 (d, J = 8 Hz, 1H), 3.77 (s, 3H), 3.62 (s, 3H).

1-(4-Chlorophenyl)-3-[4-methoxy-3-(2-methyl-2*H*-pyrazol-3-yl)-phenyl]urea. (36). 4-Methoxy-3-(2-methyl-2*H*-pyrazol-3-yl)phenylamine (0.291 g, 1.43 mmol) was treated with 4-chlorophenyl isocyanate (0.247 g, 1.57 mmol) in methylene chloride (5 mL) in a similar manner as described for **3**, providing **36** (0.415 g, 1.16 mmol, 81%) as a white solid. LCMS m/z (%) = 357 (M + H). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.21 (s, 1H), 8.07 (s, 1H), 7.58 (dd, J = 2.8, 8.9 Hz, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.44 (d, J = 2.7 Hz, 1H), 7.39 (d, J = 1.8 Hz, 1H), 7.28 (d, J = 8.8 Hz, 2H), 7.08 (d, J = 8.9 Hz, 1H), 6.20 (d, J = 1.8 Hz, 1H), 3.81 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-dichlorophenyl)urea (37). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.031 g, 0.11 mmol) was treated with 2,4-dichlorophenyl isocyanate (0.021 g, 0.11 mmol) in methylene chloride (2 mL) in a similar manner as described for **3** to afford **37** (0.036 g, 0.076 mmol, 69%) as a white solid. LCMS m/z (%) = 469 (M + $H^{79}Br^{35}Cl^{35}Cl$, 60), 471 (M + $H^{79}Br^{35}Cl^{37}$-Cl and $^{81}Br^{35}Cl^{35}Cl$, 100), 473 (M + $H^{81}Br^{35}Cl^{37}Cl^{79}Br^{37}Cl^{37}Cl$, 54), 475 (M + $H^{81}Br^{37}Cl^{37}Cl$, 4). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.81 (s, 1H), 8.36 (d, J = 9.0 Hz, 1H), 7.91 (s, 1H), 7.69 (dd, J = 2.7, 9.0 Hz, 1H), 7.50 (s, 1H), 7.48 (d, J = 2.4 Hz, 1H), 7.45 (d, J = 2.7 Hz, 1H), 7.34 (dd, J = 2.4, 9.0 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H), 3.69 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3,5-difluorophenyl)urea (38). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.032 g, 0.11 mmol) was

treated with 3,5-difluorophenyl isocyanate (14 μL, 0.11 mmol) in methylene chloride (2 mL) in a similar manner as described for **3** to afford **37** (0.038 g, 0.09 mmol, 77%) as a white solid. LCMS m/z (%) = 437 ($M + H^{79}Br$, 100), 439 ($M + H^{81}Br$, 100). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.47 (s, 1H), 8.23 (s, 1H), 7.68 (dd, J = 2.7, 9.0 Hz, 1H), 7.50 (s, 1H), 7.42 (d, J = 2.7 Hz, 1H), 7.18−7.27 (m, 2H), 7.15 (d, J = 9.0 Hz, 1H), 6.59 (ttt, J = 2.3, 9.1, 9.1 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (39). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.027 g, 0.095 mmol) was treated with 2,4-difluorophenyl isocyanate (11.5 μL, 0.095 mmol) in methylene chloride (2 mL) in a similar manner as described for **3** to afford **39** (0.030 g, 0.069 mmol, 71%) as a white solid. LCMS m/z (%) = 437 ($M + H^{79}Br$, 100), 439 ($M + H^{81}Br$, 91). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.45 (s, 1H), 8.23 (dt, J = 6.1, 9.2 Hz, 1H), 7.93 (s, 1H), 7.68 (dd, J = 2.6, 9.0 Hz, 1H), 7.49 (s, 1H), 7.44 (d, J = 2.6 Hz, 1H), 7.14 (d, J = 9.0 Hz, 1H), 7.07 (ddd, J = 2.7, 8.7, 11.3 Hz, 1H), 6.93−7.02 (m, 1H), 3.82 (s, 3H), 3.69 (s, 3H).

1-[3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(2,4-difluorophenyl)urea (40). 3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine was treated with 2,4-difluorophenyl isocyanate in methylene chloride (2 mL) in a similar manner as described for **3**, providing 26.7 mg (36%) of **40** as a white solid. LCMS m/z (%) = 393 ($M + H^{35}Cl$, 100), 395 ($M + H^{37}Cl$, 35). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.00 (s, 1H), 8.43 (s, 1H), 8.03 (m, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 7.56 (s, 1H), 7.50 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.34 (d, J = 4 Hz, 1H), 7.28 (m, J_1 = 12 Hz, J_2 = 4 Hz, 1H), 7.12 (d, J = 8 Hz, 1H), 7.01 (m, J_1 = 8 Hz, J_2 = 2 Hz, 1H), 3.72 (s, 3H), 3.56 (s, 3H).

1-[3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(3,4-difluorophenyl)urea (41). 3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (30 mg, 0.13 mmol) was treated with 3,4-difluorophenyl isocyanate (17 μL, 0.14 mmol) in methylene chloride (2 mL) in a similar manner as described for **3**, providing 18.6 mg (34%) of **41** as a white solid. LCMS m/z (%) = 393 ($M + H^{35}Cl$, 100), 395 ($M + H^{37}Cl$, 38). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.18 (s, 1H), 8.05 (s, 1H), 7.65 (m, 1H), 7.57 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.36 (s, 1H), 7.33 (d, J = 2 Hz, 1H), 7.09 (d, J = 4 Hz, 1H), 7.06 (d, J = 2 Hz, 1H), 7.04 (d, J = 8 Hz, 1H), 3.72 (s, 3H), 3.55 (s, 3H).

1-(3,4-Difluorophenyl)-3-[3-(4-fluoro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]urea (42). 3-(4-Fluoro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine was treated with 3,4-difluorophenyl isocyanate in methylene chloride (2 mL) in a similar manner as described for **3**, providing 27 mg (63% yield) of **42** as a white solid. LCMS m/z (%) = 377 ($M + H$, 100). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.28 (s, 1H), 8.12 (s, 1H), 7.74 (ddd, J_1 = 13.5 Hz, J_2 = 7.3 Hz, J_3 = 2.5 Hz, 1H), 7.63 (ddd, J_1 = 8.8 Hz, J_2 = 2.8 Hz, 1H), 7.47 (d, J = 2.8 Hz, 1H), 7.38 (d, $J_{H,F}$ = 4.4 Hz, 1H), 7.16 (m, 3H), 3.84 (s, 3H), 3.65 (s, 3H). ^{19}F NMR (376 MHz, acetone-d_6) δ: −138.89 (m, 1F), −148.38 (m, 1F), −177.40 (d, $J_{H,F}$ = 5.3 Hz, 1F).

1-(3,5-Bis-trifluoromethylphenyl)-3-[3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]urea (43). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.037 g, 0.13 mmol) was treated with 3,5-bis(trifluoromethyl)phenyl isocyanate (24.0 μL, 0.14 mmol) in methylene chloride (1 mL) in a similar manner as described for **3** to afford **43** (0.030 g, 0.06 mmol, 43%) as a white solid. LCMS m/z (%) = 537 ($M + H^{79}Br$, 99), 539 ($M + H^{81}Br$, 100). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.77 (s, 1H), 8.42 (s, 1H), 8.22 (s, 2H), 7.73 (dd, J = 2.5, 9.0 Hz, 1H), 7.51 (s, 1H), 7.46 (d, J = 2.5 Hz, 1H), 7.18 (d, J = 9.0 Hz, 1H), 3.85 (s, 3H), 3.71 (s, 3H).

1-(3,5-Bis-trifluoromethylphenyl)-3-[3-(4-chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]urea (44). 3-(4-Chloro-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine was treated with 3,5-bis(trifluoromethyl)phenyl isocyanate in methylene chloride (2 mL) in a similar manner as described for **3**, providing 21.5 mg (32%) of **44** as a white solid. LCMS m/z (%) = 493 ($M + H^{35}Cl$, 100), 495 ($M + H^{37}Cl$, 41). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.58 (s, 1H), 9.18 (s, 1H), 8.31 (s, 2H), 7.80 (s, 1H), 7.79 (s, 1H), 7.79 (dd, J_1 = 8 Hz, J_2 = 4 Hz, 1H), 7.59 (d, J = 2 Hz, 1H), 7.36 (d, = 8 Hz, 1H), 3.96 (s, 3H), 3.80 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chloro-2-trifluoromethylphenyl)urea (45). To a stirred solution of 3-(4-bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.034 g, 0.12 mol) in methylene chloride (1 mL) was added 4-chloro-2-(trifluoromethyl)phenyl isocyanate (20.0 μL, 0.13 mmol) at room temperature. White precipitated solid was filtered and washed with cold methylene chloride to afford (**45**) (0.037 g, 0.074 mmol, 60%) as a white solid. LCMS m/z (%) = 503 ($M + H^{79}Br$, 77), 505 ($M + H^{81}Br$, 100). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.82 (s, 1H), 8.22 (d, J = 9.6 Hz, 1H), 7.62−7.72 (m, 4H), 7.49 (s, 1H), 7.43 (d, J = 2.6 Hz, 1H), 7.15 (d, J = 9.0 Hz, 1H), 3.83 (s, 3H), 3.68 (s, 3H).

1-[3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenyl]-3-(4-chloro-3-trifluoromethylphenyl)urea (46). 3-(4-Bromo-2-methyl-2*H*-pyrazol-3-yl)-4-methoxyphenylamine (0.035 g, 0.12 mmol) was treated with 4-chloro-3-(trifluoromethyl)phenyl isocyanate (0.027 g, 0.12 mmol) in methylene chloride (2 mL) in a similar manner as described for **3** to afford (**46**) (0.051 g, 0.10 mmol, 81%) as a white solid. LCMS m/z (%) = 503 ($M + H^{79}Br^{35}Cl$, 78), 505 ($M + H^{81}Br^{35}Cl$, 100), 507 ($M + H^{81}Br^{37}Cl$, 28). ^{1}H NMR (400 MHz, acetone-d_6) δ: 8.52 (s, 1H), 8.27 (s, 1H), 8.13 (s, 1H), 7.74 (d, J = 8.7 Hz, 1H), 7.68 (d, J = 9.0 Hz, 1H), 7.53 (d, J = 8.7 Hz, 1H), 7.49 (s, 1H), 7.43 (s, 1H), 7.14 (d, J = 9.0 Hz, 1H), 3.82 (s, 3H), 3.68 (s, 3H).

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