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Design and Synthesis of an Orally Active Metabotropic Glutamate Receptor Subtype-2 (mGluR2) Positive Allosteric Modulator (PAM) That Decreases Cocaine Self-Administration in Rats

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The modification of 3′-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yloxy)methyl)-biphenyl-4-carboxylic acid (BINA, **1**) by incorporating heteroatoms into the structure and replacing the cyclopentyl moiety led to the development of new mGluR2 positive allosteric modulators (PAMs) with optimized potency and superior druglike properties. These analogues are more potent than **1** in vitro and are highly selective for mGluR2 vs other mGluR subtypes. They have significantly improved pharmacokinetic (PK) properties, with excellent oral bioavailability and brain penetration. The benzisothiazol-3-one derivative **14** decreased cocaine self-administration in rats, providing proof-of-concept for the use of mGluR2 PAMs for the treatment of cocaine dependence.

Introduction

Cocaine addiction is a chronic relapsing disorder affecting more than 1.6 million Americans.[1] Relapse rates among cocaine users is in the range of 94−99%, the highest among all commonly abused drugs.[2] Chronic cocaine abuse can lead to severe neurotoxicity, psychosis, lethargy, depression, or potentially death through a fatal overdose. Currently there is no effective treatment for cocaine dependence, and therefore, cocaine addiction constitutes a major public health problem. Consequently, there is a significant need to identify new therapeutic agents for the treatment of cocaine and other psychomotor stimulant addictions. Recent findings suggest that neuroadaptations in glutamatergic transmission produced by repeated exposure to cocaine or other drugs of abuse are likely to contribute to the maintenance of addictive behaviors including drug use, craving, and relapse to drug taking in humans.[3] Specifically, it has been shown that repeated cocaine exposure alters the function of group II metabotropic glutamate receptors (mGluRs).[4a] The group II mGluRs include the mGluR2[a] and mGluR3 subtypes, which couple to $G_{i/o}$ proteins to negatively regulate the activity of adenylyl cyclase.[4b] Brain regions implicated in different aspects of drug abuse and drug dependence, including the cerebral cortex, hippocampus, striatum, amygdala, frontal cortex, and nucleus accumbens, display high levels of mGluR2 and mGluR3 binding,[5] suggesting a role for the mGluR2/3 subtypes in the development of cocaine dependence and as potential targets for therapeutic agents.[3a,e,f,6]

Orthosteric (glutamate site) mGluR2/3 agonists such as LY379268[6g] are constrained amino acid analogues that do not exhibit selectivity for mGluR2 versus mGluR3, presumably because of the high degree of sequence homology at the glutamate binding site for these two receptors.[6h] LY379268 has been shown to decrease glutamate levels[7] and to attenuate cocaine self-administration both in rats[6c,8] and in squirrel monkeys.[6a] However, LY379268 also inhibits responding for food and food-seeking behavior,[6c,e,9] suggesting that mGluR2/3 agonists exhibit nonselective actions on responding for drug and nondrug reinforcers. We recently initiated investigations to determine the effect of selective activation of mGluR2 on cocaine dependence.[8] Localization studies suggest that mGluR2 acts predominantly as a presynaptic autoreceptor to modulate the release of glutamate into the synaptic cleft.[10] In recent years, there have been several reports on the use of high-throughput screening (HTS) for the identification of small molecule mGluR2 positive allosteric modulators (PAMs).[11] The activity of these compounds is of interest because of their subtype selectivity, ability to overcome receptor desensitization, and potential for improved druglike properties.[12] The use of a selective mGluR2 PAM in an appropriate in vivo model therefore represents an attractive approach to elucidate the role of mGluR2 in cocaine dependence. We previously disclosed the structure−activity relationship (SAR) around a series of pyrimidine derivatives with activity as mGluR2 PAMs.[11b] The synthesis and characterization of

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[a] Abbreviations: mGluR2, metabotropic glutamate receptor subtype 2; PAM, positive allosteric modulator; BINA, 3′-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid; HTS, high-throughput screening; PK, pharmacokinetic; POC, proof-of-concept; AUC, area under curve; LOQ, limit of quantitation; AIBN, 2,2′-azobisisobutyronitrile; NBS, *N*-bromosuccinimide; HEK, human embryonic kidney; GIRK, G protein inwardly rectifying potassium; PBS, phosphate buffered saline; DMEM, Dulbecco's modified Eagle medium; HEPES, 4-(2-hydroxyethyl)-1-piperazineethanesulfonic acid; FBS, fetal bovine serum.

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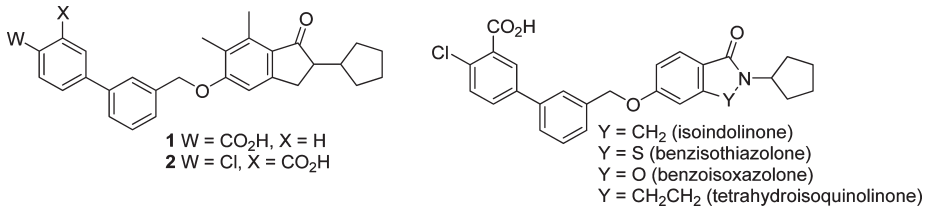


Figure 1. Incorporation of heteroatoms into BINA (**1**).

3′-((2-cyclopentyl-6,7-dimethyl-1-oxo-2,3-dihydro-1*H*-inden-5-yloxy)methyl)biphenyl-4-carboxylic acid (BINA, **1**) have been previously reported,[13] and we have shown that this compound possesses antipsychotic and anxiolytic effects in mice.[14] Most relevant to the present report, we recently showed that compound **1**, unlike mGluR2/3 agonists, decreased cocaine self-administration in rats at doses that did not affect responding for food.[8] A recent report by the Merck group on a series of oxazolobenzimidazole-based mGluR2 PAMs that are orally active in an in vivo model of schizophrenia prompts us to disclose our own efforts on the development of orally active mGluR2 PAMs.[15b]

While compound **1** is brain penetrant and selective, it lacks potency for mGluR2 both in vitro and in vivo and has suboptimal pharmacokinetic (PK) properties. We therefore set out to design and synthesize new selective mGluR2 PAMs based on the compound **1** scaffold in order to improve both potency and PK properties. These new PAMs are suitable for in vivo proof-of-concept (POC) studies to evaluate the potential of mGluR2 as a therapeutic target for the treatment of cocaine dependence. We hypothesized that modifying the indanone ring of **1** by incorporating heteroatoms may lead to analogues with improved properties (Figure 1). Interestingly, to date, there have been no reports on the synthesis and evaluation of analogues of compound **1** in which the indanone ring has been systematically modified in this way. In addition, as far as we are aware, there have been no studies documenting the effects of modifying the cyclopentyl ring in this scaffold. Furthermore, despite several recent reports disclosing mGluR2 PAMs,[11,15] none have been evaluated in an in vivo model of drug dependence.

Chemistry

Initially, we synthesized and tested compound **2**, an analogue of compound **1** previously reported to be roughly 4-fold more potent than **1** at mGluR2 (Figure 1).[13] The in vitro potency of the compounds was assessed using a thallium flux assay performed in HEK-GIRK cells expressing rat mGluR2.[16] In this assay compound **1** exhibited an EC_{50} value of 380 nM, while compound **2** had an EC_{50} of 180 nM, confirming an improved potency of **2** compared with **1** (Table 1). We therefore incorporated the 4-chlorobiphenyl-3-carboxylic acid moiety from **2** into the design of the new analogues.

We next focused on the synthesis of isoindolinone analogues (**8a**−**k**). As depicted in Scheme 1, the preparation of **8a**−**k** commenced with the conversion of commercially available 4-hydroxyphthalic acid **3** into the corresponding phthalic anhydride derivative **4** under thermal conditions, which was further converted to the phthalimide derivatives **5a**−**k** by treatment with the appropriate amine derivative. Regioselective reduction of the 3-carbonyl group with zinc in acetic acid afforded the desired 5-hydroxyisoindolinone derivatives **6a**−**k**. To verify the regioselectivity of the reduction, intermediate **6a** (R^1 = cyclopentyl) was also synthesized via an alternative procedure to confirm the structure unambiguously.[17] Completion of the synthesis of compounds **8a**−**k** was achieved in two steps using an O-alkylation reaction with methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate to give the ester derivatives **7a**−**k** which were saponified to the corresponding acid derivatives **8a**−**k** using LiOH in THF.

The synthesis of an analogue of compound **1** based on the benzisothiazol-3-one scaffold is illustrated in Scheme 2. Methyl 4-methoxy thiosalicylate **9**[18] was converted to the corresponding amide **10** by treatment with cyclopentylamine in the presence of trimethylaluminum. The cyclization to access the benzisothiazol-3-one derivative **11** was accomplished by a PIFA-mediated in situ formation of an *N*-acylnitrenium ion and its intramolecular trapping by the thiol moiety.[19] Demethylation of **11** was achieved with BBr_3 in hot benzene, followed by O-alkylation with methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate to provide **13**. Hydroxide-mediated demethylation led to the formation of byproducts; however, clean saponification of **13** was accomplished with lithium iodide to complete the synthesis of **14**.

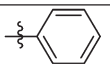
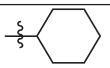
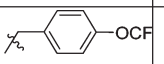
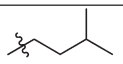
We also designed and synthesized an analogue of compound **1** based on the isoxazol-3-one scaffold (**21**). Our approach to the synthesis of **21** began with the preparation of *N*-cyclopentylbenzohydroxamic acid derivative **18** as shown in Scheme 3. The synthesis began with 4-methoxysalicylic acid **15**, which was transformed to **18** using a previously described procedure.[20] Thus, 4-methoxysalicylic acid **15** was acetylated at the phenolic hydroxyl group prior to conversion to the acid chloride derivative **16**. *N*-Cyclopentylhydroxylamine **17** was reacted with **16** to provide hydroxamic acid **18** as a colorless solid. Cyclization of **18** under Mitsunobu conditions afforded *N*-cyclopentylbenzisoxazolinone **19**, which was converted to the desired analogue **21** via intermediate **20** using the same conditions as those described for the preparation of compounds **8** and **14**.

In addition, we designed and synthesized an analogue of compound **1** (**28**) based on the tetrahydroisoquinolinone scaffold. Our approach to the synthesis of **28** is outlined in Scheme 4. Thus, commercially available 3-methoxyphenethylamine was alkylated with iodocyclopentane to provide *N*-(3-methoxyphenethyl)cyclopentanamine (**23**). Treatment of **23** with methyl chloroformate in the presence of triethylamine gave methyl cyclopentyl(3-methoxyphenethyl)carbamate **24**. Carbamate **24** was subjected to the Bischler−Napieralski cyclization conditions of Wang et al.[21] ($POCl_3$−P_2O_5) to afford the corresponding tetrahydroisoquinolone derivative **25**. Compound **25** was then converted to the target BINA analogue **28** in three steps as described for the other analogues.

Results and Discussion

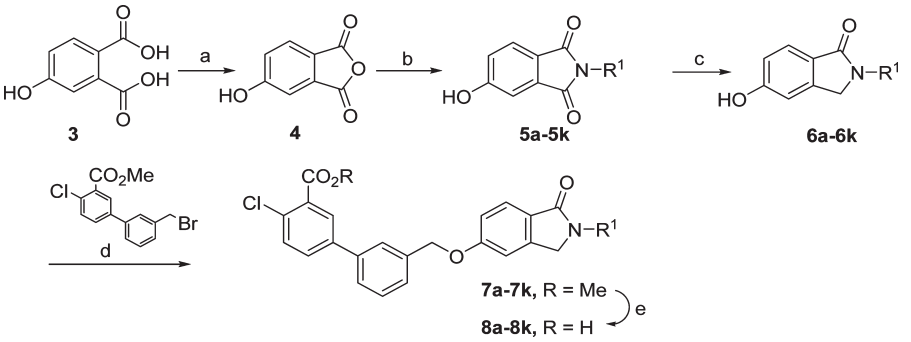
The new analogues **8a**−**k**, **14**, **21**, and **28** were tested, along with **1** and **2**, to determine in vitro activity, and the data are summarized in Table 1. For these in vitro experiments, a thallium flux assay was performed in HEK-GIRK cells[16]

Table 1. In Vitro Data for mGluR2 PAMs

Compound	R^1	mGluR2 PAM EC_{50} μM[a]	% Glutamate Max[a]	Permeability (log P)[b]	Plasma stability[c]	Microsomal stability[c]
1		0.38 ± 0.13	83.2 ± 10.0	-6.2	66	20
2		0.18 ± 0.05	77.3 ± 8.0	NT	NT	NT
8a		0.05 ± 0.02	81.4 ± 11.7	-5.5	100	42
8b		0.07 ± 0.03	88.1 ± 13.6	-6.1	98	91
8c		0.08 ± 0.04	85.7 ± 15.5	-6.5	100	73
8d		0.09 ± 0.04	90.3 ± 17.2	-5.6	100	76
8e		0.10 ± 0.05	63.9 ± 7.5	-6.3	99	43
8f		0.22 ± 0.18	64.9 ± 8.2	-5.6	100	98
8g		0.26 ± 0.12	86.2 ± 21.3	-6.6	100	100
8h		0.27 ± 0.13	63.3 ± 3.6	-6.5	99	1
8i		0.35 ± 0.04	86.7 ± 15.2	-7.8	100	100
8j		0.06 ± 0.03	85.3 ± 10.6	-5.8	94	21
8k		> 10	ND	-4.9	100	96
14		0.17 ± 0.03	63.0 ± 3.3	-5.4	86	45
21		0.31 ± 0.05	64.0 ± 3.4	-6.3	100	35
28		0.30 ± 0.03	66.9 ± 10.1	-6.1	100	36

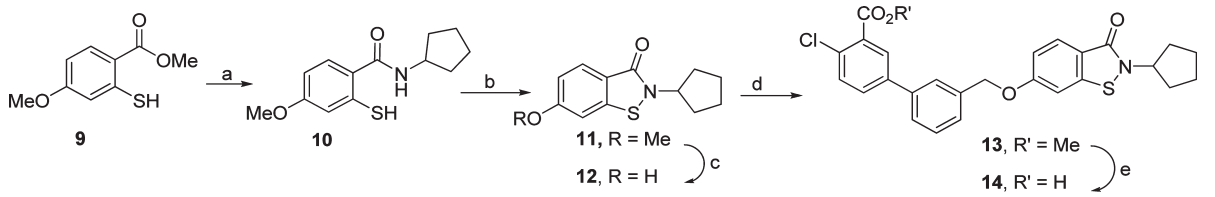
[a] mGluR2 PAM EC_{50} μM data and % glutamate max data represent the mean ± SEM for at least three independent experiments performed in triplicate. [b] Permeability is monitored by measuring the amount of compound that can diffuse through a polar brain lipid membrane to predict BBB permeability.[22] [c] Percent remaining after incubation for 60 min at 37 °C.

Scheme 1. Synthesis of 4-Chloro-3′-((2-cyclopentyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid Derivatives **8a**−**k**[a]



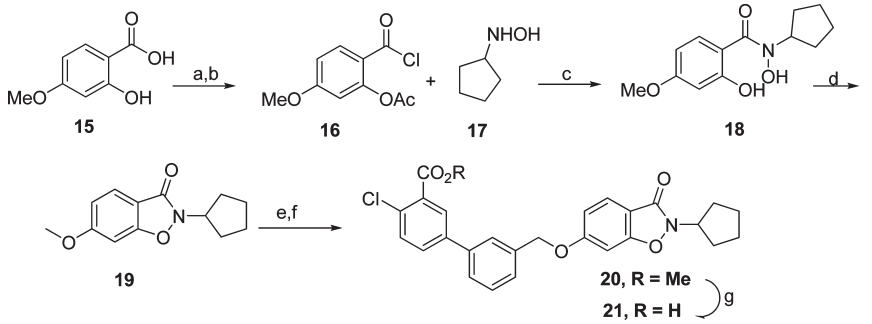
[a] Reagents and conditions: (a) Δ; (b) R^1NH_2, toluene, 4 Å molecular sieves, 110 °C, 12 h; (c) Zn/AcOH, 5 min; (d) K_2CO_3, acetone, 60 °C, 2.5 h; (e) LiOH, THF, 80 °C, 1 h.

Scheme 2. Synthesis of 3-Chloro-3′-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yloxy)methyl)biphenyl-4-carboxylic Acid **14**[a]



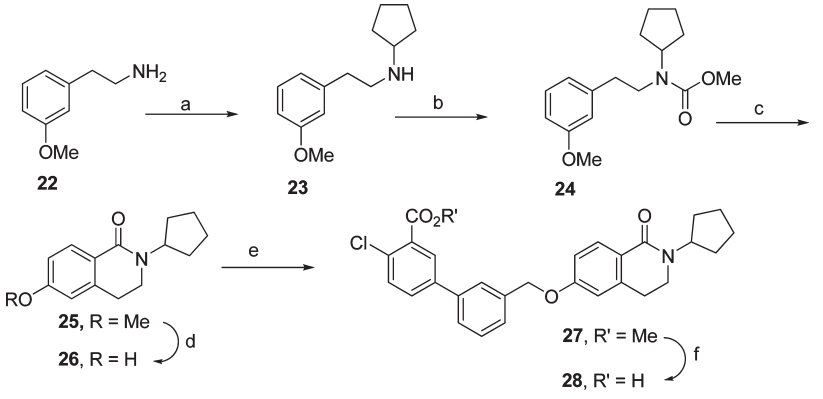
[a] Reagents and conditions: (a) $AlMe_3$, cyclopentylamine, CH_2Cl_2, 0 to −60 °C, 12 h; (b) PIFA, TFA, 0 °C, CH_2Cl_2, 1 h; (c) (i) BBr_3, C_6H_6, 80 °C, 1 h, (ii) H_2O, 100 °C, 1 h; (d) $ArCH_2Br$, K_2CO_3, MeCN, 80 °C, 12 h; (e) LiI, pyridine, 110 °C, 12 h.

Scheme 3. Synthesis of 4-Chloro-3′-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[*d*]isoxazol-6-yloxy)methyl)biphenyl-3-carboxylic Acid **21**[a]



[a] Reagents and conditions: (a) (i) AcCl, Py, CH_2Cl_2, 0 °C to room temp, 30 min; (ii) H_2O, 1 h; (b) $COCl_2$, CH_2Cl_2, 60 °C, 1 h; (c) 1 M Na_2CO_3, THF, CH_2Cl_2, 0 °C to room temp, 1 h; (d) TPP, DEAD, THF, 0 °C to room temp, 30 min, MeOH, AcOH; (e) (i) BBr_3, C_6H_6, 80 °C, 1 h, (ii) H_2O, 100 °C, 1 h; (f) $ArCH_2Br$, K_2CO_3, MeCN, 80 °C, 12 h; (g) LiI, Py, 110 °C, 12 h.

Scheme 4. Synthesis of 4-Chloro-3′-((2-cyclopentyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)methyl)biphenyl-3-carboxylic Acid **28**[a]



[a] Reagents and conditions: (a) iodocyclopentane, microwave, AcCN, 110 °C, 10 min; (b) $ClCO_2Me$, TEA, Et_2O, 0 °C, 30 min, 1 h; (c) (i) P_2O_5, $POCl_3$, 100 °C, 2 h; (d) (i) BBr_3, C_6H_6, 80 °C, 1 h, (ii) H_2O, 100 °C, 1 h; (e) $ArCH_2Br$, K_2CO_3, MeCN, 80 °C, 12 h; (f) 50% aqueous NaOH, dioxane, 80 °C, 1 h.

expressing rat mGluR2. The concentration−response relationship that potentiates the effect of an EC_{20} concentration of glutamate was determined for each of the mGluR2 PAMs, and this potency is expressed as an EC_{50} value. The efficacy for potentiation of an EC_{20} concentration of glutamate is presented as a percentage of the maximal glutamate response. Compounds **8a**−**j**, **14**, **21**, and **28** were all more potent than **1**, with compound **8a** being especially potent (EC_{50} = 50 nM). Increase (**8h**) or decrease in ring size (**8d**, **8f**) or the presence of bulky aryl substituents (**8g**, **8i**) led to a decrease in potency compared with the *N*-cyclopentyl derivative **8a**. On the other hand, branching (**8b**) or lengthening of the branched chain (**8e**, **8j**) led to compounds with potency similar to that of **8a**. Interestingly simple straight chain aliphatic substitution, as in the *N*-propyl derivative (**8k**), led to complete loss of activity. Enlargement of the lactam ring in the core scaffold from five- (**8a**) to six-membered (**28**) led to a 6-fold decrease in EC_{50}. In addition, the new analogues are highly selective for mGluR2 vs other mGluR subtypes with no activity observed up to 10 μM for **8a** and **14** (data not shown). We also determined the membrane permeability, in vitro plasma stability, and microsomal stability of the analogues to predict their in vivo pharmacological profile. As shown in Table 1, several of the new analogues displayed superior druglike properties compared with **1**, suggesting that these improvements may translate to an in vivo test.

On the basis of their overall in vitro profile, an isoindolinone derivative (**8a**) and a benzothiazolone derivative (**14**) were therefore selected for an in vivo assessment of their PK properties in rats. The rat PK data for compounds **1**, **8a**, and

Table 2. In Vivo PK Data for mGluR2 PAMs in Rats after Oral Administration[a]

compd	oral dose (mg/kg)	C_{max} (μM)	T_{max} (min)	AUC (0−t) (μM·h)	$t_{1/2}$ (h)	F (%)	brain[b] (μM)	plasma[b] (μM)	brain/plasma ratio
1	10	0.097 ± 0.032	120	0.281 ± 0.097	1.3 ± 0.25	33	0.0	0.027 ± 0.008	ND
8a	10	14.4 ± 15.8	80	105.5 ± 69.1	3.4 ± 0.7	40	3.8 ± 1.2	12.3 ± 5.7	0.3
14	10	4.1 ± 1.0	110	43.3 ± 14.4	2.7 ± 1.1	86	4.8 ± 1.0	1.0 ± 0.2	4.8

[a] C_{max}: maximum concentration of the compound detected in plasma. T_{max}: time at C_{max}. AUC: area under the curve. $t_{1/2}$: terminal half-life. F: oral bioavailability. ND: Not determined. [b] Brains and plasma were harvested at or near the T_{max}.

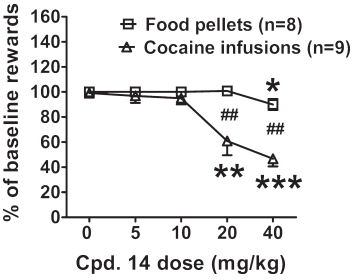


Figure 2. Effects of compound **14** on cocaine self-administration and food-maintained responding in rats. Data are expressed as percent of baseline responding (mean ± SEM). The number of baseline cocaine infusions was 20 ± 4.0 (mean ± SEM) and the number of baseline food pellets earned was 100 ± 0.0 (mean ± SEM): *, $p < 0.05$, **, $p < 0.01$, ***, $p < 0.001$ significant differences from the corresponding vehicle condition (Newman−Keuls post hoc test); ##, $p < 0.01$ significant difference between cocaine- and food- maintained responding for specific doses of compound **14** (Bonferroni post hoc test). Cpd = compound.

14 are shown in Table 2. Gratifyingly, both **8a** and **14** exhibited vastly superior PK profiles compared with **1**, with high values for C_{max}, AUC, and $t_{1/2}$. Incorporation of sulfur into the isoindolinone ring (**14**) provided a compound with similar potency to **1** but showed superior PK properties (Table 2) compared to **1**. Importantly, both **8a** and **14** had excellent oral bioavailability and were highly brain penetrant. In particular, compound **14** showed exceptional oral bioavailability (86%) and brain levels (4.8 μM) following a 10 mg/kg oral dose, with a brain/plasma ratio of 4.8. In contrast, the brain levels for **1** were below the limit of quantitation (LOQ) following oral dosing (10 mg/kg).[8] On the basis of these data, compound **14** was selected for evaluation in the cocaine self-administration procedure in rats.

The in vivo model was designed to investigate the effects of acute systemic (oral) administration of the mGluR2 PAM **14** on intravenous cocaine self-administration in rats that had 1 h access to cocaine (see Experimental Section for details). Additionally, we examined the effects of compound **14** on food-maintained responding to assess the selectivity of an orally active mGluR2 PAM on responding for cocaine compared to responding for the natural reinforcer food.

The results of the in vivo behavioral studies are shown in Figure 2. Oral administration of compound **14** significantly decreased cocaine self-administration in rats (Figure 2). Similarly, our previous work demonstrated that systemic (ip) administration of the mGluR2/3 agonist LY379268 significantly decreased cocaine self-administration in rats.[8] However, compound **14** had a much less pronounced effect on food responding compared with the effects of LY379268.[8] The effects of compound **14** on cocaine self-administration and the small effect of this compound on responding for food only at the highest dose tested (40 mg/kg) are consistent with our previous findings with compound **1**.[8] These data indicate that a selective, orally active mGluR2 PAM is as effective as an mGluR2/3 agonist at reversing the effects of cocaine self-administration in rats but with a diminished or no effect on food-maintained responding. This selectivity of the effect may be due to the selectivity of **14** for mGluR2 compared with the dual acting mGluR2/3 agonist and/or because of the modulatory properties of a mGluR2 PAM compared to the direct actions of an agonist on the receptor(s).

Conclusion

Using the mGluR2 PAM **1** as a template, we have designed and synthesized a series of new, highly potent mGluR2 PAMs. These compounds are highly selective for mGluR2 vs other mGluR subtypes and have significantly improved in vitro ADME and in vivo PK properties, providing compounds with excellent oral bioavailability and brain penetration. On the basis of these data, compound **14** was selected for in vivo studies in a model of cocaine dependence in rats, providing proof-of-concept for the use of an orally active mGluR2 PAM for the treatment of cocaine addiction.

Experimental Section

General Chemistry. All reactions were performed in oven-dried glassware under an atmosphere of argon with magnetic stirring. All solvents and chemicals used were purchased from Sigma-Aldrich or Acros and were used as received without further purification. Purity and characterization of compounds were established by a combination of liquid chromatography−mass spectrometry (LC−MS) and NMR analytical techniques and was >95% for all tested compounds. Silica gel column chromatography was carried out using prepacked silica cartridges from RediSep (ISCO Ltd.), and samples were eluted using an Isco Companion system. Melting points were reordered on a MEL-TEMP apparatus and are uncorrected. ^{1}H and ^{13}C NMR spectra were obtained using a Jeol 400 spectrometer at 400 and 100 MHz, respectively, unless otherwise mentioned, in which case a Varian 300 MHz spectrometer was used. Chemical shifts are reported in δ (ppm) relative to residual solvent peaks or TMS as internal standards. Coupling constants are reported in Hz. High-resolution ESI-TOF mass spectra were acquired at the Center for Mass Spectrometry at The Scripps Research Institute (La Jolla, CA). HPLC−MS analyses were performed on a Shimadzu 2010EV LC−MS instrument using the following conditions: Kromisil C18 column (reverse phase, 4.6 mm × 50 mm); a linear gradient from 10% acetonitrile and 90% water to 95% acetonitrile and 5% water over 4.5 min; flow rate of 1 mL/min; UV photodiode array detection from 200 to 300 nm.

5-Hydroxyisobenzofuran-1,3-dione (4).[23] 4-Hydroxyphthalic acid (10 g, 54.9 mmol) was heated at 200 °C overnight in a round bottomed flask in the absence of solvent. The resulting material was cooled and washed with ethyl acetate to obtain 5-hydroxyisobenzofuran-1,3-dione **4** as a white solid in quantitative yield.

General Procedure for the Synthesis of Thalimide Derivatives (5a−k). 4-Hydroxyphthalic anhydride **4** (5.4 g, 32.9 mmol), commercial amine (49.6 mmol), and 4 Å molecular sieves in toluene (136 mL) were stirred at reflux overnight. The reaction mixture was filtered, and the solvent was evaporated in vacuo to obtain **5a−k** as yellow solids in quantitative yield.

2-Cyclopentyl-5-hydroxyisoindoline-1,3-dione (5a).[24] ^{1}H NMR (DMSO-d_6): δ 10.8 (s,1H), 7.60 (d, J = 7.8 Hz, 1H), 7.05−7.01 (m, 2H), 4.50−4.40 (m, 1H), 1.97−1.52 (m, 8H). ^{13}C NMR

(DMSO-d_6): δ 167.7, 163.1, 134.2, 124.9, 121.0, 120.2, 109.5, 50.0, 29.2, 24.7.

5-Hydroxy-2-isopropylisoindoline-1,3-dione (5b). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65 (d, J = 8.7 Hz, 1H), 7.22−7.09 (m, 2H), 4.38−4.29 (m, 1H), 1.37 (d, J = 6.9 Hz, 6H).

2-(Cyclopropylmethyl)-5-hydroxyisoindoline-1,3-dione (5c). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (d, J = 8.1 Hz, 1H), 7.16−7.11 (m, 2H), 3.39 (d, J = 7.5 Hz, 2H), 1.11−1.06 (m, 1H), 0.47−0.39 (m, 2H), 0.32−0.28 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 163.9, 135.1, 125.9, 122.4, 121.0, 110.5, 42.4, 11.0, 4.2.

2-Cyclobutyl-5-hydroxyisoindoline-1,3-dione (5d). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.61 (d, J = 8.4 Hz, 1H), 7.06−7.04 (m, 2H), 4.59−4.50 (m, 1H), 2.79−2.68 (m, 2H), 2.16−2.10 (m, 2H), 1.78−1.66 (m, 2H).

5-Hydroxy-2-isobutylisoindoline-1,3-dione (5e). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.65 (d, J = 8.4 Hz, 1H), 7.10−7.06 (m, 2H), 3.32 (d, J = 7.2 Hz, 2H), 2.00−1.91 (m, 1H), 0.84 (d, J = 6.3 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.7, 134.9, 125.9, 121.1, 110.6, 45.3, 28.1, 20.6.

2-Cyclopropyl-5-hydroxyisoindoline-1,3-dione (5f). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.70 (+d, J = 8.4 Hz, 1H), 7.20−7.10 (m, 2H), 2.70−2.60 (m, 1H), 0.91- 0.82 (m, 4H).

5-Hydroxy-2-phenylisoindoline-1,3-dione (5g). ^{1}H NMR (DMSO-d_6): δ 11.03 (s, 1H), 7.78 (d, J = 8.2 Hz, 1H), 7.52−7.16 (m, 7H). ^{13}C NMR (DMSO-d_6): δ 166.7, 163.5, 134.3, 132.1, 128.8, 127.8, 127.3, 125.6, 120.8, 109.9.

2-Cyclohexyl-5-hydroxyisoindoline-1,3-dione (5h). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.48 (d, J = 7.8 Hz, 1H), 6.86−6.79 (m, 2H), 3.93−3.87 (m, 1H), 1.82−1.09 (m, 10H).

5-Hydroxy-2-(4-(trifluoromethoxy)benzyl)isoindoline-1,3-dione (5i). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.68−7.03 (m, 7H), 4.75 (s, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.5, 166.4, 137.2, 135.2, 130.1, 130.0, 126.2, 121.9, 121.6, 111.1, 44.7.

5-Hydroxy-2-isopentylisoindoline-1,3-dione (5j). ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.62 (d, J = 7.8 Hz, 1H), 7.07−7.02 (m, 2H), 3.54−3.49 (m, 2H), 1.47−1.40 (m, 3H), 0.89 (d, J = 6.9 Hz, 6H).

5-Hydroxy-2-propylisoindoline-1,3-dione (5k). ^{1}H NMR (DMSO-d_6): δ 7.74 (d, J = 8.2 Hz, 1H), 7.19−7.16 (m, 2H), 3.56−3.52 (m, 2H), 1.66−1.61 (m, 2H), 0.92−0.89 (m, 3H). ^{13}C NMR (DMSO-d_6): δ167.8, 163.2, 134.3, 125.1, 121.7, 120.2, 109.7, 21.4, 11.2.

General Procedure for the Synthesis of Isoindolinones (6a−k). To a solution of 1,3-dione **5a−k** (18.0 mmol) in CH_3CO_2H (129 mL) was added Zn dust (11.6 g, 180 mmol), and the mixture was heated at reflux for 5 min. The volatiles were removed in vacuo, and the residue was dissolved in water and extracted with ethyl acetate. The crude residue was purified using automated preparative HPLC to yield the desired compounds (**6a−k**) as amorphous solids.

2-Cyclopentyl-5-hydroxyisoindolin-1-one (6a). Yield: 1.7 g, 44%. ^{1}H NMR (DMSO-d_6): δ 10.10 (bs, 1H), 7.44 (d, J = 8.5 Hz, 1H), 6.89 (s, 1H), 6.83 (d, J = 7.9 Hz, 1H), 4.52−4.48 (m, 1H), 4.31 (s, 2H), 1.83−1.57 (m, 8H). ^{13}C NMR (DMSO-d_6): δ 167.2, 160.4, 144.1, 123.9, 123.7, 115.4, 109.6, 51.8, 45.4, 29.6, 23.8. LCMS calcd for $C_{13}H_{15}NO_2$ [M + H]$^+$, 218; found, 218.

5-Hydroxy-2-isopropylisoindolin-1-one (6b). Yield: 23 mg, 22%. ^{1}H NMR (DMSO-d_6): δ 10.04(s, 1H), 7.43 (d, J = 8.2 Hz, 1H), 6.89−6.81 (m, 2H), 4.38−4.31 (m, 1H), 4.28 (s, 2H), 1.16 (d, J = 6.4 Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 166.7, 160.4, 144.1, 123.9, 115.4, 109.6, 44.4, 41.9, 20.4. LRMS (ESI) calcd for $C_{11}H_{13}NO_2$ [M + H]$^+$, 192; found, 191.95.

2-(Cyclopropylmethyl)-5-hydroxyisoindolin-1-one (6c). Yield: 60 mg, 63%. LRMS (ESI) calcd for $C_{12}H_{13}NO_2$ [M + H]$^+$, 204; found, 204.

2-Cyclobutyl-5-hydroxyisoindolin-1-one (6d). Yield: 108 mg, 45%. ^{1}H NMR (DMSO-d_6): δ 7.43, (d, J = 8.2 Hz, 1H), 6.89−6.80 (m, 2H), 4.71−4.62 (m, 1H), 4.42 (s, 2H), 2.31−2.06 (m, 4H), 1.72−1.62 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 166.7, 160.6, 144.1, 124.2, 123.6, 115.5, 109.6, 45.8, 45.6, 28.1, 14.5. LRMS (ESI) calcd for $C_{12}H_{13}NO_2$ [M + H]$^+$, 204; found, 203.95.

5-Hydroxy-2-isobutylisoindolin-1-one (6e). Yield: 86 mg, 34%. ^{1}H NMR (DMSO-d_6): δ 10.07 (s, 1H), 7.45 (d, J = 8.2 Hz, 1H), 6.88−6.81 (m, 2H), 4.32 (s, 2H), 3.23 (d, J = 7.8 Hz, 2H), 2.00−1.90 (m, 1H), 0.83 (d, J = 6.8 Hz, 6H). ^{13}C NMR (DMSO-d_6): δ 167.6, 160.5, 144.1, 124.1, 123.5, 115.4, 109.5, 49.6, 49.1, 27.1, 20.0. LRMS (ESI) calcd for $C_{12}H_{15}NO_2$ [M + H]$^+$, 206; found, 205.90.

2-Cyclopropyl-5-hydroxyisoindolin-1-one (6f). Yield: 53 mg, 23%. ^{1}H NMR (DMSO-d_6): δ 7.36 (d, J = 8.2 Hz, 1H), 6.84−6.79 (m, 2H), 4.36 (s, 2H), 2.84−2.80 (m, 1H), 0.77−0.71 (m, 4H). ^{13}C NMR (DMSO-d_6): δ 168.9, 143.9, 123.8, 116.1, 109.7, 49.3, 24.9, 24.5, 5.1. LRMS (ESI) calcd for $C_{11}H_{11}NO_2$ [M + H]$^+$, 190; found, 190.00.

5-Hydroxy-2-phenylisoindolin-1-one (6g). Yield: 14 mg, 19%. ^{1}H NMR (DMSO-d_6): δ 7.83−7.81(m, 2H), 7.55−7.53 (m, 1H), 7.38−7.34 (m, 2H), 7.10−7.06 (m, 1H), 6.92−6.91 (m, 1H), 6.87−6.84 (m, 1H), 4.85 (s, 2h). LRMS (ESI) calcd for $C_{14}H_{11}NO_2$ [M + H]$^+$, 226; found, 226.

2-Cyclohexyl-5-hydroxyisoindolin-1-one (6h). Yield: 120 mg, 64%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.08 (s, 1H), 7.47 (d, J = 8.7 Hz, 1H), 6.92−6.84 (m, 2H), 4.33 (s, 2H), 3.99−3.93 (m, 1H), 1.82−1.31 (m, 10H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.4, 161.1, 144.9, 124.7, 116.1, 110.3, 50.7, 46.1, 31.4, 25.9, 25.8. LRMS (ESI) calcd for $C_{14}H_{17}NO_2$ [M + H]$^+$, 232; found, 232.0.

5-Hydroxy-2-(4-(trifluoromethoxy)benzyl)isoindolin-1-one (6i). Yield: 19 mg, 20%. LRMS (ESI) calcd for $C_{16}H_{12}F_3NO_3$ [M + H]$^+$, 324; found, 323.95.

5-Hydroxy-2-isopentylisoindolin-1-one (6j). Yield: 213 mg, 32%. ^{1}H NMR (300 MHz, DMSO-d_6): δ 7.46 (d, J = 8.1 Hz, 1H), 6.91 (s, 1H), 6.84 (d, J=8.4 Hz, 1H), 4.34 (s, 2H), 1.49−1.42 (m, 3H), 0.91 (d, J=5.4 Hz, 6H). LRMS (ESI) calcd for $C_{13}H_{17}NO_2$ [M + H]$^+$, 220; found, 219.85.

5-Hydroxy-2-propylisoindolin-1-one (6k). Yield: 12 mg, 22%. LRMS (ESI) calcd for $C_{11}H_{13}NO_2$ [M + H]$^+$, 192; found, 191.95.

Methyl 3′-(Bromomethyl)-4-chlorobiphenyl-3-carboxylate. Pd(OAc)$_2$ (0.393 g, 1.75 mmol) was added to a solution of 2-chloro-5-iodobenzoic acid (9.9 g, 35 mmol), *m*-tolylboronic acid (5.71 g, 42 mmol), and Na_2CO_3 (11.45 g, 105 mmol) in water (45 mL) under a nitrogen atmosphere. The resulting mixture was stirred at 50 °C for 2 h. The reaction mixture was cooled to room temperature and filtered. The filtrate was acidified with 1 M HCl. The precipitated 4-chloro-3′-methylbiphenyl-3-carboxylic acid was filtered, washed with water, and dried to provide a tan solid that was used without further purification in the next step (quantitative yield). ^{1}H NMR (DMSO-d_6, 300 MHz): δ 8.03 (s, 1H), 7.83 (d, J = 8.1 Hz, 1H), 7.63 (d, J = 7.8 Hz, 1H), 7.55−7.50 (m, 2H), 7.40 (t, J = 7.8 Hz,1H), 7.25 (d, J = 6.6 Hz, 1H), 2.41 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 167.4, 139.9, 139.1, 138.6, 132.7, 131.9, 131.2, 129.7, 129.5, 129.3, 128.0, 124.5, 21.8.

To a solution of 4-chloro-3′-methylbiphenyl-3-carboxylic acid (7 g, 28.5 mmol) in acetone was added K_2CO_3 (27.5 g, 199 mmol) and MeI (12.5 mL, 28 mmol). The resulting solution was heated at 50 °C for 1 h. After the mixture was cooled, the excess solvent was removed in vacuo. The crude material was dissolved in CH_2Cl_2 and washed with water. The organic layer was dried over Na_2SO_4, and the solvent was evaporated to afford methyl 4-chloro-3′-methylbiphenyl-3-carboxylate as a reddish yellow viscous liquid (7.3 g, 98%) which was used in the next step without further purification. ^{1}H NMR (DMSO-d_6): δ 8.04 (s, 1H), 7.85 (d, J = 7.8 Hz, 1H), 7.64 (d, J = 8.1 Hz, 1H), 7.52−7.47 (m, 2H), 7.38 (t, J = 7.8 Hz, 1H), 7.23 (d, J = 7.5 Hz, 1H), 3.90 (s, 3H), 2.39 (s, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz): δ 166.2, 139.9, 139.1, 138.4, 131.9, 131.7, 131.4, 131.3, 129.7, 129.6, 129.5, 128.0, 124.5, 53.3, 21.7.

A catalytic amount of AIBN was added to a solution of methyl 4-chloro-3′-methylbiphenyl-3-carboxylate (7.3 g, 28 mmol) and NBS (5.5 g, 30.8 mmol) in CCl_4. The reaction mixture was heated under reflux for 12 h. After the mixture

was cooled, the precipitated succinimide was removed by filtration. The filtrate was concentrated in vacuo to afford the crude product. Silica gel column chromatography using 4:1 hexanes/ethyl acetate afforded methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate (8.8 g, 91%) as a colorless solid. ^{1}H NMR ($CDCl_3$): δ 8.07(s, 1H), 7.68−7.45 (m, 6H), 4.58 (s, 2H), 4.00 (s, 3H). ^{13}C NMR ($CDCl_3$): δ 166.1, 139.5, 139.2, 138.7, 133.0, 131.6, 131.0, 130.4, 129.9, 129.6, 128.7, 127.7, 52.6, 33.2.

4-Chloro-3′-((2-cyclopentyl-1-oxoisoindolin-5-yloxy)methyl)-biphenyl-3-carboxylic Acid (8a). To a solution of 2-cyclopentyl-5-hydroxyisoindolin-1-one (50 mg, 0.23 mmol) in acetone (15 mL) and K_2CO_3 (181 mg, 1.31 mmol) was added methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate (92 mg, 0.27 mmol), and the mixture was heated at reflux for 1 h. The reaction mixture was filtered and the solvent was evaporated in vacuo to obtain methyl 4-chloro-3′-((2-cyclopentyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylate **7a** as a yellow oil in quantitative yield.

Crude methyl 4-chloro-3′-((2-cyclopentyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylate **7a** (109 mg, 0.23 mmol) was dissolved in tetrahydrofuran (17 mL), and 2 M LiOH (0.57 mL, 1.15 mmol) was added. The mixture was heated at reflux for 3 h. The solvent was evaporated, and the residue was dissolved in water and neutralized using 2 M HCl. The aqueous layer was extracted with ethyl acetate, and the organic layer was dried over anhydrous Na_2SO_4. The solvent was evaporated in vacuo to obtain the crude acid as a yellow solid. The crude residue was purified using automated preparative HPLC to yield the desired compound **8a** (48 mg, 46%) as an amorphous white solid. ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.78 (d, J=8.5 Hz, 1H), 7.65−7.41 (m, 6H), 7.05 (d, J = 8.5 Hz, 1H), 6.99 (s, 1H), 5.16 (s, 2H), 4.74 (m, 1H), 4.30 (s, 2H), 1.97 (m, 2H), 1.76−1.59 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 168.7, 161.5, 143.3, 139.3, 137.2, 133.5, 131.7, 131.4, 130.7, 129.7, 129.4, 127.0, 126.8, 126.0, 125.9, 125.1, 115.4, 108.7, 70.1, 52.7, 46.1, 30.1, 24.1. HRMS: calcd for $C_{27}H_{24}ClNO_4$ [M + H]$^+$, 462.1467; found, 462.1468.

Following the above-mentioned procedure, **8b**−**k** were synthesized using the appropriate starting materials.

4-Chloro-3′-((2-isopropyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8b). Amorphous white solid (14 mg, 32%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.06 (s, 1H), 7.85−7.82 (m, 2H), 7.68−7.51 (m, 5H), 7.24 (s, 1H), 7.13 (d, J = 8.4 Hz, 1H), 5.26 (s, 2H), 4.45−4.40 (m, 1H), 4.34 (s, 2H), 1.19 (d, J = 6.9 Hz, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.8, 166.6, 161.1, 144.2, 138.8, 138.3, 137.7, 132.1, 131.4, 131.0, 130.6, 129.5, 128.8, 127.6, 126.4, 126.2, 125.7, 124.1, 115.4, 109.2, 69.5, 44.8, 42.3, 20.5. LRMS (ESI): 435.95 (M + 1)$^+$. HRMS: calcd for $C_{25}H_{22}ClNO_4$, 436.131; found, 436.1309.

4-Chloro-3′-((2-(cyclopropylmethyl)-1-oxoisoindolin-5-yloxy)-methyl)biphenyl-3-carboxylic Acid (8c). Amorphous white solid (49 mg, 39%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.07 (s, 1H), 7.88−7.84 (m, 2H), 7.71−7.52 (m, 5H), 7.28 (s, 1H), 7.14 (d, J = 8.4 Hz, 1H), 5.28 (s, 2H), 4.50 (s, 2H), 3.33 (d, J = 7.5 Hz, 2H), 1.06−0.98 (m, 1H), 0.51−0.48 (m, 2H), 0.31−0.28 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.5, 167.3, 161.8, 144.8, 139.4, 138.9, 138.4, 132.8, 131.9, 131.6, 131.2, 130.1, 129.4, 128.3, 127.1, 126.9, 126.0, 124.7, 116.0, 109.8, 70.2, 50.0, 46.8, 10.6, 4.1. LRMS (ESI): 448.00 (M + H)$^+$. HRMS: calcd for $C_{26}H_{22}ClNO_4$, 448.131; found, 448.1313.

4-Chloro-3′-((2-cyclobutyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8d). Amorphous white solid (183 mg, 41%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.85−7.83 (m, 2H), 7.68−7.51 (m, 5H), 7.25 (s, 1H), 7.12 (d, J = 8.7 Hz, 1H), 5.27 (s, 2H), 4.78−4.62 (m, 1H), 4.49 (s, 2H), 2.38−2.22 (m, 2H), 2.15−2.09 (m, 2H), 1.78−1.66 (m, 2H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 166.6, 166.4, 161.1, 144.0, 138.7, 138.2, 137.6, 132.0, 131.2, 130.9, 130.5, 129.4, 128.7, 127.5, 126.3, 126.2, 125.4, 124.1, 115.4, 109.1, 69.4, 46.0, 45.7, 28.1, 14.5. LRMS (ESI): 448.00 (M + H)$^+$. HRMS: calcd for $C_{26}H_{22}ClNO_4$, 448.131; found, 448.131.

4-Chloro-3′-((2-isobutyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8e). Amorphous white solid (75 mg, 34%). ^{1}H NMR ($CDCl_3$): δ 8.17 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.66−7.62 (m, 2H), 7.55−7.41 (m, 4H), 7.07−7.05 (m, 1H), 7.00 (s, 1H), 5.17 (s, 2H), 4.33 (s, 2H), 3.39 (d, J = 7.3 Hz, 2H), 2.07−1.96 (m, 1H), 0.92 (d, J = 6.7 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 169.1, 168.2, 161.6, 143.4, 139.4, 137.2, 133.6, 131.7, 131.5, 130.7, 129.4, 127.1, 126.8, 125.9, 125.6, 125.3, 115.4, 108.7, 70.1, 50.6, 50.2, 27.8, 20.1. LRMS (ESI): 450.00 (M + H)$^+$. HRMS: calcd for $C_{26}H_{24}ClNO_4$, 450.1467; found, 450.1472.

4-Chloro-3′-((2-cyclopropyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8f). Amorphous white solid (78 mg, 23%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.86−7.81 (m, 2H), 7.67−7.51 (m, 5H), 7.21 (s, 1H), 7.12 (d, J = 7.8 Hz, 1H), 5.26 (s, 2H), 4.32 (s, 2H), 2.92−2.86 (m, 1H), 0.80−0.76 (m, 4H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 168.3, 166.8, 161.2, 144.1, 138.8, 138.3, 137.7, 132.1, 131.4, 130.9, 130.6, 129.5, 128.7, 127.6, 126.4, 126.2, 125.7, 124.0, 115.5, 108.9, 69.5, 49.5, 25.1, 5.11. LRMS (ESI): 434.05 (M + H)$^+$. HRMS: calcd for $C_{25}H_{20}ClNO_4$, 434.1154; found, 434.1150.

4-Chloro-3′-((1-oxo-2-phenylisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8g). Amorphous white solid (28 mg, 36%). ^{1}H NMR ($CDCl_3$): δ 8.20 (s, 1H), 7.86−7.36 (m, 11H), 7.15−7.05 (m, 3H), 5.19 (s, 2H), 4.77 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 169.2, 167.4, 162.2, 142.4, 139.5, 139.4, 139.3, 137.1, 133.7, 131.9, 131.7, 130.8, 129.5, 129.1, 127.1, 126.9, 126.1, 126.0, 125.8, 124.3, 119.4, 115.9, 108.4, 70.2, 50.6. LRMS (ESI): 470. (M + H)$^+$. HRMS: calcd for $C_{28}H_{20}ClNO_4$, 470.1154; found, 470.1157.

4-Chloro-3′-((2-cyclohexyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8h). Amorphous white solid (87 mg, 36%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.05 (s, 1H), 7.83 (m, 2H), 7.68−7.45 (m, 5H), 7.24 (s, 1H), 7.12 (d, J = 8.4 Hz, 1H), 5.27 (s, 2H), 4.36 (s, 2H), 3.99−3.92 (m, 1H), 1.79−1.14 (m, 10H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 167.3, 167.0, 161.7, 144.8, 139.4, 138.9, 138.4, 132.8, 131.9, 131.6, 131.2, 130.1, 129.4, 128.2, 127.0, 126.8, 126.3, 124.6, 116.0, 109.8, 70.1, 50.8, 46.3, 31.3, 25.9, 25.7. LRMS (ESI): 476.05 (M + H)$^+$. HRMS: calcd for $C_{28}H_{26}ClNO_4$, 476.1623; found, 476.1621.

4-Chloro-3′-((1-oxo-2-(4-(trifluoromethoxy)benzyl)isoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8i). Amorphous white solid (12 mg, 30%). ^{1}H NMR ($CDCl_3$): δ 8.13 (s, 1H), 7.80 (d, J = 8.5 Hz, 1H), 7.62−7.28 (m, 8H),7.14 (d, J = 7.9 Hz, 2H), 7.07−7.05 (m, 1H), 6.93 (s, 1H), 5.14 (s, 2H), 4.74 (s, 2H), 4.20 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 168.5, 161.8, 148.7, 143.4, 139.9, 139.4, 137.1, 135.8, 131.7, 131.5, 130.7, 129.5, 127.1, 126.8, 125.9, 125.4, 125.3, 121.3, 115.5, 108.9, 70.2, 49.3, 45.7. LRMS (ESI): 567.95 (M + H)$^+$. HRMS: calcd for $C_{30}H_{21}ClF_3NO_5$, 568.1133; found, 568.1136.

4-Chloro-3′-((2-isopentyl-1-oxoisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8j). Amorphous white solid (82 mg, 41%). ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.66−7.62 (m, 2H), 7.55−7.42 (m, 4H), 7.06 (dd, J = 8.5, 1.8 Hz, 1H), 6.99 (s, 1H), 5.17 (s, 2H), 4.31 (s, 2H), 3.62−3.58 (m, 2H), 1.63−1.49 (m, 3H), 0.93 (d, J = 6.1 Hz, 6H). ^{13}C NMR ($CDCl_3$): δ 168.6, 161.5, 143.3, 139.4, 137.2, 133.6, 131.8, 131.5, 130.7, 129.4, 127.1, 126.8, 125.9, 125.2, 115.3, 108.7, 70.1, 49.8, 40.8, 37.2, 25.8, 22.5. LRMS (ESI): 463.95 (M + H)$^+$. HRMS: calcd for $C_{27}H_{26}ClNO_4$, 464.1623; found, 464.1626.

4-Chloro-3′-((1-oxo-2-propylisoindolin-5-yloxy)methyl)biphenyl-3-carboxylic Acid (8k). Amorphous white solid (30 mg, 34%). ^{1}H NMR ($CDCl_3$): δ 8.18 (s, 1H), 7.78 (d, J = 8.5 Hz, 1H), 7.65−7.62 (m, 2H), 7.53−7.43 (m, 4H), 7.06 (dd, J = 8.5, 2.4 Hz, 1H), 6.99 (s, 1H), 5.17 (s, 2H), 4.31 (s, 2H), 3.54 (t, J = 7.3 Hz, 2H), 1.70−1.61 (m, 2H), 0.93 (t, J=7.3 Hz, 3H). ^{13}C NMR ($CDCl_3$): δ 168.7, 168.4, 161.5, 143.3, 139.4, 137.2, 133.5, 131.7, 131.4, 130.7, 129.5, 129.4, 127.0, 126.8, 125.9, 125.9, 125.2, 115.3, 108.7, 70.1, 49.9, 44.1, 21.7, 11.3. LRMS (ESI): 436.00 (M + H)$^+$. HRMS: calcd for $C_{25}H_{22}ClNO_4$, 436.131; found, 436.1315.

***N*-Cyclopentyl-2-mercapto-4-methoxybenzamide (10).** The title compound was prepared using the literature procedure as follows.

$AlMe_3$ (10 mmol, 2.0 M in toluene) was added dropwise to a cooled (0 °C) suspension of cyclopentylamine (0.85 g, 10 mmol) in CH_2Cl_2 (30 mL). When the addition was complete, the reaction mixture was allowed to warm to room temperature and stirring was continued for 30 min until gas evolution had ceased. A solution of methyl 2-mercapto-4-methoxybenzoate **9** (0.990 g, 5 mmol) was then added. After being stirred at 60 °C for 12 h, the mixture was cooled, and the reaction was carefully quenched with 5% aqueous HCl (20 mL). The organic layer was separated, and the aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The combined organic extracts were washed with a saturated aqueous solution of $NaHCO_3$ (15 mL) and brine. The organic phase was dried using $MgSO_4$, evaporated, and filtered and the solvent was evaporated in vacuo. The resulting residue was purified by crystallization from Et_2O to afford amide **10** as a tan solid (1.18 g, 94%). ^{1}H NMR (300 MHz, DMSO-d_6): δ 8.26 (s, 1H), 7.51 (d, J = 8.7 Hz, 1H), 7.01 (s, 1H), 6.72 (d, J = 8. One Hz, 1H), 5.62 (s, 1H), 4.16−4.14 (m, 1H), 3.78 (s, 3H), 1.99−1.80 (m, 2H), 1.79−1.68 (m, 2H), 1.66−1.53 (m, 4H). ^{13}C NMR: δ 164.6, 162.7, 142.7, 127.1, 118.4, 115.2, 105.0, 56.3, 54.8, 32.0, 23.9. LC−MS (ESI) calcd for $C_{13}H_{17}NO_2S$ $[M + H]^+$, 252.09; found, 251.95.

2-Cyclopentyl-6-methoxybenzo[*d*]isothiazol-3(2*H*)-one (11). A solution of PIFA (645 mg, 1.5 mmol) in CH_2Cl_2 (20 mL) was added at 0 °C to a solution of *N*-cyclopentyl-2-mercapto-4-methoxybenzamide 10 (251 mg, 1 mmol) and TFA (0.23 mL, 3 mmol) in CH_2Cl_2 (5 mL). The resulting mixture was gradually warmed to room temperature. After 1 h, the solvent was evaporated under reduced pressure and the resulting residue was purified by column chromatography using CH_2Cl_2 to afford the 2-cyclopentyl-6-methoxybenzo[*d*]isothiazol-3(2*H*)-one **11** as a white amorphous solid (84%, 0.210 g). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.87 (d, J = 8.5 Hz, 1H), 6.93 (s, 1H), 6.92 (d, J = 8.2 Hz, 1H), 5.50−5.01 (m, 1H), 3.86 (s, 1H), 2.13−2.12 (m, 2H), 1.83−1.67 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 165.3, 162.7, 142.2, 127.6, 118.8, 114.6, 103.1, 55.8, 55.0, 32.2, 24.4. LC−MS (ESI) calcd for $C_{13}H_{15}NO_2S$ $[M + H]^+$, 250.08; found, 249.95.

2-Cyclopentyl-6-hydroxybenzo[d]isothiazol-3(2*H*)-one (12). A solution of 2-cyclopentyl-6-methoxybenzo[d]isothiazol-3(2*H*)-one 11 (0.250 g, 1 mmol) in anhydrous C_6H_6 (20 mL) was cooled to 0 °C before BBr_3 (0.54 g, 2 mmol) was added dropwise. The mixture was gradually warmed to room temperature and then heated at 80 °C for 30 min. After that, the reaction mixture was cooled to room temperature and carefully quenched with H_2O (20 mL). The resulting mixture was then heated at reflux for 1 h and filtered. The precipitate was washed with H_2O and dried in vacuo to give the crude product. This material was purified by flash chromatography (silica gel, $CHCl_3$/MeOH, 9:1) to afford 2-cyclopentyl-6-hydroxybenzo[*d*]isothiazol-3(2*H*)-one **12** (0.200 g, 85%) as a colorless amorphous solid. ^{1}H NMR (300 MHz, DMSO-d_6): δ 10.36 (s, 1H), 7.60 (d, J = 8.5 Hz, 1H), 7.20 (s, 1H), 6.80 (d, J = 8.6 Hz, 1H), 4.84−4.81 (m, 1H), 2.12−1.98 (m, 2H), 1.75−1.60 (m, 6H). ^{13}C NMR (75 MHz, DMSO-d_6): δ 164.8, 161.3, 142.5, 127.4, 117.2, 115.6, 106.9, 54.6, 32.1, 24.4. LC−MS (ESI) calcd for $C_{12}H_{13}NO_2S$ $[M + H]^+$, 236.0667; found, 235.95.

3-Chloro-3′-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yloxy)methyl)biphenyl-4-carboxylic Acid (14). Potassium carbonate (0.052 g, 0.38 mmol) was added to a solution of 2-cyclopentyl-6- hydroxybenzo[*d*]isothiazol-3(2*H*)-one 12 (0.075 g, 0.32 mmol) and methyl 3′-(bromomethyl)-3-chlorobiphenyl-4-carboxylate (0.129 g, 0.38 mmol) in CH_3CN (5 mL). After the mixture was stirred for 12 h at 80 °C, the organic phase was evaporated under reduced pressure and the crude material was partioned between water and CH_2Cl_2. The aqueous layer was extracted with CH_2Cl_2 (3 × 15 mL). The organic layer was dried using Na_2SO_4 and evaporated to give methyl 3-chloro-3′-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[*d*]isothiazol-6-yloxy)methyl)biphenyl-4-carboxylate **13** (0.158 g, quantitative yield). The crude product was used in the next step without further purification. LC−MS (ESI) calcd for $C_{27}H_{24}NO_2S$ $[M + H]^+$, 494.11; found, 494.00.

LiI (0.042 g, 0.32 mmol) was added to a solution of the crude product (0.158 g, 0.32 mmol) in pyridine (5 mL). The reaction mixture was heated under reflux for 12 h and then cooled to room temperature. The excess solvent was removed in vacuo. The product was purified by preparative HPLC using isopropanol/water as the solvent system to afford the title compound **14** as a colorless solid (70 mg) in 46% yield. Mp: 189−191 °C. ^{1}H NMR (DMSO-d_6): δ 8.01 (s, 1H), 7.82 (d, J = 8.5 Hz, 1H), 7.80 (d, J = 8.6 Hz, 1H), 7.71−7.76 (m, 4H), 7.49−7.47 (m, 2H), 7.05 (d, J = 8.5 Hz, 1H.), 5.23 (s, 2H), 4.83−4.81 (m, 1H), 2.02−1.99 (m, 2H), 1.62−1.60 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 167.2, 164.0, 140.2, 138.7, 137.8, 131.7, 130.6, 131.0, 129.9, 129.2, 128.2, 127.2, 127.0, 126.9, 119.0, 115.73, 106.6, 70.2, 54.8, 32.2, 24.4. LC−MS (ESI) calcd for $C_{26}H_{22}ClNO_4S$ $[M + H]^+$, 480.09; found, 479.95. HRMS (ESI) calcd for $C_{26}H_{22}ClNO_4S$ $[M + H]^+$, 480.1031; found, 480.1031.

***N*-Cyclopentyl-2-dihydroxy-4-methoxybenzamide (18).** To a solution of 4-methoxysalicylic acid (0.84 g, 5 mmol) in CH_2Cl_2 was added pyridine (2.05 mL, 25 mmol) and acetyl chloride (0.89 mL, 12.5 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature over 30 min and then poured into water. The resulting biphasic mixture was stirred for 1 h and then acidified with 1 M HCl and extracted with EtOAc. The crude acetoxy derivative was then converted to the corresponding acid choride by heating with oxalyl chloride (1.3 mL, 15 mmol) in CH_2Cl_2 for 1 h at reflux. After removal of the volatile materials, the acid chloride (1.05 g, 4.38 mmol) in CH_2Cl_2 was added to a stirred mixture of sodium carbonate (1M, 17.5 mL) and C_5H_9NHOH (1.32 g, 13.2 mmol) in THF at 0 °C. The resulting mixture was stirred at room temperature for 1 h, acidified with 0.5 M HCl, and then extracted with EtOAc. The crude product was purified by column chromatography on silica gel using hexanes/ethyl acetate, affording hydroxamic acid **18** (1 g, 79%) as a colorless solid. ^{1}H NMR (DMSO-d_6): δ 7.65 (d, J = 9.1 Hz, 1H), 6.37−6.36 (overlapping doublet and singlet, 2 H), 4.10−3.98 (m, 1H), 3.70 (s, 1H), 1.69−1.63 (m, 2H), 1.55−1.52 (m, 6H). ^{13}C NMR (DMSO-d_6): δ 167.5, 162.5, 160.0, 131.4, 113.3, 105.5, 101.6, 56.6, 55.7, 29.5, 25.5. LC−MS (ESI) calcd for $C_{13}H_{17}NO_4$ $[M + H]^+$, 251.12; found, 252.00.

2-Cyclopentyl-6-methoxybenzo[*d*]isoxazol-3(2*H*)-one (19). Diethylazodicarboxylate was added dropwise to a cooled solution of hydroxamic acid **18** (0.71 g, 2.8 mmol) and triphenylphosphine (0.89 g, 3.4 mmol) in THF. The reaction mixture was warmed to room temperature and quenched with 1:1 MeOH/AcOH (0.2 mL). Concentration of the solvent followed by chromatographic separation on silica gel afforded **19** as a pale yellow solid (0.3 g, 46%). ^{1}H NMR ($CDCl_3$): δ 7.67 (d, J = 8.7 Hz, 1H), 6.78 (d, J = 8.6 Hz, 1H), 6.32 (s, 1H), 4.35−4.33 (m, 1H), 3.84 (s, 3H), 1.89−1.68 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 164.5, 162.8, 162.3, 124.9, 112.9, 109.8, 103.1, 55.8, 55.0, 32.2, 24.4. LC−MS (ESI) calcd for $C_{13}H_{15}NO_3$ $[M + H]^+$, 233.10; found, 232.90.

4-Chloro-3′-((2-cyclopentyl-3-oxo-2,3-dihydrobenzo[*d*]isoxazol-6-yloxy)methyl)biphenyl-3-carboxylic Acid (21). BBr_3 (0.54 g, 2 mmol) was added dropwise to a solution of **19** (0.232 g, 1 mmol) in anhydrous benzene (20 mL) at 0 °C. The mixture was gradually warmed to room temperature and then heated at 80 °C for 30 min. After that the reaction mixture was cooled to room temperature and carefully quenched with H_2O (20 mL). The resulting mixture was then heated at reflux for 1 h and then cooled. Extraction with EtOAc and removal of the solvent in vacuo afforded the crude demethylated product (0.170 g, 78%) which was used in the next step without further purification. A solution of 2-cyclopentyl-6-hydroxyybenzo[*d*]isoxazol-3(2*H*)-one (0.109 g, 0.5 mmol) was treated with methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate under the same conditions as described for compound **14** to give the corresponding ester in 76% yield (0.180 g). LC−MS (ESI) calcd for $C_{27}H_{24}ClNO_5$ $[M + H]^+$, 477.13; found, 478.05. The crude product obtained above was treated with LiI in

pyridine to give the final compound **21** (0.063 g, after HPLC purification) as a colorless solid in 36% yield. Mp: 185−187 °C. ^{1}H NMR (DMSO-d_6): δ 8.21 (s, 1H), 7.70−7.56 (m, 7H), 6.92 (d, J = 6.1 Hz, 1H), 5.18 (s, 2H), 4.98−4.95 (m, 1H), 2.06−2.02 (m, 2H), 1.92−1.88 (m, 4H), 1.64−1.63 (m, 2H). ^{13}C NMR (DMSO-d_6): δ 164.0, 163.4, 162.7, 139.4, 137.6, 131.7, 130.9, 129.9, 129.2, 127.1, 126.9, 125.2, 114.3, 109.4, 70.5, 95.5, 56.6, 30.2, 25.4. LC−MS (ESI) calcd for $C_{26}H_{22}ClNO_5$ [M + H]$^+$, 464.13; found, 463.95. HRMS (ESI) calcd for $C_{26}H_{22}ClNO_5$ [M + H]$^+$, 464.1259; found, 464.1261.

***N*-(3-Methoxyphenethyl)cyclopentanamine (23).** 3-Methoxyphenethylamine (4.5 mL, 30 mmol) and iodocyclopentane (1.15 mL, 10 mmol) in CH_3CN were irradiated for 10 min in a microwave reactor at 110 °C. After cooling to room temperature, the mixture was diluted with CH_2Cl_2 and washed with $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo. The crude product was separated by silica gel chromatography using hexane as eluent, and the pure product *N*-(3-methoxyphenethyl)cyclopentanamine (1.45 g, 66%) was obtained as a colorless liquid which solidified upon standing. ^{1}H NMR ($CDCl_3$): δ 8.48 (s, 1H), 7.20 (t, J = 8.0 Hz, 1H), 6.79−6.73 (overlapping doublets and singlet, 3H), 3.74 (s, 3H), 3.44−3.39 (m, 1H), 3.38−3.11 (m, 4H), 1.84−1.83 (m, 2H), 1.82−1.81 (m, 4H), 1.66−1.56 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 159.63, 140.93, 129.38, 121.07, 114.49, 111.45, 59.26, 55.18, 48.08, 32.46, 29.65, 23.84. LC−MS (ESI) calcd for $C_{14}H_{21}NO$ [M + H]$^+$, 220.16; found, 220.00.

Methyl Cyclopentyl(3-methoxyphenethyl)carbamate (24). To a solution of *N*-(3-methoxyphenethyl)cyclopentanamine **23** (1.31 g, 6 mmol) in diethyl ether was added triethylamine (1.3 mL, 9 mmol) and methyl chloroformate (0.7 mL, 9 mmol) at 0 °C. The reaction mixture was gradually warmed to room temperature and stirred for 30 min. Filtration and concentration of the solvent under reduced pressure preceded silica gel column chromatography using hexanes/ethyl acetate to afford methyl cyclopentyl(3-methoxyphenethyl)-carbamate as a pale yellow liquid (1.41 g, 84%). ^{1}H NMR ($CDCl_3$): δ 7.19 (t, J = 7.6 Hz, 1H), 6.78−6.73 (overlapping doublets and singlet, 3H), 4.27−4.24 (m, 1H), 3.78 (s, 3H), 3.70 (s, 3H), 3.28 (t, J = 7.9 Hz, 2H), 2.80 (t, J = 7.9 Hz, 2H), 1.68−1.67 (m, 2H), 1.53−1.50 (m, 6H). ^{13}C NMR ($CDCl_3$): δ 159.63, 156.74, 140.93, 129.38, 121.07, 114.49, 111.45, 57.94, 55.09, 52.30, 45.75, 36.50, 29.37, 23.50. LC−MS (ESI) valcd for $C_{16}H_{23}NO_3$ [M + H]$^+$, 278.17; found, 278.00.

2-Cyclopentyl-6-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (25). To a solution of methyl cyclopentyl(3-methoxyphenethyl)carbamate **24** (1.39 g, 5 mmol) in $POCl_3$ (20 mL) was added P_2O_5 (1.4 g, 10 mmol). The reaction mixture was heated at reflux for 2 h. Excess $POCl_3$ was removed under reduced pressure and quenched with ice−water. The mixture was neutralized with Na_2CO_3, extracted with EtOAc, and the organic phase was dried over Na_2SO_4. Concentration of the solvent followed by silica gel column chromatography using hexanes/ethyl acetate afforded 2-cyclopentyl-6-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (1.30 g, 94%). ^{1}H NMR ($CDCl_3$): δ 8.00 (d, J = 8.6 Hz, 1H), 6.81 (d, J = 8.6 Hz, 1H), 6.63 (s, 1H), 5.18−5.14 (m, 1H), 3.85 (t, J = 6.7 Hz, 1H), 2.88 (t, J = 6.7 Hz, 1H), 1.88−1.70 (m, 2H), 1.64−1.63 (m, 4H), 1.62−1.61 (m, 2H). ^{13}C NMR ($CDCl_3$): δ 164.44, 162.08, 139.97, 130.56, 123.05, 112.43, 111.79, 55.43, 53.70, 40.32, 28.96, 28.81, 24.57. LC−MS (ESI) calcd for $C_{15}H_{19}NO_2$ [M + H]$^+$, 246.14; found, 246.00.

2-Cyclopentyl-6-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (26). BBr_3 (3.7 g, 14.7 mmol) was added dropwise to a solution of 2-cyclopentyl-7-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one **25** (1.2 g, 4.9 mmol) in benzene at 0 °C. The mixture was gradually warmed to room temperature and then heated at 80 °C for 30 min. The reaction mixture was then cooled to room temperature and carefully quenched with H_2O. The resulting mixture was then heated at reflux for 1 h and then cooled. Extraction with EtOAc and removal of the solvent in vacuo followed by chromatographic separation using MeOH−$CHCl_3$ provided 2-cyclopentyl-6-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one **26** as a colorless solid (0.735 g, 65%). ^{1}H NMR (DMSO-d_6): δ 9.96 (s, 1H), 7.65 (d, J = 8.6 Hz, 1H), 6.63 (d, J = 8.5 Hz, 1H), 6.56 (s, 1H), 4.95−4.93 (m, 1H), 3.32 (t, 2H, J = 6.1 Hz), 2.73 (t, 2 H, J = 6.7 Hz), 1.73−1.64 (m, 4H), 1.53−1.45 (m, 4H). ^{13}C NMR (DMSO-d_6): 163.82, 160.69, 141.02, 130.29, 121.51, 114.28, 113.62, 53.44, 42.20, 28.79, 28.57, 24.52. LC−MS (ESI) calcd for $C_{14}H_{17}NO_2$ [M + H]$^+$, 232.13; found, 232.00.

4-Chloro-3′-((2-cyclopentyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)methyl)biphenyl-3-carboxylic Acid (28). 2-Cyclopentyl-6-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one **26** (0.106 g, 0.5 mmol) and methyl 3′-(bromomethyl)-4-chlorobiphenyl-3-carboxylate (0.208 g, 0.6 mmol) were processed according to the general procedure to provide methyl 4-chloro-3′-((2-cyclopentyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)methyl)-biphenyl-3-carboxylate **27**. NaOH (50% aqueous) was added to a solution of the crude product (0.150 g, 0.3 mmol) in dioxane (5 mL). The reaction mixture was heated at reflux for 1 h and then cooled to room temperature. Excess solvent was removed in vacuo, the residue was diluted with water and then acidified using 1 M HCl. Extraction using EtOAc followed by purification using preparative HPLC afforded **28** (0.162 g, 69% over two steps) as a colorless solid. Mp: 147−149 °C. ^{1}H NMR (DMSO-d_6): δ 8.00 (s, 1H), 7.87−7.75 (m, 3H), 7.65−7.57 (m, 2H), 7.49−7.41 (m, 2H), 6.95−6.90 (overlapping doublets and singlet, 2H), 5.20 (s, 2H), 4.97−4.93 (m, 1H), 3.34 (t, J = 6.1 Hz, 2H), 2.84 (t, J = 6.1 Hz, 2H), 1.69−1.46 (m, 8 H). ^{13}C NMR (DMSO-d_6): 163.32, 161.79, 141.60, 138.58, 137.55, 131.75, 130.99, 129.84, 129.16, 128.86, 126.45,113.78, 112.80, 69.70, 53.54, 42.20, 28.81, 28.63, 23.83. LC−MS (ESI) calcd for $C_{28}H_{26}ClNO_4$ [M + H]$^+$, 476.16; found, 476.00. HRMS (ESI) calcd for $C_{28}H_{26}ClNO_4$ [M + H]$^+$, 476.1623; found, 476.1623.

mGluR2 in Vitro Assay. Human embryonic kidney (HEK-293) cell lines coexpressing rat mGluR 2, 3, 4, 6, 7, or 8 and G protein inwardly rectifying potassium (GIRK) channels[16] were grown in growth media containing 45% DMEM, 45% F-12, 10% FBS, 20 mM HEPES, 2 mM L-glutamine, antibiotic/antimycotic, nonessential amino acids, 700 μg/mL G418, and 0.6 μg/mL puromycin at 37 °C in the presence of 5% CO_2. Rat mGluR1 and five cells were cultured as described in Hemstapat et al.[25]All cell culture reagents were purchased from Invitrogen Corp. (Carlsbad, CA) unless otherwise noted. Calcium assays were used to assess activity of compounds at mGluRs 1 and 5 as previously described in Engers et al.[26] Compound activity at the rat group II (mGluRs 2 and 3) and group III (mGluRs 4, 6, 7, and 8) mGluRs was assessed using thallium flux through GIRK channels, a method that has been described in detail.[16] Briefly, cells were plated into 384-well, black-walled, clear-bottomed poly-D-lysine-coated plates at a density of (15 000 cells/20 μL)/well in DMEM containing 10% dialyzed FBS, 20 mM HEPES, and 100 units/mL penicillin/streptomycin (assay media). Plated cells were incubated overnight at 37 °C in the presence of 5% CO_2. The following day, the medium was removed from the cells, and 20 μL/well of 1.7 μM BTC-AM, an indicator dye (Invitrogen, prepared as a stock in DMSO and mixed in a 1:1 ratio with pluronic acid F-127) in assay buffer [Hanks' balanced salt solution (Invitrogen) containing 20 mM HEPES, pH 7.3] was added to the plated cells. Cells were incubated for 1 h at room temperature, and the dye was replaced with 20 μL of assay buffer. Test compounds were diluted to 2 times their final desired concentration in assay buffer. Agonists were diluted in thallium buffer [125 mM sodium bicarbonate (added fresh the morning of the experiment), 1 mM magnesium sulfate, 1.8 mM calcium sulfate, 5 mM glucose, 12 mM thallium sulfate, and 10 mM HEPES, pH 7.3] at 5 times the final concentration to be assayed. Cell plates and compound plates were loaded onto a kinetic imaging plate reader (FDSS 6000, Hamamatsu Corporation, Bridgewater, NJ). Appropriate baseline readings were taken (10 images at 1 Hz; excitation, 470 ± 20 nm; emission, 540 ± 30 nm), and test compounds were added in a 20 μL volume and incubated for 2.5 min before the addition of 10 μL of thallium buffer with or without agonist. After the addition

of agonist, data were collected for an additional 2.5 min. Data were analyzed using Excel (Microsoft Corp, Redmond, WA). The slope of the fluorescence increase beginning 5 s after thallium/agonist addition and ending 15 s after thallium/agonist addition was calculated, corrected to vehicle and maximal agonist control slope values, and plotted in Prism software (GraphPad Software, San Diego, CA) to generate concentration−response curves. Potencies were calculated from fits using a four-point parameter logistic equation. For concentration−response curve experiments, compounds were serially diluted 1:3 into 10 point concentration−response curves and were transferred to daughter plates using an Echo acoustic plate reformatter (Labcyte, Sunnyvale, CA). Test compounds were applied and followed by EC_{20} concentrations of glutamate. For selectivity experiments, full concentration−response curves of glutamate or L-AP4 (for mGluR7) were performed in the presence of a 10 μM compound, and compounds that affected the concentration−response by less than 2-fold in terms of potency or efficacy were designated as inactive.

Microsomal Stability in Vitro Assay. Pooled rat liver microsomes (BD Biosciences, no. 452701) were preincubated with test compounds at 37.5 °C for 5 min in the absence of NADPH. The reaction was initiated by addition of NADPH and incubated under the same conditions. The final incubation concentrations were 4 μM test compound, 2 mM NADPH, and 1 mg/mL (total protein) liver microsomes in phosphate-buffered saline (PBS) at pH 7.4. One aliquot (100 μL) of the incubation mixture was withdrawn at 15 min time points and combined immediately with 100 μL of ACN/MeOH. After mixing, the sample was centrifuged at approximately 13 000 rpm for 12 min. The supernatant was filtered and transferred into an autosampler vial, and the amount of test compound was quantified using a Shimadzu LC−MS 2010EV mass spectrometer. The change of the AUC (area under the curve) of the parent compound as a function of time was used as a measure of microsomal stability. Test compounds were run in duplicate with a positive control.

Plasma Stability in Vitro Assay. A 20 μL aliquot of a 10 mM solution in DMSO of the test compound was added to 2.0 mL of heparinized rat plasma (Lampire, P1-150N) to obtain a 100 μM final solution. The mixture was incubated for 1 h at 37.5 °C. Aliquots of 100 μL were taken at 15 min intervals and diluted with 100 μL of MeOH/ACN. After mixing, the sample was centrifuged at approximately 13 000 rpm for 12 min. The supernatant was filtered and transferred into an autosampler vial, and the amount of test compound was quantified using the Shimadzu LC−MS 2010EV system. The change of the AUC of the parent compound in function of time was used as a measure of plasma stability.

Parallel Artificial Membrane Permeation Assay (PAMPA). A 96-well microtiter plate (Millipore, no. MSSACCEPTOR) was completely filled with aqueous buffer solution (pH 7.4) and covered with a microtiter filterplate (Millipore, no. MAPBMN310) to create a sort of sandwich construction. The hydrophobic filter material was impregnated with a 10% solution of polar brain lipid extract in chloroform (Avanti) as the artificial membrane, and the organic solvent was allowed to completely evaporate. Permeation studies were started by the transfer of 200 μL of a 100 μM test compound solution on top of the filter plate. In general phosphate pH 7.2 buffer was used. The maximum DMSO content of the stock solutions was < 1.5%. In parallel, an equilibrium solution lacking a membrane was prepared using the exact concentrations and specifications but lacking the membrane. The concentrations of the acceptor and equilibrium solutions were determined using the Shimadzu LC−MS 2010EV and AUC methods. The acceptor plate and equilibrium plate concentrations were used to calculate the permeability rate ($\log P_e$) of the compounds. The $\log P_e$ values were calculated using the following equation:

$$\log P_e = \log\{(C)[-\ln(1 - [\text{drug}]_{\text{acceptor}}/[\text{drug}]_{\text{equilibrium}})]\}$$

$$C = (V_D V_A)/[(V_D + V_A)(\text{area})(\text{time})]$$

Behavioral Procedures. Apparati. Intravenous cocaine self-administration and food-maintained responding took place in 12 Plexiglas experimental chambers (25 cm × 31 cm × 24 cm; MED Associates, St. Albans, VT), each housed in a sound-attenuating box (San Diego Instruments, San Diego, CA). One wall of the chamber contained two levers, measuring approximately 3 cm in width and located approximately 3 cm above the metal grid floor of the chamber. There was also an opaque disk (2.5 cm diameter) mounted 10 cm above each lever which could be illuminated by a 2.5 W, 24 V white light bulb and served as a cue light paired with cocaine or food delivery. All data collection and test session functions were controlled by computers and MED-PC IV software (MED Associates).

Food Training and Food-Maintained Responding. Methodological details of food training and food-maintained responding procedures have been described previously.[27−30] Rats were placed under food restriction ((20 g/day)/rat) and trained to lever press for 45 mg of food pellets (Research Diets, New Brunswick, NJ). Training started on a fixed-ratio 1 time-out 1 s (FR1 TO1 s) schedule of reinforcement, which then changed to FR1 TO20 s. During food training, only the active lever was used and there was no cue light presentation. Successful acquisition of the food response was defined as earning 100 pellets during a 60 min session. The training period lasted approximately 5 days. After successful acquisition of food-maintained responding, these rats were allowed to continue responding for food on an FR1 TO20 s schedule during 1 h test sessions 5−7 days per week. During these sessions, two levers (active and inactive) were present in the box. Responses on an active lever resulted in a food pellet delivery paired with a 20 s cue light presentation. Responses on inactive lever had no programmed consequences. An identical training procedure was used for both the subjects that responded for food and the rats that later were allowed to self-administer cocaine.

Cocaine Self-Administration Procedure. Methodological details of catheter construction and surgery and self-administration procedure have been described previously.[26−29] Briefly, rats were prepared with intravenous catheters inserted into the right jugular vein under isoflurane anesthesia (1−1.5% isoflurane/oxygen mixture). Cocaine self-administration training began after 7 days of recovery from surgery during daily 1 h self-administration testing sessions. These sessions were initiated by extension of both the active and inactive levers. Responses at the active lever were reinforced under an FR1 TO20 s schedule of reinforcement by an intravenous injection of cocaine (0.05 mg/kg/infusion salt) delivered over a 2 s period in a volume of 0.05 mL. Upon completion of the operant response for cocaine delivery, a cue light above the lever was turned on for 20 s and signaled the time-out period, during which responses had no consequences. Responses at the inactive lever were recorded but had no scheduled consequences. All rats were trained to self-administer cocaine for 21 days. The criteria for exhibiting stable performance (more than 10 infusions per session, less than 20% variation over three consecutive sessions) were reached by all rats during this 21-day period.

Experimental Design for Investigating the Effects of the mGluR2 PAM on Cocaine Self-Administration and Food-Maintained Responding. After completion of the cocaine self-administration training, drug treatments were initiated. Compound **14** was administered to rats (n = 9) according to a within-subjects Latin-square design. The compound was administered orally at doses of 0, 5, 10, and 20 mg/kg with 60 min pretreatment time. The highest dose (40 mg/kg) was administered to all rats after completion of the Latin-square. At least three days elapsed between drug/vehicle injections to re-establish stable self-administration behavior (less than 20% variation over three days).

To assess possible nonspecific effects, the effects of compound **14** at doses identical to those used for cocaine self-administration were assessed in a separate group of rats (n = 8) trained to lever-press for food during 1 h sessions. The FR1 TO20 s

schedule of reinforcement used for food-maintained responding was identical in all parameters to the schedule under which cocaine was self-administered.

Statistical Analyses. Intravenous self-administration and food-maintained responding data were expressed as a percentage of the baseline number of rewards earned, with baseline defined as the mean number of rewards earned during the 3 days before each drug testing session. Percent values are presented to allow for direct comparisons for data derived from the two different reinforcers (i.e., cocaine and food). Acute effects of compound **14** on cocaine self-administration and food-maintained responding were analyzed using two-way repeated-measures ANOVA, with Dose as the within-subjects factor and Reinforcer (food or cocaine) as the between-subject factor. Post hoc comparisons were conducted with Newman−Keuls and Bonferroni tests. The criterion for significance was set at 0.05.

Results. The number of baseline cocaine infusions was 20 ± 4.0 (mean ± SEM), and the number of baseline food pellets earned was 100 ± 0.0 (mean ± SEM). A two-way ANOVA on the number of baseline cocaine/food infusions earned during the three baseline days prior to the drug treatment days indicated no significant differences across days, demonstrating the stability of baseline food and cocaine self-administration in rats during the experiment (data not shown).

Systemic administration of compound **14** significantly decreased both cocaine and food self-administration in rats (Figure 2 in main text). A two-way ANOVA revealed significant main effects for the factor compound **14** Dose ($F_{4,60} = 14.88$, $p < 0.0001$), the factor Reinforcer ($F_{1,60} = 35.51$, $p < 0.0001$), and their interaction ($F_{4,60} = 8.75$, $p < 0.0001$). Post hoc tests showed a significant decrease in cocaine intake after administration of 20 mg/kg ($p < 0.01$) and 40 mg/kg ($p < 0.001$) of compound **14** compared with the vehicle treatment condition. Compound **14** had no effect on inactive lever presses at any of the doses tested (data not shown). Compound **14** also decreased food-maintained responding, and this effect was significant only at the highest dose used (40 mg/kg). Additionally, post hoc tests comparing the effects of the same dose of compound **14** on cocaine- and food-maintained responding indicated that compound **14** had more pronounced effect in decreasing cocaine compared to food self-administration (Figure 2).

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