Journal of Medicinal Chemistry

Article

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2-(Pyrrolidin-1-yl)ethyl-3,4-dihydroisoquinolin-1(2*H*)-one Derivatives as Potent and Selective Histamine-3 Receptor Antagonists

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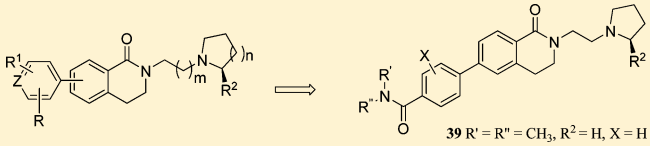
Supporting Information

ABSTRACT: On the basis of the previously reported benzimidazole 1,3′-bipyrrolidine benzamides (**1**), a new class of 2-(pyrrolidin-1-yl)ethyl-3,4-dihydroisoquinolin-1(2*H*)-one derivatives (**3**−**50**) were synthesized and evaluated as potent H_3 receptor antagonists. In particular, compound **39** exhibited potent in vitro binding and functional activities at the H_3 receptor, good selectivities against other neurotransmitter receptors and ion channels, acceptable pharmacokinetic properties, and a favorable in vivo profile.



INTRODUCTION

The histamine-3 (H_3) receptor is one of four histamine receptor subtypes (H_1−H_4), all of which are members of the larger G-protein-coupled receptor superfamily of receptors. The H_3 receptor is predominantly expressed in the central nervous system.[1] In the brain, it is located in regions associated with learning and memory such as the cerebral cortex, hippocampus, and striatum.[2] In addition to its function as a presynaptic autoreceptor, modulating histaminergic tone,[3] the H_3 receptor also acts as a heteroreceptor on nonhistaminergic neurons, inhibiting the release of other neurotransmitters, including acetylcholine,[4] norepinephrine,[5] and dopamine.[6] Accumulated neuroanatomical, neurochemical, pharmacological, and behavioral data support the concept that H_3 receptor antagonists may improve cognitive performance in disease states such as mild cognitive impairment and Alzheimer's disease and may have therapeutic value in the treatment of attention deficit hyperactivity disorder (ADHD), schizophrenia, obesity, sleep disorders, eating disorders, and neuropathic pain.[7−13]

Researchers from our laboratories recently reported the lead optimization of a series of benzimidazole analogues that originated from a screen of our focused biogenic amine library using a competitive binding assay with [^{3}H]-(*R*)-α-methylhistamine and cell membranes from HEK293T cells overexpressing human H_3 (hH_3) receptors. A few compounds (**1**, Figure 1) were identified as advanced discovery leads with single digit nanomolar potency and efficacy in both water intake and novel object recognition models in rodents.[14,15] To further investigate the SAR and build chemically diverse series of analogues, we initiated a study to constrain the amide portion of the discovery leads **1** to a six-membered lactam platform (**2**, Figure 1). Indeed, compound **2** demonstrated potent human H_3 receptor binding affinity (K_i = 0.8 nM). However, the potential mutagenic liability associated with the lead compound **1** prompted us to expand our efforts to include analogues devoid of the benzimidazole moiety. The replacement of a benzimidazole moiety with a phenyl group in compound **3** afforded reasonable potency (human H_3 K_i = 11.4 nM). Thus, improvement of the H_3 receptor binding affinity was our initial objective in progressing this new series. Herein we describe the synthesis, structure−activity relationships (SAR), and pharmacological characterization of 2-(pyrrolidin-1-yl)ethyl-3,4-dihydroisoquinolin-1(2*H*)-one derivatives, a new class of compounds as potent H_3 receptor antagonists.

CHEMISTRY

The synthesis of lactam derivatives (**3**−**50**) is depicted in the following schemes. For the synthesis of biaryl lactam analogues **3**−**15**, **24**, and **25**, an efficient and facile strategy was developed by employing Schmidt rearrangement[16] on commercially available bromoindanones (**51a**−**c**). As shown in Scheme 1, compounds **51a**−**c** were treated with sodium azide in an acidic solution to afford 3,4-dihydroisoquinolin-1(2*H*)-ones **52a**−**c**. *N*-Alkylation with allyl bromide in the presence of sodium hydride provided 2-allyl-3,4-dihydroisoquinolin-1(2*H*)-ones **53a**−**c**. Oxidation with osmium tetroxide and sodium periodate in THF−water, to give 2-(1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-acetaldehydes **54a**−**c**, was followed by reductive amination with cyclic amines to give intermediates **55a**−**c**. Palladium-mediated Suzuki−Miyaura coupling of **55a**−**c** with aryl boronic acids gave target compounds **3**−**15**, **24**, and **25**.

Received: January 3, 2012
Published: February 7, 2012

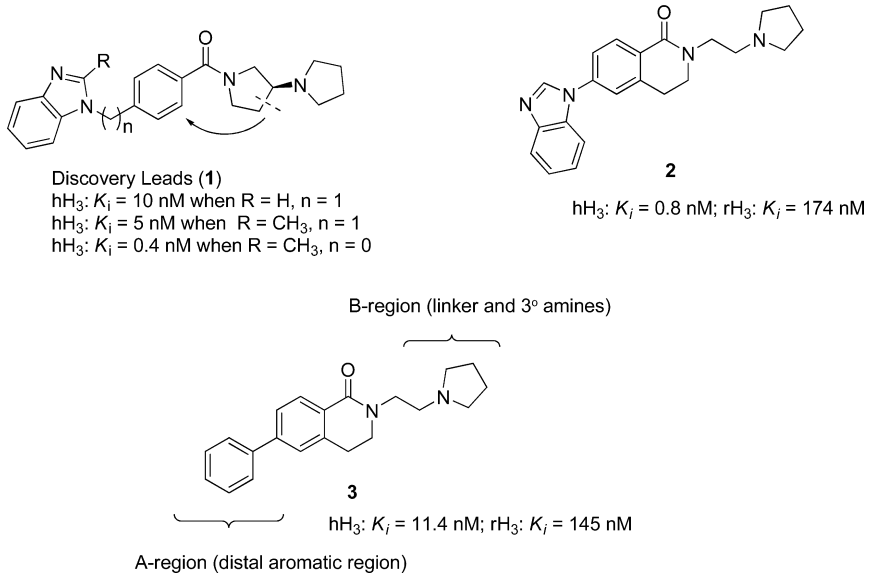
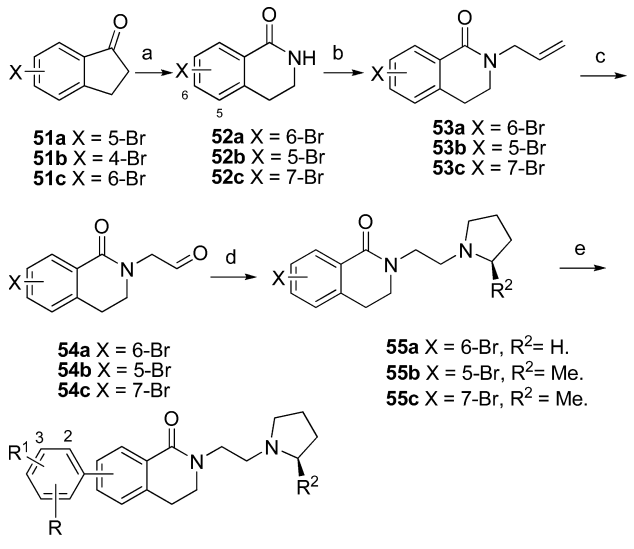


Figure 1. Design strategy.

Scheme 1[a]



3 R^2 = H, 6-phenyl
4 R^2 = H, 6-(2-fluorophenyl)
5 R^2 = H, 6-(3-fluorophenyl)
6 R^2 = H, 6-(4-fluorophenyl)
7 R^2 = H, 6-(3-cyanophenyl)
8 R^2 = H, 6-(4-cyanophenyl)
9 R^2 = H, 6-(3-(trifluoromethyl)phenyl)
10 R^2 = H, 6-(4-(trifluoromethyl)phenyl)
11 R^2= H, 6-(3-(trifluoromethoxy)phenyl)
12 R^2= H, 6-(4-(trifluoromethoxy)phenyl)
13 R^2 = H, 6-(2,4-difluorophenyl)
14 R^2 = H, 6-(3,4-difluorophenyl)
15 R^2 = H, 6-(3,5-difluorophenyl)
24 R^2 = Me, 5-(4-cyanophenyl)
25 R^2 = Me, 7-(4-cyanophenyl)

[a]Reagents and conditions: (a) NaN_3, CH_3SO_3H, CH_2Cl_2, rt; (b) NaH, allyl bromide, DMF, rt; (c) OsO_4, $NaIO_4$, THF–H_2O, 0 °C; (d) cyclic amines, $NaCNBH_3$, HOAc, MeOH, rt; (e) $ArB(OH)_2$, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane–H_2O, 90 °C.

An alternative approach to biaryl lactam compounds **18**–**23** is shown in Scheme 2. The chemistry was designed to install different cyclic amines via reductive amination as a penultimate step. To this end, Suzuki–Miyaura coupling of 2-allyl-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (**53a**) with the requisite phenyl boronic acids, followed by oxidation and reductive amination, provided the desired target compounds **18**–**23**.

Scheme 3 shows the preparation of derivatives with a three-carbon linker. *N*-Alkylation of 6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (**52a**) with 2-(2-bromoethyl)-1,3-dioxane followed by hydrolysis produced aldehyde **58**. Reductive amination of aldehyde **58** and subsequent Suzuki–Miyaura coupling with 4-cyanophenylboronic acid yielded target compounds **16** and **17**.

The preparation of isoindolinone analogue **26** is depicted in Scheme 4. Treatment of 5-bromoisoindolin-1-one (**60**) with allyl bromide and oxidation in the presence of osmium tetroxide and sodium periodate yielded 2-(5-bromo-1-oxoisoindolin-2-yl)-acetaldehyde (**62**). Reductive amination with (*R*)-2-methyl-pyrrolidine provided bromoisoindolinone **63**, which then underwent Suzuki–Miyaura coupling to afford biaryl isoindolinone **26**.

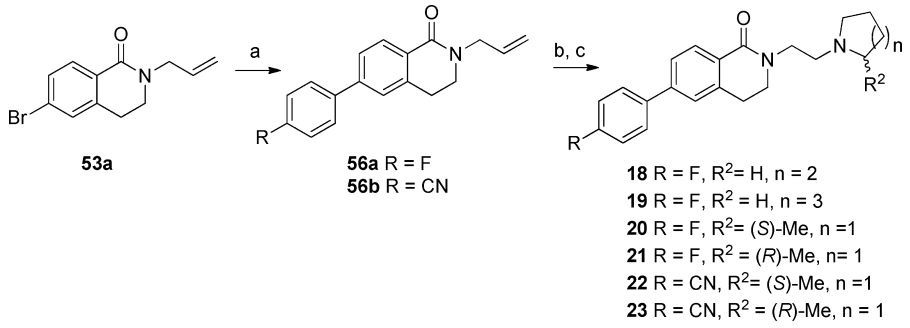
The syntheses of aryloxy-3,4-dihydroisoquinolinones **27**–**29** are shown in Scheme 5. 5-Methoxy-2,3-dihydro-1*H*-inden-1-one (**64**) underwent Schmidt rearrangement with sodium azide to afford 6-methoxy-3,4-dihydroisoquinolinone (**65**). Demethylation of aryl methyl ether **65** by boron tribromide afforded phenol **66**. Nucleophilic aromatic substitution reactions of phenol **66** with appropriate aryl halides in the presence of potassium carbonate generated aryloxy analogues **67a**–**c**. A similar reaction sequence (*N*-alkylation, oxidation, and reductive amination) to that depicted in Scheme 1 was then followed to provide the desired compounds **27**–**29**.

As shown in Scheme 6, pyridinyl analogue **30** was readily obtained by palladium-catalyzed Stille coupling of 4-tributylstannyl pyridine with 6-bromo-2-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**55a**).

Cyclopropyl ketone derivative **31** was synthesized according to Scheme 7. Suzuki–Miyaura coupling of 4-(methoxycarbonyl)-phenylboronic acid with aryl bromide **55a** followed by the ester hydrolysis generated carboxylic acid **68a**. This acid was treated with thionyl chloride to give benzoyl chloride **69a**, which was treated with *O*,*N*-dimethylhydroxylamine hydrochloride to afford Weinreb amide **70**. Addition of cyclopropylmagnesium bromide

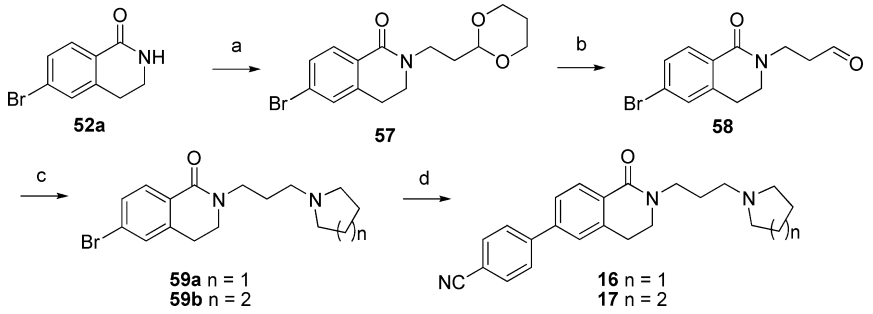
dx.doi.org/10.1021/jm300011d | J. Med. Chem. 2012, 55, 2452–2468

Scheme 2[a]



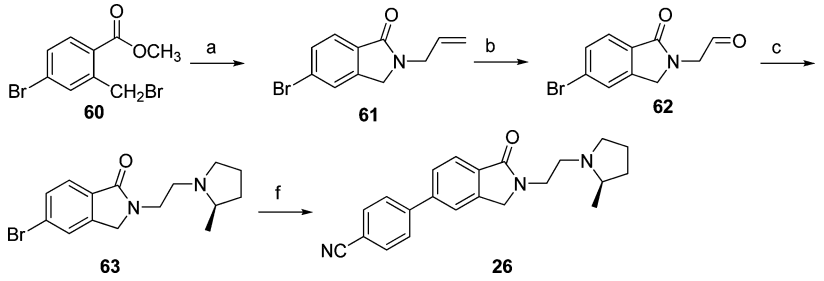
[a]Reagents and conditions: (a) $ArB(OH)_2$, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane−H_2O, 90 °C; (b) OsO_4, $NaIO_4$, THF−H_2O, 0 °C; (c) cyclic amines, $NaCNBH_3$, HOAc, MeOH, rt.

Scheme 3[a]



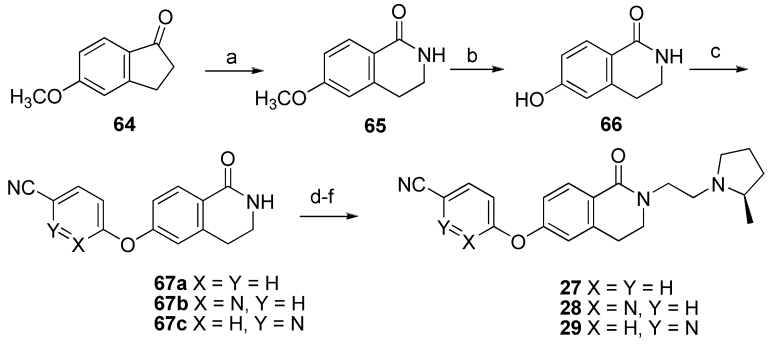
[a]Reagents and conditions: (a) NaH, 2-(2-bromoethyl)-1,3-dioxane, DMF, rt; (b) HCl (12 N), dioxane, 60 °C; (c) cyclic amines, $NaCNBH_3$, HOAc, MeOH, rt; (d) $ArB(OH)_2$, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane−H_2O, 90 °C.

Scheme 4[a]



[a]Reagents and conditions: (a) allyl amine, 50 °C; (b) OsO_4, $NaIO_4$, THF−H_2O, 0 °C; (c) (*R*)-2-methyl-pyrrolidine, $NaCNBH_3$, HOAc, MeOH, rt; (d) $ArB(OH)_2$, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane−H_2O, 90 °C.

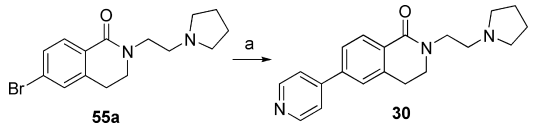
Scheme 5[a]



[a]Reagents and conditions: (a) NaN_3, CH_3SO_3H, CH_2Cl_2, rt; (b) BBr_3, CH_2Cl_2, −78 °C to rt; (c) 4-chloroarylnitrile, K_2CO_3, DMF, 90 °C; (d) NaH, allyl bromide, DMF, rt; (e) OsO_4, $NaIO_4$, THF−H_2O, 0 °C; (f) cyclic amines, $NaCNBH_3$, HOAc, MeOH, rt.

dx.doi.org/10.1021/jm300011d | *J. Med. Chem.* 2012, 55, 2452−2468

Scheme 6[a]



[a]Reagents and conditions: (a) 4-tributylstannyl pyridine, $Pd[(Ph)_3P]_4$, toluene, 90 °C.

to the Weinreb amide **70**, followed by hydrolysis, provided the desired ketone analogue **31**.

Alternatively, treatment of appropriate benzoyl chlorides **69b–e**, shown in Scheme 8, with a series of amines provided the desired amide analogues **32–50**.

RESULTS AND DISCUSSION

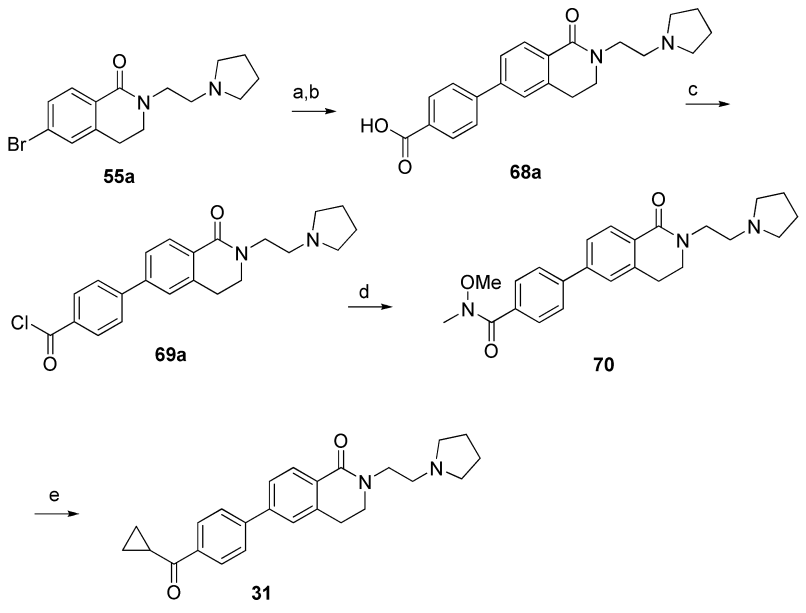
Our general approach for developing the structure–activity relationships (SAR) within this series was to dissect the pharmacophore of compound **3** into two regions (A and B; Figure 1) and to optimize each region in a systematic fashion.

We began our investigation by the introduction of substitutents on the distal phenyl ring (A region). In this study, we examined the impact of different substitutents and substitution patterns on the distal phenyl ring on H_3 receptor binding, the results of which are summarized in Table 1. Beginning with the mono fluoro substituted phenyl analogous (**4–6**), no clear preference was observed for ortho-, meta-, or para-substitution with respect to the human H_3 receptor binding. However, the para-substitution is more desired for the rat H_3 (rH_3) receptor binding (i.e., **6**, K_i = 86 nM). This observation is further supported when the rat H_3 receptor binding affinities of *meta*- and *para*-cyano (**7** and **8**), *meta*- and *para*-trifluoromethyl (**9** and **10**), and *meta*- and *para*-trifluoromethoxy (**11** and **12**) were compared. The para-substitution pattern generally resulted in more potent compounds in regard to the rat H_3 receptor binding. Bis-substitution (2,4-, 3,4-, and 3,5-) had no added benefits with respect to the H_3 receptor binding affinity when compared to the corresponding meta- and para-substituted analogues (**13–15** vs **5** and **6**). Among all the substituents investigated, the *para*-cyano substitution maximized the potency for both human and rat H_3 receptor binding.

Having found the para substitution on the distal phenyl ring to be important for H_3 receptor binding, we next focused our attention on the right-hand side of the molecule **3** (B region) to investigate the effect of a three-carbon linker on H_3 receptor binding. As shown in Table 2, the introduction of a three-carbon linker between the basic amine and the lactam core led to a decrease in rat H_3 receptor binding affinity (**16**, K_i = 270 nM vs **8**, K_i = 25 nM) albeit without a corresponding decrease in human H_3 receptor binding (**16** K_i = 6.9 nM vs **8** K_i = 3.9 nM). The effects of varying the cyclic amine ring size were also investigated, wherein the six-membered (**18**, K_i = 7.8 nM) and seven-membered (**19**, K_i = 5.7 nM) ring sizes led to some improvement in human H_3 receptor binding affinity when compared to the five-membered ring analogue **6** (K_i = 11 nM). However, compound **19** exhibited a cytochrome P450 inhibition (3A4, 47% at 3 μM) and showed reduced microsomal stability (rat, $t_{1/2}$ = 10 min). Replacement of the pyrrolidine moiety in compounds **6** and **8** with (*R*)-2-methyl pyrrolidine resulted in an approximately 5–9-fold improvement in human H_3 receptor binding affinity (**21** vs **6** and **23** vs **8**) and a 3–5-fold improvement in rat H_3 receptor binding (**21**, K_i = 23 nM, and **23**, K_i = 5.8 nM), respectively. In addition, a clear trend emerged with the (*R*)-absolute configuration being preferred when compared to the (*S*)-isomers (**20** vs **21** and **22** vs **23**) for both human and rat H_3 receptor binding.

In addition to the good in vitro H_3 receptor binding affinity of **21** and **23**, our paradigm for compound advancement required the demonstration of good selectivities against other neurotransmitter receptors, reuptakes, and ion channels. To this end, compounds **21** and **23** were further assayed for their selectivities against a panel of neurotransmitter receptors and ion channels. Despite good selectivities over several serotonin (5-HT)

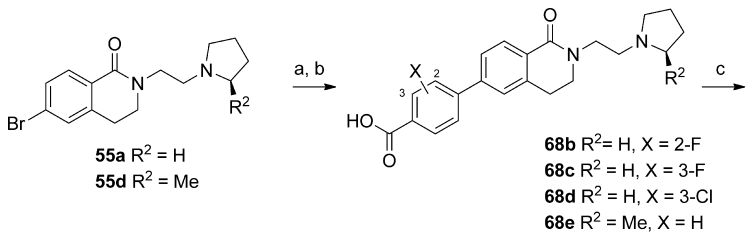
Scheme 7[a]

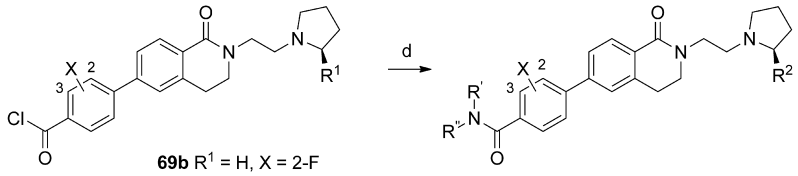


[a]Reagents and conditions: (a) 4-(methoxycarbonyl)phenylboronic acid, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane–H_2O, 90 °C; (b) NaOH, EtOH–H_2O, rt; (c) $SOCl_2$, 65 °C; (d) *N*,*O*-dimethylhydroxylamine hydrochloride, CH_2Cl_2, 0 °C to rt; (e) cyclopropyl magnesium bromide, THF, 0 °C to rt.

dx.doi.org/10.1021/jm300011d | J. Med. Chem. 2012, 55, 2452–2468

Scheme 8[a]

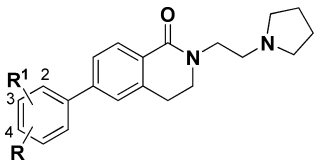




32 R^2= H, R' = H, R'' = H, X = H
33 R^2 = H, R' = H, R'' = Me, X = H
34 R^2 = H, R' = H, R'' = Et, X = H
35 R^2 = H, R' = H, R'' = ^{i}Pr, X = H
36 R^2 = H, R' = H, R'' = cyclopropyl, X = H
37 R^2 = H, R' = H, R'' = cyclobutyl, X = H
38 R^2 = H, R' = H, R'' = cyclopentyl, X = H
39 R^2 = H, R' = Me, R'' = Me, X = H
40 R^2 = H, R'R''N = pyrrolidinyl, X = H
41 R^2 = H, R'R''N = (*R*)-2-Me-pyrrolidinyl, X = H
42 R^2 = H, R'R''N = (*S*)-2-Me-pyrrolidinyl, X = H
43 R^2 = H, R'R''N = pyrrolidinyl, X = 2-F
44 R^2 = H, R'R''N = pyrrolidinyl, X = 3-F
45 R^2 = H, R'R''N = pyrrolidinyl, X = 3-Cl
46 R^2 = H, R' = H, R'' = Me X = 2-F
47 R^2 = H, R' = Me, R'' = Me X = 2-F
48 R^2 = Me, R' = H, R'' = Me, X = H
49 R^2 = Me, R' = H, R'' = Et, X = H
50 R^2 = Me, R'R''N = pyrrolidinyl, X = H

[a]Reagents and conditions: (a) $ArB(OH)_2$, $Pd[(o\text{-toly})_3P]_2Cl_2$, K_2CO_3, dioxane–H_2O, 90 °C; (b) NaOH, EtOH–H_2O, rt; (c) $SOCl_2$, 65 °C; (d) R'R''NH, THF, rt.

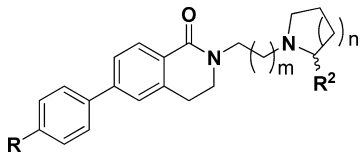
Table 1. Binding Affinity of Compounds 3–15



compd	R	R^1	binding K_i (nM) hH_3[a]	binding K_i (nM) rH_3[b]
3	H	H	11.4 ± 5.0	145
4	2-F	H	14.1 ± 6.2	174
5	3-F	H	11.6 ± 3.9	164
6	4-F	H	11.0 ± 3.9	86
7	3-CN	H	3.4 ± 0.5	73
8	4-CN	H	3.9 ± 0.8	25
9	3-CF_3	H	6.4 ± 2.1	182
10	4-CF_3	H	9.3 ± 2.2	101
11	3-OCF_3	H	28.4 ± 6.5	276
12	4-OCF_3	H	14.9 ± 3.7	178
13	2-F	4-F	8.1 ± 1.4	153
14	3-F	4-F	7.7 ± 1.1	82
15	3-F	5-F	9.0 ± 2.0	146

[a]Displacement of [^{3}H]-(*R*)-α-methylhistamine binding to cloned human H_3 receptors stably expressed in HEK293T cells. [b]Displacement of [^{3}H]-(*R*)-α-methylhistamine binding to cloned rat H_3 receptors stably expressed in HEK293T cells. Mean of three determinations with a standard error of ±20%.

Table 2. Binding Affinity of Compounds 16–23



compd	R	R^2	*m*	*n*	binding K_i (nM) hH_3	binding K_i (nM) rH_3
16	CN	H	2	1	6.9 ± 1.1	270
17	CN	H	2	2	18.0 ± 2.3	153
18	F	H	1	2	7.8 ± 1.9	na
19	F	H	1	3	5.7 ± 1.4	47
20	F	(*S*)-2-Me	1	1	12.7 ± 2.4	110
21	F	(*R*)-2-Me	1	1	1.2 ± 0.1	23
22	CN	(*S*)-2-Me	1	1	2.1 ± 0.7	49
23	CN	(*R*)-2-Me	1	1	0.8 ± 0.4	5.8

receptor subtypes, dopamine D_2 and adrenergic α_{2A} receptor (data not shown), compounds **21** and **23** demonstrated a potent hERG (human ether a go-go) inhibition (IC_{50} = 0.3 and 0.14 μM, respectively) in an IonWorks HT assay.[17]

An effort was then undertaken to block this hERG inhibition while retaining nanomolar potency at the H_3 receptors. These data are summarized in Table 3. An initial SAR study examined the effect of the position of attachment between the distal

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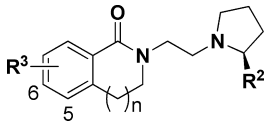
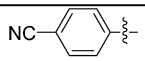
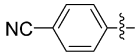
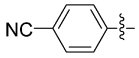
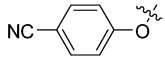
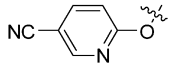
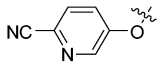
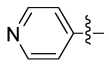
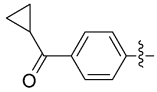
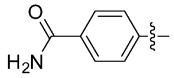
Table 3. Binding Affinity and hERG Inhibition of Compounds 24−32



compd	connectivity	R^3	R^2	n	Binding K_i (nM) hH_3	hERG % inh @10 μM
24	5		Me	1	21.7 ± 3.9	96
25	7		Me	1	2.4 ± 0.2	98
26	5		Me	0	23.8 ± 1.3	98
27	6		Me	1	0.6 ± 0.1	95
28	6		Me	1	1.2 ± 0.2	89
29	6		Me	1	0.3 ± 0.0	99
30	6		H	1	7.8 ± 1.4	93
31	6		H	1	6.0 ± 1.9	65
32	6		H	1	6.0 ± 0.5	14

aromatic ring and the lactam core on hERG affinity. It was our hope that altering the orientation of the aromatic rings in this series would improve the hERG selectivity. Unfortunately, this goal was not realized: compounds **24** and **25** displayed potent hEGR inhibition with 96% and 98% at 10 μM, respectively, in the IonWorks HT assay. Replacement of the six-membered lactam core to a five-membered lactam core had minimal impact on hERG selectivity. Compound **26** exhibited strong hERG inhibition (98% at 10 μM). Furthermore, the large loss of potency observed in compound **26** illustrates the strong preference for a six-membered lactam core over a five-membered lactam core for potent H_3 receptor binding activity. An alternative strategy of improving hERG selectivity was to reduce compound lipophilicity, such as the introduction of an ether linkage (i.e., compound **27**−**29**) between the distal aromatic ring and the lactam core or the replacement of the distal phenyl ring with a pyridinyl ring (i.e., compound **30**). As shown in Table 3, neither these modifications demonstrated improved hERG selectivity. However, the introduction of a carbonyl-containing substituent to replace the 4-cyano group in compounds **31** and **32** resulted in a substantial drop in hERG potency without disrupting human H_3 receptor binding affinity. The effect of replacing the 4-cyano substitutent with a carboxamide group, as in **32**, was particularly remarkable, furnishing a compound with only 14% hERG inhibition at 10 μM (IC_{50} = 26.3 μM) in the IonWorks HT assay.

Having identified that the primary carboxamide group at the distal phenyl ring in compound **32** is necessary for removing hERG activity, we next sought to further probe the role of secondary and tertiary carboxamides. To this end, a variety of secondary and tertiary carboxamide derivatives were prepared. Their human H_3 receptor binding affinities and hERG potencies are summarized in Table 4. The human H_3 receptor binding affinity of alkyl-substituted secondary (**33**−**38**) and tertiary carboxamides (**39** and **40**) tended to increase when compared to the primary carboxamide **32**. However, the hERG selectivity was decreased as steric bulk was added (i.e., **33** vs **35**−**38**). Replacement of the pyrrolidinyl carboxamide with (*R*)-2-methyl pyrrolidinyl or (*S*)-2-methyl pyrrolidinyl carboxamide, as in **41** and **42**, had minimal impact on human H_3 receptor binding affinity. Compounds **41** and **42** were equipotent. Interestingly, the hERG inhibition data showed a slight preference for the (*S*)-isomer **42**.

Halogen substitution of the distal aromatic ring proved to be sensitive to the hERG selectivity. Initially, the pyrrolidinyl carboxamide was held constant while the effect of halogen substitution on the distal aromatic ring was examined. In general, halogen substitution on the distal aromatic ring was likewise well-tolerated, although none proved superior to the unsubstituted analogue **40** with respect to human H_3 receptor binding affinity. However the influence of halogen substitution on hERG selectivity was noteworthy, as the 2-fluoro substitution in **43** was preferred over the 3-fluoro (**44**) and 3-chloro (**45**) substitution. The 2-fluoro substitution was then held constant while two additional carboxamides (compound **46** and **47**) were examined. The effect of replacing the pyrrolidinyl carboxamide of **43** with *N*,*N*-dimethyl carboxamide, as in **47**, was particularly striking, as compound **47** exhibited a 3-fold improvement in hERG selectivity with a IC_{50} of 32.5 μM in the IonWorks HT assay.

Replacement of the pyrrolidinyl group at the basic amine site with a (*R*)-2-methyl pyrrolidinyl group, as represented by compounds **48** and **49**, resulted in a decrease in hERG

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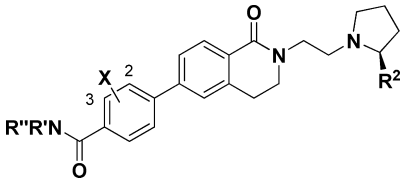
Table 4. Binding Affinity and hERG Inhibition of Compounds 33−50



compd	R^2	X	NR′R″	binding K_i (nM) hH_3	hERG IC_{50} (μM)
33	H	H	NHMe	1.3 ± 0.0	29
34	H	H	NHEt	1.2 ± 0.2	16
35	H	H	^{i}PrNH	1.9 ± 0.2	6.2
36	H	H	cyclopropylNH	2.7 ± 0.5	11
37	H	H	cyclobutylNH	2.1 ± 0.0	2.5
38	H	H	cyclopentylNH	1.9 ± 0.2	8.2
39	H	H	NMe_2	0.9 ± 0.1	11
40	H	H	pyrrolidinyl	2.4 ± 0.5	8.8
41	H	H	(*R*)-2-Me-pyrrolidinyl	1.7 ± 0.4	10.5
42	H	H	(*S*)-2-Me-pyrrolidinyl	1.7 ± 0.1	12
43	H	2-F	pyrrolidinyl	3.2 ± 0.5	11.3
44	H	3-F	pyrrolidinyl	1.3 ± 0.2	8.8
45	H	3-Cl	pyrrolidinyl	1.6 ± 0.1	9.3
46	H	2-F	NHMe	1.7 ± 0.2	3.7
47	H	2-F	NMe_2	3.1 ± 0.6	32.5
48	(*R*)-Me	H	NHMe	1.0 ± 0.2	17
49	(*R*)-Me	H	NHEt	1.0 ± 0.2	7.4
50	(*R*)-Me	H	pyrrolidinyl	0.2 ± 0.0	9.6

Table 5. Selectivity Profile of Compounds 38, 39, 41, 42, and 49−50[a]

compd	H_1 (μM)	H_2 (μM)	5-HT_{1A} (μM)	5-HT_{2B} (μM)	5-HT_6 (μM)	D_2 (μM)	α_{2A} (μM)	5-HT-T (μM)	DA-T (μM)
38	9.62	>10	8.72	>10	>10	>10	>3	0.17	>10
39	>10	>55	8.67	>10	>10	>10	>3	>3	>10
41	>10	>10	9.72	>10	>10	>10	>3	0.32	>10
42	7.01	>10	9.04	>10	>10	>10	>3	0.39	>10
49	7.23	>10	10.1	>10	>10	>10	>3	0.3	>10
50	8.75	>10	12.2	>10	>10	>10	>3	0.81	>10

[a] K_i values were determined in triplicate with standard error of <20%

selectivity. Interestingly, the hERG selectivity exhibited by **50** was slightly improved (**50** vs **40**).

We further examined six compounds (**38**, **39**, **41**, **42**, **49**, and **50**) selected from Table 4, which exhibited good human H_3 receptor binding affinity, hERG selectivity, and permeability in vitro parallel artificial membrane permeability assay (PAMPA) (data were not shown) for their selectivities against a panel of biogenic amine receptors and transporters (Table 5). In general, these compounds showed >1000-fold selectivity over all the receptors and transporters examined, with the exception of the serotonin transporter (5-HT-T). All compounds demonstrated moderate binding affinity for the serotonin transporter (K_i < 1 μM). The exception was compound **39**, which showed a low binding affinity at the serotonin transporter site (K_i > 3 μM). Compound **39** was further evaluated in [^{35}S]GTPγS binding assay to determine its inverse agonism potential at the human H_3 receptor.[18] To our delight, compound **39** reduced basal [^{35}S]GTPγS binding in membranes from HEK cells expressing the human H_3 receptor in a concentration-dependent manner with an EC_{50} value of 10.7 ± 0.3 nM and a maximal inhibition of 65% from basal.

By now we had identified compound **39**, which exhibited good binding and functional activities at the human H_3 receptor, and we then proceeded with the assessment of its drug-likeness in vitro. Compound **39** was evaluated in multispecies liver microsomal stability assays, cytochrome P450 inhibition assay, Caco-2 permeability assay, MDCK-MDR1 permeability assay, human, and rat plasma protein binding assay.

Multispecies Microsomal Stability. The metabolic stability of **39** was determined in male Sprague−Dawley rat, beagle dog, cynomolgus monkey, and mixed gender human liver microsomes using a substrate concentration of 1 μM and an incubation time of 30 min at 37 °C in the presence of NADPH and UDPGA, in combination. As shown in Table 6, compound

Table 6. Microsomal Stability Profile of Compounds 39

	phase I + II (NADPH + UDPGA)
liver microsomes	$t_{1/2}$ (min)
rat	26 min
dog	47 min
monkey	>60 min
human	69 min

dx.doi.org/10.1021/jm300011d | J. Med. Chem. 2012, 55, 2452−2468

39 was moderately metabolized in rat liver microsomes and metabolically stable in all other species tested. The formation of glutathione (GSH) adduct was not observed.

Cytochrome P450 (CYP450) Inhibition. Human liver microsomes were incubated with compound **39** at varying concentrations up to 100 μM. Compound **39** did not inhibit CYP1A2, CYP2A6, CYP2B6, CYP2C8, CYP2C9, CYP2C19, CYP2D6, and CYP3A4-mediated midazolam-1′-hydroxylation and CYP3A4-mediated testosterone-6β-hydroxylation activity at the highest concentration tested (100 μM). These results suggest that the potential for clinical drug−drug interactions with substrates of the CYPs tested is remote.

Permeability. The permeability of compound **39** was measured across Caco-2 epithelial monolayers. Compound **39** exhibited passive permeability. The apparent permeability (P_{app}) was high [P_{app} (10^{-6} cm/s) A→B, 12.1; B→A, 31.1]. The permeability directional ratio (PDR = 2.57) indicated this compound might be subjected to some efflux. In addition, in MDCK-MDR1 assay compound **39** exhibited high P-gp mediated efflux ratios (B→A/A→B = 4.6), suggesting limited brain penetration. In fact, subsequent in vivo studies (rats, 10 mg/kg, po) validated these in vitro results, as compound **39** demonstrated some potential to penetrate the brain with brain ($AUC_{0\rightarrow\infty/}$ = 642 h·ng/g) and plasma ($AUC_{0\rightarrow\infty/}$ = 2369 h·ng/g) ratios (B/P) = 0.27.

Plasma Protein Binding. Plasma protein binding of compound **39** was determined by ultrafiltration and Biacore analysis. In ultrafiltration experiments, the free fractions of compound **39** in human and rat plasma were 59% and 50%, respectively. In Biacore assays, compound **39** was found to be bound to human serum albumin and to α_1-acid glycoprotein at low level.

At this point, we have identified a molecule that met our primary in vitro criteria. We then proceeded to evaluate this compound in vivo.

The hydrochloride salt of compound **39** was used in the following in vivo studies and its structure was confirmed by single crystal X-ray analysis (Supporting Information). Compound **39** was formulated with 2% Tween/0.5% methyl cellulose (MC) in water for oral administration and DMSO/80% polyethylene glycol (PEG) 200 for the IV route of the administration.

Pharmacokinetic Profile. The pharmacokinetics of compound **39** have been characterized in male Long Evans rats after a single bolus intravenous dose of 2 mg/kg and a single oral dose of 10 mg/kg. The IV bolus pharmacokinetics of compound **39** exhibited high clearance (87 mL/min/kg), moderate volume of distribution (2.1 L/kg), and short elimination half-life (0.3 h). Upon oral administration at 10 mg/kg, compound **39** was quickly absorbed (T_{max} = 0.3 h) and had a short terminal half-life ($t_{1/2}$ = 0.8 h) and good oral bioavailability (F = 85%). Upon oral dosing at 10 mg/kg, compound **39** showed a maximum plasma concentration (C_{max}) of 989 ng/mL and a systemic exposure ($AUC_{0-\infty}$) of 1648 h·ng/mL.

The pharmacokinetics of **39** was also determined in male beagle dogs after a single bolus intravenous dose of 2 mg/kg and observed a moderate plasma clearance of 23 mL/min/kg, volume of distribution (3.1 L/kg), and short elimination half-life (1.6 h). The oral bioavailability of compound **39** when dosed at 10 mg/kg is 57%.

In Vivo Functional Activity: Dipsogenia Assay. To demonstrate functional antagonism at the H_3 receptor in vivo, compound **39** was tested in the rat dipsogenia model.[19]

Administration of the H_3 agonist (*R*)-α-methylhistamine produces a robust increase in drinking behavior in rodents that is mediated through brain H_3 receptors. The increased drinking behavior can be measured by recording the amount of water an animal consumes during a 1 h period following dosing with the agonist. Pretreatment with compound **39**, at doses of 3 or 10 mg/kg ip (P < 0.05), produced a significant block in the agonist-induced drinking response (Figure 2). These effects

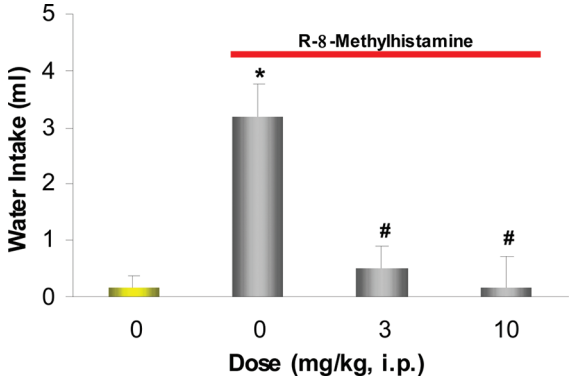


Figure 2. Effect of **39** on (*R*)-α-methylhistamine induced water consumption in rats. **39** was administered 30 min prior to (*R*)-α-methylhistamine. *p < 0.05 versus vehicle; #p < 0.05 versus (*R*)-α-methyl histamine alone.

confirm both on-target activity as well as brain penetration for compound **39**.

Compound **39** was then evaluated in two animal models of cognition.

Novel Object Recognition Assay (NOR). In the novel object recognition model, rats are allowed to explore a pair of identical objects (training) and then returned to their home cages. After a period of time, the animals are presented with one previously explored "familiar" object and an unexplored "novel" object. The animal will spontaneously explore the novel object more than the familiar one. Memory for the familiar object is recorded as greater time spent exploring the novel object. When the time between training and the testing trial is increased to 48 h, the animal no longer remembers the familiar object and will spend equal amounts of time exploring both objects during the trial.[20] Compound **39** with rat H_3 binding affinity 35 nM was able to enhance recognition memory (Figure 3), with the minimal effective dose (MED) for **39** being

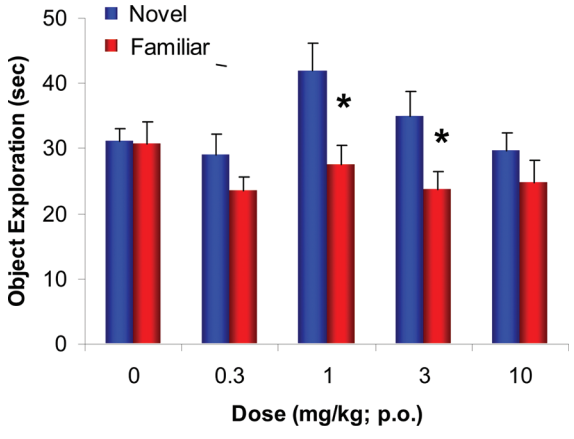


Figure 3. Compound **39** reverses the time-induced cognitive deficit in novel object recognition in rats, *p < 0.05 novel versus familiar.

dx.doi.org/10.1021/jm300011d | J. Med. Chem. 2012, 55, 2452−2468

1 mg/kg, po ($P < 0.05$). However, compound **39** shows an inverted U-shaped dose−response curve and is more active at lower doses than at higher does. In fact, inverted U-shaped dose−response curves are typical of memory enhancing compounds, with improvement occurring over a narrow range of doses.[21]

Social Odor Recognition (SOR) Assay. In mouse social odor recognition assay, male mice are allowed to explore wooden beads scented with odors from the test mouse or a stranger mouse. Memory (24 h later) is reflected as preferential exploration of a new odor over the previously experienced odor. Memory deficits in the SOR model can be induced by treatment with the NMDA receptor antagonist MK-801 (dizocipine).[22] Compound **39** was able to reverse the MK-801 induced memory deficit (Figure 4), with the MED value of 1.0 mg/kg po ($P < 0.05$).

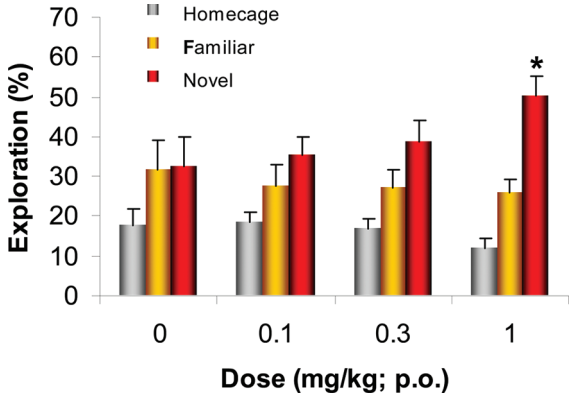


Figure 4. Compound **39** reverses the MK-801 induced memory deficit in social odor recognition in mice, *$p < 0.05$ novel versus familiar.

Drug Safety Study. The preclinical safety of compound **39** was evaluated in a screening Ames bacterial mutagenicity assay. Compound **39** was negative at all dosages tested in the bacterial reverse mutation assay with *Salmonella typhimurium*. 14-Day repeat dose toxicity studies were also carried out in rats (60, 200, and 600 mg/kg/day) and dogs (20, 60, and 120 mg/kg/day). In dogs, arrhythmia and QTc prolongation at 20 mg/kg/day were observed. Convulsions were also observed in dogs at dose ≥60 mg/kg/day. In rats, clinical evidence of respiratory distress and epithelial hyperplasia were observed at 600 mg/kg/day. The maximum tolerated dose (MTD) of compound **39** is 200 mg/kg/day in rats and 20 mg/kg/day in dogs.

CONCLUSION

In summary, we have identified a potent and selective series of H_3 receptor antagonists. From the SAR discussed, we have defined a three-part pharmacophores, in which the six-membered lactam core, two carbon linker between the basic amine and the lactam core, and para-substituted carboxamide at the distal aromatic ring are required for potent and selective H_3 receptor antagonist. Compound **39** from this series was chosen for further profiling in vitro and in vivo. This compound demonstrates antagonist activity at the H_3 receptor within the central nervous system by a reversal of H_3 agonist (*R*)-α-methylhistamine induced drinking behavior in the rat. Furthermore, compound **39** exhibited good efficacy in two cognitive behavioral assays. Thus, compound **39** represents an important advancement in this area.

EXPERIMENTAL SECTION

General Method. Melting points were determined on a Thomas−Hoover melting point apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Varian Unity Plus 400 instrument. Chemical shifts are reported in δ values (part per million, ppm) relative to an internal standard of tetramethylsilane in DMSO-d_6. Nominal (lower solution) mass spectra were acquired on either a Waters LCT or an Applied Biosystems API 3000 mass spectrometer. High resolution mass spectra (HRMS) were acquired on either a Waters LCT or an Agilent TOF mass spectrometer. Compound purity was determined by a LC-MS with 230 and 254 nm wavelengths. All LC-MS experiments were done on an Agilent 1100 HPLC coupled with an Agilent single quadrupole mass spectrometer. All final compounds reported here have purity of ≥95%.

General Procedure A: Preparation of Aryl-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one Hydrochloride Compounds. The following compounds (**3**−**15**) were prepared from the appropriate starting materials, as described below.

To a solution of an appropriate bromo-2-[2-(pyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (**55a**−**c**, 1 mmol) and appropriate aryl boronic acid (2 mmol) in dioxane (25 mL) was treated with dichlorobis(*tri-o*-tolyphosphine)-palladium(II) (0.05 mmol), potassium carbonate (2.5 mmol), and water (2 mL). The reaction mixture was allowed to stir at 90 °C for 0.5−2 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was partitioned between 1.0 N NaOH and CH_2Cl_2 and extracted with CH_2Cl_2. The combined organic phases were concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in dichloromethane with 0.5% ammonium hydroxide) to afford the free amine of the desired compound as a colorless oil. The oil was dissolved in ethanol, treated with 1.0 M HCl in diethyl ether, stirred for 10 min, and filtered. The filter cake was washed with diethyl ether and dried to afford the desired product, generally, as a white solid.

6-Phenyl-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (3). Yield 26% as a white solid, hydrochloride salt; mp 218−220 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.97 (m, 2H), 3.00−3.06 (m, 4H), 3.37 (m, 2H), 3.58−3.62 (m, 4H), 3.79 (t, J = 6.14 Hz, 2H), 7.35−7.39 (m, 1H), 7.45 (m, 2H), 7.59−7.63 (m, 2H), 7.67−7.69 (m, 2H), 7.91 (d, J = 8.11 Hz, 1H), 9.63 (br, 1H). HRMS: calcd for $C_{21}H_{24}N_2O$ + H^+, 321.19614; found (ESI, [M + H]$^+$), 321.1958.

6-(2-Fluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (4). Yield 31% as a white solid, hydrochloride salt; mp 211−213 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.97 (m, 2H), 3.05 (m, 4H), 3.37 (m, 2H), 3.61 (m, 4H), 3.79 (t, J = 5.80 Hz, 2H), 7.27−7.32 (m, 2H), 7.41−7.54 (m, 4H), 7.93 (d, J = 8.12 Hz, 1H), 9.68 (br, 1H). HRMS: calcd for $C_{21}H_{23}FN_2O$ + H^+, 339.18672; found (ESI, [M + H]$^+$), 339.1867.

6-(3-Fluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (5). Yield 51% as a white solid, hydrochloride salt; mp 182−184 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.94 (m, 2H), 3.04−3.08 (m, 4H), 3.35−3.39 (m, 2H), 3.56−3.62 (m, 4H), 3.79 (t, J = 6.14 Hz, 2H), 7.18−7.23 (m, 1H), 7.46−7.56 (m, 3H), 7.65−7.68 (m, 2H), 7.91 (d, J = 8.0 Hz, 1H), 9.78 (br, 1H). HRMS: calcd for $C_{21}H_{23}FN_2O$ + H^+, 339.18672; found (ESI, [M + H]$^+$), 339.1871.

6-(4-Fluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroiso-quinolin-1(2*H*)-one Hydrochloride (6). Yield 77% as a white solid, hydrochloride salt; mp 207−209 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.96 (m, 2H), 3.03−3.08 (m, 4H), 3.35−3.37 (m, 2H), 3.57−3.62 (m, 4H), 3.79 (t, J = 6.34 Hz, 2H), 7.28 (t, J = 8.90 Hz, 2H), 7.57−7.61 (m, 2H), 7.71−7.74 (m, 2H), 7.89 (d, J = 8.05 Hz, 1H), 10.08 (br, 1H). HRMS: calcd for $C_{21}H_{23}FN_2O$ + H^+, 339.18672; found (ESI, [M + H]$^+$), 339.1869.

3-[1-Oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzo-nitrile (7). Yield 49% as a white solid, hydrochloride salt; mp 204−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.96 (m, 2H), 2.97−3.09 (m, 4H), 3.34−3.38 (m, 2H), 3.55−3.63 (m, 4H), 3.77−3.81 (m, 2H), 7.66 (t, J = 7.76 Hz, 1H), 7.72 (m, 2H), 7.83 (d, J = 7.76 Hz, 1H), 7.92 (d, J = 9.09 Hz, 1H),

8.05 (dd, J = 8.11, 2.2 Hz, 1H), 8.18 (d, J = 1.51 Hz, 1H), 9.66 (br, 1H). HRMS: calcd for $C_{22}H_{23}N_3O + H^+$, 346.19139; found (ESI, $[M + H]^+$), 346.1915.

4-[1-Oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]-benzonitrile (8). Yield 40% as a white solid, hydrochloride salt; mp 249−251 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.94 (m, 2H), 3.03−3.09 (m, 4H), 3.37 (m, 2H), 3.59−3.63 (m, 4H), 3.78−3.81 (m, 2H), 7.69−7.72 (m, 2H), 7.88−7.95 (m, 5H), 9.83 (br, 1H). HRMS: calcd for $C_{22}H_{23}N_3O + H^+$, 346.19139; found (ESI, $[M + H]^+$), 346.1925.

2-(2-Pyrrolidin-1-ylethyl)-6-[3-(trifluoromethyl)phenyl]-3,4-dihydroisoquinolin-1(2*H*)-one (9). Yield 28% as a white solid, hydrochloride salt; mp 138−139 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.96 (m, 2H), 3.03−3.10 (m, 4H), 3.37 (m, 2H), 3.57−3.63 (m, 4H), 3.80 (t, J = 6.14 Hz, 2H), 7.70−7.75 (m, 4H), 7.93 (d, J = 8.58 Hz, 1H), 7.99−8.01 (m, 2H), 10.1 (br, 1H). HRMS: calcd for $C_{22}H_{23}F_3N_2O + H^+$, 389.18352; found (ESI, $[M + H]^+$), 389.1830.

2-(2-Pyrrolidin-1-ylethyl)-6-[4-(trifluoromethyl)phenyl]-3,4-dihydroisoquinolin-1(2*H*)-one (10). Yield 51% as a white solid, hydrochloride salt; mp 243−244 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.96 (m, 2H), 3.07 (m, 4H), 3.37 (m, 2H), 3.60 (m, 4H), 3.79 (m, 2H), 7.67−7.70 (m, 2H), 7.79−7.81 (m, 2H), 7.89−7.95 (m, 3H), 9.60 (br, 1H). HRMS: calcd for $C_{22}H_{23}F_3N_2O + H^+$, 389.18352; found (ESI, $[M + H]^+$), 389.1841;

2-(2-Pyrrolidin-1-ylethyl)-6-[3-(trifluoromethoxy)phenyl]-3,4-dihydroisoquinolin-1(2*H*)-one (11). Yield 51% as a white solid, hydrochloride salt; mp 135−137 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.96 (m, 2H), 3.03−3.09 (m, 4H), 3.37 (m, 2H), 3.52−3.62 (m, 4H), 3.79 (t, J = 6.03 Hz, 1H), 7.38 (d, J = 8.23 Hz, 1H), 7.59 (t, J = 8.0 Hz, 1H), 7.67 (m, 3H), 7.74 (d, J = 8.11 Hz, 1H), 7.92 (d, J = 7.88 Hz, 1H), 9.93 (br, 1H). HRMS: calcd for $C_{22}H_{23}F_3N_2O_2 + H^+$, 405.17844; found (ESI, $[M + H]^+$), 405.1787.

2-(2-Pyrrolidin-1-ylethyl)-6-[4-(trifluoromethoxy)phenyl]-3,4-dihydroisoquinolin-1(2*H*)-one (12). Yield 59% as a white solid, hydrochloride salt; mp 209−210 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (m, 2H), 1.98 (m, 2H), 3.00−3.09 (m, 4H), 3.33−3.39 (m, 4H), 3.56−3.63 (m, 4H), 3.80 (t, J = 6.04 Hz, 2H), 7.46 (d, J = 8.23 Hz, 2H), 7.63−7.66 (m, 2H), 7.81−7.86 (m, 2H), 7.93 (d, J = 8.01 Hz, 1H), 9.85 (br, 1H). HRMS: calcd for $C_{22}H_{23}F_3N_2O_2 + H^+$, 405.17844; found (ESI, $[M + H]^+$), 405.1793.

6-(2,4-Difluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (13). Yield 50% as a white solid, hydrochloride salt; mp 225−226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.98 (m, 2H), 3.00−3.08 (m, 4H), 3.36−3.39 (m, 2H), 3.60−3.63 (m, 4H), 3.79−3.82 (m, 2H), 7.20 (td, J = 8.24, 2.09 Hz, 1H), 7.38 (m, 1H), 7.45−7.49 (m, 2H), 7.56−7.62 (m, 1H), 7.93 (d, J = 8.0 Hz, 1H), 9.85 (br, 1H). HRMS: calcd for $C_{21}H_{22}F_2N_2O + H^+$, 357.17729; found (ESI, $[M + H]^+$), 357.1772.

6-(3,4-Difluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (14). Yield 32% as a white solid, hydrochloride salt; mp 179−180 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.97 (m, 2H), 2.99−3.07 (m, 4H), 3.32−3.39 (m, 2H), 3.53−3.62 (m, 4H), 3.75−3.80 (m, 2H), 7.48−7.58 (m, 2H), 7.63−7.65 (m, 2H), 7.78−7.85 (m, 1H), 7.90 (d, J = 7.88 Hz, 1H), 9.88 (br, 1H). HRMS: calcd for $C_{21}H_{22}F_2N_2O + H^+$, 357.17729; found (ESI, $[M + H]^+$), 357.1771.

6-(3,5-Difluorophenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (15). Yield 32% as a white solid, hydrochloride salt; mp 196−198 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.98 (m, 2H), 3.02−3.08 (m, 4H), 3.33−3.39 (m, 2H), 3.59−3.63 (m, 4H), 3.78−3.80 (m, 2H), 7.25−7.30 (m, 1H), 7.49 (m, 2H), 7.71−7.73 (m, 2H), 7.92 (d, J = 8.70 Hz, 1H), 9.72 (br, 1H). HRMS: calcd for $C_{21}H_{22}F_2N_2O + H^+$, 357.17729; found (ESI, $[M + H]^+$), 357.1777.

4-[1-Oxo-2-(3-pyrrolidin-1-ylpropyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzo-nitrile (16). Using essentially the general procedure A and employing 4-cyano phenyl boronic acid and 6-bromo-2-[3-(pyrrolidin-1-yl)propyl]-3,4-dihydroisoquinolin-1(2*H*)-one (**59a**), 71 mg (68%) of the desired prodcut was obtained as a white solid, hydrochloride salt; mp 192−193 °C.; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.91−1.99 (m, 4H), 2.92 (m, 2H), 3.03−3.09 (m, 4H), 3.46 (m, 2H), 3.52−3.59 (m, 4H), 7.68−7.70 (m, 2H), 7.87−7.96 (m, 5H). HRMS: calcd for $C_{23}H_{25}N_3O + H^+$, 360.20704; found (ESI, $[M + H]^+$), 360.2072.

4-[1-Oxo-2-(3-piperidin-1-ylpropyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzonitrile (17). The title compound was prepared according to the procedure described for **16**, substituting pyrrolidine in place of piperidine, 92 mg (60%) of the desired prodcut was obtained as a white solid; mp 249−250 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.36 (m, 1H), 1.63−1.72 (m, 5H), 1.94−1.98 (m, 2H), 2.79 (m, 2H), 2.97 (m, 2H), 3.05 (t, J = 6.47 Hz, 2H), 3.42 (m, 2H), 3.53 (t, J = 6.71 Hz, 2H), 3.57 (m, J = 6.46 Hz, 2H), 7.68−7.70 (m, 2H), 7.88−7.94 (m, 5H), 9.87 (br, 1H). HRMS: calcd for $C_{24}H_{27}N_3O + H^+$, 374.22269; found (ESI, $[M + H]^+$), 374.2232.

6-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (18). This compound was prepared in two steps from 2-allyl-6-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**56a**) as described below. The reported yields represent the yields obtained for the final step of the sequence. (1) 2-(6-(4-Fluorophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetaldehyde was prepared generally according to the general procedure B in step 3 and employing 2-allyl-6-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (1.06 g, 3.6 mmol) as starting material. The desired product was obtained as a colorless oil in 97% yield. (2) 6-(4-Fluorophenyl)-2-(2-piperidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one. A solution of 2-(6-(4-fluorophenyl)-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetaldehyde (0.1 g, 0.35 mmol) and piperidine (0.03 g, 0.35 mmol) in methanol was treated with sodium cyanoborohydride (33 mg, 0.53 mmol) and acetic acid (0.042 mL, 0.88 mmol), stirred at room temperature overnight, diluted with 1 N NaOH, and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in CH_2Cl_2 with 0.5% ammonium hydroxide) to afford the free amine of the title product as a colorless oil. The oil was dissolved in ethanol, treated with Etheral HCl, stirred, and filtered. The desired product was obtained as a white hydrochloride salt; Yield 47%; mp 241−243 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.33−1.36 (m, 1H), 1.67−1.80 (m, 5H), 2.85−2.94 (m, 2H), 3.06 (t, J = 6.61 Hz, 2H), 3.24−3.28 (m, 2H), 3.51−3.54 (m, 2H), 3.62 (t, J = 6.62 Hz, 2H), 3.84 (t, J = 6.5 Hz, 2H), 7.30 (t, J = 8.82 Hz, 2H), 7.59−7.63 (m, 2H), 7.72−7.76 (m, 2H), 7.91 (d, J = 8.12 Hz, 1H), 9.73 (br, 1H). HRMS: calcd for $C_{22}H_{25}FN_2O + H^+$, 353.20237; found (ESI, $[M + H]^+$), 353.2025.

2-(2-Azepan-1-ylethyl)-6-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (19). The title compound was prepared according to the procedure described in **18**, substituting piperidine in place of azepane. Yield 58%; mp 215−217 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52−1.54 (m, 4H), 1.71−1.85 (m, 4H), 3.05 (t, J = 6.5 Hz, 2H), 3.14−3.21 (m, 2H), 3.32−3.35 (m, 2H), 3.41−3.46 (m, 2H), 3.62 (t, J = 6.5 Hz, 2H), 3.83 (t, J = 6.61 Hz, 2H), 7.30 (t, J = 6.85 Hz, 2H), 7.60−7.63 (m, 2H), 7.71−7.76 (m, 2H), 7.91 (d, J = 8.0 z, 1H), 9.62 (br, 1H). HRMS: calcd for $C_{23}H_{27}FN_2O + H^+$, 367.21802; found (ESI, $[M + H]^+$), 367.2181.

6-(4-Fluorophenyl)-2-{2-[(2*S*)-2-methylpyrrolidin-1-yl]ethyl}-3,4-dihydroiso-quinolin-1(2*H*)-one (20). The title compound was prepared according to the procedure described in **18** and employing (*S*)-2-methylpyrrolidine. Yield 30% as a white solid, hydrochloride salt; mp 244−247 °C; $[\alpha]_D^{25}$ = +37.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.49 Hz, 3H), 1.51−1.61 (m, 1H), 1.83−1.95 (m, 2H), 2.11−2.20 (m, 1H), 3.05 (t, J = 6.38 Hz, 2H), 3.18−3.20 (m, 2H), 3.37−3.46 (m, 1H), 3.51−3.62 (m, 1H), 3.62−3.78 (m, 4H), 3.92−4.02 (m, 1H), 7.30 (t, J = 8.80 Hz, 2H), 7.60−7.63 (m, 2H), 7.73−7.76 (m, 2H), 7.92 (d, J = 8.0 Hz, 1H), 9.23 (br, 1H). HRMS: calcd for $C_{22}H_{25}FN_2O + H^+$, 353.20237; found (ESI, $[M + H]^+$), 353.2024.

6-(4-Fluorophenyl)-2-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}-3,4-dihydroisoqui-nolin-1(2*H*)-one (21). The title compound was prepared according to the procedure described in **18** and employing (*R*)-2-methylpyrrolidine Yield 26% as a white solid, hydrochloride salt; mp 236−238 °C; $[\alpha]_D^{25}$ = −33.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.49 Hz, 3H), 1.51−1.59

(m, 1H), 1.85−1.97 (m, 2H), 2.12−2.17 (m, 1H), 3.02−3.05 (m, 2H), 3.10−3.18 (m, 2H), 3.37−3.41 (m, 1H), 3.50−3.56 (m, 1H), 3.60−3.72 (m, 4H), 3.85−3.97 (m, 1H), 7.28 (t, J = 8.81 Hz, 2H), 7.58−7.61 (m, 2H), 7.70−7.74 (m, 2H), 7.90 (d, J = 8.0 Hz, 1H), 9.76 (br, 1H). HRMS: calcd for $C_{22}H_{25}FN_2O$ + H^+, 353.20237; found (ESI, $[M + H]^+$), 353.2024.

4-(2-{2-[(2*S*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzonitrile (22). The title compound was prepared according to the procedure described in **18** and employing **56b** and (*S*)-2-methylpyrrolidine. Yield 42% as a white solid, hydrochloride salt; mp 268−271 °C; $[\alpha]_D^{25}$ = +39.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.49 Hz, 3H), 1.51−1.61 (m, 1H), 1.84−2.00 (m, 2H), 2.11−2.19 (m, 1H), 3.04−3.07 (m, 2H), 3.14−3.17 (m, 2H), 3.36−3.44 (m, 1H), 3.51−3.59 (m, 1H), 3.60−3.70 (m, m, 4H), 3.91−3.98 (m, 1H), 7.70−7.72 (m, 2H), 7.88−7.96 (m, 5H), 9.58 (br, 1H). HRMS: calcd for $C_{23}H_{25}N_3O$ + H^+, 360.20704; found (ESI, $[M + H]^+$), 360.2074.

4-(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzonitrile (23). The title compound was prepared according to the procedure described in **18** and employing **56b** and (*R*)-2-methylpyrrolidine. Yield 30% as a white solid, hydrochloride salt; mp 268−270 °C; $[\alpha]_D^{25}$ = −39.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (d, J = 6.03 Hz, 3H), 1.78 (m, 1H), 1.80−2.00 (m, 2H), 2.05−2.10 (m, 1H), 3.05 (m, 2H), 3.10−3.18 (m, 2H), 3.43−3.49 (m, 1H), 3.50−3.75 (m, 5H), 3.89−4.00 (m, 1H), 7.69−7.71 (m, 2H), 7.90−7.95 (m, 5H), 9.52 (br, 1H). HRMS: calcd for $C_{23}H_{25}N_3O$ + H^+, 360.20704; found (ESI, $[M + H]^+$), 360.2072.

4-(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-5-yl)benzonitrile (24). Using essentially the general procedure A and employing 4-cyano phenyl boronic acid and (*R*)-7-bromo-2-[2-(2-methylpyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (**55b**), the title compound was prepared. Yield 58% as a white solid, hydrochloride salt; mp 203−205 °C; $[\alpha]_D^{25}$ = −47.0° (c = 1% solution in MeOH). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 6.46 Hz, 3H), 1.55−1.60 (m, 1H), 1.86−1.96 (m, 2H), 2.10−2.16 (m, 1H), 2.86−2.90 (m, 2H), 3.08−3.17 (m, 2H), 3.37−3.41 (m, 1H), 3.48−3.53 (m, 3H), 3.64−3.72 (m, 2H), 3.88−3.93 (m, 1H), 7.43−7.49 (m, 2H), 7.57 (d, J = 8.29 Hz, 2H), 7.91−7.97 (m, 3H), 9.95 (br, 1H). HRMS: calcd for $C_{23}H_{25}N_3O$ + H^+, 360.20704; found (ESI, $[M + H]^+$ obsd), 360.2071.

4-(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-7-yl)benzonitrile (25). Using essentially the general procedure A and employing 4-cyano phenyl boronic acid and (*R*)-7-bromo-2-[2-(2-methylpyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (**55c**), the title compound was prepared. Yield 44% as a white solid, hydrochloride salt; mp 205−207 °C; $[\alpha]_D^{25}$ = −3.00° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.47 Hz, 3H), 1.56−1.59 (m, 1H), 1.87−1.94 (m, 2H), 2.13−2.17 (m, 1H), 3.02−3.05 (m, 2H), 3.12−3.19 (m, 2H), 3.31−3.42 (m, 1H), 3.53−3.58 (m, 1H), 3.61−3.72 (m, 4H), 3.93−3.99 (m, 1), 7.43 (d, J = 7.93 Hz, 1H), 7.83−7.95 (m, 5H), 8.49 (d, J = 2.44 Hz, 1H), 9.67 (br, 1H). HRMS: calcd for $C_{23}H_{25}N_3O$ + H^+, 360.20704; found (ESI, $[M + H]^+$), 360.2074.

4-(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-2,3-dihydro-1*H*-isoindol-5-yl)-benzonitrile (26). Using the general procedure A and employing (*R*)-5-bromo-2-[2-(2-methylpyrrolidin-1-yl)-ethyl]isoindolin-1-one (**63**) and 4-cyano phenyl boronic acid, the desired product was obtained as a white hydrochloride salt; mp 214−216 °C; $[\alpha]_D^{25}$ = −54.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (d, J = 6.47 Hz, 3H), 1.51−1.57 (m, 1H), 1.83−2.00 (m, 2H), 2.12−2.19 (m, 1H), 3.11−3.24 (m, 2H), 3.33−3.45 (m, 1H), 3.63−3.69 (m, 2H), 3.76−3.84 (m, 1H), 3.96−4.02 (m, 1H), 4.57 (s, 2H), 7.77 (dd, J = 7.81, 3.29 Hz, 1H), 7.84 (dd, J = 7.81, 1.22 Hz, 1H), 7.91−7.96 (m, 4H), 8.00 (s, 1H), 9.37 (br, 1H). HRMS: calcd for $C_{22}H_{23}N_3O$ + H^+, 346.19139; found (ESI, $[M + H]^+$ obsd), 346.1914.

4-[(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroiso-quinolin-6-yl)oxy]benzonitrile (27). This compound was prepared in three steps from 4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile (**67a**) as described below. (1) 4-(2-Allyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile was prepared generally according to the general procedure B in step 2 and employing 4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-benzonitrile (**67a**), 0.2 g (88%) of the desired product was obtained as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.93 (t, J = 6.6 Hz, 2H), 3.45 (t, J = 6.5 Hz, 2H), 4.05−4.07 (m, 2H), 5.16 (m, 2H), 5.74−5.82 (m, 1H), 7.00−7.03 (m, 2H), 7.16 (dd, J = 6.72, 2.08 Hz, 2H), 7.84 (dd, J = 6.72, 1.81 Hz, 2H), 7.90 (d, J = 7.99 Hz, 1H). (2) 4-(1-Oxo-2-(2-oxoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-benzonitrile was prepared generally according to the general procedure B in step 3 and employing 4-(2-allyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile, 0.23 g (88%) of 4-(1-oxo-2-(2-oxoethyl)-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile was obtained as a colorless oil. (3) The title compound **27** was prepared using the general procedure B in step 4 and employing 4-(1-oxo-2-(2-oxoethyl)-1,2,3,4-tetrahydroiso-quinolin-6-yloxy)benzonitrile (0.42 mmol) and (*R*)-2-methylpyrrolidine hydrochloride (62 mg, 0.51 mmol), 71 mg (41%) of 4-[(2-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroiso-quinolin-6-yl)oxy]benzonitrile was obtained as a white hydrochloride salt, mp 254−255 °C; $[\alpha]_D^{25}$ = −33.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.47 Hz, 3H), 1.56−1.59 (m, 1H), 1.85−1.96 (m, 2H), 2.11−2.17 (m, 1H), 2.97 (t, J = 6.58 Hz, 2H), 3.08−3.17 (m, 2H), 3.37−3.41 (m, 1H), 3.50−3.69 (m, 5H), 3.88−3.94 (m, 1H), 7.02−7.05 (m, 2H), 7.15 (d, J = 8.91 Hz, 2H), 7.85 (d, J = 8.79 Hz, 2H), 7.91 (d, J = 8.66 Hz, 1H), 9.64 (br, 1H). HRMS: calcd for $C_{23}H_{25}N_3O_2$ + H^+, 376.20195; found (ESI, $[M + H]^+$ calcd), 376.2020.

6-[(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]nicotinonitrile (28). The title compound was prepared according to the procedure described in **27** and employing 6-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-nicotinonitrile (**67b**) and 96 mg (36%) of 6-[(2-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-oxy]-nicotinenitrile was obtained as a white hydrochloride salt, mp 184−185 °C; $[\alpha]_D^{25}$ = −33.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, J = 6.47 Hz, 3H), 1.55−1.59 (m, 1H), 1.85−1.96 (m, 2H), 2.11−2.18 (m, 1H), 2.97−3.00 (m, 2H), 3.11−3.16 (m, 2H), 3.37−3.41 (m, 1H), 3.50−3.59 (m, 5H), 3.93−3.97 (m, 1H), 7.12−7.14 (m, 2H), 7.29 (d, J = 8.66 Hz, 1H), 7.89−7.92 (m, 1H), 8.32 (d, J = 8.66, 2.32 Hz, 1H), 8.62 (s, 1H), 9.69 (br, 1H). HRMS: calcd for $C_{22}H_{24}N_4O_2$ + H^+, 377.19720; found (ESI, $[M + H]^+$), 377.1976.

5-[(2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)oxy]pyridine-2-carbonitrile (29). The title compound was prepared according to the procedure described in **27** and employing 5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)picolinonitrile (**67c**); 21 mg (13%) of the title compound was obtained as a white hydrochloride salt; mp 218−220 °C; $[\alpha]_D^{25}$ = −34.0° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (d, J = 6.49 Hz, 3H), 1.51−1.61 (m, 1H), 1.82−1.95 (m, 2H), 2.10−2.20 (m, 1H), 2.97 (m, 2H), 3.10−3.15 (m, 2H), 3.35−3.43 (m, 1H), 3.50−3.70 (m, 5H), 3.85−3.92 (m, 1H), 7.11 (m, 2H), 7.60 (dd, J = 8.58, 2.78 Hz, 1H), 7.92 (d, J = 8.34 Hz, 1H), 8.06 (d, J = 8.58 Hz, 1H), 8.54 (d, J = 2.66 Hz, 1H), 9.63 (br, 1H). HRMS: calcd for $C_{22}H_{24}N_4O_2$ + H^+, 377.19720; found (ESI, $[M + H]^+$ obsd), 377.1975.

6-Pyridin-4-yl-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (30). To a solution of 6-bromo-2-[2-(pyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one **55a** (0.15 g, 0.46 mmol) and 4-tributylstannyl pyrridine (0.68 g, 1.9 mmol) in toluene (20 mL) was added tetrakis (triphenylphosphine)palladium (0) (27 mg, 0.02 mmol) at 90 °C. The reaction mixture was heated at 90 °C for 18 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was partitioned between 1 N aqueous sodium hydroxide and dichloromethane. The aqueous phase was separated and extracted with dichloromethane (3 × 150 mL). The organic phases were combined and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10%

methanol in dichloromethane with 0.5% ammonium hydroxide) to afford the title compound as a colorless oil. The oil was dissolved in ethanol and made into its hydrochloride salt (36 mg) as a white solid, mp 216−218 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.96 (m, 2H), 3.00−3.05 (m, H), 3.11 (t, J = 6.72 Hz, 2H), 3.35−3.40 (m, 2H), 3.55−3.60 (m, 2H), 3.63 (t, J = 6.43 Hz, 2H), 3.82 (t, J = 6.26 Hz, 2H), 7.87−7.89 (m, 2H), 7.99 (d, J = 8.70 Hz, 1H), 8.13 (d, J = 6.03 Hz, 2H), 8.84 (d, J = 5.68 Hz, 2H), 10.13 (br, 1H). HRMS: calcd for $C_{20}H_{23}N_3O$ + H^+, 322.19139; found (ESI, [M + H]$^+$), 322.1926.

6-[4-(Cyclopropylcarbonyl)phenyl]-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydro-isoquinolin-1(2*H*)-one (31). To a solution of *N*-methoxy-*N*-methyl-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoqui-nolin-6-yl)benzamide **70** (0.14 g, 0.34 mmol) in anhydrous tetrahydrofuran (20 mL) was added cyclopropyl magnesium bromide (0.5 M solution in tetrahydrofuran solution, 2.0 mL, 1.4 mmol) at 0 °C. The reaction mixture was allowed to warm slowly to room temperature and stirred overnight. The reaction mixture was quenched with saturated aqueous ammonium chloride and extracted with methylene chloride. The aqueous phase was extracted with methylene chloride (3 × 100 mL). The organic layers were combined, dried (sodium sulfate), and filtered, and the solvent was concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in methylene chloride with 0.5% ammonium hydroxide) to afford 6-[4-(cyclopropylcarbonyl)phenyl]-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydro-isoquinolin-1(2*H*)-one as a colorless oil. The oil was dissolved in ethanol and made into its hydrochloride salt 48.4 mg (33%) as a white solid; mp 244−246 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.01−1.04 (m, 4H), 1.83 (m, 2H), 1.96 (m,2H), 2.88−2.92 (m, 1H), 3.02 (m, 2H), 3.09 (t, J = 6.58 Hz, 2H), 3.34−3.38 (m, 2H), 3.57 (m, 2H), 3.62 (t, J = 6.47 Hz, 2H), 3.80 (t, J = 6.22 Hz, 2H), 7.69−7.72 (m, 2H), 7.86 (d, J = 8.54 Hz, 2H), 7.94 (d, J = 7.93 Hz, 1H), 8.11 (d, J = 8.54 Hz, 2H), 10.25 (br, 1H). HRMS: calcd for $C_{25}H_{28}N_2O_2$ + H^+, 389.22235; found (ESI, [M + H]$^+$), 389.2228.

4-[1-Oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (32). A mixture of thionyl chloride (3 mL) and 4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic acid (**68a**) (0.10 g, 0.27 mol) was stirred at reflux temperature for 1 h, cooled to room temperature, and concentrated in vacuo to afford 4-(1-Oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroiso-quinolin-6-yl)benzoyl chloride (**69a**) as a desired product. Then **69a** was dissolved in THF, cooled to 0 °C, treated with ammonia, warmed to room temperature, stirred for 1 h at room temperature, diluted with 1 N NaOH, and extracted with CH_2Cl_2. The combined extracts were washed sequentially with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in methylene chloride with 0.5% ammonium hydroxide) to afford the desired product as a colorless oil. The oil was dissolved in ethanol, treated with Etheral HCl, stirred, and filtered. The filter cake was washed with ether, and the desired product was obtained as a white hydrochloride salt. Yield 67% as a white solid, hydrochloride salt; mp 268−270 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82−1.85 (m, 2H), 1.94−1.99 (m, 2H), 3.01−3.10 (m, 4H), 3.35−3.40 (m, 2H), 3.57−3.63 (m, 4H), 3.80 (t, J = 6.11 Hz, 2H), 7.37 (s, 1H), 7.66−7.70 (m, 2H), 7.77 (d, J = 8.42 Hz, 2H), 7.92−7.96 (m, 3H), 8.01 (br, 1H), 9.97 (br, 1H). HRMS: calcd for $C_{22}H_{25}N_3O_2$ + H^+, 364.20195; found (ESI, [M + H]$^+$ obsd), 364.2021.

***N*-Methyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (33).** Using the procedure described in **32** and employing methylamine (1.0 M in THF), the desired product was obtained as a white hydrochloride salt; mp 235−236 °C; Yield: 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (m, 2H), 1.94 (m, 2H), 2.77 (d, J = 4.51 Hz, 3H), 3.07 (m, 4H), 3.37 (m, 2H), 3.60 (m, 4H), 3.79 (m, 2H), 7.67−7.70 (m, 2H), 7.78 (d, J = 8.54 Hz, 2H), 7.90−7.94 (m, 3H), 8.45−8.48 (m, 1H), 9.55 (br, 1H). HRMS: calcd for $C_{23}H_{27}N_3O_2$ + H^+, 378.21760; found (ESI, [M + H]$^+$), 378.2177.

***N*-Ethyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (34).** Using the procedure described in **32** and employing ethylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; mp 255−257 °C; yield 65%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.09 (t, 7.20 Hz, 3H), 1.83 (m, 2H), 1.94 (m, 2H), 3.05−3.09 (m, 4H), 3.27 (m, 2H), 3.37 (m, 2H), 3.59−3.62 (m, 4H), 3.79 (t, J = 5.61 Hz, 2H), 7.66−7.69 (m, 2H), 7.78 (d, J = 8.42 Hz, 2H), 7.90−7.94 (m, 3H), 8.50 (m, 1H), 9.66 (br, 1H). HRMS: calcd for $C_{24}H_{29}N_3O_2$ + H^+, 392.23325; found (ESI, [M + H]$^+$), 392.2336.

***N*-Isopropyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (35).** Using the procedure described in **32** and employing isopropylamine, the desired product was obtained as a white hydrochloride salt; mp 257−259 °C; yield 56%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.14 (d, J = 6.59 Hz, 6H), 1.83 (m, 2H), 1.94 (m, 2H), 3.04−3.09 (m, 4H), 3.37 (m, 1H), 3.59−3.63 (m, 4H), 3.79 (t, J = 6.1 Hz, 2H), 7.66−7.69 (m, 2H), 7.77 (d, J = 8.54 Hz, 2H), 7.92 (m, 3H), 8.25 (d, J = 7.80 Hz, 1H), 9.86 (br, 1H). HRMS: calcd for $C_{25}H_{31}N_3O_2$ + H^+, 406.24890; found (ESI, [M + H]$^+$), 406.2491.

***N*-Cyclopropyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (36).** Using the procedure described in **32** and employing cyclopropylamine, the desired product was obtained as a white hydrochloride salt; mp 222−224 °C; yield 70%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.54−0.56 (m, 2H), 0.65−0.69 (m, 2H), 1.82 (m,2H), 1.94 (m, 2H), 2.81−2.84 (m, 1H), 3.02−3.08 (m, 4H), 3.37 (m, 2H), 3.58−3.62 (m, 4H), 3.79 (t, J = 6.11 Hz, 2H), 7.66−7.69 (m, 2H), 7.76 (d, J = 8.41 Hz, 2H), 7.88−7.93 (m, 3H), 8.46 (d, J = 4.27 Hz, 1H), 9.65 (br, 1H). HRMS: calcd for $C_{25}H_{29}N_3O_2$ + H^+, 404.23325; found (ESI, [M + H]$^+$), 404.2338.

***N*-Cyclobutyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (37).** Using the procedure described in **32** and employing cyclobutylmine, the desired product was obtained as a white hydrochloride salt; mp 255−258 °C; yield 35%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.61−1.68 (m, 2H), 1.82−1.86 (m, 2H), 1.94−2.10 (m, 4H), 2.14−2.21 (m, 2H), 3.04−3.09 (m, 4H), 3.31−3.37 (m, 2H), 3.59−3.65 (m, 4H), 3.79 (t, J = 6.10 Hz, 2H), 4.40 (m, 1H), 7.66−7.70 (m, 2H), 7.77 (d, J = 8.42 Hz, 2H), 7.92 (d, J = 8.42 Hz, 2H), 8.64 (d, J = 7.57 Hz, 1H), 9.82 (br, 1H). HRMS: calcd for $C_{26}H_{31}N_3O_2$ + H^+, 418.24890; found (ESI, [M + H]$^+$), 418.249.

***N*-Cyclopentyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (38).** Using the procedure described in **32** and employing cyclopentylamine, the desired product was obtained as a white hydrochloride salt; mp 280−282 °C; yield 44%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.47−1.53 (m, 4H), 1.63−1.69 (m, 2H), 1.83−1.89 (m, 4H), 1.94−1.97 (m, 2H), 3.04−3.09 (m, 4H), 3.33−3.38 (m, 2H), 3.59−3.62 (m, 4H), 3.79 (t, J = 6.22 Hz, 2H), 4.18−4.23 (m, 1H), 7.66−7.69 (m, 2H), 7.76 (d J = 8.42 Hz, 2H), 7.90−7.94 (m, 3H), 8.31 (t, J = 7.20 Hz, 1H), 9.82 (br, 1H). HRMS: calcd for $C_{27}H_{33}N_3O_2$ + H^+, 432.26455; found (ESI, [M + H]$^+$ calcd), 432.2645.

***N,N*-Dimethyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl]benzamide (39).** Using the procedure described in **32** and employing *N,N*-dimethylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; mp 252−254 °C; yield 62%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, 2H), 1.97 (m, 2H), 2.91 (s, 3H), 2.95 (s, 3H), 3.01−3.09 (m, 4H), 3.35−3.39 (m, 2H), 3.59−3.62 (m, 4H), 3.79 (t, J = 6.11 Hz, 2H), 7.47 (d, J = 8.17 Hz, 2H), 7.64−7.67 (m, 2H), 7.74 (d, J = 8.29 Hz, 2H), 7.92 (d, J = 8.05 Hz, 1H), 9.84 (br, 1H). HRMS: calcd for $C_{24}H_{29}N_3O_2$ + H^+, 392.23325; found (ESI, [M + H]$^+$), 392.2337.

6-[4-(Pyrrolidin-1-ylcarbonyl)phenyl]-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroiso-quinolin-1(2*H*)-one (40). Using the procedure described in **32** and employing pyrrolidine, the desired product was obtained as a white hydrochloride salt; mp 245−248 °C; yield 42%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.75−1.85 (m, 6H), 1.94−1.97 (m, 2H), 3.03−3.09 (m, 4H), 3.28−3.32 (m, 4H), 3.38 (t, J = 6.47 Hz, 2H), 3.60−3.63 (m, 4H), 3.80 (t, J = 6.22 Hz, 2H), 7.61 (d, J = 8.42 Hz, 2H), 7.63−7.67 (m, 2H), 7.74 (d, J = 8.30 Hz, 2H), 7.92 (d, J = 7.93 Hz, 1H), 10.03 (br, 1H). HRMS: calcd for $C_{26}H_{31}N_3O_2$ + H^+, 418.24890; found (ESI, [M + H]$^+$), 418.2492.

6-(4-{[(2*R*)-2-Methylpyrrolidin-1-yl]carbonyl}phenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (41). Using the procedure described for **32** and employing

(*R*)-2-methylpyrrolidine, the desired product was obtained as a white hydrochloride salt; mp 170−171 °C; yield 52%; $[\alpha]_D^{25}$ = −46.0° (*c* = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.11−1.15 (m, 3H), 1.49−1.55 (m, 1H), 1.63−1.70 (m, 1H), 1.83−1.86 (m, 4H), 1.94−2.06 (m, 4H), 3.04−3.09 (m, 4H), 3.33−3.37 (m, 1H), 3.44−3.50 (m, 1H), 3.60−3.63 (m, 4H), 3.80 (t, *J* = 6.22 Hz, 2H), 4.08−4.13 (m, 1H), 7.55−7.57 (m, 2H), 7.64−7.67 (m, 2H), 7.72 (d, *J* = 8.3 Hz, 2H), 7.92 (d, *J* = 7.93 Hz, 1H), 9.94 (br, 1H). HRMS: calcd for $C_{27}H_{33}N_3O_2$ + H$^+$, 432.26455; found (ESI, [M + H]$^+$ obsd), 432.2650.

6-(4-{[(2*S*)-2-Methylpyrrolidin-1-yl]carbonyl}phenyl)-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (42). Using the procedure described for **32** and employing (*S*)-2-methylpyrrolidine, the desired product was obtained as a white hydrochloride salt; mp 170.5−171.5 °C; yield 58%; $[\alpha]_D^{25}$ = +50.0° (*c* = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.22 (d, *J* = 5.37 Hz, 3H), 1.49−1.55 (m, 1H), 1.64−1.69 (m, 1H), 1.83−1.86 (m, 4H), 1.94−2.05 (m, 4H), 3.06−3.09 (m, 4H), 3.33−3.37 (m, 1H), 3.44−3.50 (m, 1H), 3.59−3.63 (m, 4H), 3.78−3.81 (m, 2H), 4.10−4.13 (m, 1H), 7.56 (d, *J* = 7.56 Hz, 2H), 7.58−7.68 (m, 2H), 7.74 (d, *J* = 8.29 Hz, 2H), 7.93 (d, *J* = 7.93 Hz, 1H), 9.79 (br, 1H). HRMS: calcd for $C_{27}H_{33}N_3O_2$ + H$^+$, 432.26455; found (ESI, [M + H]$^+$ obsd), 432.2649.

6-[2-Fluoro-4-(pyrrolidin-1-ylcarbonyl)phenyl]-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (43). Using the procedure described in **32** and employing 3-fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69b**) and pyrrolidine, the desired product was obtained as a white hydrochloride salt; yield 61%; mp 225−226 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81−1.96 (m, 6H), 1.98 (m, 2H), 3.05−3.11 (m, 4H), 3.33−3.47 (m, 6H), 3.59−3.66 (m, 4H), 3.81−3.84 (m, 2H), 7.44−7.62 (m, 5H), 7.96 (d, *J* = 7.81 Hz, 1H), 10.15 (br, 1H). HRMS: calcd for $C_{26}H_{30}FN_3O_2$ + H+, 436.23948; found (ESI, [M + H]$^+$ obsd), 436.2395.

6-[3-Fluoro-4-(pyrrolidin-1-ylcarbonyl)phenyl]-2-(2-pyrrolidin-1-ylethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (44). Using the procedure described for **32** and employing 2-fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69c**) and pyrrolidine, the desired product was obtained as a white hydrochloride salt; yield 59%; mp 231−232 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.80−1.88 (m, 6H), 1.94−1.98 (m, 2H), 3.02−3.11 (m, 4H), 3.23 (t, *J* = 6.51 Hz, 2H), 3.35−3.48 (m, 4H), 3.59−3.65 (m, 4H), 3.82 (t, *J* = 6.05 Hz, 2H), 7.51 (t, *J* = 7.56 Hz, 1H), 7.62−7.72 (m, 4H), 7.94 (d, *J* = 7.91 Hz, 1H), 10.26 (br, 1H). HRMS: calcd for $C_{26}H_{30}FN_3O_2$ + H$^+$, 436.23948; found (ESI, [M + H]$^+$ obsd), 436.2395.

6-(3-Chloro-4-(pyrrolidine-1-carbonyl)phenyl)-2-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (45). Using the procedure described in **32** and employing 2-chloro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69d**) and pyrrolidine, the desired product was obtained as a white hydrochloride salt; yield 48%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78−1.88 (m, 6H), 1.93−1.98 (m, 2H), 3.01−3.09 (m, 6H), 3.33−3.39 (m, 2H), 3.45 (t, *J* = 6.61 Hz, 2H), 3.58−3.63 (m, 4H), 3.80 (t, *J* = 6.02 Hz, 2H), 7.46 (d, *J* = 7.88 Hz, 1H), 7.68−7.75 (m, 3H), 7.84 (s, 1H), 7.92 (d, *J* = 8.8 Hz, 1H), 10.2 (br, 1H). HRMS: for $C_{26}H_{30}ClN_3O_2$ + H$^+$, 452.20993; found (ESI, [M + H]$^+$ obsd), 452.2099.

3-Fluoro-*N*-methyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]benzamide (46). Using the procedure described for **32** and employing 3-fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69b**) and methylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; yield 65%; mp 188−190 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83 (m, H), 1.94 (m, 2H), 2.76 (d, *J* = 4.52 Hz, 3H), 3.05−3.09 (m, 4H), 3.37 (m, 2H), 3.60−3.63 (m, 4H), 3.80 (t, *J* = 6.03 Hz, 2H), 7.51−7.55 (m, 2H), 7.63 (t, *J* = 7.88 Hz, 1H), 7.72−7.78 (m, 2H), 7.94 (d, *J* = 8.0 Hz, 1H), 8.60 (d, *J* = 4.52 Hz, 1H), 9.86 (br, 1H). HRMS: calcd for $C_{23}H_{26}FN_3O_2$ + H$^+$, 396.20818; found (ESI, [M + H]$^+$ obsd), 396.2082.

3-Fluoro-*N*,*N*-dimethyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydro-isoquinolin-6-yl]benzamide (47). Using the procedure described for **32** and employing 3-fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69b**) and *N*,*N*-dimetylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; yield 65%; mp 228−229 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83−1.88 (m, 2H), 1.94−2.02 (m, 2H), 2.93 (s, 3H), 2.98 (s, 3H), 3.01−3.11 (m, 4H), 3.35−3.42 (m, 2H), 3.60−3.65 (m, 4H), 3.83 (m, 2H), 7.33−7.40 (m, 2H), 7.52−7.60 (m, 2H), 7.60 (t, *J* = 7.91 Hz, 1H), 7.94 (d, *J* = 8.02 Hz, 1H), 10.04 (br, 1H). HRMS: calcd for $C_{24}H_{28}FN_3O_2$ + H$^+$, 410.22383; found (ESI, [M + H]$^+$ obsd), 410.2240.

***N*-Methyl-4-(2-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)benzamide (48).** Using the procedure described in **32** and employing (*R*)-4-(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69e**) and methylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; yield 63%; mp 258−260 °C; $[\alpha]_D^{25}$ = −30.0° (*c* = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, *J* = 6.47 Hz, 3H), 1.56−1.60 (m, 1H), 1.86−1.95 (m, 2H), 2.13−2.16 (m, 1H), 2.76 (d, *J* = 4.5 Hz, 3H), 3.04−3.09 (m, 2H), 3.12−3.18 (m, 2H), 3.36−3.42 (m, 1H), 3.52−3.55 (m, 1H), 3.62−3.74 (m, 4H), 3.91−3.96 (m, 1H), 7.67−7.70 (m, 2H), 7.78 (d, *J* = 8.42 Hz, 2H), 7.90−7.94 (m, 3H), 8.49 (q, *J* = 4.15 Hz, 1H), 9.81 (br, 1H). HRMS: calcd for $C_{24}H_{29}N_3O_2$ + H$^+$, 392.23325; found (ESI, [M + H]$^+$ calcd), 392.2333.

***N*-Ethyl-4-(2-{2-[(2*R*)-2-methylpyrrolidin-1-yl]ethyl}-1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)benzamide (49).** Using the procedure described in **32** and employing (*R*)-4-(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoyl chloride (**69e**) and ethylamine (1.0 M solution in THF), the desired product was obtained as a white hydrochloride salt; yield 66%; mp 228−230 °C; $[\alpha]_D^{25}$ = −28.0° (*c* = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.10 (t, *J* = 7.19 Hz, 3H), 1.32 (d, *J* = 6.34 Hz, 3H), 1.54−1.61 (m, 1H), 1.84−2.04 (m, 2H), 2.12−2.19 (m, 1H), 3.04−3.09 (m, 2H), 3.11−3.18 (m, 2H), 3.28 (m, 2H), 3.39−3.44 (m, 1H), 3.52−3.60 (m, 1H), 3.61−3.72 (m, 4H), 3.92−3.99 (m, 1H), 7.67−7.70 (m, 2H), 7.78 (d, *J* = 8.42 Hz, 2H), 7.91−7.95 (m, 3H), 8.50 (d, *J* = 5.49 Hz, 1H), 9.49 (br, 1H). HRMS: calcd for $C_{25}H_{31}N_3O_2$ + H$^+$, 406.24890; found (ESI, [M + H]$^+$ obsd), 406.2493.

2-{2-[(2*R*)-2-Methylpyrrolidin-1-yl]ethyl}-6-[4-(pyrrolidin-1-ylcarbonyl)phenyl]-3,4-dihydroisoquinolin-1(2*H*)-one (50). Using the procedure described in **32** and employing (*R*)-4-(2-(2-(2-methylpyrrolidin-1-yl)ethyl)-1-oxo-1,2,3,4-tetrahydro-isoquinolin-6-yl)benzoyl chloride (**69e**) and pyrrolidine, the desired product was obtained as a white hydrochloride salt; yield 58%; mp 243−244 °C; $[\alpha]_D^{25}$ = −33.0° (*c* = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.35 (d, *J* = 6.47 Hz, 3H), 1.54−1.59 (m, 1H), 1.77−1.97 (m, 6H), 2.13−2.18 (m, 1H), 3.06 (t, *J* = 6.23 Hz, 2H), 3.10−3.19 (m, 2H), 3.37−3.46 (m, 5H), 3.52−3.58 (m, 1H), 3.61−3.72 (m, 4H), 3.92−3.98 (m, 1H), 7.59 (d, *J* = 8.30 Hz, 2H), 7.64−7.67 (m, 2H), 7.74 (d, *J* = 8.42 Hz, 2H), 7.93 (d, *J* = 8.06 Hz, 1H), 9.59 (br, 1H). HRMS: calcd for $C_{27}H_{33}N_3O_2$ + H$^+$, 432.26455; found (ESI, [M + H]$^+$ calcd), 432.2645.

General Procedure B. Preparation of Bromo-2-[2-(pyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-ones. The following compounds (**55a**−**d**) were prepared in four steps starting from the appropriate bromo-2,3-dihydro-1*H*-inden-1-one, as described below. The reported yields represent the yields obtained for the final step of the sequence.

Step 1. To a solution of an appropriate bromo-1-indanone (5.1 mmol) in (2:1) methylene chloride:methanesulfonic acid (45 mL) at 0 °C was treated slowly with sodium azide (7.7 mmol), and the resulting mixture was allowed to warm to room temperature and stirred overnight. The reaction mixture was partitioned between methylene chloride and aqueous sodium hydroxide (50 mL, 1.0 N). The aqueous layer was extracted with methylene chloride. The combined organic layers were washed sequentially with water and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 10−100% ethyl acetate in hexanes)

dx.doi.org/10.1021/jm300011d | *J. Med. Chem.* 2012, 55, 2452−2468

to afford the desired product as a white solid, identified by MS and ^{1}H NMR.

Step 2. A suspension of sodium hydride (60% dispersion in mineral oil, 0.17 g, 4.4 mmol) in *N*,*N*-dimethylformamide at 0 °C, under nitrogen, was treated dropwise over 15 min with a solution of an appropriate bromo-3,4-dihydroisoquinolin-1(2*H*)-one (2.2 mmol) in *N*,*N*-dimethylformamide, stirred at 0 °C for an additional 20 min, treated with allyl bromide (3.3 mmol) at 0 °C, allowed to warm to room temperature, and stirred overnight. The reaction mixture was partitioned between water and methylene chloride. The aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 10−50% ethyl acetate in hexanes) to afford the desired product as a light-yellow oil, identified by MS and ^{1}H NMR.

Step 3. A solution of an appropriate 2-allyl-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (3.11 g, 12 mmol) in tetrahydrofuran and water at 0 °C was treated with sodium periodate (36 mmol), allowed to stir at 0 °C for 10 min, treated with osmium (VIII) tetraoxide (4 wt % solution in water, 1.5 mL) at 0 °C, and stirred at 0 °C for 8 h. Then the reaction mixture was poured into water and extracted with methylene chloride. The combined extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 40−100% ethyl acetate in hexanes) to afford the desired product as a colorless oil, identified by MS and ^{1}H NMR.

Step 4. A stirred solution of an appropriate 2-(bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetaldehyde (11 mmol) and an appropriate pyrrolidine (16.5 mmol) in methanol (40 mL) was treated with $NaBH_3CN$ (16.5 mmol) and acetic acid (27.5 mmol) at room temperature and stirred overnight. The reaction mixture was diluted with CH_2Cl_2 and washed with saturated $NaHCO_3$. The aqueous layer was extracted with methylene chloride. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in methylene chloride with 0.5% ammonium hydroxide) to afford the desired product as a colorless oil, identified by MS and ^{1}H NMR.

6-Bromo-2-[2-(pyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (55a). Yield 74%. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.60−1.63 (m, 4H), 2.43 (m, 4H), 2.55 (t, J = 6.84 Hz, 2H), 2.91 (t, J = 6.61 Hz, 2H), 3.51−3.55 (m, 4H), 7.48−7.53 (m, 2H), 7.72 (d, J = 8.12 Hz, 1H). MS (ES) m/z 323.1 $[M + H]^+$.

(*R*)-5-Bromo-2-[2-(2-methylpyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (55b). Yield 84%; $[\alpha]_D^{25} = -62°$ (1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (d, J = 5.98 Hz, 3H), 1.18−1.25 (m, 1H), 1.54−1.60 (m, 2H), 1.77−1.82 (m, 1H), 2.07 (q, J = 8.67 Hz, 1H), 2.12−2.18 (m, 1H), 2.23−2.28 (m, 1H), 2.91−2.98 (m, 3H), 3.09−3.14 (m, 1H), 3.58−3.62 (m, 4H), 7.26 (t, J = 7.81 Hz, 1H), 7.72 (dd, J = 8.05, 1.22 Hz, 1H), 7.85 (dd, J = 7.81 Hz, 1H). MS (ES) m/z 337.1 $[M + H]^+$.

(*R*)-7-Bromo-2-[2-(2-methylpyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (55c). Yield 40%; $[\alpha]_D^{25} = -48°$ (1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.93 (m, 3H), 1.18−1.22 (m, 1H), 1.58 (m, 2H), 1.77−1.82 (m, 1H), 2.04−2.15 (m, 2H), 2.24−2.27 (m, 1H), 2.87−2.94 (m, 3H), 3.10−3.13 (m, 1H), 3.47−3.60 (m, 4H), 7.23 (d, J = 8.11 Hz, 1H), 7.60 (dd, J = 8.11, 2.08 Hz, 1H), 7.88 (d, J = 2.08 Hz, 1H). MS (ES) m/z 337.1 $[M + H]^+$.

(*R*)-6-Bromo-2-(2-(2-methylpyrrolidin-1-yl)ethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (55d). Using the general procedure B and employing 2-(6-bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)-acetaldehyde (2.60 g, 9.7 mmol), (*R*)-2-methylpyrrolidine hydrochloride (1.4 g, 11.6 mmol), and diisopropylethylamine (2.0 mL, 11.6 mmol), the title compound was obtained as a colorless oil, 2.70 g (83%); $[\alpha]_D^{25} = -59.8°$ (c = 1.0 in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.89−0.98 (m, 3H), 1.19−1.24 (m, 1H), 1.57−1.59 (m, 2H), 1.77−1.84 (m, 1H), 2.05−2.17 (m, 2H), 2.20−2.29 (m, 1H), 2.89−2.98 (m, 3H), 3.12−3.13 (m, 1H), 3.48−3.60 (m, 4H), 7.48−7.53 (m, 2H), 7.72 (d, J = 8.18 Hz, 1H). MS (ES) m/z 337.1 $[M + H]^+$.

2-Allyl-6-(4-fluorophenyl)-3,4-dihydroisoquinolin-1(2*H*)-one (56a). Using essentially the same procedure described in **56b** and employing 2-allyl-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (1.23 g, 4.6 mmol) and 4-fluorobenzene boronic acid (2.6 g, 18 mmol), the title compound was obtained as a colorless oil, 1.06 g (81%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.00 (t, J = 6.61 Hz, 2H), 3.48 (t, J = 6.49 Hz, 2H), 4.07−4.09 (m, 2H), 5.10−5.21 (m, 2H), 5.78−5.84 (m, 1H), 7.25−7.29 (m, 2H), 7.50−7.60 (m, 2H), 7.70−7.75 (m, 2H), 7.89 (d, J = 8.0 Hz, 1H). MS (ES) m/z 282.1 $[M + H]^+$.

4-(2-Allyl-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)-benzonitrile (56b). A solution of 2-allyl-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (1.22 g, 4.6 mmol) and 4-cyanobenzene boronic acid (2.7 g, 18 mmol) in dioxane at 90 °C was treated with dichlorobis(*tri-o*-tolyphosphine)palladium(II) (0.18 g, 0.23 mmol), potassium carbonate (1.6 g, 11.5 mmol), and water, heated at 90 °C for 0.5 h, cooled to room temperature, and filtered through a pad of Celite. The filtrate was partitioned between aqueous sodium hydroxide and dichloromethane. The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 10−100% ethyl acetate in hexanes) to afford the title compound as a colorless oil, 1.04 g (79%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.02 (t, J = 6.59 Hz, 2H), 3.49 (t, J = 6.46 Hz, 2H), 4.09 (d, J = 5.49 Hz, 2H), 5.11−5.21 (m, 2H), 5.77−5.84 (m, 1H), 7.67−7.70 (m, 2H), 7.87−7.94 (m, 5H). MS (ES) m/z 289.1 $[M + H]^+$.

2-(2-(1,3-Dioxan-2-yl)ethyl)-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (57). A suspension of sodium hydride (60% dispersion in mineral oil, 0.54 g, 13.6 mmol) in DMF at room temperature, under nitrogen, was treated dropwise over 15 min with a solution of 6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (**52a**) (2.05 g, 9.1 mmol) in DMF, stirred at room temperature for 20 min, treated with 2-(2-bromoethyl)-1,3-dioxane (1.84 mL, 13.6 mmol), and stirred for 16 h. The reaction mixture was partitioned between water and CH_2Cl_2. The aqueous phase was extracted with CH_2Cl_2. The combined organic phase and extracts were washed with brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−100% ethyl acetate in hexanes) to afford the title compound as a light-yellow oil, 3.0 g (97%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.29 (m, 1H), 1.70−1.75 (m, 2H), 1.76−1.87 (m, 1H), 2.91 (t, J = 6.6 Hz, 2H), 3.42−3.49 (m, 4H), 3.64 (m, 2H), 3.94 (m, 2H), 4.55 (t, J = 5.1 Hz, 1H), 7.47−7.49 (m, 2H), 7.71 (d, J = 8.11 Hz, 1H). MS (ES) m/z 340.1 $[M + H]^+$.

3-(6-Bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)propanal (58). A solution of 2-(2-(1,3-dioxan-2-yl)ethyl)-6-bromo-3,4-dihydroisoquinolin-1(2*H*)-one (3.0 g, 8.8 mmol) in dioxane was treated dropwise with 12 N HCl (17 mL) at room temperature, heated at 60 °C for 4 h, cooled to room temperature, and concentrated in vacuo. The residue was diluted with water and extracted with ethyl acetate. The combined extracts were washed sequentially with brine and water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in methylene chloride) to afford the title compound as an off-white solid; 2.08 g (84%); mp 93−94 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.71 (td, J = 6.73, 1.74 Hz, 2H), 2.92 (t, J = 6.73 Hz, 2H), 3.53 (t, J = 6.49 Hz, 2H), 3.69 (t, J = 6.73 Hz, 2H), 7.49−7.52 (m, 2H), 7.72 (d, J = 8.12 Hz, 1H), 9.60 (t, J = 1.74 Hz, 1H).

6-Bromo-2-[3-(pyrrolidin-1-yl)propyl]-3,4-dihydroisoquinolin-1(2*H*)-one (59a). A stirred solution of 3-(6-bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)propanal (0.75 g, 2.7 mmol) and pyrrolidine (0.28 mL, 3.4 mmol) in methanol was treated with sodium cyanoborohydride (0.25 g, 4.0 mmol) and acetic acid (0.38 mL, 6.6 mmol) at room temperature and allowed to stir at room temperature overnight. The reaction mixture was diluted with 1.0 N NaOH and extracted with CH_2Cl_2. The combined extracts were dried over Na_2SO_4 and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in methylene with 0.5% ammonium hydroxide) to afford the title product as a colorless oil, 0.48 g (54%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.73−1.78 (m, 6H), 2.65−2.75 (m, 6H), 2.94 (t, J = 6.61 Hz, 2H), 3.44−3.52

(m, 4H), 7.48−7.51 (m, 2H), 7.72 (d, J = 8.23 Hz, 1H). MS (ES) m/z 337.1 $[M + H]^+$.

6-Bromo-2-(3-(piperidin-1-yl)propyl)-3,4-dihydroisoquinolin-1(2*H*)-one (59b). Using essentially the same procedure described in **59a** and employing piperidine, the title compound was obtained as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.30−1.33 (m, 2H), 1.54−1.68 (m, 2H), 1.71−1.79 (m, 2H), 2.76−2.83 (m, 2H), 2.95−2.98 (m, 4H), 3.30−3.40 (m, 2H), 3.48−3.54 (m, 4H), 7.50−7.54 (m, 2H), 7.73 (d, J = 8.3 Hz, 1H), 9.10 (br, 1H). MS (ES) m/z 351.0 $[M + H]^+$.

2-Allyl-5-bromoisoindolin-1-one (61). A mixture of methyl 4-bromo-2-(bromomethyl)benzoate (4.19 g, 13.5 mmol) and allyl amine (20 mL) was heated at 50 °C for 12 h, cooled to room temperature, diluted with CH_2Cl_2, washed sequentially with 1.0 N HCl and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−75% ethyl acetate in hexanes) to afford 2.13 g (62%) of the title compound as a white solid; mp 58−60 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 4.08−4.10 (m, 2H), 4.38 (s, 2H), 5.11−5.16 (m, 2H), 5.77−5.87 (m, 1H), 7.58 (d, J = 8.10 Hz, 1H), 7.64 (m, 1H), 7.82 (d, J = 0.8 Hz, 1H). MS (ES) m/z 252.0 $[M + H]^+$.

2-(5-Bromo-1-oxoisoindolin-2-yl)acetaldehyde (62). Using essentially the general procedure B in step 3 and employing 2-allyl-5-bromoisoindolin-1-one (2.13 g, 8.4 mmol), **62** was obtained as a light-yellow oil; 1.34 g (62%). ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53 (s, 2H), 4.47 (d, J = 7.3 Hz, 2H), 7.23 (s, 2H), 7.59−7.61 (m, 2H), 7.71 (d, J = 8.81 Hz, 1H), 9.70 (br, 1H). MS (ES) m/z 254.0 $[M + H]^+$.

(*R*)-5-Bromo-2-[2-(2-methylpyrrolidin-1-yl)ethyl]isoindolin-1-one (63). Using the general procedure B in step 4 and employing 2-(5-bromo-1-oxo-3,4-dihydroisoquinolin-2(1*H*)-yl)acetaldehyde (**62**) (0.35 g, 13 mmol), (*R*)-2-methylpyrrolidine hydrochloride (0.19 g, 15.6 mmol), and diisopropylethylamine (0.34 mL, 15.6 mmol), the title compound was obtained as a colorless oil; 0.37 g (84%); $[\alpha]_D^{25}$ = −62° (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.92 (m, 3H), 1.16−1.22 (m, 1H), 1.57−1.64 (m, 2H), 1.76−1.87 (m, 1H), 2.02−2.10 (m, 1H), 2.17−2.30 (m, 2H), 2.96−3.03 (m, 1H), 3.11−3.16 (m, 1H), 3.52−3.58 (m, 2H), 4.43−4.57 (m, 2H), 7.57 (d, J = 8.01 Hz, 1H), 7.64 (d, J = 7.65 Hz, 1H), 7.83 (s, 1H). MS (ES) m/z 337.1 $[M + H]^+$.

6-Methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (65). The title compound was prepared using the general procedure B in step 1 and employing 5-methoxy-1-indanone (4.98 g, 31 mmol), and 4.5 g (82%) of 6-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one was obtained as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.83 (t, J = 6.61 Hz, 2H), 3.28−3.32 (m, 2H), 3.76 (s, 3H), 7.23 (s, 2H), 6.81−6.85 (m, 2H), 7.68 (s, 1H), 7.72−7.74 (m, 1H). MS (ES) m/z 178.0 $[M + H]^+$.

6-Hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (66). A solution of 6-methoxy-3,4-dihydroisoquinolin-1(2*H*)-one (2.58 g, 14 mmol) in dichloromethane at −78 °C was treated with boron tribromide (2.7 mL, 28 mmol), allowed to warm to room temperature overnight, quenched with cold water, and extracted with ethyl acetate. The combined extracts were concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−15% methanol in dichloromethane) to afford the title compound as a light-brown solid; 1.8 g (75%); mp 204−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.74 (t, J = 6.59 Hz, 2H), 3.24−3.28 (m, 2H), 6.57 (m, 1H), 6.63 (dd, J = 8.42, 2.32 Hz, 1H), 7.53 (s, 1H), 7.62 (d, J = 8.41 Hz, 1H), 9.91 (s, 1H). MS (ES) m/z 162.1 $[M + H]^+$.

4-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile (67a). To a solution of (6-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (**66**) (0.5 g, 3.0 mmol) and potassium carbonate (1.1 g, 7.5 mmol) in *N*,*N*-dimethylformamide (40 mL) was added 4-fluorobenzonitrile (0.74 g, 6.0 mmol) and the reaction mixture was heated at 90 °C overnight. The reaction mixture was cooled to room temperature and partitioned between dichloromethane and water. The aqueous phase was extracted with dichloromethane (3 × 100 mL). The organic phases were combined and washed with water (3 × 100 mL). The organic layer was dried (sodium sulfate) and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in dichloromethane) to afford 0.68 g (85%) of 4-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)benzonitrile as a light-yellow oil. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.83−2.88 (m, 2H), 3.32−3.36 (m, 2H), 7.01−7.03 (m, 2H), 7.15−7.18 (m, 2H), 7.83−7.92 (m, 4H).

6-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-nicotinonitrile (67b). A solution of (6-hydroxy-3,4-dihydroisoquinolin-1(2*H*)-one (0.4 g, 2.4 mmol) and potassium carbonate (0.85 g, 6.0 mmol) in DMF was treated with 2-chloro-pyridine-5-carbonitrile (0.68 g, 4.8 mmol), heated at 90 °C overnight, cooled to room temperature, diluted with water, and extracted with CH_2Cl_2. The combined extracts were washed with water, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in dichloromethane) to afford the title compound as a white solid; 0.42 g (65%); mp 192−194 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.85 (t, J = 6.60 Hz, 2H), 3.34−3.36 (m, 2H), 7.08−7.11 (m, 2H), 7.25 (d, J = 8.69 Hz, 1H), 7.85−7.90 (m, 2H), 8.30 (dd, J = 8.69, 2.32 Hz, 1H), 8.32 (m, 1H). MS (ES) m/z 266.1 $[M + H]^+$.

5-(1-Oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-picolinonitrile (67c). The title compound was prepared according to the procedure described in **67b**, substituting 2-chloropyridine-5-carbonitrile in place of 5-chloro-2-cyanopyridine (1.7 g, 12.0 mmol); 0.45 g (28%) of 5-(1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yloxy)-picolinonitrile was obtained as a white solid; mp 185−187 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.86 (t, J = 6.60 Hz, 2H), 3.31−3.35 (m, 2H), 7.06−7.09 (m, 2H), 7.60 (dd, J = 8.70, 2.90 Hz, 1H), 7.86−7.98 (m, 2H), 8.30 (d, J = 8.58 Hz, 1H), 8.55 (t, J = 2.43 Hz, 1H). MS (ES) m/z 266.1 $[M + H]^+$.

4-(1-Oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic Acid (68a). This compound was prepared in two steps starting from 6-bromo-2-(2-(pyrrolidin-1-yl)ethyl)-3,4-dihydroisoquinolin-1(2*H*)-one (**55a**). (1) To a solution of 6-bromo-2-[2-(pyrrolidin-1-yl)ethyl]-3,4-dihydroisoquinolin-1(2*H*)-one (**55a**) (0.5 g, 1.5 mmol) and 4-methoxycarbonyl phenyl boronic acid (1.11 g, 6.2 mmol) in dioxane (20 mL) was added dichlorobis(*tri-o*-tolyphosphine)-palladium(II) (0.06 g, 0.08 mmol), potassium carbonate (0.53 g, 3.9 mmol), and water (4 mL) at 90 °C. The reaction mixture was heated at 90 °C for 0.5 h. The reaction mixture was cooled to room temperature and filtered through a pad of Celite. The filtrate was partitioned between 1 N aqueous sodium hydroxide and dichloromethane. The aqueous phase was separated and extracted with dichloromethane (3 × 100 mL). The organic phases were combined and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica gel, 0−10% methanol in dichloromethane with 0.5% ammonium hydroxide) to afford 0.49 g (84%) of the desired methyl 4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-benzoate as a white solid; mp 118−120 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.63 (m, 4H), 2.46 (m, 4H), 2.61 (m, 2H), 2.99 (t, J = 6.47 Hz, 2H), 3.56−3.59 (m, 4H), 3.84 (s, 3H), 7.64−7.68 (m, 2H), 7.82−7.84 (m, 2H),7.91 (d, J = 7.93 Hz, 1H), 8.01 (d, J = 6.71, 1.83 Hz, 2H). MS (ES) m/z 379.1 $[M + H]^+$. (2) To a solution of methyl 4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)-benzoate (1.74 g, 4.6 mmol) in ethanol (40 mL) at room temperature was added a aqueous solution (5.0 mL) of sodium hydroxide (0.36 g, 9.2 mmol). The resulting reaction mixture was stirred at room temperature for 3 h. The reaction mixture was then carefully neutralized with hydrochloric acid (2.0 N) until the pH of the solution was 7. The white precipitate was crashed out from the solution and filtered and washed with water and dried under vacuum at 78 °C overnight; 1.60 g (96%) of 4-(1-oxo-2-(2-(pyrrolidine-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic acid (**68a**) was collected as a white solid; mp 247−249 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.70 (m, 4H), 2.71 (m, 4H), 2.77 (t, J = 6.22 Hz, 2H), 2.93 (t, J = 6.59 Hz, 2H), 3.57 (t, J = 6.59 Hz, 2H), 3.64 (t, J = 6.35 Hz, 2H), 7.44 (s, 1H), 7.55−7.60 (m, 3H), 7.77 (d, J = 8.05 Hz, 2H), 7.87 (d, J = 8.05 Hz, 1H). MS (ES) m/z 365.1 $[M + H]^+$.

3-Fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic Acid (68b). The title compound was prepared according to the procedure described in **68a** and

employing 2-fluoro-4-(methoxycarbonyl)phenylboronic acid, the desired product was obtained as a white solid. MS (ES) m/z 381.1 $[M - H]^-$.

2-Fluoro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic Acid (68c). The title compound was prepared according to the procedure described in **68a** and employing 3-fluoro-4-(methoxycarbonyl)phenylboronic acid, the desired product was obtained as a white solid.

2-Chloro-4-(1-oxo-2-(2-(pyrrolidin-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic Acid (68d). The title compound was prepared according to the procedure described in **68a** and employing 3-chloro-4-(methoxycarbonyl)phenylboronic acid, the desired product was obtained as a white solid.

(*R*)-4-(2-(2-(2-Methylpyrrolidin-1-yl)ethyl)-1-oxo-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic Acid (68e). The title compound was prepared according to the procedure described in **68a** and employing **55d**, the desired product was obtained as a white solid; $[\alpha]_D^{25} = -62°$ (c = 1% solution in methanol). ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.98 (d, J = 6.10 Hz, 3H), 1.21−1.30 (m, 1H), 1.57−1.64 (m, 2H), 1.78−1.87 (m, 1H), 2.12−2.18 (m, 1H), 2.20−2.25 (m, 1H), 2.28−2.36 (m, 1H), 2.90−3.03 (m, 3H), 3.12−3.19 (m, 1H), 3.52−3.63 (m, 4H), 7.62−7.66 (m, 2H), 7.78 (d, J = 8.32 Hz, 2H), 7.90 (d, J = 8.05 Hz, 1H), 7.97−7.99 (m, 2H), 8.62 (br, 1H). MS (ES) m/z 377.2 $[M - H]^-$.

***N*-Methoxy-*N*-methyl-4-[1-oxo-2-(2-pyrrolidin-1-ylethyl)-1,2,3,4-tetrahydroiso-quinolin-6-yl]benzamide (70).** A suspension of 4-(1-oxo-2-(2-(pyrrolidine-1-yl)ethyl)-1,2,3,4-tetrahydroisoquinolin-6-yl)benzoic acid **68a** (0.55 mmol) in thionyl chloride (2 mL) was heated at reflux temperature for 1 h, cooled to room temperature, and concentrated in vacuo to afford a crude material **69a**. The residue **69a** was dissolved in THF, cooled to 0 °C, treated with treated with *N*,*O*-dimethylhydroxylamine (1.1 mmol), warmed to room temperature, stirred for 1 h at room temperature, diluted with 1 N NaOH, and extracted with CH_2Cl_2. The combined extracts were washed sequentially with saturated $NaHCO_3$ and brine, dried over Na_2SO_4, and concentrated in vacuo. The residue was purified by ISCO CombiFlash chromatography (silica, 0−10% methanol in CH_2Cl_2 with 0.5% ammonium hydroxide) to afford the free amine of the title product as a colorless oil. The oil was dissolved in ethanol, treated with Etheral HCl, stirred, and filtered. The filter cake was washed with ether and dried to provide the title compound as a white solid, hydrochloride salt; yield 58%; mp 190−191 °C. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62 (m, 4H), 2.46 (m, 4H), 2.58 (t, J = 6.72 Hz, 2H), 2.98 (t, J = 6.6 Hz, 2H), 3.24 (s, 3H), 3.53 (s, 3H), 3.54−3.59 (m, 4H), 7.61−7.65 (m, 4H), 7.75 (d, J = 8.46 Hz, 2H), 7.90 (d, J = 8.11 Hz, 1H). HRMS: calcd for $C_{24}H_{29}N_3O_3 + H^+$, 408.22817; found (ESI, $[M + H]^+$ obsd), 408.2286.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental procedures for the human and rat H_3 receptor binding assays; plasma protein binding; X-ray structure and crystal data for compound **39**. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ABBREVIATIONS USED

H_3 receptor, histamine-3 receptor; ADHD, attention deficit hyperactivity disorder; hERG, human ether a go-go; 5-HT-T, serotonin transporter; MC, methyl cellulose; PEG, polyethylene glycol; C_{max}, maximum plasma concentration; $AUC_{0-\infty}$, systemic exposure; NOR, novel object recognition; SOR, social odor recognition; MED, minimal effective dose

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