# Novel Diarylurea Based Allosteric Modulators of the Cannabinoid CB1 Receptor: Evaluation of Importance of 6-Pyrrolidinylpyridinyl Substitution

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S *Supporting Information*
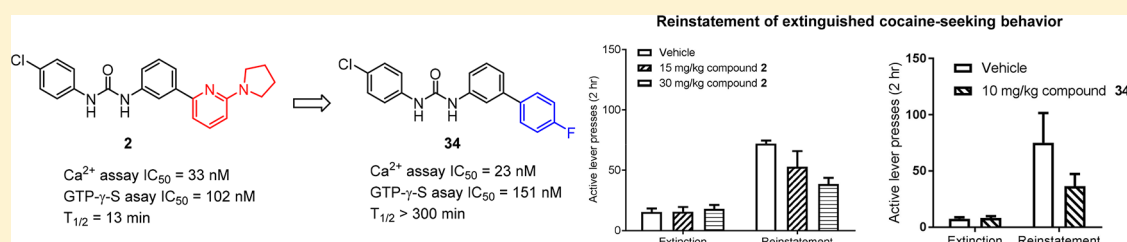
ABSTRACT: Allosteric modulators of the cannabinoid CB1 receptor have recently been reported as an alternative approach to modulate the CB1 receptor for therapeutic benefits. In this study, we report the design and synthesis of a series of diarylureas derived from PSNCBAM-1 (**2**). Similar to **2**, these diarylureas dose-dependently inhibited CP55,940-induced intracellular calcium mobilization and [^{35}S]GTP-γ-S binding while enhancing [^{3}H]CP55,940 binding to the CB1 receptor. Structure–activity relationship studies revealed that the pyridinyl ring of **2** could be replaced by other aromatic rings and the pyrrolidinyl ring is not required for CB1 allosteric modulation. **34** (RTICBM-74) had similar potencies as **2** in all in vitro assays but showed significantly improved metabolic stability to rat liver microsomes. More importantly, **34** was more effective than **2** in attenuating the reinstatement of extinguished cocaine-seeking behavior in rats, demonstrating the potential of this diarylurea series as promising candidates for the development of relapse treatment of cocaine addiction.

INTRODUCTION

The cannabinoid CB1 and CB2 receptors are components of the endocannabinoid system which is involved in many important physiological processes such as appetite control, cardiovascular regulation, learning and memory, pain regulation, and drug dependence.[1−3] Expressed abundantly in the central nervous system (CNS), the CB1 receptor has been demonstrated to be a viable target in a number of disorders including obesity, drug addiction, pain, inflammation, gastrointestinal diseases, multiple sclerosis, psychosis, schizophrenia, and osteoporosis.[1,4] The CB2 receptor is found mainly in immune cells and is responsible for modulation of cytokine release and immune cell migration. A wide range of selective and nonselective agonists and antagonists for CB1 and CB2 receptors have been developed to date. Currently, licensed cannabinoid medications all contain tetrahydrocannabinol (Δ^9-THC), the principal psychoactive constituent of the plant cannabis, or its synthetic analogue (nabilone); however, they are prescribed with many restrictions because of the adverse effects such as marijuana-like psychoactivity and addictive tendency. The CB1 selective antagonist/inverse agonist Rimonabant (SR141716A) was first approved for treatment of obesity but was subsequently withdrawn due to a risk of suicidal ideation.

An alternate approach to target the CB1-mediated signaling pathways is to develop allosteric modulators that bind to distinct binding sites from the orthosteric site. Compared to orthosteric ligands, allosteric modulators offer potential benefits such as better spatial and temporal selectivity due to their dependence on the presence of an orthosteric agonist for signaling, better subtype selectivity due to less conserved allosteric binding sites, and improved safety profiles due to the "ceiling" effect, i.e., their effect is saturable because of their dependence on endogenous ligands for signaling. Recently, several allosteric modulators have been advanced to the market as therapeutics, including cinacalcet, a positive allosteric modulator (PAM) of the calcium sensing receptor (CasR, a member of the GPCR C family),[5] and maraviroc, a negative allosteric modulator (NAM) of the CCR5 receptor,[6] demonstrating that allosteric modulation can be a safe and therapeutically relevant approach to targeting GPCRs.
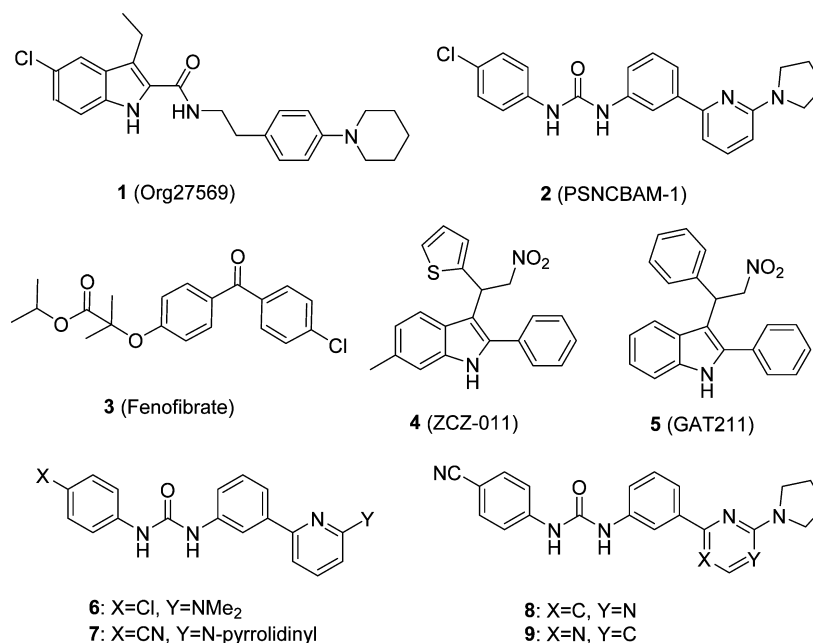
Figure 1. Structures of representative small molecule CB1 allosteric modulators.

Since discovery of the first CB1 modulator Org27569 (**1**) in 2005,[7] several NAMs and PAMs have been reported.[8] These include CB1 receptor NAMs such as PSNCBAM-1 (**2**),[9] fenofibrate (**3**),[10] and CB1 receptor PAMs ZCZ011 (**4**),[11] and GAT211 (**5**)[12] (Figure 1). Compounds **1** and **2** are two small molecule CB1 NAMs that have been the most extensively characterized. Both were reported to enhance radioligand binding levels but decrease responses stimulated by orthosteric agonists in assays such as intracellular calcium mobilization, [^{35}S]GTP-γ-S binding, cAMP accumulation, and β-arrestin recruitment.[8] Unlike **1**, which displays agonist activities in some assays such as ERK phosphorylation,[13,14] **2** showed little or no activity in the absence of an orthosteric agonist in many assays investigated thus far.[8]

Compared to the wide range of in vitro studies, the in vivo effects of these CB1 receptor NAMs have not been fully characterized.[8] In animal behavioral studies, **1** had no effects on agonist-induced antinociception and catalepsy, grooming and scratching behaviors, or drug discrimination.[15,16] However, similar to CB1 antagonists/inverse agonists, **1** has been demonstrated to reduce food intake and to attenuate CP55,940-induced hypothermia in rats, albeit not in mice.[15,16] Importantly, **1** also attenuated cue- and drug-induced reinstatement of extinguished cocaine- and methamphetamine-seeking behavior,[17] effects that have been previously observed with CB1 antagonists/inverse agonists, SR141716A and AM251 (**46**).[18−21] On the other hand, reports on the in vivo effects of **2** have been confined to only one study, in which it decreased food intake and body weight.[9] To date, **2** has not been investigated in vivo for the potential use for the treatment of drug addiction or other centrally mediated disorders.

Our group recently reported the first structure−activity relationship (SAR) study of **2** focusing on the 4-chlorophenyl and the alkyl substitution at the 6-aminopyridinyl rings (e.g., **6** and **7**).[22] More recently, a series of analogues of **2** where the pyridinyl group was replaced by a structurally similar pyrimidinyl ring, which also bears an ortho nitrogen atom, were reported (e.g., **8** and **9**).[23] In both series, the pyrrolidinyl group

was either retained or replaced with substituted amino groups, which can be considered ring-opened pyrrolidines. To expand the SAR knowledge and investigate the importance of the 6-pyrrolidinylpyridinyl group for activity as an allosteric modulator, we designed and synthesized a series of analogues where the pyrrolidinyl group of **2** was replaced or completely removed, and/or the pyridinyl ring was replaced with substituted phenyl or other aromatic moieties (Figure 2). The
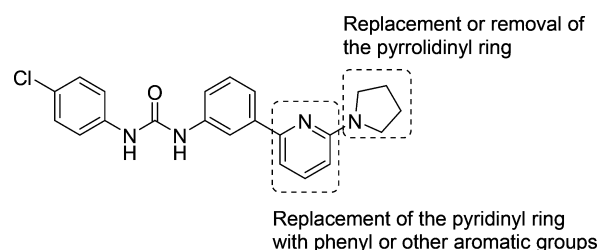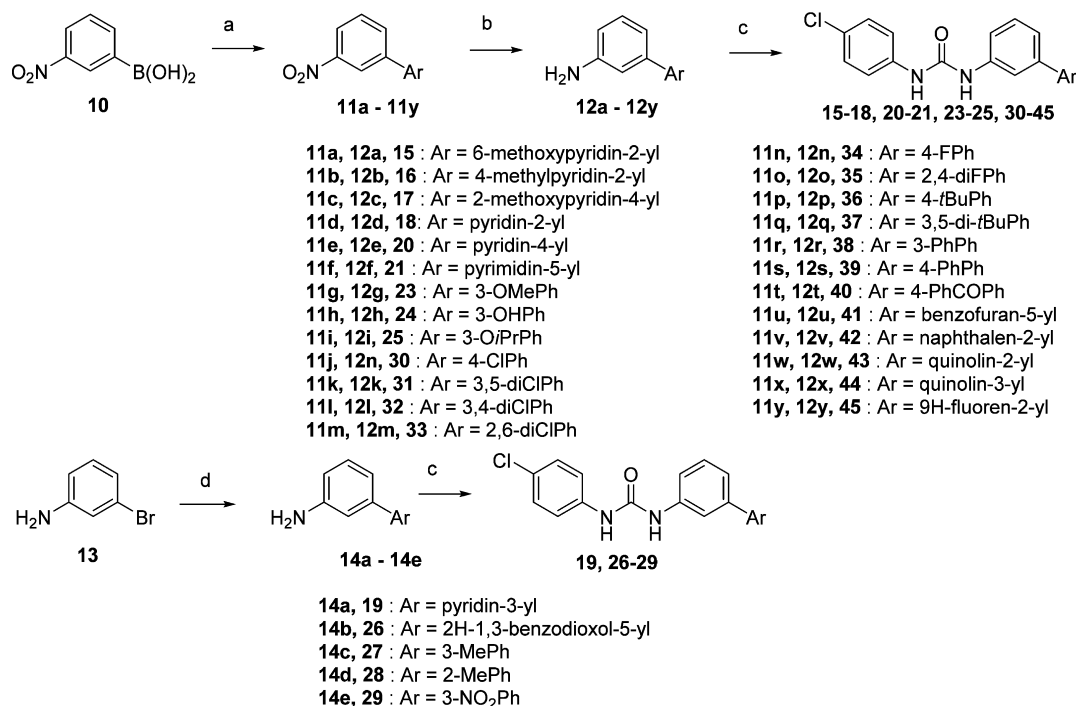

Figure 2. Structural modifications on compound **2** conducted in this study.

synthesized diarylureas were characterized in calcium mobilization and [^{35}S]GTP-γ-S binding assays for their potency as CB1 allosteric modulators. Select compounds were then assessed for metabolic stability in liver microsomes. Finally, we examined the effects of **2** and one of the diarylurea analogues (**34**) in a rat model of drug-induced reinstatement of extinguished cocaine-seeking behavior.

■ RESULTS AND DISCUSSION

Chemistry. Compounds **15**−**45** were synthesized as depicted in Scheme 1 following procedures described by us previously.[22] Briefly, commercially available 3-nitrophenyl boronic acid (**10**) underwent Suzuki coupling with the corresponding aryl bromides under basic conditions catalyzed by Pd(PPh$_3$)$_4$ to afford intermediates **11a−y**. Reduction of the nitro group in **11a−y** by transfer hydrogenation with hydrazine hydrate and Raney nickel in ethanol provided 3-substituted anilines **12a−y** in good yields. Subsequent reaction between

Scheme 1[a]

11a, 12a, 15 : Ar = 6-methoxypyridin-2-yl
11b, 12b, 16 : Ar = 4-methylpyridin-2-yl
11c, 12c, 17 : Ar = 2-methoxypyridin-4-yl
11d, 12d, 18: Ar = pyridin-2-yl
11e, 12e, 20 : Ar = pyridin-4-yl
11f, 12f, 21 : Ar = pyrimidin-5-yl
11g, 12g, 23 : Ar = 3-OMePh
11h, 12h, 24 : Ar = 3-OHPh
11i, 12i, 25 : Ar = 3-OiPrPh
11j, 12n, 30 : Ar = 4-ClPh
11k, 12k, 31 : Ar = 3,5-diClPh
11l, 12l, 32 : Ar = 3,4-diClPh
11m, 12m, 33 : Ar = 2,6-diClPh

11n, 12n, 34 : Ar = 4-FPh
11o, 12o, 35 : Ar = 2,4-diFPh
11p, 12p, 36 : Ar = 4-tBuPh
11q, 12q, 37 : Ar = 3,5-di-tBuPh
11r, 12r, 38 : Ar = 3-PhPh
11s, 12s, 39 : Ar = 4-PhPh
11t, 12t, 40 : Ar = 4-PhCOPh
11u, 12u, 41 : Ar = benzofuran-5-yl
11v, 12v, 42 : Ar = naphthalen-2-yl
11w, 12w, 43 : Ar = quinolin-2-yl
11x, 12x, 44 : Ar = quinolin-3-yl
11y, 12y, 45 : Ar = 9H-fluoren-2-yl

14a, 19 : Ar = pyridin-3-yl
14b, 26 : Ar = 2H-1,3-benzodioxol-5-yl
14c, 27 : Ar = 3-MePh
14d, 28 : Ar = 2-MePh
14e, 29 : Ar = 3-NO$_2$Ph

[a]Reagents and conditions: (a) corresponding aryl bromide, Pd(PPh$_3$)$_4$, DME, aq NaHCO$_3$, reflux, 16 h; (b) hydrazine hydrate, Raney Ni, ethanol, 50 °C, 2 h; (c) 4-chlorophenyl isocyanate, chloroform, 50 °C, 16 h; (d) corresponding aryl boronic acid, Pd(PPh$_3$)$_4$, DME, aq NaHCO$_3$, reflux, 16 h.

these anilines with 4-chlorophenyl isocyanate afforded the final diarylureas. Alternatively, the anilines **14a−e** could be prepared by Suzuki coupling between 3-bromoaniline (**13**) and corresponding aryl boronic acids and were then converted to the final products via reaction with 4-chlorophenyl isocyanate.

Biological Evaluations in Calcium Mobilization Assays. The FLIPR-based calcium mobilization assays were used as the primary screen to assess the potency of the synthesized diarylureas at CB1 and CB2 receptors as described previously.[22,24] In these assays, CHO cells that overexpress the promiscuous Gα_{16} protein (RD-HGA16 cells, Molecular Devices) were engineered to stably express the human CB1 or CB2 receptor. Compounds were evaluated for their ability to inhibit the mobilization of intracellular calcium levels stimulated by CP55,940. Table 1 shows IC$_{50}$ values of the synthesized compounds against the EC$_{80}$ concentration of CP55,940 (100 nM).

In previous studies conducted by our group and others,[22,23] the 6-pyrrolidinyl group on the pyridine ring of **2** was either retained or replaced with substituted amino groups such as dimethylamino (**6**), which can be seen as the ring opened analogues of the pyrrolidinyl ring. To explore the importance of the pyrrolidinyl substituent on the allosteric modulating activity, we first replaced the pyrrolidinyl ring with another hydrogen bond acceptor, a methoxy group. This alteration dampened the activity around 8-fold (**15**, IC$_{50}$ = 231 nM). The corresponding 4-pyridinyl analogue with a methoxy at the same position (**17**, IC$_{50}$ = 133 nM) was slightly more potent than its 2-pyridinyl analogue (**15**) but less potent than **2**. These results suggest that a hydrogen bond acceptor or electron donating group at this position is preferred. However, interestingly, when the pyrrolidinyl group was completely removed, the resulting analogue showed similar potency as **2** (**18**, IC$_{50}$ = 47 nM vs **2**, IC$_{50}$ = 33 nM), implying that the pyrrolidinyl moiety is not

required for the activity. Replacing the 2-pyridinyl ring by its regioisomers, 3- or 4-pyridinyl analogues (**19** and **20**) or a pyrimidinyl ring (**21**) resulted in slightly less potent analogues, all of which lack the pyrrolidinyl group. Activity as an allosteric modulator was significantly diminished with the 3-methyl substitution (**16**, IC$_{50}$ = 1310 nM). Together, these results suggest that the pyrrolidinyl group is not required for CB1 allosteric modulator activity.

Analogues of **2** reported thus far have either a pyridine or pyrimidine group, each of which has a nitrogen atom at the ortho position. We examined the importance of the nitrogen atom and whether the pyridinyl group can be replaced with other aromatic rings. Interestingly, substituting the pyridinyl ring with a phenyl ring led to **22** (IC$_{50}$ = 32 nM), which had nearly identical potency to **2** (IC$_{50}$ = 33 nM), suggesting that the pyridinyl group can be replaced without compromising activity. Thus, substituents of diverse electronic and steric properties were introduced onto the phenyl group to probe the substitution effect. The 3-methoxyphenyl (**23**) had an IC$_{50}$ of 81 nM, which was more potent than the corresponding pyridinyl analogue (**15**, IC$_{50}$ = 231 nM) and only slightly less potent than **22**, confirming the earlier finding that the pyrrolidinyl group was not required for activity. Several electron-donating groups such as methyl, hydroxyl, methoxy, and isopropyloxy were incorporated in the phenyl ring at the 3 position, the same meta position as the pyrrolidinylpyridinyl group on **2**. All of these analogues (**23−27**) had lower potency than **2**. The 1,3-benzodioxol-5-yl analogue (**26**) was slightly weaker. The methyl group at the 2 position (**28**, IC$_{50}$ = 190 nM) had around a 3-fold decrease in potency compared to its 3-position isomer (**27**, IC$_{50}$ = 74 nM).

We next investigated substitutions on the phenyl ring with a series of electron-withdrawing groups. A 3-nitro group (**29**, IC$_{50}$ = 27 nM) showed similar potency as **2** and the phenyl

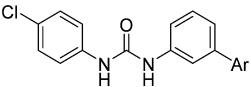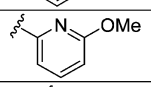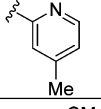**Table 1. Allosteric Modulatory Activities of Diarylureas 2 and 15−45 in the CB1 Calcium Mobilization Assays and [^{35}S]GTP-γ-S Binding Assay**
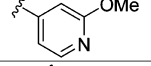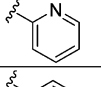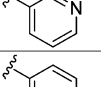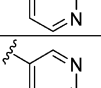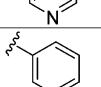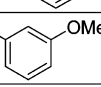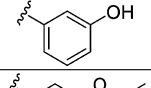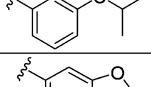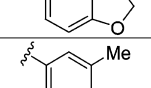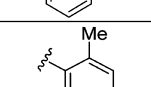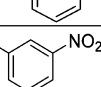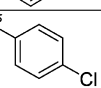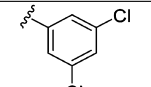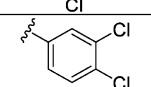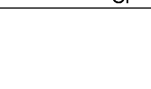
Compound	Ar	Calcium Mobilization Assay			CB1 [^{35}S]GTP-γ-S, IC$_{50}$ (nM)[d]
		CB1		CB2	
		IC$_{50}$ (nM)[a]	Agonist screen[b] (% CP55,940 E$_{max}$)	IC$_{50}$ (nM)[c]	
2		33 ± 8	28 ± 5	> 10,000	89 (71 − 112)
15		231 ± 14	2 ± 0	N.D.	N.D.
16		1,310 ± 80	3 ± 0	N.D.	N.D.
17		133 ± 6	23 ± 3	N.D.	1,320 (871 − 1,990)
18		47 ± 13	9 ± 5	N.D.	2,650 (1,590 − 4,420)
19		244 ± 45	34 ± 16	N.D.	N.D.
20		178 ± 38	15 ± 4	N.D.	405 (295 − 556)
21		290 ± 24	9 ± 0	3,400 ± 700	N.D.
22		32 ± 7	5 ± 2	N.D.	439 (212 − 908)
23		81 ± 10	13 ± 3	N.D.	827 (590 − 1,160)
24		840 ± 130	10 ± 3	N.D.	N.D.
25		141 ± 24	25 ± 9	N.D.	N.D.
26		70 ± 14	10 ± 7	N.D.	619 (497 − 772)
27		74 ± 6	8 ± 4	N.D.	459 (310 − 671)
28		190 ± 45	6 ± 5	> 10,000	N.D.
29		27 ± 2	17 ± 6	> 10,000	452 (321 − 635)
30		95 ± 9	21 ± 6	N.D.	N.D.
31		22 ± 2	16 ± 4	N.D.	299 (151 − 592)
32		30 ± 4	20 ± 3	> 10,000	464 (259 − 830)

Table 1. continued

Compound	Ar	Calcium Mobilization Assay			CB1 [^{35}S]GTP-γ-S, IC$_{50}$ (nM)^d
		CB1		CB2	
		IC$_{50}$ (nM)^a	Agonist screen^b (% CP55,940 E$_{max}$)	IC$_{50}$ (nM)^c	
33		338 ± 19	17 ± 6	N.D.	N.D.
34		23 ± 2	9 ± 2	> 10,000	153 (73 − 318)
35		18 ± 1	9 ± 3	N.D.	353 (236 − 528)
36		591 ± 48	4 ± 2	N.D.	N.D.
37		460 ± 39	10 ± 4	N.D.	N.D.
38		195 ± 40	1 ± 0	N.D.	559 (383 − 817)
39		1,340 ± 370	0	N.D.	> 10,000
40		1,570 ± 60	13 ± 3	N.D.	N.D.
41		134 ± 13	1 ± 1	N.D.	265 (216 − 326)
42		132 ± 28	7 ± 1	N.D.	1,520 (1,120 − 2,070)
43		334 ± 80	5 ± 1	N.D.	1,890 (1,360 − 2,640)
44		516 ± 70	3 ± 2	4,100 ± 1,200	651 (476 − 891)
45		1,260 ± 160	0	N.D.	N.D.

^{a}Against EC$_{80}$ (100 nM) of CP55,940 in stable human CB1-CHO-RD-HGA16 cells. Values are the mean ± SEM of at least three independent experiments in duplicate. ^{b}Agonist screens were conducted at 10 μM final concentration in stable human CB1-CHO-RD-HGA16 cells, and values are the mean ± SD of two independent experiments in duplicate. ^{c}Against EC$_{80}$ (90 nM) of CP55,940 in stable human CB2-CHO-RD-HGA16 cells. IC$_{50}$ values were determined for compounds that had >50% inhibition in antagonist screens conducted at 10 μM final concentration. Values are the mean ± SD of two independent experiments in duplicate. ^{d}Values are expressed as mean (95% confidence interval) from at least three independent experiments in duplicate. N.D.: not determined.

analogue **22**. While a weak electron withdrawing group like chloro at the 4-position (**30**) reduced potency around ~3-fold compared to **2** and **22**, inclusion of a chloro at the 3-position as in 3,5-dichloro (**31**, IC$_{50}$ = 23 nM) and 3,4-dichloro (**32**, IC$_{50}$ = 30 nM) resulted in comparable potency. The 2,6-dichloro analogue (**33**, IC$_{50}$ = 338 nM) was more than 10-fold weaker than its 3,5-dichloro or 3,4-dichloro analogues (**31** and **32**), similar to the methyl substituent which also favored the 3-position compared to the 2-position as described earlier. The significant drop in potency of the 2,6-dichloro analogue **33** could be due to the steric hindrance at the 2-*ortho*-chloro groups that forces the biaryl system to a more nonplanar spatial

arrangement. The fluoro substituent, however, did not follow the same trend as the chloro series. Both the 4-fluoro analogue, 3-(4-chlorophenyl)-1-[3-(4-fluorophenyl)phenyl]urea (RTICBM-74, **34**, IC$_{50}$ = 23 nM) and the 2,4-difluoro analogue (**35**, IC$_{50}$ = 18 nM) displayed excellent activities. This could be attributed to the unique effect of the highly electronegative fluorine atom which has a size as small as that of a hydrogen.[25,26]

While these results suggest that electron withdrawing groups are generally preferred over elctron donating groups for activity, the electronic property is not the only factor in determining the potency of these compounds at the CB1 receptor. This is clearly demonstrated by the relatively small differences in

potency between the 3-position (or meta-) substituted phenyl analogues **23**, **27**, and **29**, which have various electron densities on the phenyl group. Rather, the substituents such as the pyrrolidinyl group in **2** at the same meta position may simply occupy a binding pocket at this position. Given that its removal does not affect the potency, the interactions between the pyrrolidinyl group and binding pocket of the receptor are not essential for activity. Therefore, we briefly probed the steric requirements in the phenyl series. Substituents of large size such as *tert*-butyl, phenyl, and benzoyl seemed to be detrimental to the activity. Both the 4-*tert*-butyl (**36**) and 3,5-di-*tert*-butyl (**37**) substitutions showed a significant decrease in IC_{50} values. Both 3-phenyl (**38**) and 4-phenyl (**39**) analogues were less potent than **2**. However, **38** (IC_{50} = 195 nM) was significantly more potent than **39** (IC_{50} = 1340 nM), consistent with the earlier observations that the meta-position of the phenyl or pyridinyl ring has better tolerance for substitution than the ortho- or para-positions (**27** vs **28**, **31** vs **30**). Similarly, 4-benzoyl analogue (**40**) also possessed poor activity. Finally, several bicyclic and tricyclic aromatic rings (**41–45**) were explored. In concordance with the observation that there is a limited space at this binding pocket, the larger aromatic ring systems were not well tolerated at this region.[22]

All of these compounds were screened in the calcium mobilization assay for agonist activity at the CB1 receptor; no significant agonist effects (<30% of CP55,940 E_{max}) were observed for any of the compounds. All of these compounds were also screened for agonist and antagonist activity at the CB2 receptor to determine receptor subtype selectivity. None of the compounds had significant CB2 agonist activity (<10% of CP55,940 E_{max}). All compounds had no significant CB2 antagonist activities (<50% inhibition of CP55,940 EC_{80} concentration at 10 μM or IC_{50} values >10 μM) except compounds **21** (CB2 IC_{50} = 3.4 μM) and **44** (CB2 IC_{50} = 4.1 μM).

Effects of Diarylureas in the [^{35}S]GTP-γ-S Binding Assay. A number of representative compounds were then further evaluated in antagonizing agonist-stimulated [^{35}S]GTP-γ-S binding to CB1 receptor in mouse cerebellar membranes. The CB1 receptor agonist CP55,940 was employed as the agonist probe. Table 1 lists the potencies (IC_{50}s) of these diarylureas determined against 100 nM of CB1 agonist CP55,940 in the [^{35}S]GTP-γ-S binding assay (Figure 3).
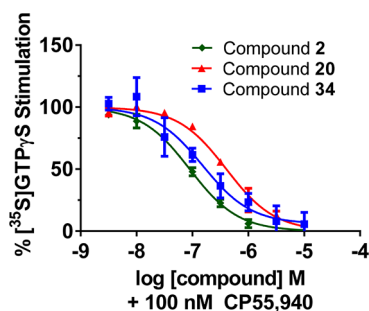

Figure 3. Curve fits for inhibition of CP55,940 (100 nM) stimulated [^{35}S]GTP-γ-S binding by compounds **2**, **20**, and **34** used to calculate IC_{50} values in Table 1. Data are expressed as percent of CP55,940 (100 nM) stimulated [^{35}S]GTP-γ-S binding. Symbols represent mean values ± SEM from three to six independent experiments carried out in duplicate.

In general, the activities of the synthesized compounds in the [^{35}S]GTP-γ-S binding assay were several fold lower than in the

calcium mobilization assay but follow the same trend, with some variations in the ranking order. In the [^{35}S]GTP-γ-S binding assay using mouse cerebellar membranes, **2** had an IC_{50} value of 89 nM against 100 nM CP55,940. It is comparable to the reported values of 42–74 nM for **2** in rat cerebellar membrane and HEK293 membrane against 50–200 nM CP55,490.[9,27] While the 2-pyridinyl (**18**) analogue was more potent than its 4-pyridinyl isomer (**20**) in the calcium mobilization assay, the latter was more active in the [^{35}S]GTP-γ-S binding assay (**18**, IC_{50} = 2647 nM, vs **20**, IC_{50} = 405 nM). Similarly, 3-methoxy-pyridin-4-yl analogue (**17**) had comparable potency in the calcium mobilization assay but weaker activity in the [^{35}S]GTP-γ-S binding assay compared to the unsubstituted pyridine-4-yl analogue (**20**) (**17**, IC_{50} = 1320 nM, vs **20**, IC_{50} = 405 nM). Within the substituted phenyl series, the 4-fluorophenyl was the most potent analogue (**34**, IC_{50} = 153 nM), demonstrating good potencies in both in vitro assays, comparable to those of compound **2**. Other phenyl analogues (**22**, **23**, **26**, **27**, **29**, **31**, **32**, **35**) with good activities (IC_{50} values <100 nM) in the calcium mobilization assay had potencies in the [^{35}S]GTP-γ-S binding assay with IC_{50} values around 300–800 nM. The 3-biphenyl analogue (**38**) had weaker activity in the calcium mobilization assay yet displayed comparable potency in the [^{35}S]GTP-γ-S binding assay to other substituted phenyl analogues, whereas 4-biphenyl (**39**) showed weak to no activity in both assays. Among the bicyclic aromatic rings, the benzofuran-5-yl (**41**) and quinoline-3-yl (**44**) had lower potencies in the calcium mobilization assay but exhibited comparable potencies in the [^{35}S]GTP-γ-S binding assay to the previous phenyl analogues. On the other hand, naphthalen-2-yl (**42**) and quinoline-3-yl (**43**) were weaker modulators in both in vitro assays.

Characterization of Allosterism. CB1 NAMs reported so far such as **2** have been characterized as PAM-antagonists, i.e., increasing agonist binding but decreasing G-protein functions.[8] Consistent with previous reports,[9,13,27] **2** dose-dependently decreased the E_{max} value of [^{35}S]GTP-γ-S binding levels stimulated by CP55,940 as expected for CB1 NAMs (Figure 4A). Similarly, **34** showed a concentration-related E_{max} reduction, confirming its allosteric mechanism (Figure 4B). In the calcium mobilization assay, the same effect was also observed for **34** (Figure 4C), similarly to **2** as previously reported by our group.[22]

Compound **2** has been reported to demonstrate positive binding cooperativity with the CB1 agonist CP55,940.[7,9,22] To determine whether **34** retains these characteristics, we conducted equilibrium binding with 1 nM [^{3}H]CP55,940 (Figure 4D). In contrast to unlabeled CP55,940, which inhibited specific binding of the radioligand, **34** increased specific binding to 214.7 ± 7.39% (199.8–229.7) with an EC_{50} value of 790 nM (467–1336). These results demonstrate positive binding cooperativity for **34** with CP55,940, consistent with the PAM-antagonist mechanism.

Metabolic Stability of Select Diarylureas. We have demonstrated that the pyrrolidinyl moiety on the pyridine is not required for allosteric modulatory activity at the CB1 receptor. Removal of the pyrrolidinyl moiety could result in smaller and more lipophilic molecules that have a better chance to cross the blood–brain barrier. Moreover, the pyridine ring could be replaced by other aromatic rings with similar size, such as substituted phenyl groups, without losing its potency and efficacy. Moreover, the substituents of various nature including size and electronic properties can be tolerated, thus allowing for optimization of other properties, such as pharmacokinetics,
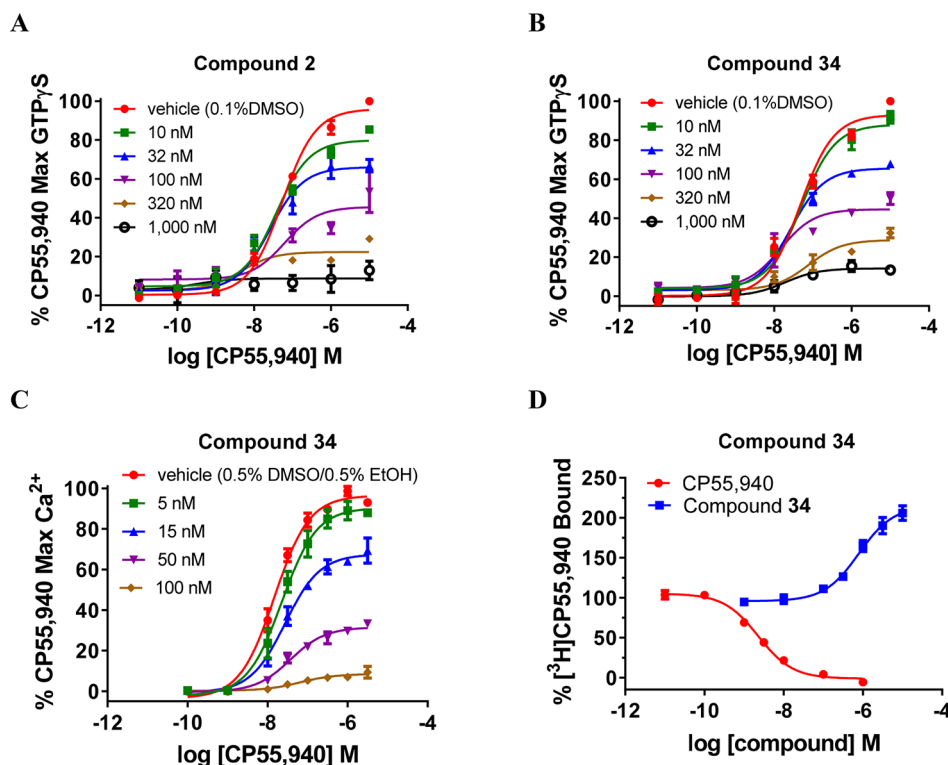
Figure 4. Insurmountable antagonism of CP55,940-stimulated $[^{35}S]GTP$-γ-S binding by diarylureas (A) compound **2** and (B) compound **34**, (C) insurmountable antagonism of CP55,940-stimulated calcium mobilization by compound **34**, and (D) positive binding cooperativity with 1 nM $[^{3}H]CP55,940$ and **34** in mouse cerebellar membranes. Data are expressed as (A,B) percent stimulation of $[^{35}S]GTP$-γ-S binding over basal, (C) percent maximal CP55,940 response, or (D) percent $[^{3}H]CP55,940$ bound. Symbols represent mean values $\pm$ SEM from three to six independent experiments carried out in duplicate (Ca^{2+}) or triplicate ($[^{35}S]GTP$-γ-S).

with appropriate structural alterations. A drug must have sufficient stability to reach its molecular targets to elicit its effects, therefore, the metabolic stability of select compounds were evaluated in rat liver microsomes.

Table 2 lists the half-lives ($T_{1/2}$) and clearance (CL) of compounds **2**, **20**, and **34**. Compound **2** was rapidly metabolized

Table 2. Stability of Select Diarylureas in Rat Liver Microsomes

compd	half-life (min)[a]	clearance (μL/min/mg)[a]
2	13.4 $\pm$ 4.1	113.7 $\pm$ 34.4
20	41.9 $\pm$ 1.3	33.1 $\pm$ 1.0
34	>300	<4.6

[a]Values are expressed as mean $\pm$ SD from two independent experiments.

with $T_{1/2}$ = 13.4 min, suggesting modest stability in first pass metabolism. When the pyrrolidinyl ring was absent, the metabolic stability increased by ~3-fold (**20**, $T_{1/2}$ = 41.9 min). Finally, replacement of the pyridinyl ring with a 4-fluorophenyl group significantly improved the metabolic stability. **34** had a half-life of more than 300 min and clearance of less than 4.6 μL/min/mg.

Compounds 2 and 34 Attenuated Reinstatement of Cocaine-Seeking Behavior. Blockade of the CB1 receptor in vivo with the antagonists/inverse agonists SR141716A and **46** has been demonstrated to reduce intake of palatable food, self-administration of several drugs of abuse, and reinstatement of food and drug-seeking behaviors.[18,19,28] We previously demonstrated that rats pretreated with **1**, the first reported

CB1 NAM, were less likely to seek drugs of abuse such as cocaine or methamphetamine after a period of extinction. Therefore, we examined whether compound **2** and one of the active diarylureas, compound **34**, would achieve the same effects in vivo.

As shown in Figure 5, a cocaine prime significantly reinstated the extinguished active lever response (t test: $t[7]$ = 16.29, $p <$ 0.0001). Pretreatment with **2** attenuated cocaine-induced reinstatement of cocaine-seeking behavior (one way ANOVA: $F[2, 22]$ = 5.174, $p < 0.05$). Post hoc analysis revealed that at the dose of 30 mg/kg, **2** significantly reduced cocaine-induced reinstatement behavior. Excitingly, **34** at 10 mg/kg produced the same degree of attenuation as that of 30 mg/kg of **2** (t test: $t[20]$ = 1.84, $p < 0.05$). While **2** and **34** had equivalent in vitro IC_{50} values in both calcium mobilization and $[^{35}S]GTP$-γ-S binding assays, **34** was effective at a lower dose than **2** in attenuating cocaine-seeking behavior. The difference in in vivo potency is likely due to the improved metabolic stability of **34** producing higher concentrations at sites of action within the CNS.

■ CONCLUSIONS

The endocannabinoid system, particularly the CB1 receptor, has shown considerable potential as a therapeutic target in a number of neuropsychiatric conditions such as mood disorders and drug addiction.[29] Although CB1 antagonists/inverse agonists have shown potential therapeutic effects in these conditions, their activity also produces untoward effects limiting their development as drug candidates. The present study describes a series of novel diarylureas derived from **2**,
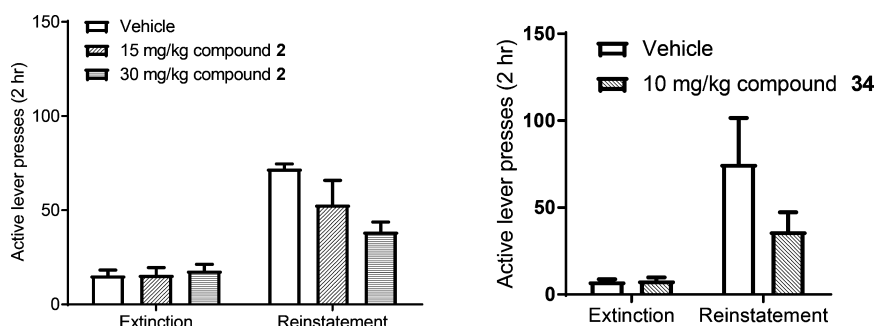
Figure 5. Compounds **2** (left) and **34** (right) attenuated the resumption of extinguished cocaine-seeking behavior of active lever responding as compared with saline treatment in rats.

a CB1 NAM without known agonist activities, as an alternate approach to manipulate this important signaling pathway and to potentially circumvent adverse side effects of orthosteric ligands.

Optimization of **2** resulted in a series of diarylureas with comparable or even greater potency as determined in calcium mobilization and [^{35}S]GTP-γ-S binding assays. SAR studies of this series of diarylureas indicated that the pyrrolidinyl ring of **2** was not necessary for the allosteric modulation of the CB1 receptor and that the pyridinyl ring of **2** could be replaced by other aromatic rings. Introducing a phenyl ring in place of the pyridinyl ring led to **34** with similar in vitro potency but with significantly improved microsomal stability. We have demonstrated for the first time that these diarylureas were effective in attenuating reinstatement of cocaine taking after a period of extinction. In this model, the optimized analogue **34** appeared more effective than the lead compound **2**, which may be partially ascribed to its improved metabolic stability. Although the in vivo effects of these diarylureas in attenuating cocaine reinstatement could not be exclusively attributed to the CB1 signaling pathway at present, the involvement of the CB1 receptor is a plausible mode of action given that similar effects were observed for the CB1 antagonist/inverse agonists SR141716A[18] and **46**,[21] and the structurally distinct CB1 NAM **1**, which has been reported to possess high selectivities against more than 40 GPCRs, including many that have been indicated in drug addiction.[17]

Currently, there are no FDA approved medications for the treatment of cocaine addiction, the relapse rate of which remains as high as 40−60%.[30] With the in vivo efficacy to attenuate reinstatement of cocaine craving, these CB1 allosteric modulators may represent promising candidates for the development of therapeutics for relapse prevention of cocaine addiction and abuse, an urgent need that is currently unfilled.

■ EXPERIMENTAL SECTION

Chemistry. All solvents and chemicals were reagent grade. Unless otherwise mentioned, all reagents and solvents were purchased from commercial vendors and used as received. Flash column chromatography was carried out on a Teledyne ISCO CombiFlash Rf system using prepacked columns. Solvents used include hexane, ethyl acetate (EtOAc), dichloromethane, methanol, and chloroform/methanol/ammonium hydroxide (80:18:2) (CMA-80). Purity and characterization of compounds were established by a combination of HPLC, TLC, mass spectrometry, and NMR analyses. Melting point was recorded by the Mel-Temp II instrument (Laboratory Devices Inc., U.S.). ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DPX-300 (300 MHz) spectrometer and were determined in chloroform-d, DMSO-d_6, or methanol-d_4 with tetramethylsilane (TMS) (0.00 ppm) or solvent peaks as the internal reference.

Chemical shifts are reported in ppm relative to the reference signal, and coupling constant (J) values are reported in hertz (Hz). Thin layer chromatography (TLC) was performed on EMD precoated silica gel 60 F254 plates, and spots were visualized with UV light or iodine staining. Low resolution mass spectra were obtained using a Waters Alliance HT/Micromass ZQ system (ESI). All test compounds were greater than 95% pure as determined by HPLC on an Agilent 1100 system using an Agilent Zorbax SB-Phenyl, 2.1 mm × 150 mm, 5 μm column using a 15 min gradient elution of 5−95% solvent B at 1 mL/min followed by 10 min at 95% solvent B (solvent A, water with 0.1% TFA; solvent B, acetonitrile with 0.1% TFA and 5% water; absorbance monitored at 220 and 280 nm).

General Procedure A. To a mixture of aryl bromide or aryl iodide (1 equiv) and boronic acid (1.1 equiv) in dimethoxyethane (0.1 M) was added 1 M aqueous NaHCO$_3$ solution (3 equiv) followed by Pd(Ph$_3$)$_4$ (0.075 equiv). The reaction mixture was refluxed overnight under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate and washed with a saturated NaHCO$_3$ solution and brine. The combined organic layers were dried over anhydrous MgSO$_4$ and filtered. The filtrate was concentrated in vacuo, and the residue was purified by column chromatography (SiO$_2$, ethyl acetate/hexanes) to give the desired product.

2-Methoxy-6-(3-nitrophenyl)pyridine (11a). **11a** was prepared from 2-bromo-6-methoxypyridine (0.12 mL, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.12 g, 50%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.89 (t, J = 1.98 Hz, 1H), 8.01 (dd, J = 0.57, 7.35 Hz, 1H), 7.64−7.74 (m, 2H), 7.41 (d, J = 7.35 Hz, 1H), 6.72−6.80 (m, 2H), 4.04 (s, 3H). MS (ESI) m/z for C$_{12}$H$_{10}$N$_2$O$_3$ [M + H]$^+$: calcd 231.1, found 231.4.

4-Methyl-2-(3-nitrophenyl)pyridine (11b). **11b** was prepared from 2-bromo-4-methylpyridine (0.11 mL, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.16 g, 73%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.84 (t, J = 1.98 Hz, 1H), 8.58 (d, J = 4.90 Hz, 1H), 8.34−8.39 (m, 1H), 8.23−8.27 (m, 1H), 7.60−7.67 (m, 2H), 7.15 (dd, J = 0.66, 4.99 Hz, 1H), 2.46 (s, 3H). MS (ESI) m/z for C$_{12}$H$_{10}$N$_2$O$_2$ [M + H]$^+$: calcd 214.1, found 214.4.

2-Methoxy-4-(3-nitrophenyl)pyridine (11c). **11c** was prepared from 2-methoxy-5-bromopyridine (0.21 mL, 1.60 mmol) and 3-nitrophenylboronic acid (0.29 g, 1.76 mmol) following the general procedure A as white solid (0.34 g, 85%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.36−8.46 (m, 2H), 8.17−8.25 (m, 1H), 7.79−7.88 (m, 2H), 7.58−7.66 (m, 1H), 6.88 (d, J = 8.48 Hz, 1H), 4.00 (s, 3H). MS (ESI) m/z for C$_{12}$H$_{10}$N$_2$O$_3$ [M + H]$^+$: calcd 231.1, found 231.5.

2-(3-Nitrophenyl)pyridine (11d). **11d** was prepared from 2-bromopyridine (1.00 g, 6.33 mmol) and 3-nitrophenylboronic acid (1.16 g, 6.96 mmol) following the general procedure A as orange solid (0.85 g, 67%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.86 (t, J = 1.88 Hz, 1H), 8.75 (td, J = 1.20, 4.94 Hz, 1H), 8.37 (td, J = 1.39, 7.77 Hz, 1H), 8.27 (ddd, J = 0.94, 2.21, 8.15 Hz, 1H), 7.85 (d, J = 1.70 Hz, 2H), 7.66 (t, J = 8.01 Hz, 10H), 7.62−7.70 (m, 1H), 7.34 (ddd, J = 2.45, 4.76, 6.17 Hz, 1H). MS (ESI) m/z for C$_{11}$H$_8$N$_2$O$_2$ [M + H]$^+$: calcd 201.1, found 201.4.

4-(3-Nitrophenyl)pyridine (11e). **11e** was prepared from 4-bromopyridine hydrochloride (0.19 g, 1.0 mmol) and 3-nitrophenylboronic

acid (0.18 g, 1.1 mmol) following the general procedure A as brown solid (0.13 g, 67%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.73–8.78 (m, 1H), 7.62–7.74 (m, 3H), 7.51–7.59 (m, 2H), 7.43–7.50 (m, 2H). MS (ESI) m/z for C$_{11}$H$_8$N$_2$O$_2$ [M + H]$^+$: calcd 201.1, found 201.4.

5-(3-Nitrophenyl)pyrimidine (11f). **11f** was prepared from 5-bromopyrimidine (0.16 g, 1.0 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.1 mmol) following the general procedure A as light-yellow solid (0.10 g, 52%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.29–9.32 (m, 1H), 9.03 (s, 2H), 8.48 (t, J = 1.98 Hz, 1H), 8.33–8.38 (m, 1H), 7.94 (qd, J = 0.93, 7.75 Hz, 1H), 7.71–7.79 (m, 1H). MS (ESI) m/z for C$_{10}$H$_7$N$_3$O$_2$ [M + H]$^+$: calcd 202.1, found 202.4.

1-(3-Methoxyphenyl)-3-nitrobenzene (11g). **11g** was prepared from 2-bromo-3-methoxybenzene (0.30 g, 1.6 mmol) and 3-nitrophenylboronic acid (0.29 g, 1.8 mmol) following the general procedure A as white solid (0.24 g, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.33–8.40 (m, 1H), 8.13 (td, J = 1.06, 8.24 Hz, 1H), 7.80–7.88 (m, 1H), 7.54 (t, J = 8.01 Hz, 1H), 7.29–7.41 (m, 1H), 7.13 (dd, J = 0.85, 7.63 Hz, 1H), 7.04–7.09 (m, 1H), 6.86–6.94 (m, 1H), 3.82 (s, 3H).

1-(3-Hydroxyphenyl)-3-nitrobenzene (11h). **11h** was prepared from 2-bromo-3-hydroxybenzene (0.30 g, 1.7 mmol) and 3-nitrophenylboronic acid (0.32 g, 1.9 mmol) following the general procedure A as white solid (0.24 g, 64%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (d, J = 1.70 Hz, 1H), 8.16–8.25 (m, 1H), 7.85–7.95 (m, 1H), 7.56–7.65 (m, 1H), 7.33–7.40 (m, 1H), 7.20 (br s, 1H), 7.13 (br s, 1H), 6.88–7.00 (m, 1H), 5.42 (br s, 1H).

1-(3-Nitrophenyl)-3-(propan-2-yloxy)benzene (11i). **11i** was prepared from 1-bromo-3-(propan-2-yloxy)benzene (0.30 g, 1.7 mmol) and 3-nitrophenylboronic acid (0.28 g, 1.7 mmol) following the general procedure A as yellow liquid (0.30 g, 84%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.44 (t, J = 1.98 Hz, 1H), 8.15–8.24 (m, 1H), 7.90 (td, J = 1.25, 7.86 Hz, 1H), 7.54–7.65 (m, 1H), 7.33–7.44 (m, 1H), 7.10–7.20 (m, 2H), 6.95 (dd, J = 1.88, 8.10 Hz, 1H), 4.64 (spt, J = 6.06 Hz, 1H), 1.34–1.43 (m, 6H).

1-(4-Chlorophenyl)-3-nitrobenzene (11j). **11j** was prepared from 1-iodo-4-chlorobenzene (0.30 g, 1.25 mmol) and 3-nitrophenylboronic acid (0.23 g, 1.38 mmol) following the general procedure A as white solid (0.24 g, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.37–8.43 (m, 1H), 8.21 (ddd, J = 1.04, 2.26, 8.19 Hz, 1H), 7.88 (ddd, J = 1.04, 1.74, 7.77 Hz, 1H), 7.62 (t, J = 8.01 Hz, 1H), 7.51–7.58 (m, 2H), 7.41–7.50 (m, 2H).

1,3-Dichloro-4-(3-nitrophenyl)benzene (11k). **11k** was prepared from 1-bromo-3,5-dichlorobenzene (0.30 g, 1.32 mmol) and 3-nitrophenylboronic acid (0.24 g, 1.46 mmol) following the general procedure A as white solid (0.29 g, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.41 (t, J = 1.79 Hz, 1H), 8.27 (dd, J = 1.22, 8.19 Hz, 1H), 7.87 (d, J = 7.72 Hz, 1H), 7.62–7.70 (m, 1H), 7.50 (d, J = 1.70 Hz, 2H), 7.43 (t, J = 1.70 Hz, 1H).

1,2-Dichloro-4-(3-nitrophenyl)benzene (11l). **11l** was prepared from 1-iodo-3,4-dichlorobenzene (0.30 g, 1.10 mmol) and 3-nitrophenylboronic acid (0.20 g, 1.21 mmol) following the general procedure A as white solid (0.19 g, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.40 (t, J = 1.98 Hz, 1H), 8.21–8.27 (m, 1H), 7.87 (td, J = 1.25, 7.68 Hz, 1H), 7.71 (d, J = 2.07 Hz, 1H), 7.64 (t, J = 8.01 Hz, 1H), 7.55–7.59 (m, 1H), 7.46 (dd, J = 2.17, 8.38 Hz, 1H).

1,3-Dichloro-2-(3-nitrophenyl)benzene (11m). **11m** was prepared from 2-bromo-1,3-dichlorobenzene (0.30 g, 1.32 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as yellow solid (0.23 g, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.26–8.34 (m, 1H), 8.18 (d, J = 1.70 Hz, 1H), 7.59–7.68 (m, 2H), 7.41–7.49 (m, 2H), 7.29–7.35 (m, 1H).

1-(4-Fluorophenyl)-3-nitrobenzene (11n). **11n** was prepared from 1-bromo-4-fluorobenzene (0.30 g, 1.71 mmol) and 3-nitrophenylboronic acid (0.31 g, 1.88 mmol) following the general procedure A as white solid (0.35 g, 93%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.39 (s, 1H), 8.19 (d, J = 7.54 Hz, 1H), 7.86 (d, J = 7.72 Hz, 1H), 7.57–7.62 (m, 2H), 7.18 (t, J = 8.57 Hz, 2H).

1-(2,4-Difluorophenyl)-3-nitrobenzene (11o). **11o** was prepared from 1-bromo-2,4-difluorobenzene (0.19 g, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.17 g, 71%). ^{1}H NMR (300 MHz, CDCl$_3$) δ

8.37 (s, 1H), 8.23 (td, J = 1.08, 8.19 Hz, 1H), 7.85 (dd, J = 1.13, 7.72 Hz, 1H), 7.59–7.67 (m, 1H), 7.46 (dt, J = 6.31, 8.62 Hz, 1H), 6.92–7.06 (m, 2H).

1-(4-tert-Butylphenyl)-3-nitrobenzene (11p). **11p** was prepared from 1-bromo-4-*tert*-butylbenzene (0.30 g, 1.41 mmol) and 3-nitrophenylboronic acid (0.26 g, 1.55 mmol) following the general procedure A as colorless liquid (0.15 g, 42%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.43 (t, J = 1.88 Hz, 1H), 8.12–8.18 (m, 1H), 7.87–7.92 (m, 1H), 7.48–7.60 (m, 5H), 1.37 (s, 9H).

1,3-Di-tert-butyl-5-(3-nitrophenyl)benzene (11q). **11q** was prepared from 1-bromo-3,5-di-*tert*-butylbenzene (0.30 g, 1.1 mmol) and 3-nitrophenylboronic acid (0.20 g, 1.2 mmol) following the general procedure A as colorless liquid (0.22 g, 63%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.41–8.44 (m, 1H), 8.19 (td, J = 1.08, 8.19 Hz, 1H), 7.91 (dd, J = 0.47, 7.82 Hz, 1H), 7.59–7.63 (m, 1H), 7.52 (t, J = 1.51 Hz, 1H), 7.42 (d, J = 1.70 Hz, 2H), 1.40 (s, 21H).

1-(3-Nitrophenyl)-3-phenylbenzene (11r). **11r** was prepared from 1-bromo-3-phenylbenzene (0.17 mL, 1.0 mmol) and 3-nitrophenyl-boronic acid (0.18 g, 1.1 mmol) following the general procedure A as colorless liquid (0.27 g, 98%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.52 (t, J = 1.98 Hz, 1H), 8.21–8.26 (m, 1H), 7.98 (td, J = 1.27, 7.82 Hz, 1H), 7.81–7.84 (m, 1H), 7.63–7.69 (m, 4H), 7.59–7.63 (m, 2H), 7.45–7.50 (m, 2H), 7.39–7.43 (m, 1H).

1-(4-Phenylphenyl)-3-nitrobenzene (11s). **11s** was prepared from 1-bromo-4-phenylbenzene (0.30 g, 1.29 mmol) and 3-nitrophenylboronic acid (0.24 g, 1.42 mmol) following the general procedure A as white solid (0.21 g, 58%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.50 (t, J = 1.98 Hz, 1H), 8.20 (ddd, J = 0.75, 2.12, 8.24 Hz, 1H), 7.95 (td, J = 1.18, 7.82 Hz, 1H), 7.71 (d, J = 0.94 Hz, 4H), 7.62–7.66 (m, 3H), 7.44–7.51 (m, 2H), 7.37–7.42 (m, 1H).

[4-(3-Nitrophenyl)phenyl](phenyl)methanone (11t). **11t** was prepared from (4-iodophenyl)(phenyl)methanone (0.31 g, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as brown solid (0.18 g, 60%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.49–8.55 (m, 1H), 8.28 (dd, J = 1.79, 7.63 Hz, 1H), 7.91–8.01 (m, 3H), 7.81–7.87 (m, 2H), 7.73–7.78 (m, 2H), 7.60–7.71 (m, 2H), 7.49–7.56 (m, 2H).

5-(3-Nitrophenyl)-1-benzofuran (11u). **11u** was prepared from 5-bromo-1-benzofuran (0.13 mL, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.20 g, 84%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.47 (t, J = 1.98 Hz, 1H), 8.18 (ddd, J = 1.04, 2.21, 8.24 Hz, 1H), 7.90–7.96 (m, 1H), 7.81–7.85 (m, 1H), 7.68–7.71 (m, 1H), 7.58–7.64 (m, 2H), 7.51–7.56 (m, 1H), 6.85 (dd, J = 0.85, 2.17 Hz, 1H).

2-(3-Nitrophenyl)naphthalene (11v). **11v** was prepared from 2-bromonaphthalene (0.41 g, 2.00 mmol) and 3-nitrophenylboronic acid (0.37 g, 2.20 mmol) following the general procedure A as white solid (0.37 g, 74%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.57 (t, J = 1.98 Hz, 1H), 8.22 (ddd, J = 0.94, 2.17, 8.19 Hz, 1H), 8.08 (d, J = 1.51 Hz, 1H), 8.01–8.06 (m, 1H), 7.96 (d, J = 8.48 Hz, 1H), 7.86–7.93 (m, 2H), 7.74 (dd, J = 1.88, 8.48 Hz, 1H), 7.64 (t, J = 8.01 Hz, 1H), 7.52–7.57 (m, 2H).

2-(3-Nitrophenyl)quinoline (11w). **11w** was prepared from 2-bromoquinoline (0.18 g, 0.84 mmol) and 3-nitrophenylboronic acid (0.15 g, 0.93 mmol) following the general procedure A as white solid (0.02 g, 11%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.05 (t, J = 1.88 Hz, 1H), 8.53–8.58 (m, 1H), 8.28–8.34 (m, 2H), 8.20 (d, J = 8.48 Hz, 1H), 7.94 (d, J = 8.67 Hz, 1H), 7.88 (d, J = 8.10 Hz, 1H), 7.75–7.82 (m, 1H), 7.70 (t, J = 8.01 Hz, 1H), 7.55–7.63 (m, 1H).

3-(3-Nitrophenyl)quinoline (11x). **11x** was prepared from 3-bromoquinoline (0.14 mL, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.08 g, 33%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.19 (d, J = 2.26 Hz, 1H), 8.55–8.60 (m, 1H), 8.38 (d, J = 2.26 Hz, 1H), 8.29 (dd, J = 1.41, 8.19 Hz, 1H), 8.17 (d, J = 8.48 Hz, 1H), 8.05 (d, J = 7.91 Hz, 1H), 7.93 (d, J = 8.10 Hz, 1H), 7.79 (dt, J = 1.32, 7.72 Hz, 1H), 7.72 (t, J = 8.01 Hz, 1H), 7.60–7.67 (m, 1H).

2-(3-Nitrophenyl)-9H-fluorene (11y). **11y** was prepared from 2-bromo-9*H*-fluorene (0.25 mL, 1.00 mmol) and 3-nitrophenylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as

yellow solid (0.07 g, 26%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.51 (t, J = 1.98 Hz, 1H), 8.19 (ddd, J = 0.94, 2.26, 8.10 Hz, 1H), 7.97 (qd, J = 0.94, 7.72 Hz, 1H), 7.84−7.91 (m, 2H), 7.81 (d, J = 4.71 Hz, 2H), 7.62−7.67 (m, 1H), 7.56−7.60 (m, 1H), 7.40 (d, J = 6.97 Hz, 1H), 7.36 (dd, J = 1.32, 7.35 Hz, 1H), 3.99 (s, 2H).

3-(Pyridin-3-yl)aniline (14a). **14a** was prepared from 3-bromoaniline (0.11 mL, 1.00 mmol) and 3-pyridinylboronic acid (0.18 g, 1.10 mmol) following the general procedure A as white solid (0.10 g, 59%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.81 (d, J = 1.70 Hz, 1H), 8.56 (dd, J = 1.41, 4.80 Hz, 1H), 7.77−7.85 (m, 1H), 7.31 (dd, J = 4.71, 7.91 Hz, 1H), 7.24 (t, J = 7.72 Hz, 1H), 6.91−6.98 (m, 1H), 6.83−6.88 (m, 1H), 6.71 (td, J = 1.11, 7.96 Hz, 1H), 3.83 (br s, 2H). MS (ESI) m/z for C$_{11}$H$_{10}$N$_2$ [M + H]$^+$: calcd 171.1, found 171.0.

3-(2H-1,3-Benzodioxol-5-yl)aniline (14b). **14b** was prepared from 3-bromoaniline (0.19 mL, 1.74 mmol) and (2H-1,3-benzodioxol-5-yl)boronic acid (0.32 g, 2.08 mmol) following the general procedure A as yellow liquid (0.08 g, 60%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 6.95−7.04 (m, 2H), 6.81−6.90 (m, 4H), 6.61−6.66 (m, 1H), 6.55−6.61 (m, 2H), 6.41 (d, J = 2.64 Hz, 1H), 6.24 (dd, J = 2.54, 8.38 Hz, 1H), 5.89 (s, 2H), 3.73 (br s, 2H). MS (ESI) m/z for C$_{13}$H$_{11}$NO$_2$ [M + H]$^+$: calcd 213.1, found 213.2.

3-(3-Methylphenyl)aniline (14c). **14c** was prepared from 3-bromoaniline (0.11 mL, 1.00 mmol) and 3-methylphenylboronic acid (0.16 g, 1.10 mmol) following the general procedure A as yellow liquid (0.12 g, 66%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.29−7.39 (m, 3H), 7.12−7.22 (m, 2H), 6.96−7.00 (m, 1H), 6.90 (t, J = 1.98 Hz, 1H), 6.67 (ddd, J = 0.94, 2.26, 7.91 Hz, 1H), 3.73 (br s, 2H), 2.41 (s, 3H).

3-(2-Methylphenyl)aniline (14d). **14d** was prepared from 3-bromoaniline (0.11 mL, 1.00 mmol) and 2-methylphenylboronic acid (0.15 g, 1.10 mmol) following the general procedure A as yellow liquid (0.15 g, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.20−7.29 (m, 5H), 6.61−6.74 (m, 3H), 3.69 (br s, 2H), 2.28 (s, 3H). MS (ESI) m/z for C$_{13}$H$_{13}$N [M + H]$^+$: calcd 184.1, found 184.2.

3-(3-Nitrophenyl)aniline (14e). **14e** was prepared from 3-bromoaniline (0.19 mL, 1.74 mmol) and 3-nitrophenylboronic acid (0.32 g, 1.91 mmol) following the general procedure A as white solid (0.08 g, 21%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.37−8.45 (m, 1H), 8.17 (ddd, J = 0.94, 2.26, 8.10 Hz, 1H), 7.83−7.92 (m, 1H), 7.57 (t, J = 7.91 Hz, 1H), 7.21−7.28 (m, 1H), 6.96−7.03 (m, 1H), 6.92 (t, J = 1.88 Hz, 1H), 6.72−6.78 (m, 1H), 3.82 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_{10}$N$_2$O$_2$ [M + H]$^+$: calcd 215.1, found 215.0.

General Procedure B. To a solution of nitrobenzene derivative (1 equiv) in ethanol (0.1 M) was added hydrazine hydrate (15 equiv). The reaction was stirred at 50 °C for 15 min and an excess of Raney nickel slurry in water (1.2 equiv) was added slowly. After 1 h, the bubbling ceased and the mixture was cooled to room temperature and filtered through Celite. The filtrate was condensed under reduced pressured, and the residue was either used for the next step without purification or purified by column chromatography (SiO$_2$, ethyl acetate/hexanes) to afford the desired product.

3-(6-Methoxypyridin-2-yl)aniline (12a). **12a** was prepared from **11a** (0.23 g, 1.00 mmol) following the general procedure B as colorless liquid (0.20 g, quant yield). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.54 (dd, J = 7.54, 8.10 Hz, 1H), 7.36−7.41 (m, 2H), 7.17−7.27 (m, 2H), 6.62−6.70 (m, 2H), 4.00 (s, 3H), 3.65−3.81 (m, 2H). MS (ESI) m/z for C$_{12}$H$_{12}$N$_2$O [M + H]$^+$: calcd 201.1, found 201.1.

3-(4-Methylpyridin-2-yl)aniline (12b). **12b** was prepared from **11b** (0.16 g, 0.73 mmol) following the general procedure B as yellow solid (0.10 g, 76%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.52 (d, J = 3.96 Hz, 1H), 7.51 (s, 1H), 7.27 (d, J = 5.09 Hz, 3H), 7.04 (d, J = 3.58 Hz, 1H), 6.65 (br s, 1H), 3.63 (br s, 2H), 2.39 (s, 3H). MS (ESI) m/z for C$_{12}$H$_{12}$N$_2$ [M + H]$^+$: calcd 184.1, found 184.4.

3-(2-Methoxypyridin-4-yl)aniline (12c). **12c** was prepared from **11c** (0.30 g, 1.30 mmol) following the general procedure B as colorless liquid (0.17 g, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.35 (d, J = 2.07 Hz, 1H), 7.71−7.78 (m, 1H), 7.18−7.28 (m, 1H), 6.91 (td, J = 1.25, 7.68 Hz, 1H), 6.76−6.85 (m, 2H), 6.67 (ddd, J = 0.75, 2.26, 7.91 Hz, 1H), 3.97 (s, 3H), 3.34 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_{12}$N$_2$O [M + H]$^+$: calcd 201.1, found 201.2.

3-(Pyridin-2-yl)aniline (12d). **12d** was prepared from **11d** (0.85 g, 4.24 mmol) following the general procedure B, and the crude product was used for the next step without purification.

3-(Pyridin-4-yl)aniline (12e). **12e** was prepared from **11e** (0.13 g, 0.65 mmol) following the general procedure B as white solid (0.07 g, 65%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.61−8.66 (m, 1H), 7.63−7.72 (m, 3H), 7.52−7.56 (m, 1H), 7.45−7.50 (m, 3H). MS (ESI) m/z for C$_{11}$H$_{10}$N$_2$ [M + H]$^+$: calcd 171.1, found 171.0.

3-(Pyrimidin-5-yl)aniline (12f). **12f** was prepared from **11f** (0.10 g, 0.52 mmol) following the general procedure B as white solid (0.09 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.19 (s, 1H), 8.90−8.94 (m, 2H), 7.26−7.33 (m, 1H), 6.95 (dd, J = 0.85, 7.63 Hz, 1H), 6.86 (t, J = 1.88 Hz, 1H), 6.78 (td, J = 1.13, 8.10 Hz, 1H), 3.85 (br s, 2H). MS (ESI) m/z for C$_{10}$H$_9$N$_3$ [M + H]$^+$: calcd 172.1, found 172.5.

3-(3-Methoxyphenyl)aniline (12g). **12g** was prepared from **11g** (0.21 g, 0.92 mmol) following the general procedure B as colorless liquid (0.15 g, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.28−7.35 (m, 1H), 7.17−7.23 (m, 1H), 7.14 (d, J = 7.72 Hz, 1H), 7.09 (d, J = 2.26 Hz, 1H), 6.97 (d, J = 7.54 Hz, 1H), 6.84−6.90 (m, 2H), 6.65 (dd, J = 1.51, 7.91 Hz, 1H), 3.83 (s, 3H), 3.70 (br s, 2H). MS (ESI) m/z for C$_{13}$H$_{13}$NO [M + H]$^+$: calcd 200.1, found 200.2.

3-(3-Hydroxyphenyl)aniline (12h). **12h** was prepared from **11h** (0.24 g, 1.12 mmol) following the general procedure B as white solid (0.11 g, 54%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21−7.29 (m, 1H), 7.13−7.19 (m, 1H), 7.07 (d, J = 7.16 Hz, 1H), 7.02 (s, 1H), 6.91 (d, J = 6.78 Hz, 1H), 6.82 (d, J = 1.51 Hz, 2H), 6.60 (d, J = 5.46 Hz, 1H), 3.65 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_{11}$NO [M + H]$^+$: calcd 185.1, found 185.9.

3-[3-(Propan-2-yloxy)phenyl]aniline (12i). **12i** was prepared from **11i** (0.30 g, 1.16 mmol) following the general procedure B. The crude was used for the next step without purification.

3-(4-Chlorophenyl)aniline (12j). **12j** was prepared from **11j** (0.22 g, 0.94 mmol) following the general procedure B as yellow solid (0.18 g, 94%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.41 (d, J = 8.29 Hz, 2H), 7.24−7.35 (m, 3H), 7.14 (d, J = 7.91 Hz, 1H), 6.85−6.94 (m, 1H), 6.62 (dd, J = 1.41, 8.01 Hz, 1H), 3.66 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_{10}$ClN [M + H]$^+$: calcd 204.1, found 204.4.

3-(3,5-Dichlorophenyl)aniline (12k). **12k** was prepared from **11k** (0.29 g, 1.09 mmol) following the general procedure B as colorless liquid (0.21 g, 82%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.42 (d, J = 1.88 Hz, 2H), 7.31 (t, J = 1.88 Hz, 1H), 7.19−7.23 (m, 1H), 6.89−6.94 (m, 1H), 6.81−6.84 (m, 1H), 6.68−6.74 (m, 1H), 3.76 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_9$Cl$_2$N [M + H]$^+$: calcd 238.0, found 238.3.

3-(3,4-Dichlorophenyl)aniline (12l). **12l** was prepared from **11l** (0.18 g, 0.67 mmol) following the general procedure B as colorless liquid (0.14 g, 88%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.63 (d, J = 1.70 Hz, 1H), 7.44−7.50 (m, 1H), 7.34−7.40 (m, 1H), 7.18−7.24 (m, 1H), 6.92 (d, J = 7.72 Hz, 1H), 6.83 (s, 1H), 6.70 (dd, J = 1.22, 7.82 Hz, 1H), 3.76 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_9$Cl$_2$N [M + H]$^+$: calcd 238.0, found 238.3.

3-(2,6-Dichlorophenyl)aniline (12m). **12m** was prepared from **11m** (0.26 g, 0.97 mmol) following the general procedure B as yellow solid (0.23 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.38 (d, J = 8.10 Hz, 2H), 7.24 (d, J = 7.91 Hz, 2H), 6.69−6.78 (m, 1H), 6.64 (d, J = 6.97 Hz, 1H), 6.57 (s, 1H), 3.72 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_9$Cl$_2$N [M + H]$^+$: calcd 238.0, found 238.1.

3-(4-Fluorophenyl)aniline (12n). **12n** was prepared from **11n** (0.32 g, 1.47 mmol) following the general procedure B as yellow liquid (0.22 g, 80%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.21−7.54 (m, 3H), 7.09 (d, J = 7.35 Hz, 1H), 6.99 (t, J = 7.91 Hz, 1H), 6.82 (d, J = 7.35 Hz, 1H), 6.72 (s, 1H), 6.55 (d, J = 6.40 Hz, 1H), 3.60 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_{10}$FN [M + H]$^+$: calcd 188.1, found 188.1.

3-(2,4-Difluorophenyl)aniline (12o). **12o** was prepared from **11o** (0.17 g, 0.71 mmol) following the general procedure B as colorless liquid (0.15 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.30−7.41 (m, 1H), 7.16−7.25 (m, 1H), 6.75−6.95 (m, 4H), 6.67 (d, J = 7.72 Hz, 1H), 3.69 (br s, 2H). MS (ESI) m/z for C$_{12}$H$_9$F$_2$N [M + H]$^+$: calcd 206.1, found 206.2.

3-(4-tert-Butylphenyl)aniline (12p). 12p was prepared from 11p (0.15 g, 0.53 mmol) following the general procedure B as yellow liquid (0.14 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.40−7.46 (m, 2H), 7.33−7.39 (m, 2H), 7.14 (t, J = 7.82 Hz, 1H), 6.92 (d, J = 7.72 Hz, 1H), 6.83 (s, 1H), 6.59 (dd, J = 1.41, 7.82 Hz, 1H), 3.64 (br s, 2H), 1.28 (s, 10H). MS (ESI) m/z for C$_{16}$H$_{19}$N [M + H]$^+$: calcd 226.2, found 226.2.

3-(3,5-Di-tert-butylphenyl)aniline (12q). 12q was prepared from 11q (0.22 g, 0.71 mmol) following the general procedure B as yellow oil (0.18 g, 91%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.35−7.43 (m, 3H), 7.18−7.23 (m, 1H), 6.99 (d, J = 7.72 Hz, 1H), 6.90 (s, 1H), 6.67 (dd, J = 1.32, 7.91 Hz, 1H), 3.26−4.11 (m, 2H), 1.37 (s, 18H). MS (ESI) m/z for C$_{20}$H$_{27}$N [M + H]$^+$: calcd 282.2, found 282.4.

3-(3-Phenylphenyl)aniline (12r). 12r was prepared from 11r (0.27 g, 0.98 mmol) following the general procedure B as colorless liquid (0.18 g, 73%). MS (ESI) m/z for C$_{18}$H$_{15}$N [M + H]$^+$: calcd 246.1, found 246.3.

3-(4-Phenylphenyl)aniline (12s). 12s was prepared from 11s (0.20 g, 0.73 mmol) following the general procedure B as yellow solid (0.18 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.61−7.68 (m, 6H), 7.45 (t, J = 7.44 Hz, 2H), 7.36 (d, J = 7.16 Hz, 1H), 7.21−7.28 (m, 1H), 7.04 (d, J = 7.72 Hz, 1H), 6.95 (d, J = 1.88 Hz, 1H), 6.68 (dd, J = 1.32, 7.91 Hz, 1H), 3.72 (br s, 2H). MS (ESI) m/z for C$_{18}$H$_{15}$N [M + H]$^+$: calcd 246.1, found 246.2.

3-(4-Benzoylphenyl)aniline (12t). 12t was prepared from 11t (0.18 g, 0.59 mmol) following the general procedure B as yellow solid (0.14 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.72−7.83 (m, 4H), 7.59 (d, J = 8.29 Hz, 2H), 7.51 (d, J = 7.35 Hz, 1H), 7.43 (d, J = 7.54 Hz, 2H), 7.14−7.20 (m, 1H), 6.96 (d, J = 7.72 Hz, 1H), 6.85−6.89 (m, 1H), 6.62−6.69 (m, 1H), 3.65 (br s, 2H). MS (ESI) m/z for C$_{19}$H$_{15}$NO [M + H]$^+$: calcd 274.1, found 274.2.

3-(1-Benzofuran-5-yl)aniline (12u). 12u was prepared from 11u (0.20 g, 0.84 mmol) following the general procedure B as white solid (0.12 g, 66%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.75 (d, J = 1.32 Hz, 1H), 7.63 (d, J = 2.07 Hz, 1H), 7.45−7.55 (m, 2H), 7.18−7.26 (m, 1H), 6.98−7.03 (m, 1H), 6.91 (t, J = 1.98 Hz, 1H), 6.78 (dd, J = 0.66, 2.17 Hz, 1H), 6.66 (ddd, J = 0.94, 2.31, 7.86 Hz, 1H), 3.71 (br s, 2H). MS (ESI) m/z for C$_{14}$H$_{11}$NO [M + H]$^+$: calcd 210.1, found 210.2.

3-(Naphthalen-2-yl)aniline (12v). 12v was prepared from 11v (0.26 g, 1.05 mmol) following the general procedure B as white solid (0.11 g, 46%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.00 (s, 1H), 7.84−7.91 (m, 3H), 7.71 (dd, J = 1.60, 8.57 Hz, 1H), 7.44−7.50 (m, 2H), 7.26 (d, J = 2.83 Hz, 1H), 7.12 (d, J = 7.16 Hz, 1H), 7.04 (s, 1H), 6.71 (d, J = 7.16 Hz, 1H). MS (ESI) m/z for C$_{16}$H$_{13}$N [M + H]$^+$: calcd 220.1, found 220.2.

3-(Quinolin-2-yl)aniline (12w). 12w was prepared from 11w (0.02 g, 0.10 mmol) following the general procedure B as yellow solid (0.02 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.21 (dd, J = 5.84, 8.48 Hz, 2H), 7.80−7.87 (m, 2H), 7.73 (ddd, J = 1.41, 6.97, 8.38 Hz, 1H), 7.58 (t, J = 1.98 Hz, 1H), 7.52−7.56 (m, 1H), 7.45−7.51 (m, 1H), 7.31 (t, J = 7.82 Hz, 1H), 6.77−6.82 (m, 1H), 3.46 (br s, 2H). MS (ESI) m/z for C$_{15}$H$_{12}$N$_2$ [M + H]$^+$: calcd 221.1, found 221.2.

3-(Quinolin-3-yl)aniline (12x). 12x was prepared from 11x (0.08 g, 0.33 mmol) following the general procedure B as yellow solid (0.07 g, quant). ^{1}H NMR (300 MHz, CDCl$_3$) δ 9.15 (d, J = 2.26 Hz, 1H), 8.25 (d, J = 2.07 Hz, 1H), 8.13 (d, J = 8.29 Hz, 1H), 7.85 (d, J = 8.10 Hz, 1H), 7.70 (ddd, J = 1.41, 6.92, 8.43 Hz, 1H), 7.52−7.59 (m, 1H), 7.26−7.33 (m, 1H), 7.09 (dd, J = 0.94, 7.72 Hz, 1H), 7.00 (t, J = 1.98 Hz, 1H), 6.75 (ddd, J = 0.75, 2.26, 7.91 Hz, 1H), 3.86 (br s, 2H). MS (ESI) m/z for C$_{15}$H$_{12}$N$_2$ [M + H]$^+$: calcd 221.1, found 221.2.

3-(9H-Fluoren-2-yl)aniline (12y). 12y was prepared from 11y (0.07 g, 0.26 mmol) following the general procedure B as white solid (0.05 g, 71%). ^{1}H NMR (300 MHz, CDCl$_3$) δ 7.77−7.83 (m, 2H), 7.74 (d, J = 0.75 Hz, 1H), 7.52−7.60 (m, 2H), 7.35−7.42 (m, 1H), 7.31 (dd, J = 1.22, 7.44 Hz, 1H), 7.20−7.28 (m, 2H), 7.03−7.07 (m, 1H), 6.97 (t, J = 1.98 Hz, 1H), 6.68 (ddd, J = 0.75, 2.31, 7.86 Hz, 1H), 3.94 (s, 2H), 3.73 (br s, 2H). MS (ESI) m/z for C$_{19}$H$_{15}$N [M + H]$^+$: calcd 258.1, found 258.2.

General Procedure C. To a solution of aryl amine (1 equiv) in anhydrous chloroform (0.04 M) was added 4-chlorophenyl isocyanate (1 equiv) at room temperature. The reaction mixture was then heated at 60 °C for 16 h. The precipitated product was filtered and thoroughly washed with dichloromethane.

3-(4-Chlorophenyl)-1-[3-(6-methoxypyridin-2-yl)phenyl]urea (15). 15 was prepared from 12a (0.08 g, 0.5 mmol) following the general procedure C as white solid (0.14 g, 82%); mp 212−213 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (d, J = 3.96 Hz, 2H), 8.14−8.18 (m, 1H), 7.76−7.83 (m, 1H), 7.69 (d, J = 8.10 Hz, 1H), 7.56 (d, J = 9.42 Hz, 1H), 7.48−7.54 (m, 3H), 7.41 (d, J = 7.91 Hz, 1H), 7.32−7.38 (m, 2H), 6.80 (d, J = 8.29 Hz, 1H), 3.97 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 153.6, 152.5, 140.0, 139.9, 138.9, 138.7, 129.1, 128.6, 125.3, 120.2, 119.8, 119.0, 116.4, 112.9, 109.3, 52.8. MS (ESI) m/z for C$_{19}$H$_{16}$ClN$_3$O$_2$ [M + H]$^+$: calcd 354.1, found 354.3.

3-(4-Chlorophenyl)-1-[3-(4-methylpyridin-2-yl)phenyl]urea (16). 16 was prepared from 12b (0.09 g, 0.55 mmol) following the general procedure C as white solid (0.12 g, 64%); mp 195−196 °C. ^{1}H NMR (300 MHz, CDCl$_3$) δ 8.50 (d, J = 5.09 Hz, 1H), 7.87 (s, 1H), 7.61 (d, J = 7.54 Hz, 1H), 7.51 (s, 1H), 7.39 (td, J = 7.91, 15.82 Hz, 2H), 7.20−7.24 (m, 4H), 7.07−7.16 (m, 3H), 2.41 (s, 3H). ^{13}C NMR (75 MHz, CDCl3) δ 157.0, 153.2, 149.1, 148.5, 140.4, 138.7, 136.9, 129.6, 129.0, 128.7, 123.6, 122.5, 122.1, 121.6, 121.3, 119.4, 21.2. MS (ESI) m/z for C$_{19}$H$_{17}$ClN$_3$O [M + H]$^+$: calcd 338.1, found 338.5.

3-(4-Chlorophenyl)-1-[3-(2-methoxypyridin-4-yl)phenyl]urea (17). 17 was prepared from 12c (0.03 g, 0.15 mmol) following the general procedure C as white solid (0.03 g, 57%); mp 187−189 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.05 (br s, 1H), 8.96 (br s, 1H), 8.43 (s, 1H), 7.69−8.04 (m, 2H), 7.20−7.61 (m, 7H), 6.92 (d, J = 7.54 Hz, 1H), 3.90 (br s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 163.1, 152.5, 144.5, 140.2, 138.7, 137.6, 137.5, 129.4, 128.5, 125.3, 120.0, 119.8, 117.4, 116.2, 110.6, 53.2. MS (ESI) m/z for C$_{19}$H$_{16}$ClN$_3$O$_2$ [M + H]$^+$: calcd 353.1, found 353.4.

3-(4-Chlorophenyl)-1-[3-(pyridin-2-yl)phenyl]urea (18). 18 was prepared from 12d (0.05 g, 0.29 mmol) following the general procedure C as white solid (0.05 g, 53%); mp 218−220 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89−8.96 (m, 2H), 8.67 (d, J = 4.71 Hz, 1H), 8.25 (d, J = 1.70 Hz, 1H), 7.87−7.91 (m, 1H), 7.67 (d, J = 7.72 Hz, 1H), 7.45−7.55 (m, 4H), 7.30−7.38 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 155.9, 152.5, 149.5, 140.0, 139.3, 138.7, 138.5, 137.2, 129.1, 128.6, 125.3, 122.6, 120.2, 119.8, 119.0, 116.5. MS (ESI) m/z for C$_{18}$H$_{14}$ClN$_3$O [M + H]$^+$: calcd 324.1, found 324.2.

3-(4-Chlorophenyl)-1-[3-(pyridin-3-yl)phenyl]urea (19). 19 was prepared from 14a (0.05 g, 0.29 mmol) following the general procedure C as white solid (0.05 g, 53%); mp 195−198 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (br s, 1H), 8.85 (br s, 2H), 8.59 (d, J = 2.83 Hz, 1H), 8.02 (d, J = 7.35 Hz, 1H), 7.82 (br s, 1H), 7.38−7.55 (m, 5H), 7.33 (d, J = 7.35 Hz, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 148.5, 147.5, 140.3, 138.6, 137.7, 135.7, 134.1, 129.6, 128.6, 125.4, 123.9, 120.6, 119.8, 118.1, 116.7. MS (ESI) m/z for C$_{18}$H$_{14}$ClN$_3$O [M + H]$^+$: calcd 324.1, found 324.3.

3-(4-Chlorophenyl)-1-[3-(pyridin-4-yl)phenyl]urea (20). 20 was prepared from 12e (0.03 g, 0.15 mmol) following the general procedure C as white solid (0.03 g, 33%); 195−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.92 (s, 1H), 8.89 (s, 1H), 8.65 (d, J = 5.27 Hz, 2H), 7.93 (s, 1H), 7.65 (d, J = 5.46 Hz, 2H), 7.46−7.54 (m, 3H), 7.43 (d, J = 8.10 Hz, 2H), 7.34 (d, J = 8.67 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 150.2, 147.1, 140.4, 138.6, 137.8, 129.7, 128.6, 125.4, 121.2, 120.5, 119.8, 119.1, 116.5. MS (ESI) m/z for C$_{18}$H$_{14}$ClN$_3$O [M + H]$^+$: calcd 324.1, found 324.1.

3-(4-Chlorophenyl)-1-[3-(pyrimidin-5-yl)phenyl]urea (21). 21 was prepared from 12f (0.03 g, 0.15 mmol) following the general procedure C as white solid (0.03 g, 33%); mp 198−199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (s, 1H), 9.09 (s, 2H), 8.95 (d, J = 19.21 Hz, 2H), 7.83 (s, 1H), 7.55 (s, 1H), 7.49−7.53 (m, 2H), 7.47 (s, 1H), 7.42 (s, 1H), 7.34 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.3, 154.6, 152.5, 140.4, 138.6, 134.4, 133.4, 129.8, 128.6, 125.5, 120.7, 119.8, 118.9, 116.7. MS (ESI) m/z for C$_{17}$H$_{13}$ClN$_4$O [M − H]$^-$: calcd 323.1, found 323.3.

3-(4-Chlorophenyl)-1-(3-phenylphenyl)urea (22). **22** was prepared from 3-biphenylamine (0.05 g, 0.29 mmol) following the general procedure C as white solid (0.05 g, 53%); mp 228−230 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (br s, 1H), 8.86 (br s, 1H), 7.80 (br s, 1H), 7.62 (d, J = 7.91 Hz, 2H), 7.44−7.54 (m, 4H), 7.29−7.42 (m, 5H), 7.27 (td, J = 1.98, 4.33 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.8, 140.3, 140.1, 138.7, 129.3, 128.9, 128.6, 127.5, 126.6, 125.3, 120.4, 119.8, 117.4, 116.6. MS (ESI) m/z for C$_{17}$H$_{13}$ClN$_4$O [M − H]$^-$: calcd 321.1, found 321.2.

3-(4-Chlorophenyl)-1-[3-(3-methoxyphenyl)phenyl]urea (23). **23** was prepared from **12g** (0.02 g, 0.1 mmol) following the general procedure C as white solid (0.02 g, 57%); mp 194−196 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.82 (s, 1H), 7.76 (br s, 1H), 7.49 (br s, 2H), 7.22−7.44 (m, 6H), 7.16 (d, J = 13.37 Hz, 2H), 6.95 (br s, 1H), 3.82 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 159.7, 152.5, 141.8, 140.7, 140.0, 138.7, 130.0, 129.3, 128.6, 125.4, 120.5, 119.8, 119.0, 117.6, 116.7, 113.0, 112.2, 55.1. MS (ESI) m/z for C$_{20}$H$_{17}$ClN$_2$O$_2$ [M − H]$^-$: calcd 351.1, found 351.4.

3-(4-Chlorophenyl)-1-[3-(3-hydroxyphenyl)phenyl]urea (24). **24** was prepared from **12h** (0.02 g, 0.1 mmol) following the general procedure C as white solid (0.02 g, 44%); mp 187−190 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (s, 1H), 8.90 (s, 1H), 7.51 (d, J = 8.29 Hz, 1H), 7.18−7.38 (m, 4H), 6.98−7.10 (m, 2H), 6.90−6.97 (m, 1H), 6.74 (d, J = 18.84 Hz, 2H), 6.54 (d, J = 8.67 Hz, 1H), 5.14 (s, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.7, 142.5, 141.6, 140.9, 140.0, 138.7, 129.9, 129.2, 128.6, 119.8, 117.2, 116.5, 115.1, 114.0, 113.3, 113.1, 112.1. MS (ESI) m/z for C$_{19}$H$_{15}$ClN$_2$O$_2$ [M − H]$^-$: calcd 337.1 found 337.5.

3-(4-Chlorophenyl)-1-[3-(3-isopropylphenyl)phenyl]urea (25). **25** was prepared from **12i** (0.03 g, 0.13 mmol) following the general procedure C as white solid (0.03 g, 60%); mp 190−192 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.90 (br s, 1H), 8.82 (br s, 1H), 7.77 (br s, 1H), 7.46−7.54 (m, 2H), 7.29−7.43 (m, 5H), 7.26 (d, J = 7.35 Hz, 1H), 7.15 (d, J = 6.78 Hz, 1H), 7.09 (br s, 1H), 6.93 (d, J = 5.27 Hz, 1H), 4.60−4.78 (m, 1H), 1.30 (d, J = 5.84 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.9, 152.5, 141.8, 140.7, 140.1, 138.7, 130.0, 129.2, 128.5, 125.3, 120.4, 119.8, 118.8, 117.5, 116.7, 69.2, 21.8. MS (ESI) m/z for C$_{22}$H$_{21}$ClN$_2$O$_2$ [M − H]$^-$: calcd 379.1, found 379.3.

1-[3-(2H-1,3-Benzodioxol-5-yl)phenyl]-3-(4-chlorophenyl)urea (26). **26** was prepared from **14b** (0.09 g, 0.40 mmol) following the general procedure C as white solid (0.09 g, 59%); mp 224−225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.73−8.90 (m, 2H), 7.71 (s, 1H), 7.44−7.56 (m, 3H), 7.28−7.39 (m, 4H), 7.07−7.23 (m, 2H), 6.98−7.03 (m, 1H), 6.07 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 147.9, 146.8, 140.5, 139.9, 138.6, 134.6, 129.2, 128.6, 125.3, 120.2, 119.8, 117.1, 116.4, 108.6, 107.0, 101.1. MS (ESI) m/z for C$_{20}$H$_{15}$ClN$_2$O$_3$ [M + H]$^+$: calcd 367.1, found 367.4.

3-(4-Chlorophenyl)-1-[3-(3-methylphenyl)phenyl]urea (27). **27** was prepared from **14c** (0.13 g, 0.82 mmol) following the general procedure C as white solid (0.11 g, 41%); mp 195−196 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.81 (s, 1H), 7.79 (s, 1H), 7.48−7.53 (m, 2H), 7.43 (s, 1H), 7.31−7.40 (m, 6H), 7.23−7.27 (m, 1H), 7.19 (d, J = 7.16 Hz, 1H), 2.38 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.9, 140.2, 140.0, 138.6, 138.0, 129.3, 128.8, 128.6, 128.1, 127.2, 125.4, 123.7, 120.4, 119.8, 117.4, 116.6, 21.1. MS (ESI) m/z for C$_{20}$H$_{17}$ClN$_2$O [M + H]$^+$: calcd 337.1, found 337.5.

3-(4-Chlorophenyl)-1-[3-(2-methylphenyl)phenyl]urea (28). **28** was prepared from **14d** (0.15 g, 0.82 mmol) following the general procedure C as white solid (0.11 g, 41%); mp 194−195 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.85 (s, 1H), 8.78 (s, 1H), 7.45−7.51 (m, 4H), 7.37 (d, J = 3.77 Hz, 1H), 7.27−7.36 (m, 5H), 7.20 (d, J = 4.71 Hz, 1H), 6.94 (d, J = 7.16 Hz, 1H), 2.24 (s, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 141.8, 141.3, 139.3, 138.6, 138.5, 134.6, 130.3, 129.3, 128.6, 127.3, 125.9, 125.5, 125.3, 122.6, 119.8, 119.7, 118.9, 116.9, 20.1. MS (ESI) m/z for C$_{20}$H$_{17}$ClN$_2$O [M − H]$^-$: calcd 357.1, found 335.3.

3-(4-Chlorophenyl)-1-[3-(3-nitrophenyl)phenyl]urea (29). **29** was prepared from **14e** (0.04 g, 0.19 mmol) following the general procedure C as white solid (0.06 g, 82%); mp 198−200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (d, J = 1.88 Hz, 2H), 8.37 (s, 1H), 8.22 (dd, J = 1.70, 7.91 Hz, 1H), 8.09 (d, J = 7.91 Hz, 1H), 7.88 (s, 1H), 7.77 (t, J = 8.01 Hz, 1H), 7.43−7.50 (m, 4H), 7.36−7.42 (m, 1H), 7.33 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 148.4, 141.8, 140.4, 138.6, 138.4, 133.1, 130.5, 129.7, 128.6, 125.5, 122.2, 120.9, 120.6, 119.8, 118.5, 116.7. MS (ESI) m/z for C$_{19}$H$_{14}$ClN$_3$O$_3$ [M − H]$^-$: calcd 366.1, found 366.5.

3-(4-Chlorophenyl)-1-[3-(4-chlorophenyl)phenyl]urea (30). **30** was prepared from **12j** (0.05 g, 0.23 mmol) following the general procedure C as white solid (0.08 g, 94%); mp 194−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.02 (s, 1H), 8.98 (s, 1H), 7.86 (t, J = 1.79 Hz, 1H), 7.78 (s, 1H), 7.56−7.69 (m, 2H), 7.53 (d, J = 2.64 Hz, 1H), 7.50 (d, J = 3.01 Hz, 1H), 7.45−7.48 (m, 1H), 7.35−7.40 (m, 1H), 7.32−7.35 (m, 1H), 7.31 (d, J = 3.39 Hz, 1H), 7.27 (dd, J = 1.51, 4.52 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.2, 139.5, 139.1, 138.6, 132.4, 129.4, 128.8, 128.6, 128.3, 125.4, 120.3, 119.8, 117.8, 116.5. MS (ESI) m/z for C$_{19}$H$_{14}$Cl$_2$N$_2$O [M − H]$^-$: calcd 355.1, found 355.3.

3-(4-Chlorophenyl)-1-[3-(3,5-dichlorophenyl)phenyl]urea (31). **31** was prepared from **12k** (0.03 g, 0.19 mmol) following the general procedure C as white solid (0.045 g, 91%); 203−206 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.88 (s, 1H), 7.83 (d, J = 2.07 Hz, 1H), 7.79 (s, 1H), 7.68−7.73 (m, 1H), 7.58−7.64 (m, 1H), 7.43−7.52 (m, 3H), 7.38−7.42 (m, 2H), 7.27−7.37 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.3, 138.6, 137.8, 134.6, 129.6, 128.9, 128.6, 126.9, 126.6, 125.3, 120.6, 119.9, 118.7, 116.8. MS (ESI) m/z for C$_{19}$H$_{13}$Cl$_3$N$_2$O [M − H]$^-$: calcd 391.0, found 390.9.

3-(4-Chlorophenyl)-1-[3-(3,4-dichlorophenyl)phenyl]urea (32). **32** was prepared from **12l** (0.03 g, 0.13 mmol) following the general procedure C as white solid (0.03 g, 61%); mp 197−198 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.98 (s, 1H), 8.92 (s, 1H), 7.82−7.90 (m, 2H), 7.69−7.76 (m, 1H), 7.62 (dd, J = 1.88, 8.48 Hz, 1H), 7.53 (s, 2H), 7.48−7.56 (m, 2H), 7.38−7.46 (m, 2H), 7.29−7.37 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.9, 140.3, 138.6, 138.1, 131.7, 131.0, 130.2, 129.5, 128.6, 128.3, 126.8, 125.4, 120.5, 119.8, 118.3, 116.6. MS (ESI) m/z for C$_{19}$H$_{13}$Cl$_3$N$_2$O [M − H]$^-$: calcd 391.0, found 390.9.

3-(4-Chlorophenyl)-1-[3-(2,6-dichlorophenyl)phenyl]urea (33). **33** was prepared from **12m** (0.02 g, 0.15 mmol) following the general procedure C as white solid (0.04 g, 69%); mp 201−202 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (br s, 2H), 7.59 (d, J = 2.64 Hz, 2H), 7.37−7.53 (m, 7H), 7.28−7.36 (m, 2H), 6.80−6.92 (m, J = 6.97 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 139.6, 138.8, 138.6, 136.9, 133.8, 130.1, 128.9, 128.6, 128.4, 125.4, 122.7, 119.8, 118.7, 118.0. MS (ESI) m/z for C$_{19}$H$_{13}$Cl$_3$N$_2$O [M − H]$^-$: calcd 391.0, found 391.1.

3-(4-Chlorophenyl)-1-[3-(4-fluorophenyl)phenyl]urea (34). **34** was prepared from **12n** (0.03 g, 0.16 mmol) following the general procedure C as white solid (0.05 g, 92%); mp 222−225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.91 (s, 1H), 8.85 (s, 1H), 7.79 (s, 1H), 7.61−7.69 (m, 2H), 7.45−7.54 (m, 3H), 7.36−7.41 (m, 2H), 7.34 (s, 2H), 7.31 (d, J = 3.01 Hz, 2H), 7.23−7.28 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.1, 139.8, 138.7, 129.4, 128.9, 128.6, 128.6, 128.5, 126.6, 125.4, 120.4, 119.8, 117.4, 116.6, 115.8, 115.5. MS (ESI) m/z for C$_{19}$H$_{14}$ClFN$_2$O [M − H]$^-$: calcd 339.1, found 339.6.

3-(4-Chlorophenyl)-1-[3-(2,4-difluorophenyl)phenyl]urea (35). **35** was prepared from **12o** (0.04 g, 0.20 mmol) following the general procedure C as white solid (0.05 g, 66%); 198−199 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.95 (d, J = 3.77 Hz, 2H), 7.75 (s, 1H), 7.61−7.69 (m, 1H), 7.52−7.60 (m, 3H), 7.47−7.52 (m, 1H), 7.43−7.47 (m, 1H), 7.37−7.42 (m, 2H), 7.23−7.32 (m, 1H), 7.20 (d, J = 6.97 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.4, 139.8, 138.6, 134.7, 131.9, 131.8, 131.7, 131.7, 129.1, 128.6, 125.4, 122.4, 119.8, 118.6, 117.8, 112.2, 112.1, 111.9, 111.8, 104.8, 104.5, 104.1. MS (ESI) m/z for C$_{19}$H$_{13}$ClF$_2$N$_2$O [M − H]$^-$: calcd 357.1, found 357.5.

3-(4-Chlorophenyl)-1-[3-(4-tert-butylphenyl)phenyl]urea (36). **36** was prepared from **12p** (0.01 g, 0.20 mmol) following the general procedure C as white solid (0.01 g, 48%); 195−198 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (s, 1H), 8.86 (s, 1H), 7.75 (s, 1H), 7.46−7.58 (m, 6H), 7.30−7.43 (m, 4H), 7.25 (d, J = 7.35 Hz, 1H),

1.32 (s, 9H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 149.9, 140.7, 140.0, 138.7, 137.4, 129.3, 128.6, 126.3, 125.7, 125.3, 120.3, 119.8, 117.2, 116.4, 34.2, 31.1. MS (ESI) m/z for $C_{23}H_{23}ClN_2O$ [M − H]$^-$: calcd 377.2, found 377.4.

3-(4-Chlorophenyl)-1-[3-(3,5-ditert-butylphenyl)phenyl]urea (37). **37** was prepared from **12q** (0.06 g, 0.21 mmol) following the general procedure C as white solid (0.03 g, 54%); mp 197−200 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.86 (s, 1H), 8.82 (s, 1H), 7.61 (br s, 1H), 7.50 (d, J = 6.78 Hz, 3H), 7.31−7.44 (m, 6H), 7.22−7.27 (m, 1H), 1.34 (s, 18H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 142.0, 140.0, 139.8, 138.7, 129.2, 128.6, 126.6, 125.3, 121.1, 120.9, 120.7, 119.7, 117.1, 116.9, 34.6, 31.3. MS (ESI) m/z for $C_{27}H_{31}ClN_2O$ [M − H]$^-$: calcd 433.2, found 433.6.

3-(4-Chlorophenyl)-1-[3-(3-phenylphenyl)phenyl]urea (38). **38** was prepared from **12r** (0.11 g, 0.72 mmol) following the general procedure C as white solid (0.16 g, 56%); mp 191−193 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.89 (s, 1H), 8.83 (s, 1H), 7.86 (br s, 2H), 7.75 (d, J = 7.16 Hz, 2H), 7.61−7.69 (m, 2H), 7.58 (d, J = 7.35 Hz, 1H), 7.47−7.54 (m, 4H), 7.36−7.46 (m, 4H), 7.33 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 141.0, 140.9, 140.7, 140.1, 140.1, 138.6, 129.6, 129.4, 128.9, 128.6, 127.6, 126.9, 125.9, 125.8, 125.4, 125.0, 120.7, 119.8, 117.6, 116.8. MS (ESI) m/z for $C_{25}H_{19}ClN_2O$ [M − H]$^-$: calcd 397.1, found 397.1.

3-(4-Chlorophenyl)-1-[3-(4-phenylphenyl)phenyl]urea (39). **39** was prepared from **12s** (0.01 g, 0.20 mmol) following the general procedure C as white solid (0.01 g, 48%); 195−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.93 (br s, 1H), 8.88 (br s, 1H), 7.88 (s, 1H), 7.70−7.84 (m, 6H), 7.47−7.58 (m, 4H), 7.40 (d, J = 5.09 Hz, 3H), 7.31−7.38 (m, 3H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 140.2, 140.2, 139.6, 139.2, 138.7, 129.4, 129.0, 128.6, 127.5, 127.2, 127.1, 126.6, 126.5, 125.4, 120.3, 119.8, 117.6, 116.5. MS (ESI) m/z for $C_{25}H_{19}ClN_2O$ [M − H]$^-$: calcd 397.1, found 397.0.

3-(4-Chlorophenyl)-1-[3-(4-benzoylphenyl)phenyl]urea (40). **40** was prepared from **12t** (0.03 g, 0.11 mmol) following the general procedure C as white solid (0.04 g, 81%); mp 194−197 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.87 (d, J = 1.88 Hz, 2H), 7.88 (s, 1H), 7.79−7.86 (m, 4H), 7.74−7.78 (m, 2H), 7.66−7.72 (m, 1H), 7.54−7.62 (m, 2H), 7.46−7.51 (m, 2H), 7.43 (d, J = 4.52 Hz, 2H), 7.36−7.41 (m, 1H), 7.32 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 195.3, 152.5, 144.3, 140.3, 139.6, 138.6, 137.2, 135.8, 132.6, 130.4, 129.6, 129.5, 128.6, 128.6, 126.7, 125.4, 120.7, 119.8, 118.3, 116.8. MS (ESI) m/z for $C_{26}H_{19}ClN_2O_2$ [M − H]$^-$: calcd 425.1, found 425.3.

1-[3-(1-Benzofuran-5-yl)phenyl]-3-(4-chlorophenyl)urea (41). **41** was prepared from **12u** (0.09 g, 0.55 mmol) following the general procedure C as white solid (0.12 g, 60%); mp 224−225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.82 (s, 1H), 8.05 (d, J = 2.07 Hz, 1H), 7.87 (d, J = 5.84 Hz, 2H), 7.66−7.71 (m, 1H), 7.47−7.60 (m, 3H), 7.27−7.40 (m, 5H), 7.04 (d, J = 1.32 Hz, 1H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 154.0, 152.5, 146.6, 141.2, 140.0, 138.7, 135.6, 129.3, 128.6, 127.9, 127.2, 125.4, 123.4, 120.7, 119.8, 119.2, 118.7, 117.0, 117.0, 111.5, 107.0. MS (ESI) m/z for $C_{21}H_{15}ClN_2O_2$ [M − H]$^-$: calcd 361.1, found 361.4.

3-(4-Chlorophenyl)-1-[3-(naphthalen-2-yl)phenyl]urea (42). **42** was prepared from **12v** (0.11 g, 0.68 mmol) following the general procedure C as white solid (0.14 g, 55%); mp 225−226 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.00 (d, J = 6.40 Hz, 2H), 8.15 (s, 1H), 7.97−8.04 (m, 2H), 7.91−7.96 (m, 2H), 7.79 (dd, J = 1.51, 8.67 Hz, 1H), 7.46−7.56 (m, 4H), 7.42 (s, 3H), 7.32 (d, J = 8.85 Hz, 2H), 7.21 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.6, 140.6, 140.0, 138.5, 137.5, 133.2, 132.2, 129.5, 128.6, 128.5, 128.1, 127.4, 126.5, 126.2, 125.6, 125.1, 125.0, 120.9, 120.0, 117.7, 116.9. MS (ESI) m/z for $C_{23}H_{17}ClN_2O$ [M − H]$^-$: calcd 371.1, found 371.3.

3-(4-Chlorophenyl)-1-[3-(quinolin-2-yl)phenyl]urea (43). **43** was prepared from **12w** (0.01 g, 0.09 mmol) following the general procedure C as white solid (0.02 g, 59%); mp 224−225 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.96 (s, 1H), 8.87 (s, 1H), 8.46 (d, J = 8.48 Hz, 1H), 8.32 (s, 1H), 8.04−8.09 (m, 1H), 8.00 (d, J = 7.72 Hz, 1H), 7.75−7.86 (m, 2H), 7.55−7.64 (m, 2H), 7.46−7.52 (m, 2H), 7.33 (d, J = 8.85 Hz, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 156.1,

152.6, 147.4, 139.9, 139.3, 138.4, 137.3, 130.1, 129.4, 128.9, 128.6, 127.8, 126.9, 126.6, 125.6, 121.2, 120.1, 119.7, 118.8, 117.2. MS (ESI) m/z for $C_{22}H_{16}ClN_3O$ [M + H]$^+$: calcd 374.1, found 374.0.

3-(4-Chlorophenyl)-1-[3-(quinolin-3-yl)phenyl]urea (44). **44** was prepared from **12x** (0.05 g, 0.33 mmol) following the general procedure C as white solid (0.08 g, 63%); mp 221−222 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.21 (d, J = 2.26 Hz, 1H), 8.94 (d, J = 7.54 Hz, 2H), 8.60 (d, J = 2.07 Hz, 1H), 8.04−8.13 (m, 2H), 7.98 (s, 1H), 7.79 (dt, J = 1.51, 7.63 Hz, 1H), 7.63−7.70 (m, 1H), 7.46−7.55 (m, 5H), 7.36 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 149.4, 146.9, 140.4, 138.6, 137.7, 132.9, 132.8, 129.7, 129.5, 128.6, 128.6, 128.4, 127.6, 127.0, 125.4, 120.9, 119.8, 118.2, 117.0. MS (ESI) m/z for $C_{22}H_{16}ClN_3O$ [M + H]$^+$: calcd 374.1, found 374.3.

3-(4-Chlorophenyl)-1-[3-(9H-fluoren-2-yl)phenyl]urea (45). **45** was prepared from **12y** (0.03 g, 0.18 mmol) following the general procedure C as white solid (0.05 g, 67%); mp 283−286 °C. ^{1}H NMR (300 MHz, DMSO-d_6) δ 8.88 (s, 1H), 8.84 (s, 1H), 7.99 (d, J = 7.91 Hz, 1H), 7.90−7.96 (m, 2H), 7.85 (s, 1H), 7.60−7.69 (m, 2H), 7.49−7.55 (m, 2H), 7.30−7.43 (m, 7H), 4.01 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6) δ 152.5, 143.8, 143.3, 141.1, 140.7, 140.5, 140.1, 138.9, 138.7, 129.3, 128.6, 126.8, 125.5, 125.4, 125.1, 123.3, 120.5, 120.4, 120.1, 119.8, 117.3, 116.6. MS (ESI) m/z for $C_{26}H_{19}ClN_2O$ [M − H]$^-$: calcd 409.1, found 409.5.

Calcium Mobilization Assay. CHO-RD-HGA16 cells (Molecular Devices, CA) stably expressing the human CB1 receptor were plated into 96-well black-walled assay plates at 25000 cells/well in 100 μL of Ham's F12 (supplemented with 10% fetal bovine serum, 100 units of penicillin/streptomycin, and 100 μg/mL Normocin) and incubated overnight at 37 °C, 5% CO$_2$. Calcium 5 dye (Molecular Devices, CA) was reconstituted according to the manufacturer's instructions. The reconstituted dye was diluted 1:40 in prewarmed (37 °C) assay buffer (1× HBSS, 20 mM HEPES, 2.5 mM probenecid, pH 7.4 at 37 °C). Growth medium was removed, and the cells were gently washed with 100 μL of prewarmed (37 °C) assay buffer. The cells were incubated for 45 min at 37 °C, 5% CO$_2$, in 200 μL of the diluted Calcium 5 dye solution. For antagonist assays to determine IC$_{50}$ values, the EC$_{80}$ concentration of CP55,940 was prepared at 10× the desired final concentration in 0.25% BSA/0.5% DMSO/0.5% EtOH/assay buffer, aliquoted into 96-well polypropylene plates, and warmed to 37 °C. Serial dilutions of the test compounds were prepared at 10× the desired final concentration in 2.25% BSA/4.5% DMSO/4.5% EtOH/ assay buffer. After the dye loading incubation period, the cells were pretreated with 25 μL of the test compound serial dilutions and incubated for 15 min at 37 °C. After the pretreatment incubation period, the plate was read with a FLIPR Tetra (Molecular Devices, CA). Calcium-mediated changes in fluorescence were monitored every 1 s over a 90 s time period, with the Tetra adding 25 μL of the CP55,940 EC$_{80}$ concentration at the 10 s time point (excitation/ emission: 485/525 nm). Relative fluorescence units (RFU) were plotted against the log of compound concentrations. Data were fit to a three-parameter logistic curve to generate IC$_{50}$ values (GraphPad Prism 6.0, CA). For the modulation experiments, the above procedure was followed except that cells were pretreated with a single concentration of test compound (prepared at 10× the desired concentration in 2.25% BSA/4.5% DMSO/4.5% EtOH/assay buffer) and the Tetra added serial dilutions of CP55,940 (prepared at 10× the desired concentration in 0.25% BSA/0.5% DMSO/0.5% EtOH/assay buffer). For agonist screens, the above procedure was followed except that cells were pretreated with 2.25% BSA/4.5% DMSO/4.5% EtOH/assay buffer and the Tetra added single concentration dilutions of the test compounds prepared at 10× the desired final concentration in 0.25% BSA/0.5% DMSO/0.5% EtOH/assay buffer. Test compound RFUs were compared to the CP55,940 E_{max} RFUs to generate % E_{max} values. For the CB2 agonist screens and IC$_{50}$ determinations, the same procedures were followed except that stable human CB2-CHO-RD-HGA16 cells were used. CB2 antagonist screens were conducted similar to the IC$_{50}$ experiments except that a single concentration of test compound was used instead of serial dilutions and test compound RFUs were compared to the CP55,940 EC$_{80}$ RFUs to generate % inhibition values.

Membrane Preparation. Cerebella from adult male CD-1 mice were dissected on ice, snap frozen, and stored at −80 °C until the day of the experiment. Cerebella were homogenized by polytron in membrane buffer (50 mM Tris, 3 mM MgCl$_2$, 0.2 mM EGTA, 100 mM NaCl, pH 7.4) on ice and centrifuged for 10 min at 40000g at 4 °C. The supernatant was discarded, and the pellet was suspended in membrane buffer, homogenized, and centrifuged again for 10 min at 40000g. The pellet was resuspended in membrane buffer and protein quantified by the Bradford method.

[^{35}S]GTP-γ-S Binding Assay. Cerebellar membranes were preincubated in assay buffer (membrane buffer containing 1 mg/mL bovine serum albumin; BSA) for 10 min with 3 units/mL adenosine deaminase then incubated for 60 min at 30 °C with 30 μM GDP and 0.1 nM [^{35}S]GTP-γ-S or 90 min with 1 nM [^{3}H]CP55,940. Serial dilutions of test compounds were done in 100% DMSO with final assay DMSO concentration of 0.1%. Nonspecific binding was determined by adding 30 μM unlabeled GTP-γ-S or 1 μM unlabeled CP55,940. Reactions were terminated by vacuum filtration through GF/C filter plates (PerkinElmer). GTP-γ-S inhibition curves for test compounds were normalized to CP55,940 (100 nM) stimulation in the absence of test compound (i.e., vehicle = 100%). Curve fits were accomplished using Graphpad Prism 6.0 and where GTP-γ-S data were fit to three-parameter nonlinear regression, with bottom and top constrained to >0 and = 100, respectively, for IC$_{50}$ calculation. Values were considered significantly different when 95% confidence intervals did not overlap.

[^{3}H]CP55,940 Equilibrium Binding Assay. Cerebellar membranes were incubated in assay buffer for 90 min at 30 °C with 1 nM [^{3}H]CP55,940 and multiple concentrations of **34**. Nonspecific binding was determined by adding 1 μM unlabeled CP55,940. Reactions were terminated by vacuum filtration through GF/C filter plates (PerkinElmer). Binding data were fit to three-parameter nonlinear regression using Graphad Prism 6.0.

Metabolic Stability Assessment. was performed by Paraza Pharma Inc. (Montreal, Canada). Compounds were incubated with rat liver microsomes at 37 °C for a total of 45 min. The reaction was performed at pH 7.4 in 100 mM potassium phosphate buffer containing 0.5 mg/mL of rat liver microsomal protein. Phase I metabolism was assessed by adding NADPH to a final concentration of 1 mM and collecting samples at time points 0, 5, 15, 30, and 45 min. All collected samples were quenched 1:1 with ice-cold stop solution (1 μM labetalol and 1 μM glyburide in acetonitrile) and centrifuged to remove precipitated protein. Resulting supernatants were further diluted 1:4 with acetonitrile:water (1:1). Samples were analyzed by LC/MS/MS and calculations for half-life, and in vitro clearance were accomplished using Microsoft Excel (2007).

Reinstatement of Extinguished Cocaine-Seeking Behavior. Adult male Sprague−Dawley rats (Harlan, Indianapolis, IN) weighing 280−300 g were used in the study. Animals were housed individually on a 12/12 h light/dark cycle (behavioral experiments were conducted during the light period) with free access to water and food except during experimental sessions. Animals were maintained and experiments conducted in accordance with the Institutional Animal Care and Use Committee, University at Buffalo, and with the 2011 Guide for the Care and Use of Laboratory Animals (Institute of Laboratory Animal Resources on Life Sciences, National Research Council, National Academy of Sciences, Washington, DC.

Drug self-administration, extinction, and reinstatement: The reinstatement procedure was descriebd in detail elsewhere.[17,31] Briefly, rats were surgically implanted with a chronic indwelling jugular catheter. After one-week recovery, rats were trained to press the active lever (left lever) for infusion of cocaine (0.75 mg/kg/inf) under a fixed ratio [FR] schedule (starting FR = 1, which was increased to FR 5 within 5 training sessions) schedule during daily 2 h sessions for 14 days. Reinforcer deliveries were accompanied by the presentation of a stimulus light over the active lever followed by a 30 s time-out period, during which lever presses had no programmed consequence. Following acquisition of cocaine self-administration, extinction of drug-seeking behavior took place during 2 h daily sessions in which lever pressing produced no consequence. All other conditions

remained unchanged. After 7 days of extinction, all rats reached the extinction criteria (total responses less than 20% of the training sessions).

Drug-induced reinstatement test was conducted on the day following the last extinction session. Rats were pretreated with vehicle, compounds **2** (15, 30 mg/kg), or **34** (10 mg/kg) 10 min prior to a priming injection of cocaine (10 mg/kg, ip) administered immediately before the start of the reinstatement session.

Data analyses: Data are expressed as mean ± SEM. Differences in active lever responding between the last extinction session and reinstatement session were determined with paired t tests (within subjects comparison). The effects of compounds **2** on reinstatement were analyzed by a one-way analysis of variance (ANOVA) followed by post hoc Bonferroni's test (between subjects comparison). The effects of compounds **34** on reinstatement was analyzed by Student's t test. $P < 0.05$ was considered statistically significant.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.jmedchem.7b00707.

> HPLC analysis results of target compounds (PDF)
> Molecular formula strings with biological data (CSV)

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Author Contributions
The manuscript was written through contributions of all authors. All authors have given approval to the final version of the manuscript.

Notes
The authors declare no competing financial interest.

■ ABBREVIATIONS USED

CB1, cannabinoid 1 receptor; DCM, dichloromethane; 1,2-DCE, 1,2-dichloroethane; DME, 1,2-dimethoxyethane; FLIPR, fluorometric imaging plate reader; GPCR, G-protein-coupled receptor; HPLC, high performance liquid chromatography; IC$_{50}$, half-maximum inhibitory concentration; MS, mass spectrometry; NAM, negative allosteric modulator; NMR, nuclear magnetic resonance; PAM, positive allosteric modulator; SAR, structure−activity relationship; TLC, thin-layer chromatography

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