Bioorganic & Medicinal Chemistry 16 (2008) 6707–6723

Contents lists available at ScienceDirect

Bioorganic & Medicinal Chemistry

journal homepage: www.elsevier.com/locate/bmc

Studies toward the discovery of the next generation of antidepressants. Part 6: Dual 5-HT$_{1A}$ receptor and serotonin transporter affinity within a class of arylpiperazinyl-cyclohexyl indole derivatives

Dahui Zhou [a,*], Ping Zhou [a], Deborah A. Evrard [a], Kristin Meagher [a], Michael Webb [a], Boyd L. Harrison [a], Donna M. Huryn [a], Jeannette Golembieski [b], Geoffrey A. Hornby [b], Lee E. Schechter [b], Deborah L. Smith [b], Terrance H. Andree [b], Richard E. Mewshaw [a,*]

[a] Chemical and Screening Sciences, Wyeth Research, CN 8000, Princeton, NJ 08543-8000, USA
[b] Neuroscience' Discovery Research, Wyeth Research, CN 8000, Princeton, NJ 08543-8000, USA

ARTICLE INFO

Article history:
Received 6 March 2008
Revised 29 May 2008
Accepted 29 May 2008
Available online 5 June 2008

Keywords:
Serotonin transporter
5-HT$_{1A}$ receptor

ABSTRACT

Based on the previously reported discovery lead, 3-(*cis*-4-(4-(1*H*-indol-4-yl)piperazin-1-yl)cyclohexyl)-5-fluoro-1*H*-indole (**2**), a series of related arylpiperazin-4-yl-cyclohexyl indole analogs were synthesized then evaluated as 5-HT transporter inhibitors and 5-HT$_{1A}$ receptor antagonists. The investigation of the structure–activity relationships revealed the optimal pharmacophoric elements required for activities in this series. The best example from this study, 5-(piperazin-1-yl)quinoline analog (*trans*-**20**), exhibited equal binding affinities at 5-HT transporter (K_i = 4.9 nM), 5-HT$_{1A}$ receptor (K_i = 6.2 nM) and functioned as a 5-HT$_{1A}$ receptor antagonist.

© 2008 Elsevier Ltd. All rights reserved.

1. Introduction

Selective serotonin reuptake inhibitors (SSRIs) have achieved great success in treating depression and related illnesses and have fewer and less-severe side effects than first generation drugs, such as tricyclic antidepressants (TCAs) and non-selective monoamine oxide (MAO) inhibitors. However, clinical efficacy is seen only after prolonged treatment with SSRIs.[1] It is speculated that this delayed onset of action is attributed to the SSRI-induced increase in serotonin (5-HT) levels in the vicinity of the serotonergic cell bodies. The excess serotonin activates somatodendritic 5-HT$_{1A}$ autoreceptors, causing a decrease in neuronal firing, which in turn decreases the release of serotonin in major forebrain areas. In practice, sustained treatment with SSRIs can effectively desensitize the pre-synaptic 5-HT$_{1A}$ autoreceptor and allow for the desired increase in 5-HT levels in the forebrain.[2–4]

It has been proposed that the addition of a 5-HT$_{1A}$ receptor antagonist component to the action of a SSRI can limit the negative feedback through blockade of the 5-HT$_{1A}$ autoreceptor, allowing an immediate increase in synaptic 5-HT levels in desired post-synaptic brain regions. Preclinical evidence using in vivo microdialysis has shown that co-administration of fluoxetine and the selective 5-HT$_{1A}$ receptor antagonist WAY-100635 produces an immediate increase in 5-HT levels in rat frontal cortex. This effect is not observed with acute fluoxetine treatment alone.[5–7] In support of this hypothesis, clinical trials performed by Artigas[8] and Blier[9] demonstrated that the combination of (±)-pindolol, a non-selective 5-HT$_{1A}$ partial agonist, with the SSRI paroxetine shortened the onset of antidepressant action to a period of 3–7 days, in contrast to 2–3 weeks required with the SSRI alone. Therefore, the concept of developing a dual-acting agent that combines blockade of both the 5-HT$_{1A}$ receptor and 5-HT transporter in one molecule has been proposed. Several groups have reported their efforts and design strategies toward the construction of such a hybrid 5-HT$_{1A}$ receptor antagonist and 5-HT transporter inhibitor.[10–14]

The current study expands efforts initiated in 2001 to incorporate 5-HT transporter and 5-HT$_{1A}$ receptor activity into a single molecule. 4-(1*H*-Indol-3-yl)cyclohexylamines were used as a starting point to introduce the 5-HT$_{1A}$ pharmacophore, resulting in a novel class of indolylcyclohexylamines (**1**, Fig. 1).[10] Disappointingly, incorporation of the methoxy-substituted tetrahydroisoquinoline as a 5-HT$_{1A}$ receptor pharmacophore resulted in compounds having only weak affinity for the 5-HT$_{1A}$ receptor. As a continuation of our investigation, we decided to replace the tetrahydroisoquinoline moiety with 1-(4-indolyl)piperazine, a more optimal 5-HT$_{1A}$ receptor pharmacophoric group. As a result, *cis*-1-(4-indolyl)piperazine analog *cis*-**2** (Fig. 1), which exhibited high binding affinity for 5-HT transporter (K_i = 5.3 nM) and moderate affinity for 5-HT$_{1A}$ receptor (K_i = 36.6 nM), was chosen as a new discovery lead.[15] In order to further advance this series, we then turned our attention to the Regions **A** and **B** of the compound

* Corresponding authors. Tel.: +1 732 274 4423; fax: +1 732 274 4505.
E-mail address: zhoud@wyeth.com (D. Zhou).

0968-0896/$ - see front matter © 2008 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2008.05.075

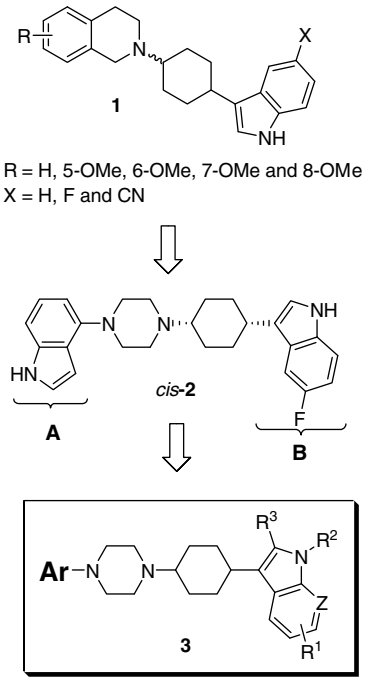


Figure 1. Compound design.

cis-**2**, in attempts to further enhance the potency at both 5-HT transporter and 5-HT_{1A} receptor sites. Our strategy was to systematically explore different 4-(indol-3-yl)cyclohexyl moieties (**B**-region, exemplified by generic structure **3**, Fig. 1) and alternative aryl piperazines (**A**-region) as replacements for the 1-(4-indolyl)piperazine. Herein, we describe the synthesis and biological evaluation of a series of arylpiperazin-4-yl-cyclohexyl indole derivatives (**3**) that demonstrated potent and selective dual activities as 5-HT reuptake inhibitors and 5-HT_{1A} receptor antagonists.

2. Chemistry

The current SAR study began with an evaluation of the effect of various cyclohexyl-3-indoles on the binding affinities at the 5-HT transporter and the 5-HT_{1A} receptor. The synthesis began with the preparation of several 4-(indol-3-yl)-cyclohexanones **28a**–**28m** as shown in Scheme 1. Condensation of the requisite indoles with 1,4-cyclohexanedione mono-ethylene ketal under basic conditions afforded compounds **25a**–**25h**. Reduction of the resulting alkenes **25a**–**25h** and deketalization of compounds **26a**–**26h** provided the 4-(1*H*-indol-3-yl)-cyclohexanones **28a**–**28h**.[16] N-Alkylation of compounds **26b** and **26d** with alkyl halides, followed by hydrolysis of compounds **27i**–**28m** under acidic conditions generated 4-(indol-3-yl)cyclohexanones **28i**–**28m**.

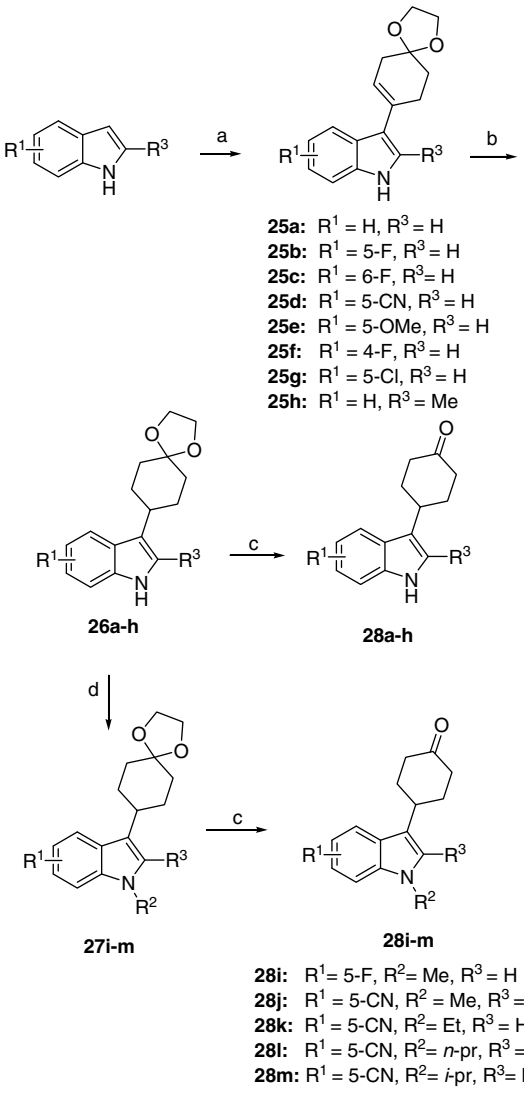
Reductive alkylation of 4-(piperazin-1-yl)-1*H*-indole (**29**)[15] with the 4-(indol-3-yl)-cyclohexanones **28a**–**28m** afforded target compounds **2** and **4**–**15** in excellence yield (Scheme 2). The *cis* and *trans* isomers were separated by column chromatography.

To investigate of the effects of different heteroaryl piperazines (**A**-region) on affinities at 5-HT transporter and 5-HT_{1A} receptor sites, (piperazin-1-yl)-1*H*-benzo[*d*]imidazole analogs **16**–**18** were prepared by reductive alkylation of (piperazin-1-yl)-1*H*-benzo[*d*]imidazoles **30a**–**30c**[17,18] with 4-(1*H*-indol-3-yl)-cyclohexanone **28a** (Scheme 3).

To further expand the SAR, 5-quinoline analogs **19** and **20** were synthesized in a 4-step sequence starting from commercially available 5-hydroxyquinoline (Scheme 4). Buchwald coupling[19] between the 5-(trifluoromethylsulfonyloxy)quinoline (**31**) and 1-*tert*-butyl-4-piperazine carboxylate afforded compound **32**. Deprotection and reductive alkylation of 5-(piperazin-1-yl)quinoline (**33**) with 4-(indol-3-yl)cyclohexanones **28b** and **28d** generated the target compounds **19** and **20**.

Next, 8-(piperazin-1-yl)quinoline analogs **21** and **22** were prepared (Scheme 5). Reaction of commercially available 8-aminoquinoline with bis-(2-chloroethyl)-benzylamine afforded compound **34**. Debenzylation with vinyl chloroformate followed by reductive alkylation with 4-(indol-3-yl)-cyclohexanones **28b** and **28d** provided compounds **21** and **22** (Scheme 5).

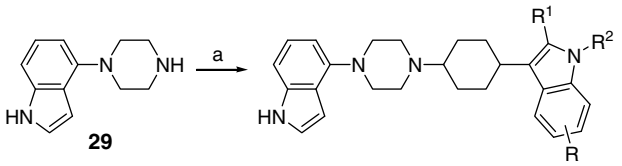
Finally, in order to further expand our SAR, quinoxaline 23, 1-naphthalenyl-piperazine **24** and the 7-azoindole analog **25** were prepared (Schemes 6 and 7). Reductive alkylation of compound **40**[20] and **29**[15] with cyclohexanones **28b** and 4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)cyclohexanone **41** afforded compounds **24** and **25**.



Scheme 1. Reagents: (a) 1,4-cyclohexanedione mono-ethylene ketal, KOH, methanol; (b) Pd–C 10%, ethanol–EtOAc or PtO_2, ethanol when R^1 = Cl; (c) 1 N HCl/THF (1:1); (d) NaH, R^2Br, DMF.

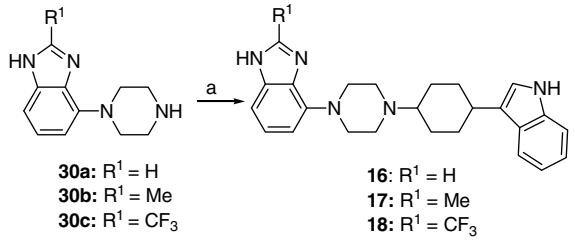
3. Results and discussion

Both the **B**-region indole moiety and the **A**-region heteroaryl moiety of the compound *cis*-**2** (Fig. 1) were systematically varied to establish the structure–activity relationship (SAR) of this series

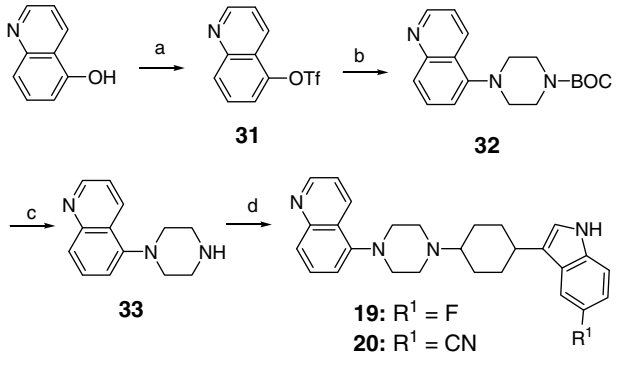


2: R = 5-F, $R^1 = R^2 = H$
4: R = H, $R^1 = R^2 = H$
5: R = H, $R^1 = H$, R^2 = Me
6: R = 6-F, $R^1 = R^2 = H$
7: R = 4-F, $R^1 = R^2 = H$
8: R = 5-CN, $R^1 = R^2 = H$
9: R = 5-CN, $R^1 = H$, R^2 = Me
10: R = 5-CN, $R^1 = H$, R^2 = Et
11: R = 5-CN, $R^1 = H$, R^2 = *n*-Pr
12: R = 5-CN, $R^1 = H$, R^2 = *i*-Pr
13: R = 5-OMe, $R^1 = R^2 = H$
14: R = 5-Cl, $R^1 = R^2 = H$
15: R = H, R^1 = Me, $R^2 = H$

Scheme 2. Reagents: (a) 4-(1*H*-indol-3-yl)-cyclohexanone, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.

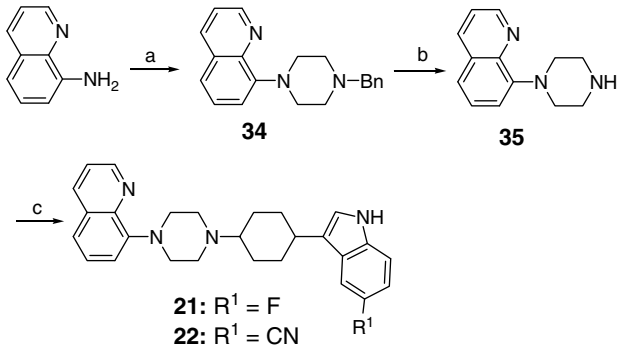


Scheme 3. Reagents: (a) 4-(1*H*-indol-3-yl)-cyclohexanone, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.

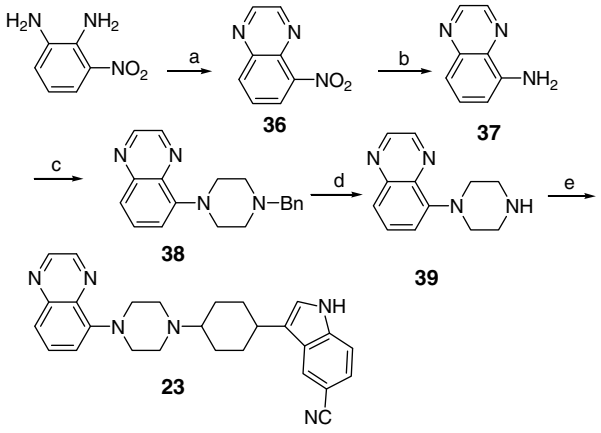


Scheme 4. Reagents: (a) Tf_2O, Et_3N, dichloromethane; (b) *tert*-butyl piperazine-1-carboxylate, $Pd(OAc)_2$, BINAP, Cs_2CO_3, tetrahydrofuran; (c) TFA, dichloromethane; (d) 4-(indol-3-yl)cyclohexaones, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.

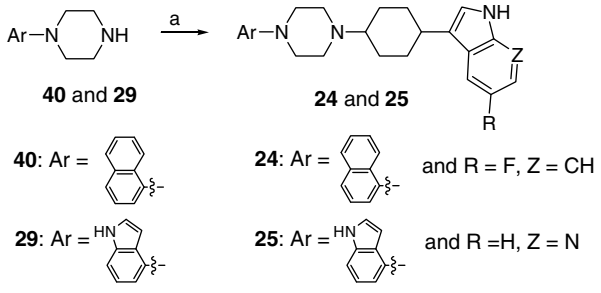
of compounds,. The following SAR Tables 1–6 examine each of these variables in turn. Compounds were evaluated in vitro to determine the binding affinities for both the serotonin transporter (r-5-HT-T) and 5-HT_{1A} receptor (h-5-HT_{1A}). Compounds that exhibited high binding affinity at both the 5-HT_{1A} receptor and the 5-HT transporter were further evaluated for their 5-HT_{1A} receptor intrinsic activity ($GTP\gamma S^{35}$ E_{max}) and selectivity over the α_1 adrenergic receptor. WAY-100635 (a 5-HT_{1A} receptor antagonist) and fluoxetine (a 5-HT transporter inhibitor) are shown as reference standards (Table 1).



Scheme 5. Reagents: (a) bis-(2-chloroethyl)-benzylamine, 1-butanol; (b) vinyl chloroformate followed by HCl (12 N)/dioxane (1:1) then ethanol reflux; (c) 4-(indol-3-yl)cyclohexaones, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.



Scheme 6. Reagents: (a) glyoxal; (b) Fe, HOAc; (c) bis(2-chloroethyl)-benzylamine, 1-butanol; (d) Pd–C 10%, ammonium formate, ethanol; (e) 3-(4-oxocyclohexyl)-1*H*-indole-5-carbonitrile, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.

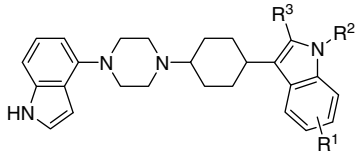


Scheme 7. Reagents: (a) 4-(5-fluoro-1*H*-indol-3-yl)cyclohexanone or 4-(1*H*-pyrrolo[2,3-*b*]pyridin-3-yl)cyclohexanone, $NaBH(OAc)_3$, HOAc, 1,2-dichloroethane.

As noted previously, *cis*-3-(4-(4-(1*H*-indole-4-yl)piperazin-1-yl)cyclohexyl)-5-fluoro-1*H*-indole (*cis*-**2**) was identified as a promising lead, but this observation was based only on the 4-(5-fluoro-1*H*-indol-3-yl) moiety in the **B**-region. Therefore, to more completely probe the effect of the **B**-region indolyl moiety on the affinities at the 5-HT transporter and 5-HT_{1A} receptor, we decided to systematically examine substituents at various positions in this region, while maintaining the 1-(4-indolyl)piperazine (**29**) as the 5-HT_{1A} receptor pharmacophore in the **A**-region.

As shown in Table 1, within each pair of geometric isomers in the 3-{4-[4-(1*H*-indol-4-yl)-piperazin-4-yl]cyclohexyl}-indole series (i.e., **2**, **4**–**15**), the *cis* isomers were more potent for 5-HT transporter affinity than their corresponding *trans* isomers. Also,

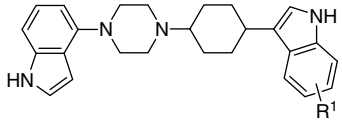
Table 1
3-{4-[4-(1*H*-Indol-4-yl)-1-piperazinyl]cyclohexyl}indoles **2**, **4**–**16**[a]



Compound	R^1	R^2	R^3	r-5-HT-T K_i[b] (nM)		h-5-HT_{1A} K_i[c] (nM)	
				cis	*trans*	*cis*	*trans*
Fluoxetine				2.7 (racemic)		nd	
WAY-100635				nd		0.9 (achiral)	
2	5-F	H	H	5.3	48.5	36.7	4.62
4	H	H	H	38	155	32	5.3
5	5-F	Me	H	11.6	67.5	124	90
6	6-F	H	H	12.7	35% at 100 nM	33.5	5.4
7	4-F	H	H	27% at 100 nM	0% at 100 nM	117.3	22.2
8	5-CN	H	H	1.6	8.5	69.6	3.5
9	5-CN	Me	H	3.3	102	232.9	53.2
10	5-CN	Et	H	13.4	58.2	563.5	827.6
11	5-CN	Pr	H	26.7	62.5	819.8	46% at 1 μM
12	5-CN	*i*-Pr	H	38.5	16% at 100 nM	694.2	46% at 1 μM
13	5-OMe	H	H	25% at 100 nM	45% at 1 μM	60.3	2.9
14	5-Cl	H	H	28% at 100 nM	20% at 100 nM	325.7	58.3
15	H	H	Me	4% at 100 nM	12% at 100 nM	87.1	13

nd, not determined.
[a] K_i values are the mean of at least two experiments performed in triplicate, determined from nine concentrations and all K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[21] Percentages represent inhibition of binding at the concentration indicated.
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]paroxetine.[22]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[23]

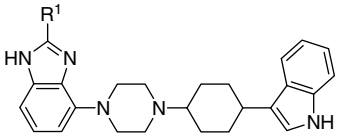
Table 2
Intrinsic activity at 5-HT_{1A} receptor and the selectivity over α_1 adrenergic receptor



Compound	R^1	h-5-HT_{1A} K_i (nM)	GTPγS^{35} E_{max}[a] (%)	r-α_1 K_i[b] (nM)
cis-**2**	5-F	36.7	10	196
trans-**2**	5-F	4.6	43	16% at 100 nM
cis-**4**	H	32	0	2430
cis-**6**	6-F	33.5	0	266
cis-**8**	5-CN	69.6	0	65
trans-**8**	5-CN	3.5	11	26

[a] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor.[24] E_{max} refers to maximal agonist effect relative to 5-HT.
[b] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]prazosin.[25]

Table 3
Benzimidazolepiperazines **16**–**18**[a]



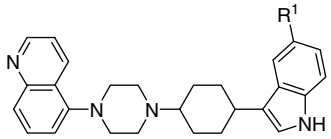
Compound	R^1	r-5-HT-T K_i[b] (nM)	h-5-HT_{1A} K_i[c] (nM)	GTPγS^{35} E_{max}[d] (%)	r-α_1 K_i[e] (nM)
cis-**16**	H	13	7.9	0	34
trans-**16**	H	75	1.7	0	4.2
cis-**17**	Me	61	10.7	0	23.1
trans-**17**	Me	115	3	0	3
cis-**18**	CF_3	105	16.1	0	118
trans-**18**	CF_3	75	3.6	29	11

[a] K_i values are the mean of at least two experiments performed in triplicate, determined from nine concentrations and all *K*i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[21]
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]paroxetine.[22]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[23]
[d] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor.[24] E_{max} refers to maximal agonist effect relative to 5-HT.
[e] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]prazosin.[25]

substituents at the C5-position of the **B**-region indole moiety had a significant influence on the binding affinity for the 5-HT transporter in both *cis* and *trans* isomeric series. For example, the C5-cyano analogs showed a 24-fold (*cis*-**8**) and an 18-fold (*trans*-**8**) increase in binding affinity compared to the non-substituted analogs (*cis*-**4** and *trans*-**4**). The C5-fluoro derivatives showed a sevenfold (*cis*-**2**) and 23-fold (*trans*-**2**) increase in binding affinity compared to the corresponding non-substituted analogs (*cis*-**4** and *trans*-**4**). In contrast, the C5-methoxy analogs (*cis*-**13** and *trans*-**13**) and C5-chloro analogs (*cis*-**14** and *trans*-**14**) were almost devoid of the transporter affinity compared to the corresponding non-substituted analogs (*cis*-**4** and *trans*-**4**). A consistent trend was followed by both *cis* and *trans* isomers demonstrating that C5-CN > C5-F > H ≫ C5-Cl ~ C5-OMe with respect to 5-HT transporter binding affinity.

The presence of fluorine at the C4-, C5-, and C6- positions of the **B**-region indole moiety was also found to have great impact on 5-HT transporter affinity for both *cis* and *trans* isomers. The C5-fluoro analogs (*cis*-**2** and *trans*-**2**) had optimized 5-HT transporter binding affinity compared to their corresponding C6-fluoro (*cis*-**6** and *trans*-**6**) and C4-fluoro analogs (*cis*-**7** and *trans*-**7**). In fact, compounds bearing a C4-fluoro at the **B**-region indole moiety (*cis*-**7** and *trans*-**7**) displayed dramatically lower binding affinity for 5-HT transporter.

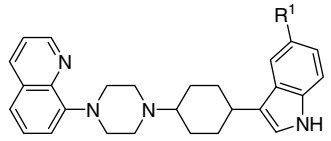
Table 4
5-(Piperazin-1-yl)quinoline Analogs **19**–**20**[a]



Compound	R^1	r-5-HT-T K_i[b] (nM)	h-5-HT_{1A} K_i[c] (nM)	GTPγS^{35} E_{max}[d] (%)	r-α_1 K_i[e] (nM)
cis-**19**	F	13.8	97.2	0	nd
trans-**19**	F	73	8.3	0	156
cis-**20**	CN	3.5	58.1	0	522
trans-**20**	CN	4.9	6.2	3	293

nd, not determined.
[a] K_i values are the mean of at least two experiments performed in triplicate, determined from nine concentrations and all *K*i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[21]
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]paroxetine.[22]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DAPT.[23]
[d] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor.[24] E_{max} refers to maximal agonist effect relative to 5-HT.
[e] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]prazosin.[25]

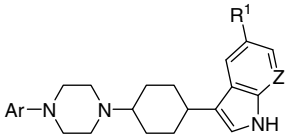
Table 5
8-(Piperazin-1-yl)quinoline Analogs **21**–**22**[a]

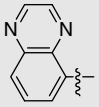
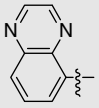
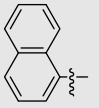
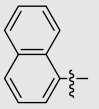
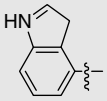
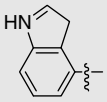


Compound	R^1	r-5-HT-T K_i[b] (nM)	h-5-HT_{1A} K_i[c] (nM)	GTPγS^{35} E_{max}[d] (%)	r-α_1 K_i[e] (nM)
cis-**21**	F	4.6	69.7	20	177.0
trans-**21**	F	39.3	6.5	66	82.0
cis-**22**	CN	1.3	43.9	23	78.0
trans-**22**	CN	20.0	2.9	0	66.0

[a] K_i values are the mean of at least two experiments performed in triplicate, determined from nine concentrations and all K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[21]
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]paroxetine.[22]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DAPT.[23]
[d] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor.[24] E_{max} refers to maximal agonist effect relative to 5-HT.
[e] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]prazosin.[25]

Table 6
Other piperazine analogs **23**–**25**[a]



Compound	Ar	R^1	Z	r-5-HT-T K_i[b] (nM)	h-5-HT_{1A} K_i[c] (nM)	GTPγS^{35} E_{max}[d] (%)	r-α_1 K_i[e] (nM)
cis-**23**		CN	C	1.1	156.2	0	60.5
trans-**23**		CN	C	13.6	9.1	11	47.6
cis-**24**		F	C	640	46% at 1 μM	34	nd
trans-**24**		F	C	38% at 1 μM	42.6	71	nd
cis-**25**		H	N	0% at 100 nM	15.8	nd	nd
trans-**25**		H	N	18% at 100 nM	7.8	nd	nd

nd, not determined.
[a] K_i values are the mean of at least two experiments performed in triplicate, determined from nine concentrations and all K_i values were calculated from IC_{50} values using the method of Cheng and Prusoff.[21] Percentages represent inhibition of binding at the concentration indicated.
[b] Binding affinity at rat cortical 5-HT reuptake sites labeled with [^{3}H]paroxetine.[22]
[c] Binding affinity at human 5-HT_{1A} receptors in CHO cells labeled with [^{3}H]-8-OH-DPAT.[23]
[d] Stimulation of GTPγS^{35} binding in CHO cells expressing 5-HT_{1A} receptor.[24] E_{max} refers to maximal agonist effect relative to 5-HT.
[e] Binding affinity at rat cortical α_1 adrenergic receptors labeled with [^{3}H]prazosin.[2]

Introduction of a C2-methyl group to the **B**-region indole moiety also had a detrimental effect on the binding affinity for 5-HT transporter in both *cis* and *trans* isomeric series (i.e., *cis*-**15** and *trans*-**15**), with only 4% and 12% inhibition in r-5-HT transporter binding assay at 100 nM, respectively.

Further exploration of the SAR of the N-alkylations of the **B**-region indole moiety revealed that replacement of the *N*-proton with *N*-alkyl substitutents showed a consistent trend toward decreased 5-HT transporter binding affinity for both *cis* and *trans* isomers (e.g., *cis*- and *trans*-**8** vs *cis*- and *trans*-**9**, **10**, **11**, and **12**), suggesting that the binding pocket of the 5-HT transporter appears to be sensitive to steric bulk.

Having investigated the effects of modifying the **B**-region indole moiety on 5-HT transporter affinity, we next focused our attention on understanding the effects of these modifications on affinity at the 5-HT_{1A} receptor.

As summarized in Table 1, within each pair of geometric isomers in the 3-{4-[4-(1*H*-indol-4-yl)-piperazin-4-yl]cyclohexyl}-indole series (i.e., **2**, **4**–**15**), the *trans* isomers always demonstrated more potent binding affinity for the 5-HT_{1A} receptor than their corresponding *cis* isomers. Changing different substituents at C5-position of **B**-region indole moiety (e.g., non-substituted, C5-fluoro, C5-cyano and C5-methoxy) had minimal impact on the binding affinity at 5-HT_{1A} receptor for both *cis* and *trans* isomers (*cis*- and *trans*-**4** vs **2**, **8** and **13**), suggesting that there exists a large tolerance of the 5-HT_{1A} receptor toward electronic effects at C5-position of **B**-region indole moiety. For example, *cis*- and *trans*-**8** isomers were equipotent to the corresponding *cis*- and *trans*-**13** isomers in the h-5-HT_{1A} receptor binding assay.

The C5- and C6-fluoro substituted analogs (*cis*- and *trans*-**2** vs *cis*- and *trans*-**6**) showed comparable potency with respect to the binding affinity at the 5-HT_{1A} receptor. However, the C4-fluoro analogs (*cis*- and *trans*-**7**) demonstrated reduced binding affinity at the 5-HT_{1A} receptor.

Furthermore, as depicted in Table 1, replacement of *N*-proton of the **B**-region indole moiety with *N*-alkyls led to a decrease in the binding affinity at the 5-HT_{1A} receptor for both *cis* and *trans* isomers (*cis*- and *trans*-**8** vs **9**, **10**, **11**, and **12**).

We further examined six compounds (i.e., *cis*-**2**, *trans*-**2**, *cis*-**4**, *cis*-**6**, *cis*-**8**, and *trans*-**8**) selected from Table 1, which exhibited good binding affinities at both 5-HT_{1A} receptor and the 5-HT transporter, for their intrinsic activity at the 5-HT_{1A} receptor as well as selectivity against the α_1 adrenergic receptor (Table 2).

These six compounds were tested in vitro using a GTPγS^{35} binding assay to determine their agonist/antagonist properties at the 5-HT_{1A} receptor. Four *cis* analogs (*cis*-**2**, *cis*-**4**, *cis*-**6**, and *cis*-**8**) appeared to be antagonists or very weak partial agonists (E_{max} values expressed as a percentage of the maximal activity of 5-HT), indicating that antagonism of the 5-HT_{1A} receptor was more readily achieved for *cis* isomers in this series. With respect to the selectivity for the 5-HT_{1A} receptor over the α_1 adrenergic receptor, *cis*-**4** was observed to have the best profile. The C5-fluoro (*cis*-**2** and *trans*-**2**), C6-fluoro (*cis*-**6**), and C5-cyano (*trans*-**8**) analogs exhibited moderate selectivity (5- to 8-fold).

By now we had developed a clear picture of the **B**-region indole moiety requirements for potent binding at 5-HT transporter and 5-HT_{1A} receptor when employing the 1-(4-indolyl)piperazine motif as a 5-HT_{1A} receptor pharmacophore. Most critical was to have a C5-fluoro or a C5-cyano substitution on the **B**-region indole ring. With respect to α_1 adrenergic receptor selectivity, no substitution on the **B**-region indole ring was optimal, although the corresponding *cis*-4 analog was less potent for 5-HT transporter binding affinity when compared to C5-fluoro (*cis*-**2**) or C5-cyano (*cis*-**8**) analogs.

Having identified the *cis*-**4** analog to be selective for the 5-HT_{1A} receptor over the α_1 adrenergic receptor, we set out to further increase the binding affinities at 5-HT transporter and 5-HT_{1A} receptor by modifying the **A**-region aryl moiety while maintaining the 4-(1*H*-indol-3-yl)cyclohexyl moiety constant. As a result, a 7-(piperazin-1-yl)benzo-[*d*]imidazole moiety was introduced as a surrogate for the 1-(4-indolyl)piperazine. As shown in Table 3, compared to the 1-(4-indolyl)piperazine analog *cis*-**4**, benzoimidazole analogs *cis*- and *trans*-**16**–**18** exhibited a trend toward the improvement of the binding affinity for the 5-HT_{1A} receptor (e.g., 2- to 18-fold), but failed to improve the binding affinity for the 5-HT transporter, with the exception of compound *cis*-**16,** which showed a threefold increase in binding affinity for the 5-HT transporter. As noted previously (Table 2), all the *cis* isomers (*cis*-**16**–**18**) appeared as 5-HT_{1A} receptor antagonists. Interestingly, three *trans* isomers (*trans*-**16**–**18**) also had low 5-HT_{1A} receptor intrinsic activity. Benzoimidazole analog *cis*-**16** demonstrated potent and balanced affinity for 5-HT transporter and 5-HT_{1A} receptor and functioned as a 5-HT_{1A} receptor antagonist, albeit at the cost of reduction of the selectivity for the 5-HT_{1A} receptor over the α_1 adrenergic receptor (e.g., *cis*-**16**: fourfold).

Further exploration of the SAR of **A**-region of *cis*-**2** is revealed in Tables 4–6. Compared to the 1-(4-indolyl)piperazine analogs (*cis*- and *trans*-**2** and **8**), 5-(piperazin-1-yl)quinoline analogs (*cis*- and *trans*-**19** and **20**) gave no improvement in binding affinity for 5-HT transporter and 5-HT_{1A} receptor. However, the selectivity for the 5-HT_{1A} receptor over the α_1 adrenergic receptor was improved in the analogs of *cis*- and *trans*-**20**. 5-(Piperazin-1-yl)quinoline analog *trans*-**20** exhibited nearly equal potencies for both 5-HT transporter and 5-HT_{1A} receptor. In addition, analog *trans*-**20** showed nearly 50-fold 5-HT_{1A} receptor selectivity over the α_1 adrenergic receptor.

8-(Piperazin-1-yl)quinoline replacement for the 5-(piperazin-1-yl)quinoline was likewise well-tolerated (Table 5) with respect to the binding affinities at 5-HT transporter and 5-HT_{1A} receptor, with the exception of *trans*-**22** that showed a fourfold loss of the binding affinity for 5-HT transporter compared to *trans*-**20**. As a consequence, none of the compounds proved superior to the *trans*-**20** analog. In addition, replacement of 5-(piperazin-1-yl)quinoline with 8-(piperazin-1-yl)-quinoline resulted in decreased selectivity for the 5-HT_{1A} receptor over the α_1 adrenergic receptor.

For completeness, 5-(piperazin-1-yl)quinoxaline analogs were also explored, albeit to a lesser extent (Table 6). Replacement of 5-(piperazin-1-yl)quinoline and 8-(piperazin-1-yl)quinoline with 5-(piperazin-1-yl)quinoxaline provided no improvement in binding affinities for the 5-HT transporter and 5-HT_{1A} receptor, as well as the selectivity over the α_1 adrenergic receptor (*cis*- and *trans*-**23**).

To further examine the effect of the heteroatoms in the aromatic ring (**A**-region), we prepared the naphthalenyl-piperazine analogs *cis*- and *trans*-**24**. A deterioration of binding affinities at both the 5-HT transporter and the 5-HT_{1A} receptor was observed when heteroaryl piperazines (**29**, **30**, **33**, **35**, and **39**) were replaced by naphthalenyl-piperazine **40**. The *cis*- and *trans*-**24** analogs also showed an increase in 5-HT_{1A} receptor intrinsic activity. Both *cis*-**24** and *trans*-**24** functioned as partial 5-HT_{1A} receptor agonists. The reduction in binding affinities at the 5-HT transporter and the 5-HT_{1A} receptor, and increase in agonism at 5-HT_{1A} receptor for compounds *cis*- and *trans*-**24** may be due to the elimination of the hydrogen-bonding interaction between the ligand and the 5-HT transporter and 5-HT_{1A} receptor, suggesting that hydrogen-bonding interaction in the **A**-region is critical for achieving activities at both 5-HT transporter and 5-HT_{1A} receptor sites in this class of molecules.

The final SARs examined in this investigation entailed replacement the **B**-region 3-cyclohexyl-indole moiety with 3-cyclohexyl-7-azoindole **41** (Table 6). Both isomers (*cis*- and *trans*-**25**) were devoid of 5-HT transporter affinity, but maintained potent binding affinity for 5-HT_{1A} receptor, strongly indicating that 3-cyclohexyl-7-azoindole moiety was not a desirable 5-HT transporter pharmacophoric modification.

4. Conclusion

In this study, we synthesized a class of arylpiperazine-4-yl-cyclohexyl indole derivatives (**4**–**25**). The goal of creating a single molecular entity with dual activities as both a 5-HT transporter inhibitor and a 5-HT_{1A} receptor antagonist has been achieved. Through structural modifications of 3-(*cis*-4-(4-(1*H*-indol-4-yl)piperazin-1-yl)cyclohexyl)-5-fluoro-1*H*-indole (*cis*-**2**), we have developed a thorough understanding of the interactions between the arylpiperazineyl-indole derivatives and the 5-HT transporter and 5-HT_{1A} receptor. The heteroaryl piperazines of **A**-region and the 3-cyclohexyl-indoles of **B**-region in the structure **3** are clearly critical, as the naphthalenyl-piperazine (*cis*- and *trans*-**24**) and 3-cyclohexyl-azoindole (*cis*- and *trans*-**25**) replacements significantly decreased the dual activities at both 5-HT transporter and 5-HT_{1A} receptor. Furthermore, our studies demonstrated that the substitution pattern on the **B**-region indole ring in structure **3** was very important and that C5-cyano and C5-fluoro were preferred with respect to the binding affinities at 5-HT transporter and 5-HT_{1A} receptor. Finally, selectivity for the 5-HT_{1A} receptor over the α_1 adrenergic receptor in this series of compounds spans a wide range, with selectivity ratios from 0.2- to 75-fold. The most interesting compound identified from this study is the 5-(piperazin-1-yl)quinoline analog *trans*-**20**, which exhibited nearly equal potencies at both 5-HT transporter (K_i = 4.9 nM) and 5-HT_{1A} recep-

tor (K_i = 6.2 nM), and functioned as a full 5-HT_{1A} receptor antagonist. In addition, *trans*-**20** showed nearly 50-fold 5-HT_{1A} receptor selectivity over the α_1 adrenergic receptor.

5. Experimental

5.1. General method: Chemistry

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 $CDCl_3$ or DMSO-d_6. Mass spectra were recorded on a Micromass LCT spectrometer. CHN combustion analyses were determined on either a Perkin-Elmer 2400 analyzer or were performed by Robertson Microlit (Madison, NJ). Solvents and reagents were used as purchased.

5.1.1. 3-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-6-fluoro-1*H*-indole (25c)

A solution of 6-fluoro-indole (5.14 g, 38 g, 38 mmol), 1,4-cyclohexanedione mono-ethylene ketal (5.9 g, 38 mmol), and potassium hydroxide (7.6 g, 190 mol) in 50 mL methanol was heated to reflux for 18 h. The mixture was poured into water (150 mL) and extracted with methylene chloride (2× 200 mL). The organic layer was dried over anhydrous magnesium sulfate, filtered, and solvent was removed in vacuo. Chromatography (25% ethyl acetate/hexanes) afforded 10 g (96.3%) of the title product as a white solid: mp 196–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.78–1.82 (m, 2H), 2.38 (m, 2H), 2.54–2.57 (m, 2H), 3.91 (s, 4H), 5.99–6.01 (m, 1H), 6.83–6.88 (m, 1H), 7.12 (dd, J = 10.12, 2.64 Hz, 1H), 7.35 (d, J = 2.40 Hz, 1H), 7.70–7.76 (m, 1H), 11.13 (br, 1H). Anal. Calcd for $C_{16}H_{16}FNO_2$: C, 70.32; H, 5.90; N, 5.13. Found: C, 70.62; H, 5.91; N, 5.08.

5.1.2. 3-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-5-cyano-1*H*-indole (25d)

This compound was prepared in a similar fashion as described above (**25c**) by replacing 6-fluoroindole with 5-cyanoindole (29.98 g, 0.21 mol) to afford 29.32 g (50%) of the title compound as a white solid: mp 158–160 °C; MS (ESI) *m/z* 279 ([M+H]$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82 (t, J = 4.0 Hz, 2H), 2.41 (m, 2H), 2.58 (t, J = 4.0 Hz, 2H), 3.92 (s, 4H), 6.08 (m, 1H), 7.43 (d, J = 4.0 Hz, 1H), 7.53 (d, J = 4.0 Hz, 1H), 8.25 (s, 1H), 11.66 (br, 1H).

5.1.3. 3-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-4-fluoro-1*H*-indole (25f)

This compound was prepared in a similar fashion as described above (**25c**) by replacing 6-fluoroindole with 4-fluoroindole (3 g, 22 mmol) to afford the title compound in quantitative yield as a white solid: mp at 140 °C sublimated; MS (EI) *m/z* 273 (M$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ1.95 (t, J = 6.56 Hz, 2H), 2.02 (t, J = 7.24 Hz, 2H), 2.70 (m, 2H), 4.03 (s, 4H), 5.94 (m, 1H), 7.06–7.14 (m, 2H), 8.10 (br, 1H).

5.1.4. 3-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-5-chloro-1*H*-indole (25g)

This compound was prepared in a similar fashion as described above (**25c**) by replacing 6-fluoroindole with 5-chloroindole (5 g, 33 mmol) to afford 9.14 g (96%) of the title compound as a white solid: mp 178–181 °C; MS (EI) *m/z* 273 (M$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.96 (t, J = 6.6 Hz, 2H), 2.53 (m, 2H), 2.65–2.70 (m, 2H), 4.04 (s, 4H), 6.06–6.09 (m, 1H), 7.13 (d, J = 2.0 Hz, 1H), 7.15 (dd, J = 5.24, 2.6 Hz, 1H), 7.25 (m, 1H), 7.84 (d, J = 2.0 Hz, 1H), 8.11 (br, 1H).

5.1.5. 3-(1,4-Dioxa-spiro[4,5]dec-7-en-8-yl)-2-methyl-1*H*-indole (25h)

This compound was prepared in a similar fashion as described above (**25c**) by replacing 6-fluoroindole with 2-methylindole (4.76 g, 30.4 mmol) to afford 2.35 g (62%) of the title product as a white solid: mp 136–137 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (t, J = 6.36 Hz, 2H), 2.33 (s, 3H), 2.38 (m, 2H), 2.50–2.54 (m, 2H), 3.92 (s, 4H), 6.88–6.92 (m, 2H), 6.94–6.98 (m, 1H), 7.21 (d, J = 7.92 Hz, 1H), 7.40 (d, J = 7.68 Hz, 1H), 10.84 (s, 1H). Anal. Calcd for $C_{17}H_{19}NO_2$: C, 75.81; H, 7.11; N, 5.70. Found: C, 75.47; H, 7.26; N, 5.13.

5.1.6. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole (26c)

A mixture of 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-6-fluoro-1*H*-indole **25c** (9.54 g, mmol) and 10% palladium on carbon (0.35 g) in ethanol (80 mL) was hydrogenated under 45 Psi for 18 h. The catalyst was filtered off, and then a solution of methylene/methanol (80 mL) was used to dissolve any solids within the Celite. The was solvent removed in vacuo to afford 5.83 g (60%) of the title product as an off-white solid, which was triturated with ethyl ether (40 mL) to afford a white solid: mp 158–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.61–1.76 (6H, m), 1.90–1.93 (2H, m), 2.77–2.82 (1H, m), 3.88 (4H, s), 6.77–6.82 (1H, m), 7.05–7.09 (1H, m), 7.49–7.52 (1H, m), 10.81 (1H, br). Anal. Calcd for $C_{16}H_{18}FNO_2$: C, 69.80; H, 6.59; N, 5.09. Found: C, 69.74; H, 6.48; N, 5.13.

5.1.7. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-cyano-1*H*-indole (26d)

This compound was prepared in a similar fashion as described above (**26c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]-dec-7-en-8-yl)-5-cyano-1*H*-indole (54.6 g) to afford 52.1 g (95%) of the title compound as a white solid in 95% (52.1 g) yield: mp 153–155 °C; MS (ESI) *m/z* 281 ([M+H]$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.64–1.76 (m, 6H), 1.94 (m, 2H), 2.88 (m, 1H), 3.88 (s, 4H), 7.30 (s, 1H), 7.38 (d, J = 4.0 Hz, 1H), 7.47 (d, J = 4.0 Hz, 1H), 8.09 (s, 1H), 11.36 (br, 1H).

5.1.8. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-4-fluoro-1*H*-indole (26f)

This compound was prepared in a similar fashion as described above (**26c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-4-fluoro-1*H*-indole (6.3 g) to afford 4.44 g (70%) of the title compound as a white solid: mp 161–162 °C; MS (EI) *m/z* 275 (M$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.72–1.90 (m, 6H), 2.12–2.15 (m, 2H), 3.03–3.06 (m, 1H), 3.99 (s, 4H), 6.71–6.76 (m, 1H), 6.93 (m, 1H), 7.04–7.12 (m, 2H), 8.02 (br, 1H). Anal. Calcd for $C_{16}H_{18}FNO_2$: C, 69.08; H, 6.59; N, 5.09. Found: C, 69.05; H, 6.56; N, 4.87.

5.1.9. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-chloro-1*H*-indole (26g)

A mixture of 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-5-chloro-1*H*-indole (0.18 g) and platinum oxide (0.02 g) in ethanol (20 mL) with ten drops of acetic acid was hydrogenated under 45 Psi overnight. The catalyst was filtered off and the solvent removed in vacuo. Chromatography (25% ethyl acetate/hexanes) afforded 0.16 g (88%) of the title product as a white solid: mp 205–206.5 °C; MS (FAB) *m/z* 291 ([M+H]$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.71–1.79 (m, 4H), 1.81–1.87 (m, 2H), 2.04–2.083 (m, 2H), 2.82–2.86 (m, 1H), 3.99 (s, 3H), 6.99 (m, 1H), 7.12 (dd, J = 8.56, 1.96 Hz, 1H), 7.26 (t, J = 4.30 Hz, 1H), 7.60 (d, J = 2.0 Hz, 1H), 8.02 (br, 1H).

5.1.10. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-2-methyl-1*H*-indole (26h)

This compound was prepared in a similar fashion as described above (**26c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-7-

en-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-2-methyl-1*H*-indole (2.39 g, 8.9 mmol) to afford 2.34 g (97%) of the title compound as a white solid: mp 166–168 °C; MS (EI) *m/z* 271 (M^+); The mother liquor was concentrated to afford another 1.2 g of the title product as a yellow solid. ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58–1.65 (m, 4H), 1.74–1.77 (m, 2H), 2.06–2.13 (m, 2H), 2.31 (s, 3H), 2.74–2.80 (m, 1H), 3.86–3.95 (m, 4H), 6.84–6.99 (m, 2H), 7.18–7.20 (m, 1H), 7.46 (d, J = 7.68 Hz, 1H), 10.61 (s, 1H). Anal. Calcd for $C_{17}H_{21}NO_2$: C, 75.25; H, 7.80; N, 5.16. Found: C, 75.17; H, 7.99; N, 5.12.

5.1.11. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-cyano-1-methyl-indole (27j)

(a) To a suspension of sodium hydride (60%, 1.74 g, 0.073 mol) in anhydrous *N,N*-dimethylformamide (100 mL) was added 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-5-cyano-1*H*-indole (9.9 g, 0.035 mol) at room temperature. The mixture was stirred for 30 min at room temperature, then methyl iodide (9 mL, 0.14 mol) was added at room temperature. The reaction was allowed to stir for 1 h, then quenched with water (50 mL). The mixture was extracted with methylene chloride (3× 150 mL) and water (3× 150 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo. Chromatography (5% methanol/methylene chloride) afforded 2.54 g (24%) of 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-5-cyano-1-methyl-indole as a light yellow solid: mp 65–67 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81 (t, J = 6.60 Hz, 2H), 2.39–2.46 (m, 2H), 2.53–2.56 (m, 2H), 2.84–2.90 (m, 1H), 3.79 (s, 3H), 3.91 (s, 4H), 6.46 (s, 1H), 6.07 (m, 1H), 7.50 (dd, J = 8.56, 1.56 Hz, 1H), 7.56 (s, 1H), 7.60 (d, J = 8.56 Hz, 1H), 8.25 (m, 1H). Anal. Calcd for $C_{18}H_{18}N_2O_2$: C, 73.45; H, 6.16; N, 9.52. Found: C, 73.17; H, 6.24; N, 9.43. (b) A mixture of 3-(1,4-dioxa-spiro[4,5]dec-7-en-8-yl)-5-cyano-1-methyl-indole (3.77 g) and 10% palladium on carbon (0.99 g) in ethanol/tetrahydrofuran (200:80 mL) was hydrogenated under 45 Psi for 5 h. The catalyst was filtered off and the solvent was removed in vacuo to afford a white powder which was washed with ethanol/hexanes (1:1) and dried under vacuum for 4 h to afford 2.75 g (12%) of the title product: mp 170–172 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.62–1.76 (m, 6H), 1.92–1.94 (m, 2H), 2.88 (m, 1H), 3.77 (s, 3H), 3.88 (s, 4H), 7.30 (m, 1H), 7.45 (dd, J = 8.56, 1.52 Hz, 1H), 7.55 (d, J = 8.56 Hz, 1H), 8.10–8.11 (m, 1H). Anal. Calcd for $C_{18}H_{20}N_2O_2$: C, 72.95; H, 6.80; N, 9.45. Found: C, 72.79; H, 6.82; N, 9.35.

5.1.12. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-cyano-1-ethyl-indole (27k)

To a suspension of sodium hydride (60%, 1.63 g, 0.068 mol) in anhydrous *N,N*-dimethylformamide (150 mL) was added 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-5-cyano-1*H*-indole (9.0 g, 0.032 mol) at room temperature. The mixture was stirred for 30 min at room temperature then ethylbromide (14.6 g, 0.13 mol) was added at room temperature. The reaction was allowed to stir overnight, and then quenched with water (50 mL). The mixture was extracted with methylene chloride (3× 150 mL) and water (3× 150 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed in vacuo. Chromatography (hexanes) afforded 5.5 g (69%) of the title product as a white solid: mp 124–126 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, J = 7.24 Hz, 3H), 1.63–1.76 (m, 6H), 1.93–1.94 (m, 2H), 2.83 (m, 1H), 3.88 (s, 4H), 4.18 (q, J = 7.04 Hz, 2H), 7.37 (s, 1H), 7.43 (dd, J = 8.56, 1.52 Hz, 1H), 7.60 (d, J = 8.56 Hz, 1H), 8.10 (m, 1H). Anal. Calcd for $C_{19}H_{20}N_2O_2$: C, 73.52; H, 7.14; N, 9.02. Found: C, 73.56; H, 6.93; N, 8.95.

5.1.13. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-cyano-1-*N*-propyl-indole (27l)

This compound was prepared in a similar fashion as described above (**27k**) by replacing ethylbromide with *n*-propylbromide (13.1 g, 11 mmol) to afford 4.33 g (75%) of the title compound as an oil: MS (EI) *m/z* 324 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.79 (t, J = 7.24 Hz, 3H), 1.62–1.78 (m, 8H), 1.92–1.96 (m, 2H), 2.88 (m, 1H), 3.87 (s, 4H), 4.11 (t, J = 7.00 Hz, 2H), 7.35 (s, 1H), 7.42 (dd, J = 8.56, 1.52 Hz, 1H), 7.62 (d, J = 8.56 Hz, 1H), 8.10 (m, 1H).

5.1.14. 3-(1,4-Dioxa-spiro[4,5]dec-8-yl)-5-cyano-1-*iso*-propyl-indole (27m)

This compound was prepared in a similar fashion as described above (**27k**) by replacing ethylbromide with isopropylbromide (10.2 g, 83 mmol) in 62% yield (6.44 g) as a white solid: mp 114.5–116 °C; MS (EI) *m/z* 324 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41–1.45 (m, 6H), 1.65–1.94 (m, 8H), 2.86 (m, 1H), 3.88 (s, 4H), 4.75 (m, 1H), 7.43 (m, 1H), 7.46(m, 1H), 7.60–7.65 (m, 1H), 8.09 (s, 1H).

5.1.15. 4-(6-Fluoro-1*H*-3-indolyl)-cyclohexanone (28c)

A solution of 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole (5.4 g) in 150 mL (1:1) tetrahydrofuran/hydrochloric acid (1 N) was allowed to stir at room temperature for 16 h, followed by the addition of 4.49 g sodium bicarbonate. The mixture was extracted with methylene chloride (3× 100 mL), washed with brine (3× 150 mL). The organic layer was dried over anhydrous magnesium sulfate and filtered. The solvent was removed to afford a light brown solid that was boiled in ethyl acetate/hexanes (1:1). The mixture was cooled to room temperature, and solid was collected and dried under vacuum to afford 19.3 g (99%) of the title compound as a white solid: mp 102–105 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79–1.90 (m, 2H), 2.22–2.29 (m, 4H), 2.57–2.66 (m, 2H), 3.25–3.32 (m, 1H), 6.80–6.85 (m, 1H), 7.08–7.13 (m, 1H), 7.58–7.62 (m, 1H), 10.89 (br, 1H). Anal. Calcd for $C_{14}H_{14}NOF$: C, 72.71; H, 6.10; N, 6.06. Found: C, 72.77; H, 5.98; N, 5.96.

5.1.16. 3-(4-Oxo-cyclohexyl)-1*H*-indole-5-carbo-nitrile (28d)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-5-cyano-1*H*-indole (6 g) to afford 4.0 g (81%) of the title compound as a white solid: mp 162.5–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ1.82–1.93 (m, 2H), 2.22–2.30 (m, 4H), 2.58–2.67 (m, 2H), 3.33–3.39 (m, 1H), 7.34 (m, 1H), 7.40 (m, 1H), 7.50 (m, 1H), 8.24 (s, 1H), 11.42 (s, 1H). Anal. Calcd for $C_{15}H_{14}N_2O$: C, 75.61; H, 5.92; N, 11.76. C, 75.82; H, 6.06; N, 11.72.

5.1.17. 4-(5-Methoxy-1*H*-3-indolyl)-cyclohexanone (28e)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-5-methoxy-1*H*-indole (5.9 g) to afford 4.2 g (85%) of the title compound as a white solid: mp 103–106 °C; MS (EI) *m/z* 243 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.92–2.03 (m, 2H), 2.40–2.47 (m, 2H), 2.49–2.63 (m, 4H), 3.27–3.34 (m, 1H), 3.89 (s, 3H), 6.88 (dd, J = 8.80, 2.40 Hz, 1H), 6.97 (d, J = 2.40 Hz, 1H), 7.07 (d, J = 2.40 Hz, 1H), 7.27 (d, J = 8.8 Hz, 1H), 7.93 (s, 1H).

5.1.18. 4-(4-Fluoro-1*H*-3-indolyl)-cyclohexanone (28f)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-4-fluoro-1*H*-indole (4.0 g) to afford 3.7 g (63%) of the title compound as a white

solid: mp 104–106 °C; MS (EI) *m/z* 231 (M^+); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.82–1.95 (m, 2H), 2.43–2.63 (m, 6H), 3.46–3.54 (m, 1H), 6.75–6.80 (m, 1H), 6.94 (m, 1H), 7.07–7.15 (m, 2H), 8.14 (br, 1H).

5.1.19. 4-(5-Chloro-1*H*-3-indolyl)-cyclohexanone (28g)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-5-chloro-1*H*-indole (2.1 g) to afford 1.1 g (60%) of the title compound as a clear oil. MS (FAB) *m/z* 248 ([M+H]$^+$); ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.90–2.00 (m, 2H), 2.39–2.45 (m, 2H), 2.50–2.62 (m, 4H), 3.26–3.30 (m, 1H), 7.02 (d, J = 2.44 Hz, 1H), 7.16 (dd, J = 8.80, 1.96 Hz, 1H), 7.29 (d, J = 8.56 Hz, 1H), 7.61 (d, J = 2.0 Hz, 1H), 8.04 (br, 1H).

5.1.20. 4-(2-Methyl-1*H*-3-indolyl)-cyclohexanone (28h)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-2-methyl-1*H*-indole (2.2 g) to afford 1.6 g (88%) of the title compound as a yellow thick oil: MS (EI) *m/z* 227 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.95–1.99 (m, 2H), 2.21–2.30 (m, 4H), 2.37 (s, 3H), 2.56–2.64 (m, 2H), 3.27–3.32 (m, 1H), 6.84–6.88 (m, 1H), 6.91–6.95 (m, 1H), 7.19–7.20 (m, 1H), 7.50–7.52 (m, 1H), 10.68 (s, 1H).

5.1.21. 4-(5-Fluoro-1-methyl-1*H*-indol-3-yl)cyclo-hexanone (28i)

To a suspension of sodium hydride (60%, 0.18 g, 4.5 mmol) in anhydrous *N,N*-dimethylformamide (10 mL) at room temperature was added 4-(5-fluoro-1*H*-indol-3-yl) cyclohexasnone (0.7 g, 3.0 mmol), and the mixture was stirred for 0.5 h. Then to the above solution was added iodomethane (0.21 mL, 3.3 mmol) at room temperature, and the resulting mixture was stirred for another 0.5 h and quenched with water. The mixture was extracted with methylene chloride (3× 50 mL), and the organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (30% ethyl acetate/hexanes) afforded 0.35 g (46%) of the title product as a yellow solid: mp 102.5–104.5 °C; MS (EI) *m/z* 245 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.89 (m, 2H), 2.37–2.43 (m, 2H), 2.50–2.62 (m, 4H), 3.25–3.31 (m, 1H), 3.76 (s, 3H), 6.89 (s, 1H), 6.96–7.02 (m, 1H), 7.20–7.23 (m, 1H), 7.27–7.31 (m, 1H).

5.1.22. 4-(5-Cyano-1-methyl-3-indolyl)-cyclo-hexanone (28j)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-5-cyano-1-methyl-indole (5.5 g) to afford 2.1 g of the title compound as a white solid: mp 150–152 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.32 (t, J = 7.24 Hz, 3H), 1.81–1.88 (m, 2H), 2.22–2.30 (m, 4H), 2.58–2.66 (m, 2H), 3.32–3.39 (m, 1H), 4.19 (q, J = 7.24 Hz, 2H), 7.42 (m, 1H), 7.45 (dd, J = 8.60, 1.52 Hz, 1H), 7.62 (d, J = 8.60 Hz, 1H), 8.23 (m, 1H). Anal. Calcd for $C_{15}H_{15}N_2O$: C, 76.16; H, 6.39; N, 11.10. Found: C, 75.84; H, 6.34; N, 10.9.

5.1.23. 4-(5-Cyano-1-ethyl-3-indolyl)-cyclo-hexanone (28k)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole with 3-(1,4-dioxa-spiro[4,5]-dec-8-yl)-5-cyano-1-ethyl-indole (6.77 g, 22 mmol) to afford 4.33 g (75%) of the title compound as a white solid: mp 124 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86 (m, 2H), 2.21–2.30 (m, 4H), 3.32–3.35 (m, 1H), 3.77 (s, 3H), 7.34 (s, 1H), 7.47 (dd, J = 8.56, 1.52 Hz, 1H), 7.57 (d, J = 8.56 Hz, 1H), 8.26 (m, 1H). Anal. Calcd for $C_{17}H_{18}N_2O$: C, 76.66; H, 6.81; N, 10.52. Found: C, 76.30; H, 6.82; N, 10.25.

5.1.24. 4-(5-Cyano-1-*n*-propyl-3-indolyl)-cyclo-hexanone (28l)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole with 3-(1,4-dioxa-spiro[4,5]-dec-8-yl)-5-cyano-1-*n*-propyl-indole (2.6 g, 8.2 mmol) to afford 1.7 g (73%) of the title compound as a white solid: mp 103–104 °C; MS (EI) *m/z* 280 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.80 (t, J = 7.48 Hz, 3H), 1.71–1.76 (m, 2H), 1.82–1.92 (m, 2H), 2.22–2.29 (m, 4H), 2.58–2.66 (m, 2H), 3.31 (m, 1H), 4.12 (t, J = 7.00 Hz, 2H), 7.40 (s, 1H), 7.44 (dd, J = 8.56, 1.52 Hz, 1H), 7.64 (d, J = 8.56 Hz, 1H), 8.25 (m, 1H). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.99. Found: C, 76.80; H, 7.10; N, 9.82.

5.1.25. 4-(5-Cyano-1-isopropyl-3-indolyl)-cyclo-hexanone (28m)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-indole with 3-(1,4-dioxa-spiro[4,5]-dec-8-yl)-5-cyano-1-isopropyl-indole (5.86 g, 16 mmol) to afford 3.5 g (63%) of the title compound as a white solid: mp 106–107 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.41 (d, J = 6.6 Hz, 6H), 1.45–1.94 (m, 2H), 2.22–2.29 (m, 4H), 2.58–2.67 (m, 2H), 3.34–3.39 (m, 1H), 4.78 (m, 1H), 7.44 (dd, J = 8.56, 1.32 Hz, 1H), 7.52 (s, 1H), 7.65 (d, J = 8.56 Hz, 1H), 8.25 (m, 1H). Anal. Calcd for $C_{18}H_{20}N_2O$: C, 77.11; H, 7.19; N, 9.0. Found: C, 76.85; H, 7.16; N, 9.

5.1.26. 5-Fluoro-3-[*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*cis*-2)

A solution of 4-(5-fluoro-1*H*-indol-3-yl)-cyclohexanone (0.56 g, 2.5 mmol), 1-(indol-4-yl)piperazine (0.5 g, 2.5 mmol), sodium triacetoxyborohydride (0.78 g, 3.5 mmol), and acetic acid (0.14 mL, 2.5 mmol) in 1,2-dichloroethane (11 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL), and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (10% methanol/ethyl acetate) afforded 0.54 g (52%) of the title product as a white solid: mp 85–87 °C. The HCl salt was prepared in ethyl acetate: mp 215–217 °C; ^{1}H NMR (400 MHz, DMSO-d_6)δ 1.81–1.92 (m, 4H), 2.01–2.04 (m, 2H), 2.16–2.19 (m, 2H), 3.18–3.39 (m, 6H), 3.60–3.69 (m, 4H), 6.43–6.44 (m, 1H), 6.48 (d, J = 7.3 Hz, 1H), 6.87–6.92 (m, 1H), 6.98 (t, J = 7.9 Hz, 1H), 7.08 (d, J = 7.9 Hz, 1H), 7.26–7.35 (m, 3H), 7.43–7.44 (m, 1H), 10.41 (br s, 1H), 11.05 (s, 1H), 11.14 (s, 1H). Anal. Calcd for $C_{26}H_{29}FN_4 \cdot HCl \cdot 0.36C_4H_8O_2$: C, 67.37; H, 6.88; N, 11.45. Found: C, 67.18; H, 6.72; N, 11.18.

5.1.27. 5-Fluoro-3-[*trans*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*trans*-2)

The *trans* compound was isolated at the same time as the *cis*-**2** isomer in 30% yield (0.31 g) as a white solid: mp 112–114 °C. The HCl salt was prepared in ethanol: mp 280 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54–1.62 (m, 2H), 1.71–1.80 (m, 2H), 2.12–2.15 (m, 2H), 2.29–2.32 (m, 2H), 2.72–2.78 (m, 1H), 3.23–3.43 (m, 5H), 3.56–4.03 (m, 4H), 6.47–6.48 (m, 1H), 6.52 (d, J = 7.5 Hz, 1H), 6.86–6.92 (m, 1H), 7.00 (t, J = 7.9 Hz, 1H), 7.10 (d, J = 7.9 Hz, 1H), 7.18–7.19 (m, 1H), 7.28–7.38 (m, 3H), 10.78 (br s, 1H), 10.94 (s, 1H), 11.17 (s, 1H). Anal. Calcd for $C_{26}H_{29}FN_4 \cdot HCl$: Calcd C, 66.81; H, 6.81; N, 11.99. Found: C, 66.44; H, 6.66; N, 11.74.

5.1.28. 3-[*cis*-4-[4-(1*H*-Indol-4-yl)-1-piperazinyl]-cyclo-hexyl]-1*H*-indole (*cis*-4)

A solution of 4-(1*H*-indol-3-yl)-cyclohexanone[10] (0.53 g, 2.5 mmol), 1-(indol-4-yl)piperazine (0.5 g, 2.5 mmol), sodium

triacetoxyborohydride (0.78 g, 3.5 mmol), and acetic acid (0.14 mL, 2.5 mmol) in 1,2-dichloroethane (11 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL), and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (10% methanol/ethyl acetate) afforded 0.52 g (53%) of the title product as a white solid: mp 85–87 °C. The HCl salt was prepared in ethyl acetate: mp 198–200 °C (off-white solid); MS (FAB) *m/z* 399 ($[M+H]^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82–1.93 (m, 4H), 1.98–2.10 (m, 2H), 2.17–2.23 (m, 2H), 3.20–3.40 (m, 6H), 3.60–3.70 (m, 4H), 6.42–6.48 (m, 1H), 6.50 (d, J = 7.47 Hz, 1H), 6.94–7.10 (m, 4H), 7.26–7.35 (m, 3H), 7.53 (d, J = 7.91 Hz, 1H), 10.47 (br, 1H), 10.92 (s, 1H), 11.16 (s, 1H); Anal. Calcd. for $C_{26}H_{30}N_4$·1HCl·1.25H_2O: C, 68.25; H, 7.38; N, 12.25. Found: C, 68.12; H, 7.16; N, 11.93.

5.1.29. 3-[*trans*-4-[4-(1*H*-Indol-4-yl)-1-pipera-zinyl]-cyclohexyl]-1*H*-indole (*tans*-4)

The *trans* compound was isolated at the same time as the *cis*-**4** isomer in 21% yield (0.21 g) as a white solid: mp 105–107 °C. The HCl salt (off-white solid) was prepared in ethyl acetate: mp 305 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6)δ 1.54–1.64 (m, 2H), 1.73–1.82 (m, 2H), 2.15–2.18 (m, 2H), 2.30–2.33 (m, 2H), 2.76–2.83 (m, 1H), 3.25–3.42 (m, 5H), 3.59–3.79 (m, 4H), 6.48–6.50 (m, 1H), 6.54 (d, J = 7.47 Hz, 1H), 6.94–7.12 (m, 5H), 7.29–7.34 (m, 2H), 7.58 (d, J = 7.69 Hz, 1H), 10.81–10.82 (m, 2H), 11.17 (s, 1H); MS (FAB) *m/z* 399 ($[M+H]^+$); Anal. Calcd for $C_{26}H_{30}N_4$·HCl·1.25H_2O: C, 68.25; H, 7.38; N, 12.25. Found: C, 68.12; H, 7.16; N, 11.93.

5.1.30. 5-Fluoro-3-{*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl}-1-methyl-1*H*-indole (*cis*-5)

This compound was prepared in a similar fashion as described above (*cis*-**4**) by replacing 4-(1*H*-3-indolyl)-cyclohexone with 4-(5-fluoro-1-methyl-3-indolyl)-cyclohexone (0.34 g, 1.4 mmol) to afford 0.24 g (34%) of the title product as a clear oil. HCl salt was prepared in ethanol: mp 247–249 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.84–1.89 (m, 2H), 2.03–2.05 (m, 2H), 2.13–2.16 (m, 2H), 3.24–3.38 (m, 6H), 3.61–3.71 (m, 4H), 3.76 (s, 3H), 6.48 (m, 1H), 6.53 (d, J = 7.44 Hz, 1H), 6.95–7.01 (m, 2H), 7.10 (d, J = 8.12 Hz, 1H), 7.28–7.34 (m, 2H), 7.39 (dd, J = 8.80, 4.40 Hz, 1H), 7.48 (m, 1H), 10.59 (br, 1H), 11.17 (s, 1H). Anal. Calcd for $C_{27}H_{31}FN_4$·2HCl·0.25H_2O: C, 63.84; H, 6.65; N, 11.03. Found: C, 63.88; H, 6.51; N, 10.77.

5.1.31. 5-Fluoro-3-{*trans*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl}-1-methyl-1*H*-indole (*trans*-5)

The *trans* compound was isolated at the same time as the *cis*-**5** isomer as a white solid. The HCl salt was prepared in ethanol: mp 275–277 °C; MS (EI) *m/z* 430 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6): ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.52–1.61 (m, 2H), 1.72–1.80 (m, 2H), 2.11–2.14 (m, 2H), 2.30–2.32 (m, 2H), 2.72–2.78 (m, 1H), 3.28–3.45 (m, 5H), 3.59–3.62 (m, 2H), 3.72 (s, 3H), 3.74 (m, 1H), 6.51 (M, 1H), 6.56 (d, J = 7.48 Hz, 1H), 6.94–7.03 (m, 2H), 7.12 (d, J = 8.12 Hz, 1H), 7.18 (s, 1H), 7.30 (t, J = 2.64 Hz, 1H), 7.36–7.40 (m, 2H), 10.84 (br, 1H), 11.18 (s, 1H). Anal. Calcd for $C_{27}H_{31}FN_4$·2HCl: C, 64.41; H, 6.61; N, 11.13. Found: C, 64.10, H, 6.57, N, 10.77.

5.1.32. 6-Fluoro-3-[*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl] cyclohexyl]-1*H*-indole (*cis*-6)

This compound was prepared in a similar fashion as described above (*cis*-**4**) by replacing 4-(1*H*-indol-3-yl)-cyclohexanone with 4-(6-fluoro-1*H*-indol-3-yl)-cyclohexanone (1.15 g, 5.0 mmol) to afford 1.06 g (51%) of the title product as a white foam. The HCl salt was prepared in ethanol: mp 250–252 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.81–1.91 (m, 4H), 1.97–2.02 (m, 2H), 2.17–2.19 (m, 2H), 3.27–3.39 (m, 6H), 3.61–3.69 (m, 4H), 6.49 (br, 1H), 6.54 (m, 1H), 6.79–6.80 (m, 1H), 6.99 (t, J = 7.68 Hz, 1H), 7.08–7.09 (m, 1H), 7.11 (m, 1H), 7.28 (t, J = 2.84 Hz, 1H), 7.35 (d, J = 1.52 Hz, 1H), 7.52 (dd, J = 8.76, 5.72 Hz, 1H), 10.63 (br, 1H), 11.02 (s, 1H), 11.78 (s, 1H). Anal. Calcd for $C_{26}H_{29}FN_4$·2HCl·0.75H_2O: C, 62.09; H, 6.51; N, 11.14. Found: C, 62.20; H, 6.50; N, 11.16.

5.1.33. 6-Fluoro-3-[*trans*-4-[4-(1*H*-indol-4-yl)-1-pipera-zinyl] cyclohexyl]-1*H*-indole (*trans*-6)

The *trans* compound was isolated at the same time as the *cis*-**6** isomer in 27% yield (0.55 g) as a white foam. The HCl salt was prepared in ethanol: mp 319–320 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52–1.62 (m, 2H), 1.72–1.81 (m, 2H), 2.13–2.16 (m, 2H), 2.30–2.32 (m, 2H), 2.74–2.80 (m, 1H), 3.28–3.42 (m, 5H), 3.59–3.62 (m, 2H), 3.71–3.74 (m, 2H), 6.50 (br, 1H), 6.54 (m, 1H), 6.79–6.84 (m, 1H), 7.00 (t, J = 7.68 Hz, 1H), 7.08–7.12 (m, 3H), 7.30 (t, J = 2.88 Hz, 1H), 7.526 (dd, J = 8.76, 5.48 Hz, 1H), 10.90 (br, 1H), 10.91 (s, 1H), 11.18 (s, 1H). Anal. Calcd for $C_{26}H_{29}FN_4$·1.5HCl·0.25H_2O: C, 65.64; H, 6.57; N, 11.78. Found: C, 65.62; H, 6.59; N, 11.64.

5.1.34. 4-Fluoro-3-[*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*cis*-7)

A solution of 4-(4-fluoro-1*H*-indol-3-yl)-cyclohexanone (0.88 g, 3.8 mmol), 1-(indol-4-yl)piperazine (0.7 g, 3.5 mmol), sodium triacetoxy-borohydride (1.1 g, 5.2 mmol), and acetic acid (0.4 mL, 7 mmol) in 1,2-dichloroethane (20 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL), and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (5–7% methanol/ethyl acetate) afforded 1.14 g (79%) of the title product as a white foam. The HCl salt was prepared in ethanol: mp 283–285 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83–2.04 (m, 6H), 2.14–2.17 (m, 2H), 3.15–3.18 (m, 2H), 3.21–3.37 (m, 4H), 3.62–3.74 (m, 4H), 6.44 (s, 1H), 6.48 (d, J = 7.24 Hz, 1H), 6.67–6.72 (m, 1H), 7.00–7.09 (m, 2H), 7.08 (d, J = 8.36 Hz, 1H), 7.17 (d, J = 7.88 Hz, 1H), 7.26–7.28 (m, 1H), 7.36–7.34 (m, 1H), 10.14 (br, 1H), 1113 (br, 1H), 11.24 (br, 1H). Anal. Calcd for $C_{26}H_{29}FN_4$·HCl·0.25H_2O: C, 68.26; H, 6.72; N, 12.25. Found: C, 68.16; H, 6.74; N, 12.04.

5.1.35. 4-Fluoro-3-[*trans*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*trans*-7)

The *trans* compound was isolated at the same time as the *cis*-**7** isomer in 17% yield (0.24 g) as a white solid: mp 206–208 °C. The HCl salt was prepared in ethanol: mp 297–299 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.49–1.58 (m, 2H), 1.70–1.79 (m, 2H), 2.17 (m, 2H), 2.30 (m, 2H), 2.84–2.90 (m, 1H), 3.18–3.24 (m, 2H), 3.34–3.42 (m, 3H), 3.52–3.89 (m, 4H), 6.46 (s, 1H), 6.52 (t, J = 7.48 Hz, 1H), 6.68–6.73 (m, 1H), 7.00–7.04 (m, 2H), 7.09 (m, 1H), 7.14–7.17 (m, 2H), 7.28–7.30 (m, 1H), 10.50 (br, 1H), 11.1 (br, 1H). Anal. Calcd for $C_{26}H_{29}FN_4$·HCl·H_2O: C, 66.30; H, 6.85; N, 11.90. Found: C, 66.17; H, 6.51; N, 11.70.

5.1.36. 3-{4-[(1,4-*cis*)-4-(1*H*-Indol-4-yl)-pipera-zinyl-1-yl]-cyclohexyl}-1*H*-indole-5-carbonitrile (*cis*-8)

This compound was prepared in a similar fashion as described above (*cis*-**4**) by replacing 4-(4-fluoro-1*H*-indol-3-yl)-cyclohexanone with 4-(5-cyano-1*H*-indol-3-yl)-cyclohexanone[10] (0.71 g, 3.0 mmol) to afford 0.38 g (30%) of the title product. The HCl salt (off-white solid) was prepared in ethyl acetate: mp 216–218 °C; MS (EI) *m/z* 423 (M^+); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83–1.93 (m, 4H), 2.03–2.04 (m, 2H), 2.18–2.21 (m, 2H), 3.19–3.40 (m,

7H), 3.52–3.70 (m, 5H), 6.40–6.46 (m, 1H), 6.49 (d, J = 7.47 Hz, 1H), 6.98 (t, J = 7.91 Hz, 1H), 7.08 (d, J = 7.91 Hz, 1H), 7.28 (t, J = 2.70 Hz, 1H), 7.40–7.42 (m, 1H), 7.50–7.52 (m, 1H), 7.58–7.60 (m, 1H), 8.11–8.12 (m, 1H), 10.42 (br, 1H), 11.15 (s, 1H), 11.58 (s, 1H). Anal. Calcd for $C_{27}H_{29}N_5 \cdot HCl \cdot 1.5H_2O$: C, 66.25; H, 6.94; N, 13.64. Found: C, 66.05; H, 6.54; N, 13.28.

5.1.37. 3-{4-[(1,4-*trans*)-4-(1*H*-indol-4-yl)-pipera-zinyl-1-yl]cyclohexyl}-1*H*-indole-5-carbonitrile (*trans*-8)

The *trans* compound was isolated at the same time as the *cis*-8 isomer in 25% yield (0.32 g). The HCl salt (white solid) was prepared in ethyl acetate: mp 310 °C (dec); MS FAB *m/z* 424 ($[M+H]^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58–1.81 (m, 4H), 2.14–2.18 (m, 2H), 2.29–2.32 (m, 2H), 2.82–2.88 (m, 1H), 3.18–3.24 (m, 2H), 3.34–3.46 (m, 3H), 3.60–3.63(m, 2H), 3.72–3.76 (m, 2H), 6.45–6.48 (m, 1H), 6.51 (d, J = 7.47 Hz, 1H), 7.00(t, J = 7.47 Hz, 1H), 7.08–7.11 (m, 1H), 7.29–7.33 (m, 2H), 7.38–7.41 (m, 1H), 7.49–7.51 (m, 1H), 8.20–8.22 (m, 1H), 10.47 (br, 1H), 11.15 (s, 1H), 11.45 (s, 1H). Anal. Calcd for $C_{27}H_{29}N_5 \cdot HCl \cdot 0.75H_2O$: C, 68.48; H, 6.71; N, 14.79. Found: C, 68.43; H, 6.54; N, 14.63.

5.1.38. 3-{(1,4-*cis*)-4-[4-(1*H*-Indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1-methyl-1*H*-indole-5-carbonitrile (*cis*-9)

A solution of 4-(5-cyano-1-methyl-3-indolyl)cyclohexa-none (0.75 g, 3 mmol), 1-(indol-4-yl)piperazine (0.6 g, 3 mmol), sodium triacetoxyborohydride (0.95 g, 4.5 mmol), and acetic acid (0.34 mL, 6 mmol) in 1,2-dichloroethane (20 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL), and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (10% methanol/ethyl acetate) afforded 0.73 g (56%) of the title product as a white solid: mp 274–275 °C. The HCl salt was prepared in ethyl acetate: mp 285.5–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.83–1.93 (m, 4H), 2.00–2.07 (m, 2H), 2.15–2.17 (m, 2H), 3.20–3.42 (m, 6H), 3.61–3.71 (m, 4H), 3.82 (s, 3H), 6.45 (m, 1H), 6.50 (d, J = 7.44 Hz, 1H), 6.98 (t, J = 7.92 Hz, 1H), 7.09 (d, J = 8.12 Hz, 1H), 7.28 (t, J = 2.64 Hz, 1H), 7.48 (dd, J = 8.56, 1.52 Hz, 1H), 7.58–7.62 (m, 2H), 8.14 (m, 1H), 10.40 (br, 1H), 11.14 (s, 1H). Anal. Calcd for $C_{28}H_{31}N_5 \cdot 1.0HCl \cdot 1.0H_2O$: C, 68.35; H, 6.96; N, 14.23. Found: C, 68.02; H, 6.40; N, 14.18.

5.1.39. 3-{(1,4-*trans*)-4-[4-(1*H*-Indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1-methyl-1*H*-indole-5-carbonitrile (*tran*-9)

The *trans* compound was isolated at the same time as the *cis*-**9** isomer in 33% yield (0.42 g) as a white solid: mp 239–240 °C. The HCl salt was prepared in ethyl acetate: mp 286–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ 1.58–1.64 (m, 2H), 1.73–1.82 (m, 2H), 2.12–2.15 (m, 2H), 2.31–2.34 (m, 2H), 2.82–2.88 (m, 1H), 3.31–3.46 (m, 5H), 3.60–3.63 (m, 2H), 3.72–3.75 (m, 2H), 3.79 (s, 3H), 6.52 (m, 1H), 6.58 (d, J = 7.48 Hz, 1H), 7.01 (t, J = 7.72 Hz, 1H), 7.12 (d, J = 8.12 Hz, 1H), 7.30 (t, J = 2.84 Hz, 1H), 7.33 (s, 1H), 7.47 (dd, J = 8.60, 1.56 Hz, 1H), 7.57 (d, J = 8.60 Hz, 1H), 8.23 (m, 1H), 10.96 (br, 1H), 11.20 (s, 1H). Anal. Calcd for $C_{28}H_{31}N_5 \cdot 2HCl \cdot 0.5H_2O$: C, 64.73; H, 6.60; N, 13.65. Found: C, 64.55; H, 6.42; N, 13.41.

5.1.40. 1-Ethyl-3-{(1,4-*cis*)-4-[4-(1*H*-indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1*H*-indole-5-carbonitrile (*cis*-10)

A solution of 4-(5-cyano-1-ethyl-indol-3-yl)-cyclohexanone (1.5 g, 5.6 mmol), 1-(indol-4-yl)piperazine (1.19 g, 5.9 mmol), sodium triacetoxyborohydride (1.73 g, 8.2 mmol), and acetic acid (0.9 mL, 15 mmol) in 1,2-dichloroethane (30 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 80 mL), and washed with brine (3× 80 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (2.5% methanol/ethyl acetate) afforded 0.98 g (39%) of the title product as a white solid: mp decomposed at 226 °C. The HCl salt was prepared in ethyl acetate: mp 245 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.38 (t, J = 7.2 Hz, 3H), 1.82–1.99 (m, 4H), 2.01–2.10 (m, 2H), 2.13–2.18 (m, 2H), 3.26–3.41 (m, 6H), 3.62–3.75 (m, 4H), 4.25 (t, J = 7.24 Hz, 2H), 6.48 (m, 1H), 6.54 (d, J = 7.24 Hz, 1H), 6.99 (d, J = 7.92 Hz, 1H), 7.10 (t, J = 8.12 Hz, 1H), 7.30 (t, J = 2.44 Hz, 1H), 7.48 (dd, J = 8.56, 1.52 Hz, 1H), 7.65 (d, J = 8.56 Hz, 1H), 7.70 (s, 1H), 8.14 (m, 1H), 10.06 (br, 1H), 11.18 (br, 1H). Anal. Calcd for $C_{29}H_{33}N_5 \cdot 2HCl \cdot 0.25H_2O$: C, 65.84; H, 6.76; N, 13.24. Found: C, 65.97; H, 6.74; N, 13.40.

5.1.41. 1-Ethyl-3-{(1,4-*trans*)-4-[4-(1*H*-indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1*H*-indole-5-carbonitrile (*trans*-10)

The *trans* compound was isolated at the same time as the *cis*-**10** isomer in 19% yield (0.48 g) as a light brown solid: mp decomposed at 110 °C. The HCl salt was prepared in ethyl acetate: mp 250 °C (decomposed); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.34 (t, J = 7.24 Hz, 3H), 1.58–1.64 (m, 2H), 1.67–1.81 (m, 2H), 2.16 (m, 2H), 2.34 (m, 2H), 2.82–2.89 (m, 1H), 3.41–3.47 (m, 5H), 3.62–3.65 (m, 2H), 3.74–3.76 (m, 2H), 4.22 (q, J = 7.24 Hz, 2H), 6.56 (m, 1H), 6.62 (d, J = 7.68 Hz, 1H), 7.03 (d, J = 7.68 Hz, 1H), 7.15 (d, J = 8.12 Hz, 1H), 7.33 (t, J = 2.64 Hz, 1H), 7.41 (s, 1H), 7.47 (dd, J = 8.56, 1.52 Hz, 1H), 7.64 (d, J = 8.80 Hz, 1H), 8.24 (m, 1H), 11.07 (br, 1H), 11.20 (br, 1H). Anal. Calcd for $C_{29}H_{33}N_5 \cdot 2HCl$: C, 66.40; H, 6.73; N, 13.35. Found: C, 66.32; H, 6.67; N, 13.10.

5.1.42. 3-{(1,4-*cis*)-4-[4-(1*H*-Indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1-propyl-1*H*-indole-5-carbonitrile (*cis*-11)

A solution of 4-(5-cyano-1-*n*-propyl-indol-3-yl)-cyclohexa-none (1.68 g, 6 mmol), 1-(indol-4-yl)piperazine (1.27 g, 6.3 mmol), sodium triacetoxyborohydride (1.84 g, 8.9 mmol), and acetic acid (0.94 mL, 16 mmol) in 1,2-dichloroethane (80 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (20 mL), extracted with methylene chloride (3× 100 mL), and washed with brine (3× 100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (10% methanol/ethyl acetate) afforded 0.42 g (15%) of the title product as a white powder. The HCl salt was prepared in ethanol: mp 200–206 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.84 (t, J = 7.44 Hz, 3H), 1.76–1.96 (m, 6H), 2.04–2.08 (m, 2H), 2.15–2.18 (m, 2H), 3.33–3.43 (m, 6H), 3.64–3.71 (m, 4H), 4.18 (t, J = 7.04 Hz, 2H), 6.50 (m, 1H), 6.56 (d, J = 7.48 Hz, 1H), 7.01 (d, J = 7.72 Hz, 1H), 7.12 (t, J = 8.12 Hz, 1H), 7.30 (t, J = 2.64 Hz, 1H), 7.47 (dd, J = 8.56, 0.88 Hz, 1H), 7.66 (d, J = 8.56 Hz, 1H), 7.70 (s, 1H), 8.14 (m, 1H), 10.76 (br, 1H), 11.19 (br, 1H). Anal. Calcd for $C_{30}H_{35}N_5 \cdot 2HCl \cdot 0.75H_2O$: C, 65.27; H, 7.03; N, 12.69. Found: C, 65.18; H, 6.97; N, 12.68.

5.1.43. 3-{(1,4-*trans*)-4-[4-(1*H*-Indol-4-yl)-pipera-zin-1-yl]-cyclohexyl}-1-propyl-1*H*-indole-5-carbonitrile (*trans*-11)

The *trans* compound was isolated at the same time as the *cis*-**11** isomer in 14% yield (0.39 g) as a white foam. The HCl salt was prepared in ethanol: mp decomposed >245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 0.83 (t, J = 7.24 Hz, 3H), 1.57–1.66 (m, 2H), 1.60–1.68 (m, 4H), 2.15–2.17 (m, 2H), 2.31–2.34 (m, 2H), 2.84–2.89 (m, 1H), 3.25–3.29 (m, 2H), 3.30–3.39 (m, 3H), 3.62–3.64 (m, 2H), 3.74–3.77 (m, 2H), 4.15 (t, J = 7.04 Hz, 2H), 6.51 (m, 1H), 6.56 (d, J = 7.28 Hz, 1H), 7.02 (d, J = 7.68 Hz, 1H), 7.12 (t, J = 8.16 Hz, 1H), 7.31 (t, J = 2.84 Hz, 1H), 7.40 (s, 1H), 7.45–7.47 (m, 1H), 7.65 (d, J = 8.36 Hz, 1H), 8.24 (m, 1H), 10.70 (br, 1H), 11.19 (s, 1H). Anal. Calcd for $C_{30}H_{35}N_5 \cdot 2HCl$: C, 66.90; H, 6.93; N, 13.00. Found: C, 66.68; H, 6.97; N, 12.96.

5.1.44. 3-{(1,4-*cis*)-4-[4-(1*H*-Indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1-isopropyl-1*H*-indole-5-carbonitrile (*cis*-12)

A solution of 4-(5-cyano-1-*n*-propyl-indol-3-yl)-cyclohexanone (1.68 g, 6 mmol), 1-(indol-4-yl)piperazine (1.27 g, 6.3 mmol), sodium triacetoxyborohydride (1.84 g, 8.9 mmol), and acetic acid (0.94 mL, 16 mmol) in 1,2-dichloroethane (80 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (20 mL), extracted with methylene chloride (3× 100 mL), and washed with brine (3× 100 mL). The organic layer was dried over anhydrous sodium sulfate, and filtered. Chromatography (10% methanol/ethyl acetate) afforded 0.49 g (18%) of the title product as a white powder. The HCl salt was prepared in ethanol: mp 285–286 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.49 (d, J = 6.59 Hz, 6H), 1.81–1.87 (m, 2H), 1.92–1.98 (m, 4H), 2.03–2.08 (m, 2H), 3.27–3.40 (m, 6H), 3.67–3.69 (m, 4H), 4.81 (m, 1H), 6.44 (m, 1H), 6.49 (d, J = 7.47 Hz, 1H), 6.99 (t, J = 7.69 Hz, 1H), 7.09 (d, J = 8.13 Hz, 1H), 7.28 (m, 1H), 7.45 (dd, J = 8.56, 1.54 Hz, 1H), 7.67 (d, J = 8.55 Hz, 1H), 7.76 (m, 1H), 8.13 (m, 1H), 10.72 (br, 1H), 11.14 (s, 1H). Anal. Calcd for $C_{30}H_{35}N_5$·HCl·0.5H_2O: C, 70.50; H, 7.30; N, 13.70. Found: C, 70.86; H, 7.12; N, 13.56.

5.1.45. 3-{(1,4-*trans*)-4-[4-(1*H*-Indol-4-yl)-piperazin-1-yl]-cyclohexyl}-1-isopropyl-1*H*-indole-5-carbo-nitrile (*trans*-12)

The *trans* compound was isolated at the same time as the *cis*-**12** isomer in 12% yield (0.34 g) as a white foam. The HCl salt was prepared in ethanol: mp decomposed >245 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.42 (s, 3H), 1.44 (s, 3H), 1.62–1.68 (m, 2H), 1.72–1.74 (m, 2H), 2.13–2.16 (m, 2H), 2.30–2.33 (m, 2H), 2.82–2.85 (m, 1H), 3.20–3.26 (m, 2H), 3.35–3.42 (m, 3H), 3.59–3.62 (m, 2H), 3.71–3.75 (m, 2H), 4.77–4.80 (m, 1H), 6.47 (m, 1H), 6.51 (d, J = 7.24 Hz, 1H), 7.00 (d, J = 8.16, Hz, 1H), 7.09 (t, J = 7.72 Hz, 1H), 7.29 (t, J = 2.84 Hz, 1H), 7.43 (d, J = 1.52 Hz, 1H), 7.45 (d, J = 1.54 Hz, 1H), 7.49 (s, 1H), 7.66 (d, J = 8.56 Hz, 1H), 8.22 (m, 1H), 10.67 (br, 1H), 11.15 (s, 1H). Anal. Cacld for $C_{30}H_{35}N_5$·2HCl: C, 66.90; H, 6.93; N, 13.00. Found: C, 66.68; H, 6.97; N, 12.96.

5.1.46. 5-Methoxy-3-[*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*cis*-13)

A solution of 4-(5-methoxy-1*H*-indol-3-yl)-cyclohexanone (1.2 g, 5 mmol), 1-(indol-4-yl)piperazine (1 g, 5 mmol), sodium triacetoxy-borohydride (1.47 g, 6.2 mmol), and acetic acid (0.28 mL, 4 mmol) in 1,2-dichloroethane (20 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL) and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (2.5% methanol/ethyl acetate) afforded 1.18 g (55%) of the title product as a white solid: mp 105–108 °C. The HCl salt was prepared in ethyl acetate: mp 280–281 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.84–1.86 (m, 4H), 2.02 (m, 2H), 2.16–2.19 (m, 2H), 3.14–3.20 (m, 3H), 3.25–3.40 (m, 3H), 3.60–3.71 (m, 4H), 3.75 (s, 3H), 6.44 (s, 1H), 6.48 (d, J = 7.48 Hz, 1H), 6.70–6.73 (m, 1H), 6.96–7.00 (m, 2H), 7.08 (d, J = 7.92 Hz, 1H), 7.23 (d, J = 8.8 Hz, 1H), 7.26–7.30 (m, 2H), 10.15 (br, 1H), 10.75 (br, 1H), 11.13 (br, 1H). Anal. Calcd for $C_{27}H_{32}N_4O$·HCl·0.25H_2O: C, 69.07; H, 7.19; N, 11.93. Found: C, 69.18; H, 7.19; N, 11.80.

5.1.47. 5-Methoxy-3-[*trans*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*trans*-13)

The *trans* compound was isolated at the same time as the *cis*-**13** isomer in 20% yield (0.43 g) as a white foam. The HCl salt was prepared in ethyl acetate: mp 194–196 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.55–1.61 (m, 2H), 1.72–1.78 (m, 2H), 2.15–2.18 (m, 2H), 2.28–2.31 (m, 2H), 2.73–2.79 (m, 1H), 3.16–3.22 (m, 2H), 3.34–3.45 (m, 3H), 3.58–3.65 (m, 2H), 3.72 (m, 2H), 3.76 (s, 3H), 6.46 (s, 1H), 6.51 (d, J = 7.47 Hz, 1H), 6.71 (dd, J = 8.8, 2.4 Hz, 1H), 6.98–7.11 (m, 4H), 7.22 (d, J = 8.8 Hz, 1H), 7.29–7.30 (m, 1H), 10.37 (br, 1H), 10.64 (s, 1H), 11.15 (s, 1H). Anal. Calcd for $C_{27}H_{32}N_4O$·HCl·1.5H_2O: C, 66.65; H, 7.15; N, 11.52. Found: C, 66.65; H, 7.06; N, 11.44.

5.1.48. 5-Chloro-3-[*cis*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*cis*-14)

A solution of 4-(5-chloro-1*H*-indol-3-yl)-cyclohexanone (0.78 g, 3.1 mmol), 1-(indol-4-yl)piperazine (0.6 g, 3 mmol), sodium triacetoxy-borohydride (0.95 g, 4.5 mmol), and acetic acid (0.34 mL, 6 mmol) in 1,2-dichloroethane (20 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (10 mL), extracted with methylene chloride (3× 60 mL), and washed with brine (3× 60 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (5% methanol/ethyl acetate) afforded 0.84 g (65%) of the title product as a white foam. The HCl salt was prepared in ethanol: mp 279–281 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.85 (m, 4H), 2.03 (m, 2H), 2.60 (m, 2H), 3.16 (m, 2H), 3.22–3.45 (m, 4H), 3.61–3.70 (m, 4H), 6.43–6.49 (m, 2H), 6.98 (t, J = 7.9 Hz, 1H), 7.02–7.09 (m, 2H), 7.27 (t, J = 2.8 Hz, 1H), 7.36 (m, 1H), 7.42 (m, 1H), 7.56 (m, 1H), 10.10 (br, 1H), 11.13 (br, 1H), 11.15 (br, 1H). Anal. Calcd for $C_{26}H_{29}ClN_4$·HCl·0.25H_2O: C, 65.46; H, 6.69; N, 11.45. Found: C, 65.14; H, 6.73; N, 11.33.

5.1.49. 5-Chloro-3-[*trans*-4-[4-(1*H*-indol-4-yl)-1-piperazinyl]-cyclohexyl]-1*H*-indole (*tans*-14)

The *trans* compound was isolated at the same time as the *cis*-**14** isomer in 24% yield (0.32 g) as a white foam. The HCl salt was prepared in ethanol: mp 314–315.5 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.53–1.63 (m, 2H), 1.65–1.80 (m, 2H), 2.12–2.15 (m, 2H), 2.30–2.33 (m, 2H), 2.75–2.79 (m, 1H), 3.18–3.28 (m, 2H), 3.34–3.46 (m, 3H), 3.59–3.62 (m, 2H), 3.72–3.76 (m, 2H), 6.46 (s, 1H), 6.51 (m, 1H), 6.98–7.10 (m, 3H), 7.19–7.20 (m, 1H), 7.27–7.30 (m, 1H), 7.33–7.36 (m, 1H), 7.64 (m, 1H), 10.37 (br, 1H), 11.03 (br, 1H), 11.14 (br, 1H). Anal. Calcd for $C_{26}H_{29}ClN_4$·HCl·0.25H_2O: C, 65.65; H, 6.60; N, 11.62. Found: C, 65.50; H, 6.50; N, 11.30.

5.1.50. 3-[*cis*-4-[4-(1*H*-Indol-4-yl)-1-piperazinyl]-cyclohexyl]-2-methyl-1*H*-indole (*cis*-15)

A solution of 4-(1*H*-indol-3-yl)-cyclohexanone (1.44 g, 6.33 mmol), 1-(indol-4-yl)piperazine (1.27 g, 6.33 mmol), sodium triacetoxyborohydride (1.88 g, 8.86 mmol), and acetic acid (0.76 mg, 12.6 mmol) in 1,2-dichloroethane (100 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (80 mL), extracted with methylene chloride (3× 300 mL), and washed with brine (150 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. The solvent was removed under vacuum to afford an off-white solid. Trituration of the solid with warm methylene chloride (80 mL) followed by filtration afforded 0.88 g of the title product as a white solid. The mother liquor was concentrated and chromatographed (2% methanol/methylene chloride) to afford another 0.18 g (total 40.7%) of the title product as a white solid: mp 279–280 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.65–1.68 (m, 2H), 1.89–1.96 (m, 2H), 2.27–2.36 (m, 4H), 2.40 (s, 3H), 2.91–2.97 (m, 1H), 3.37–3.45 (m, 2H), 3.50–3.52 (m, 1H), 3.60–3.70 (m, 4H), 3.79–3.83 (m, 2H), 6.59 (m, 1H), 6.64–6.67 (m, 1H), 6.85–6.98 (m, 1H), 6.91–6.96 (m, 1H), 7.03 (t, J = 7.68 Hz, 1H), 7.14–7.20 (m, 2H), 7.32 (t, J = 2.88 Hz, 1H), 7.78 (d, J = 7.68 Hz, 1H), 10.48 (br, 1H), 10.67 (br, 1H), 11.24 (br, 1H). The HCl salt was prepared in ethanol: mp 200–203 °C. Anal. Calcd for $C_{27}H_{32}N_4$·2HCl·0.75H_2O: C, 64.99; H, 7.17; N, 11.23. Found: C, 65.05; H, 7.07; N, 11.23.

5.1.51. 3-[*trans*-4-[4-(1*H*-Indol-4-yl)-1-pipera-zinyl]-cyclohexyl]-2-methyl-1*H*-indole (*trans*-15)

The *trans* compound was isolated at the same time as the *cis*-**15** isomer in 25.7% yield (0.67 g) as a white foam; ^{1}H NMR (400 MHz, DMSO-d_6) δ1.73–1.85 (m, 4H), 1.98–2.04 (m, 2H), 2.30 (m, 2H), 2.34 (s, 3H), 2.74–2.75 (m, 1H), 3.46–3.62 (m, 7H), 3.73–3.75 (m, 2H), 6.59 (m, 1H), 6.65–6.67 (m, 1H), 6.85–6.89 (m, 1H), 6.92–6.96 (m, 1H), 7.02 (t, J = 7.68 Hz, 1H), 7.16 (d, J = 8.16 Hz, 1H), 7.21 (d, J = 7.88 Hz, 1H), 7.33 (t, J = 2.84 Hz, 1H), 10.72 (br, 1H), 11.26 (br, 2H). The HCl salt was prepared in ethanol: mp >310 °C. Anal. Calcd for $C_{27}H_{32}N_4$·2HCl: C, 66.80; H, 7.06; N, 11.54. Found: C, 66.84; H, 6.87; N, 11.37.

5.1.52. 4-{*cis*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]-piperazin-1-yl}-1*H*-benzimidazole (*cis*-16)

To a solution of 4-piperazin-1-yl-1*H*-benzoimidazole (0.51 g, 2.5 mmol), 4-(1*H*-3-indolyl)-cyclohexanone (0.53 g, 2.5 mmol), and sodium tracetoxyborohydride (0.79 g, 3.7 mmol) in dichloroethane (30 mL) was added acetic acid (0.29 mL, 5.0 mmol), and stirred overnight at room temperature. The reaction was quenched with 1 N NaOH (50 mL) and extracted in methylene chloride (2× 100 mL) and 50% ethyl acetate/methanol (3× 100 mL). The organic fractions were combined, dried over sodium sulfate, concentrated, filtered and chromatographed twice (5% methanol/ethyl acetate) yielding 0.35 g (34%) of the title product as a white solid. The HCl salt was generated from ethyl acetate yielding a white solid: mp 217–219 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57–1.68 (m, 4H), 1.86–2.03 (m, 4H), 2.28 (m, 1H), 2.62–2.69 (m, 4H), 2.95–2.69 (m, 4H), 2.95–3.05 (m, 2H), 3.43–3.49 (m, 3H), 6.45 (d, J = 6.49 Hz, 1H), 6.88 (t, J = 7.42 Hz, 1H), 6.97–7.04 (m, 3H), 7.06 (m, 1H), 7.27 (d, J = 8.11 Hz, 1H), 7.55 (d, J = 7.77 Hz, 1H), 7.99 (s, 1H), 10.67 (s, 1H), 12.29 (s, 1H). Anal. Calcd for $C_{25}H_{29}N_5$: C, 75.16; H, 7.32; N, 17.53. Found: C, 74.82; H, 7.21; N, 17.05.

5.1.53. 4-{*trans*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]-piperazin-1-yl}-1*H*-benzimidazole (*trans*-16)

The *trans* isomer was isolated at the same time as *cis*-**16** affording 0.2 g (20%) of the title product as a white solid. The HCl salt was generated from Et_2O/EtOH to give white solid: mp dec >215 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.53–1.62 (m, 2H), 1.69–1.76 (m, 2H), 2.13–2.16 (m, 2H), 2.25–2.29 (m, 2H), 2.75–2.81 (m, 1H), 3.20–3.49 (m, 4H), 3.57–3.66 (m, 2H), 3.86–4.01 (m, 2H), 6.88–6.95 (m, 1H), 7.06 (m, 1H), 7.29–7.52 (m, 3H), 7.30 (m, 1H), 7.55 (d, J = 8.0 Hz, 1H), 8.98 (br, 1H), 10.63 (br, 1H), 10.87 (s, 1H). Anal. Calcd for $C_{25}H_{29}N_5$·0.5H_2O: C, 73.50; H, 7.40; N, 17.14. Found: C, 73.79; H, 7.11; N, 17.02.

5.1.54. 4-{*cis*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]-piperazin-1-yl}-2-methyl-1*H*-benzimidazole (*cis*-17)

This compound was prepared as described for *cis*-**16** by replacing 4-piperazin-1-yl-1*H*-benzoimidazole with 4-piperazin-1-yl-2-methyl-1*H*-benzoimidazole (0.34 g, 1.6 mmol) to afford 0.35 g (54%) of the title compound as a white foam: mp dec >190 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.86–1.88 (m, 4H), 1.98–2.03 (m, 2H), 2.23–2.32 (m, 2H), 2.76 (s, 3H), 3.34–3.40 (m, 6H), 3.53–3.61 (m, 2H), 3.68–3.78 (m, 2H), 6.94–6.98 (m, 2H), 7.04–7.12 (m, 1H), 7.32–7.55 (m, 4H), 7.58 (m, 1H), 10.82 (br, 1H), 10.93 (s, 1H), 14.8 (br, 1H). Anal. Calcd for $C_{26}H_{31}N_5$·2HCl·0.45H_2O: C, 63.14; H, 6.91; N, 14.16. Found: C, 63.41; H, 7.30; N, 13.65.

5.1.55. 4-{*trans*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]piperazin-1-yl}-2-methyl-1*H*-benzimidazole (*trans*-17)

The *trans* isomer was isolated at the same time as *cis*-**17** affording 0.11 g (17%) of the title product as a white solid: mp dec >220 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.52–1.66 (m, 2H), 1.74–1.83 (m, 2H), 2.16–2.19 (m, 2H), 2.30–2.32 (m, 2H), 2.77 (s, 3H), 2.75–2.83 (m, 1H), 3.32–3.46 (m, 5H), 3.52–3.63 (m, 2H), 3.72–3.84 (m, 2H), 6.94–6.98 (m, 2H), 7.03–7.10 (m, 2H), 7.32–7.37 (m, 3H), 7.58–7.60 (m, 1H), 10.81 (s, 1H), 10.99 (br, 1H), 14.65 (br, 1H). Anal. Calcd for $C_{26}H_{31}N_5$·2HCl·1H_2O: C, 61.90; H, 6.99; N, 13.88. Found: C, 61.88; H, 7.17; N, 13.44.

5.1.56. 4-{*cis*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]-piperazin-1-yl}-2-(trifluoromethyl)-1*H*-benzimidazole (*cis*-18)

This compound was prepared as described for *cis*-**16** by replacing 4-piperazin-1-yl-1*H*-benzoimidazole with 4-piperazin-1-yl-2-(trifluoro-methyl)-1*H*-benzoimida-zole (0.4 g, 1.48 mmol) to afford 0.17 g (25%) of the title product as a white solid. The HCl salt was generated from ethyl acetate yielding a white solid: mp above 207 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.79–1.92 (m, 4H), 1.98–2.08 (m, 2H), 2.18–2.24 (m, 2H), 3.23–3.48 (m, 4H), 3.66–3.68 (m, 2H), 3.98 (m, 2H), 4.34 (m, 2H), 6.72–6.76 (m, 1H), 6.93–6.98 (m, 1H), 7.02–7.08 (m, 1H), 7.19–7.21 (m, 1H), 7.24–7.30 (m, 1H), 7.33–7.35 (m, 2H), 7.52–7.54 (m, 1H), 10.36 (br, 1H), 10.9 (s, 1H), 14.0 (br, 1H). Anal. Calcd for $C_{26}H_{28}F_3N_5$·HCl·H_2O: C, 59.82; H, 5.99; N, 13.42. Found: C, 60.18; H, 5.84; N, 13.29.

5.1.57. 4-{*trans*-4-[4-(1*H*-Indol-3-yl)cyclohexyl]-piperazin-1-yl}-2-(trifluoromethyl)-1*H*-benzimidazole (*trans*-18)

The *trans* isomer was isolated at the same time as *cis*-**18** affording 0.18 g (9%) of the title product as a beige solid. The HCl salt was generated from ethyl acetate yielding a white solid: mp above 200 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.54–1.60 (m, 2H), 1.63–1.77 (m, 2H), 2.15–2.18 (m, 2H), 2.29–2.32 (m, 2H), 2.76–2.82 (m, 1H), 3.17–3.19 (m, 2H), 3.28–3.40 (m, 3H), 3.66–3.68 (m, 2H), 4.43 (m, 2H), 6.75 (d, J = 5.93 Hz, 1H), 6.96 (m, 1H), 7.03–7.10 (m, 2H), 7.21–7.28 (m, 1H), 7.30–7.35 (m, 2H), 7.54–7.58 (m, 1H), 10.5 (br, 1H), 10.89 (s, 1H), 14.0 (m, 1H). Anal. Calcd for $C_{26}H_{28}F_3N_5$·HCl·0.75H_2O: C, 60.34; H, 5.94; N, 13.53. Found: C, 60.37; H, 5.68; N, 13.43.

5.1.58. 5-(Trifluoromethylsulfonyloxy)-quinoline (31)

A solution of 5-hydroxy-quinoline (8 g, 55 mmol) and potassium carbonate (15.2 g, 110 mmol) in anhydrous pyridine (60 mL) under nitrogen was cooled to −20 °C. Tf_2O (13.97 mL, 83 mmol) was added drop-wise via syringe. The reaction mixture was stirred 1 h at −20 °C, then warmed to 0 °C for 1 h then stirred at room temperature for 48 h. The reaction mixture was then poured into water (200 mL) and extracted in methylene chloride (2× 200 mL). The aqueous layer was acidified with 1 N HCl (100 mL) and back extracted with methylene chloride (2× 200 mL). The organic fractions were dried over anhydrous sodium sulfate and concentrated and purified by column chromatography (40% ethyl acetate/hexanes) affording 13.97 g (90%) of the title product as a pink oil; MS (EI) m/z 277 (M^+). ^{1}H NMR (400 MHz, DMSO-d_6) δ 7.77–7.82 (m, 2H), 7.90 (t, J = 7.92 Hz, 1H), 8.17–8.20 (m, 1H), 8.37–8.40 (m, 1H), 9.07 (m, 1H).

5.1.59. 1-*tert*-Butyl-4-(5-quinolinyl)piperazine carboxylate (32)

To an oven-dried 200 mL flask was added cesium carbonate (19.87 g, 61 mmol), palladium acetate (0.49 g, 2.2 mmol) and BINAP (1.18 g, 1.9 mmol). The solids were flushed with nitrogen for 10 min. A solution of 5-(trifluoromethylsulfonyl-oxy)quinoline (12 g, 43 mmol) and 1-*tert*-butyl-4-piperazine carboxylate (9.67 g, 52 mmol) in THF was then added slowly to the reaction flask. The reaction mixture was stirred at room temperature for 0.5 h then at 65 °C overnight. The resulting solution was diluted with ether, filtered through a bed of Celite, washed with ether (50 mL) and ethyl acetate (50 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, filtered, and chromatography three times (10% methanol/methylene chloride) yielding

1.57 g (12%) of pure product as a beige solid: mp 116–118 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.43 (s, 9H), 3.00 (m, 4H), 3.60 (m, 4H), 7.19 (dd, J = 7.24, 1.12 Hz, 1H), 7.52 (dd, J = 8.56, 4.20 Hz, 1H), 7.63–7.72 (m, 2H), 8.50–8.53 (m, 1H), 8.86–8.88 (m, 1H). Anal. Calcd for $C_{18}H_{23}N_3O_2$: C, 68.98; H, 7.40; N, 13.41. Found: C, 69.09; H, 7.33; N, 13.08.

5.1.60. 5-(1-Piperazinyl)-quinoline (33)

To a solution of 1-*tert*-butyl-4-(5-quinolinyl)piperazine carboxylate (1.57 g, 5 mmol) in methylene chloride (2 mL) at 0 °C were added a per-cooled, premixed, solution of TFA (10 mL), methylene chloride (20 mL) and methanol (10 drops). The reaction was warmed slowly to room temperature and allowed to stir overnight. The resulting solution was concentrated, dissolved in water (5 mL), and methylene chloride (5 mL) and made alkaline with sodium bicarbonate to pH 9. The aqueous portion was extracted ethyl acetate (6× 100 mL) and concentrated yielding 1.0 g (100%) of a yellow oil which solidified upon standing and was not purified further. ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.06 (m, 4H), 3.17 (m, 4H), 3.62 (br, 1H), 7.19 (dd, J = 7.0, 1.08 Hz, 1H), 7.50 (dd, J = 8.56, 4.16 Hz, 1H), 7.64–7.72 (m, 2H), 8.50 (m, 1H), 8.87 (m, 1H).

5.1.61. 5-{4-[(1,4-*cis*)-4-(5-Fluoro-1*H*-indol-3-yl)-cyclohexyl]-piperazin-1-yl}-quinoline (*cis*-19)

To a solution of 5-(1-piperazinyl)quinoline (0.5 g, 2.35 mmol), 4-(5-fluoro-1*H*-3-indolyl)-cyclohexanone (0.54 g, 2.35 mmol) and sodium traxetoxyborohydride (0.74 g, 3.5 mmol) in dichloroethane (20 mL) was added acetic acid (0.27 mL, 4.7 mmol) and stirred overnight at room temperature. The reaction was quenched with 1 N NaOH (50 mL) and extracted in methylene chloride (3× 100 mL). The organic fractions were combined, dried over anhydrous sodium sulfate, concentrated, filtered, and chromatographed (5% methanol/ethyl acetate) yielding 0.41 g (41%) of the title product as a pale yellow solid: mp 220–223 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58–1.70 (m, 4H), 1.94–2.04 (m, 4H), 2.37 (m, 1H), 2.75 (m, 4H), 2.92–2.97 (m, 1H), 3.07 (m, 4H), 6.88 (m, 1H), 7.18 (m, 1H), 7.29 (dd, J = 8.76, 4.80 Hz, 1H), 7.35 (dd, J = 10.52, 2.44 Hz, 1H), 7.49 (dd, J = 8.56, 4.20 Hz, 1H), 7.63–7.69 (m, 2H), 8.47 (dd, J = 8.56, 1.56 Hz, 1H), 8.86 (dd, J = 3.92, 1.52 Hz, 1H), 10.82 (br, 1H). Anal. Calcd for $C_{27}H_{29}FN_4{\cdot}0.12C_4H_8O_2$: C, 75.16; H, 6.88; N, 12.76. Found: C, 74.83; H, 6.86; N, 12.60.

5.1.62. 5-{4-[(1,4-*trans*)-4-(5-Fluoro-1*H*-indol-3-yl)-cyclohexyl]-piperazin-1-yl}-quinoline (*trans*-19)

The trans isomer was isolated at the same time as the *cis*-**19** isomer affording 0.18 g (18%) of the title product as a white solid: mp 210–211 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.46–1.56 (m, 4H), 2.00–2.06 (m, 4H), 2.52–2.69 (m, 1H), 2.83 (m, 4H), 3.04 (m, 4H), 6.88 (m, 1H), 7.15 (d, J = 2.20 Hz, 1H), 7.18 (dd, J = 6.60, 1.56 Hz, 1H), 7.27–7.33 (m, 2H), 7.50 (dd, J = 8.56, 4.16 Hz, 1H), 7.63–7.69 (m, 2H), 8.47 (m, 1H), 8.86 (m, 1H), 10.83 (s, 1H). Anal. Calcd for $C_{27}H_{29}FN_4{\cdot}0.20C_4H_8O_2$: C, 74.84; H, 6.91; N, 12.56. Found: C, 74.45; H, 6.79; N, 12.35.

5.1.63. 3-[(1,4-*cis*)-4-(4-Quinolin-5-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*cis*-20)

This compound was prepared in the same manner as the *cis*-**19** isomer by replacing 4-(5-fluoro-1*H*-3-indolyl)-cyclohexanone with 4-(5-cyano-1*H*-3-indolyl)-cyclohexanone (0.54 g, 2.35 mmol) afforded 0.41 (41%) of the *cis* isomer as a white solid. The HCl salt was generated from ethyl acetate yielding a white solid: mp >270 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85–1.92 (m, 4H), 2.01–2.06 (m, 2H), 2.21–2.26 (m, 2H), 3.34–3.51 (m, 6H), 3.56–3.64 (m, 4H), 7.28 (d, J = 7.25 Hz, 1H), 7.41 (dd, J = 8.57, 1.32 Hz, 1H), 7.51 (d, J = 8.57 Hz, 1H), 7.59 (m, 2H), 7.74 (t, J = 8.35 Hz, 1H), 7.80 (d, J = 8.57 Hz, 1H). Anal. Calcd for $C_{28}H_{29}N_5{\cdot}HCl{\cdot}H_2O$: C, 68.63; H, 6.58; N, 14.29. Found: C, 68.99; H, 6.54; N, 14.06.

5.1.64. 3-[(1,4-*trans*)-4-(4-Quinolin-5-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*trans*-20)

The *trans* isomer was isolated at the same time as the *cis*-**20** isomer affording 0.18 g (18%) as a beige solid. The HCl salt was generated from ethyl acetate yielding a white solid: mp 210–211 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.85–1.95 (m, 4H), 2.04–2.06 (m, 2H), 2.20–2.23 (m, 2H), 3.34–3.56 (m, 6H), 3.61–3.64 (m, 4H), 7.27 (d, J = 7.28 Hz, 1H), 7.41 (dd, J = 8.36, 1.32 Hz, 1H), 7.51 (d, J = 8.56 Hz, 1H), 7.58–7.61 (m, 2H), 7.74 (t, J = 8.36 Hz, 1H), 7.80 (d, J = 8.60 Hz, 1H), 8.12 (d, J = 0.64 Hz, 1H), 8.63 (d, J = 8.36 Hz, 1H), 8.95 (dd, J = 4.20, 1.32 Hz, 1H), 10.71 (br, 1H), 11.58 (s, 1H). Anal. Calcd for $C_{28}H_{29}N_5{\cdot}HCl{\cdot}0.40H_2O$: C, 70.18; H, 6.48; N, 14.61. Found: C, 70.23; H, 6.21; N, 14.45.

5.1.65. 8-(4-Benzyl-piperazin-1-yl)quinoline (34)

A solution of 8-amino-quinoline (12.9 g, 89 mmol) and bis(2-chloroethyl)-benzylamine (26.0 g, 112 mmol) in *n*-butanol (65 mL) was allowed to heat at 85 °C for 11 h. The mixture was poured into 50% sodium hydroxide, extracted with methylene chloride and water. The organic layer was dried over anhydrous magnesium sulfate, and filtered. The solvent was removed in vacuo. Chromatography (5% methanol/methylene chloride) afforded 12.3 g of the title product as a solid: mp 116.5–118 °C. The HCl salt was prepared in ethyl acetate: mp 209–210 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.36–3.58 (m, 6H), 3.69–3.73 (m, 2H), 4.41 (s, 2H), 7.45–7.49 (m, 3H), 7.57–7.58 (m, 1H), 7.70–7.74 (m, 3H), 7.84–7.89 (m, 1H), 8.80 (br, 1H), 9.06 (m, 1H), 11.72 (br, 1H). Anal. Calcd for $C_{20}H_{21}N_3{\cdot}2HCl{\cdot}0.5H_2O$: C, 62.34; H, 6.28; N, 10.91. Found: C, 62.37; H, 6.55; N, 10.80.

5.1.66. 8-(Piperazin-1-yl)-quinoline (35)

To a solution of 8-(4-benzyl-piperazin-1-yl)quinoline (2.6 g, 8.7 mmol) in methylene chloride (30 mL) was added vinyl chloroformate (1.1 mL, 13 mmol) at room temperature slowly. The reaction mixture was refluxed for 2 h, and then concentrated in vacuo. The residue was dissolved in hydrochloric acid (12 N, 20 mL) and stirred at room temperature for 1 h. The mixture was concentrated; the residue was taken up with 40 mL ethanol and heated up to 50 °C for 2 h. The solvent was removed in vacuo, the residue was dissolved in 1.0 N sodium hydroxide/ethyl acetate, and extracted with ethyl acetate and washed with water. The organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo. Chromatography (10–30% methanol/methylene chloride plus ammonium hydroxide) afforded 1.86 g (90%) of the title product as a yellow oil. The HCl salt was prepared in ethanol; MS (EI) m/z 213 $(M)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 3.41 (br, 4H), 3.47 (br, 4H), 7.46 (m, 1H), 7.63–7.68 (m, 1H), 7.74–7.77 (m, 2H), 8.63 (m, 1H), 9.00–9.17 (m, 1H), 9.25 (br, 2H). Anal. Calcd for $C_{13}H_{15}N_3{\cdot}2HCl{\cdot}H_2O$: C, 51.30; H, 6.30; N, 13.81. Found: C, 51.67; H, 6.36; N, 13.32.

5.1.67. 8-{4-[(1,4-*cis*)-4-(5-Fluoro-1*H*-indol-3-yl)-cyclohexyl]-piperazin-1-yl}-quinoline (*cis*-21)

A solution of 4-(5-fluoro-1-indol-3-yl)-cyclohexanone (0.54 g, 2.3 mmol), 8-(piperazin-1-yl)-quinoline (0.5 g, 2.3 mmol), sodium triacetoxyborohydride (0.75 g, 3.5 mmol), and acetic acid (0.27 mL, 4.7 mmol) in 1,2-dichloroethane (20 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (20 mL), extracted with methylene chloride (3× 100 mL), and washed with brine (3× 100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (5% methanol/ethyl acetate) afforded 0.46 g (46%) of the title product as a white solid: mp 122–125 °C. The

HCl salt was prepared in ethanol: mp 209–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55–1.64 (m, 2H), 1.74–1.82 (m, 2H), 2.13–2.16 (m, 2H), 2.32–2.35 (m, 2H), 2.73–2.80 (m, 1H), 3.34–3.45 (m, 4H), 3.58–3.74 (m, 5H), 6.86–6.92 (m, 1H), 7.19 (m, 1H), 7.30–7.38 (m, 2H), 7.48 (m, 1H), 7.66 (m, 1H), 7.76–7.79 (m, 2H), 8.65 (m, 1H), 9.0 (m, 1H), 10.79 (br, 1H), 10.93 (br, 1H). Anal. Calcd for $C_{27}H_{29}FN_4 \cdot 3HCl$: C, 60.28; H, 6.00; N, 10.42. Found: C, 60.23; H, 6.29; N, 10.21.

5.1.68. 8-{4-[(1,4-*trans*)-4-(5-Fluoro-1*H*-indol-3-yl)-cyclohexyl]-piperazin-1-yl}-quinoline (*trans*-21)

The *trans* compound was isolated at the same time as the *cis*-**21** isomer in 25% yield (0.25 g) as a white solid: mp 207.5–209 °C. The HCl salt was prepared in ethanol: mp 286–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.82–1.94 (m, 4H), 2.04–2.07 (m, 2H), 2.17–2.19 (m, 2H), 3.24 (m, 1H), 3.34–3.59 (m, 6H), 3.64–3.71 (m, 3H), 6.87–6.92 (m, 1H), 7.28–7.34 (m, 2H), 7.44 (m, 1H), 7.63–7.67 (m, 1H), 7.74–7.79 (m, 2H), 8.64 (br, 1H), 9.00 (br, 1H), 10.55 (br, 1H), 11.05 (br, 1H). Anal. Calcd for $C_{27}H_{29}FN_4 \cdot HCl$: C, 64.67; H, 6.23; N, 11.17. Found: C, 64.74; H, 6.27; N, 11.06.

5.1.69. 3-[(1,4-*cis*)-4-(4-Quinolin-8-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*cis*-22)

A solution of 4-(5-cyano-1-indol-3-yl)-cyclohexanone (1.47 g, 6.2 mmol), 8-(piperazin-1-yl)-quinoline (1.32 g, 6.2 mmol), sodium triacetoxyborohydride (2.0 g, 7.2 mmol), and acetic acid (0.71 mL, 12 mmol) in 1,2-dichloroethane (40 mL) was allowed to stir at room temperature overnight. The reaction was quenched with 1 N sodium hydroxide (20 mL), extracted with methylene chloride (3× 100 mL), and washed with brine (3× 100 mL). The organic layer was dried over anhydrous sodium sulfate and filtered. Chromatography (5% methanol/ethyl acetate) afforded 1.48 g (55%) of the title product as a white solid: mp 149–151 °C. The HCl salt was prepared in ethanol: mp 282–283 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.84–1.96 (m, 4H), 2.05–2.07 (m, 2H), 2.19–2.21 (m, 2H), 3.33 (m, 1H), 3.39–3.44 (m, 3H), 3.53–3.55 (m, 2H), 3.65–3.67 (m, 2H), 3.78 (m, 2H), 7.40 (dd, J = 8.36, 1.32 Hz, 1H), 7.50 (m, 2H), 7.59 (m, 1H), 7.68 (m, 1H), 7.82 (m, 2H), 8.12 (m, 1H), 8.72 (br, 1H), 9.04 (m, 1H), 10.71 (br, 1H), 11.58 (s, 1H). Anal. Calcd for $C_{28}H_{29}N_5 \cdot 2HCl \cdot 0.75H_2O$: C, 66.43; H, 6.28; N, 13.42. Found: C, 64.46; H, 6.29; N, 13.37.

5.1.70. 3-[(1,4-*trans*)-4-(4-Quinolin-8-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*trans*-22)

The *trans* compound was isolated at the same time as the *cis*-**22** isomer in 26% yield (0.55 g) as a white solid: mp 276–278 °C. The HCl salt was prepared in ethanol: mp 286–288 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57–1.66 (m, 2H), 1.73–1.82 (m, 2H), 2.14–2.17 (m, 2H), 2.33–2.35 (m, 2H), 2.83–2.89 (m, 1H), 3.14–3.20 (m, 2H), 3.38–3.50 (m, 3H), 3.62–3.65 (m, 3H), 3.62–3.65 (m, 2H), 4.00–4.08 (m, 2H), 7.33 (m, 2H), 7.40 (dd, J = 8.36, 1.56 Hz, 1H), 7.50 (d, J = 8.36 Hz, 1H), 7.56–7.69 (m, 3H), 8.20 (s, 1H), 8.45 (br, 1H), 8.93 (m, 1H), 10.59 (br, 1H), 11.45 (s, 1H). Anal. Calcd for $C_{28}H_{29}FN_5 \cdot 2HCl \cdot 0.5H_2O$: C, 64.98; H, 6.23; N, 13.53. Found: C, 65.28; H, 5.96; N, 13.30.

5.1.71. 5-Nitro-quinoxaline (36)

To a room temperature solution of 3-nitro-*o*-phenylenediamine (10 g, 65.3 mmol) in ethanol (50 mL) was added glyoxal (40% in water, 22.47 mL). The reaction mixture was heated at reflux for 1 h, then diluted with water (100 mL). The cooled mixture was extracted with methylene chloride (2× 300 mL) and the organic layers were combined and washed again with water (500 mL), dried over sodium sulfate and concentrated yield a bright orange solid which was recrystallized from ethyl acetate/hexanes to give 10.96 g (96%) of the title product as a solid mp: 90–92 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 8.00–8.04 (m, 1H), 8.39–8.43 (m, 1H), 9.10–9.14 (m, 1H). Anal. Calcd for $C_8H_5N_3O_2$:C, 54.86; H, 2.88; N, 23.99. Found: C, 55.12; H, 3.05; N, 24.05.

5.1.72. 5-Amino-quinoxaline (37)

To a three-neck 250 mL round-bottomed flask equipped with a reflux condenser, and nitrogen inlet was added 5-nitro-quinoxaline (4 g, 22.8 mmol) dissolved in acetic acid (60 mL). The mixture was heated to boiling, removed from heat, and solid iron powder (3.83 g, 68.6 mmol) was added. Vigorous boiling was observed. The reaction mixture was heated at reflux for 10 min and them poured into water (100 mL) and ice. The aqueous solution was filtered and basified to pH > 10 with 1 M sodium hydroxide, and extracted in ethyl acetate (3× 200 mL). The organic layers were combined and washed again with water (500 mL), dried over sodium sulfate and concentrated. The resulting oil was purified by column chromatography (40% ethyl acetate/hexanes) yielding a bright orange solid 2.03 g (61%); mp: 87–90 °C; ^{1}H NMR (MHz, DMSO-d_6) δ 6.13 (s, 2H), 6.90 (dd, J = 7.68, 1.32 Hz, 1H), 7.16 (dd, J = 8.12, 1.12 Hz, 1H), 7.52 (t, J = 8.12 Hz, 1H), 8.71 (s, 1H), 8.84 (s, 1H). Anal. Calcd for $C_8H_7N_3$: C, 66.19; H, 4.86 N, 28.95. Found: C, 66.25; H, 4.96; N, 29.26.

5.1.73. 5-(1-Piperazinyl)quinoxaline (39)

To a solution of 5-amino-quinoxaline (2.8 g, 19.3 mmol) in BuOH (50 mL) were added bis(2-chloroethyl)-benzylamine (8.42 g, 38.6 mmol) and triethyl amine (5.34 mL, 38.6 mmol). The reaction was stirred at 100 °C overnight. A second portion of triethyl amine (5.34 mL, 38.6 mmol) was added and the reaction stirred at 100 °C an additional 24 h. The cooled solution was made alkaline with NaOH (2.5 N, 500 mL) and extracted with ethyl acetate (3× 200 mL). The organic fractions were combined, dried over sodium sulfate, concentrated and chromatography (40% ethyl acetate/hexanes) yielding 1.0 g (17%) of 1-benzyl-4-(quinoxalinyl)piperazine 38 as a gold oil. To a solution of 1-benzyl-4-(quinoxalin-yl)piperazine **38** (1.0 g, 3.3 mmol) in anhydrous methylene chloride at room temperature under nitrogen was added vinyl chloroformate (0.34 mL, 3.9 mmol) drop-wise. The reaction mixture was heated at reflux for 2 h. The reaction was cooled, concentrated to dryness, and concentrated HCl (25 mL) and 1,4-dioxane (25 mL) were added. The resulting solution was stirred at ambient temperature overnight. The solution was basified with sodium hydroxide (2.5 N, 300 mL) and extracted into ethyl acetate (3× 200 mL). The organic layers were combined, dried over sodium sulfate, concentrated, and chromatographed (10% MeOH/CH_2Cl_2/NH_4OH) to give 0.45 g (64%) of the title product as an orange solid: mp 106–108 °C; MS (ESI) m/z 215 $(M+H)^+$; ^{1}H NMR (400 MHz, DMSO-d_6) δ 2.93–2.95 (m, 4H), 3.24–3.36 (m, 4H), 7.15–7.17 (m, 1H), 7.58–7.60 (m, 1H), 7.67–7.72 (m, 1H), 8.85 (m, 1H), 8.88 (m, 1H).

5.1.74. 3-[(1,4-*cis*)-4-(4-Quinoxalin-5-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*cis*-23)

A solution of 4-(5-cyano-1*H*-indolyl)-cyclo-hexanone (0.43 g, 1.87 mmol), 5-(1-piperazinyl)-quinoxaline (0.4 g, 1.87 mmol), acetic acid (0.22 mL, 3.7 mmol), and sodium triacetoxyborohydride (0.59 g, 2.8 mmol) in dichloroethane (50 mL) was stirred at room temperature overnight. The reaction was quenched with NaOH (1 N, 100 mL) and extracted with methylene chloride (3× 100 mL). The organic fractions were combined, dried over sodium sulfate, and filtered. The resulting oil was purified by column chromatography (5% MeOH in EtOAc) yielding 0.13 g (16%) of the title

product as a yellow solid: mp 223–225 °C; MS (ESI) *m/z* 437 ([M+H]$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ1.62–1.67 (m, 4H), 1.71–2.06 (m, 4H), 2.31–2.35 (m, 1H), 2.65–2.72 (s, 3H), 3.03–3.06 (m, 1H), 3.21–3.40 (m, 5H), 7.19–7.21 (m, 1H), 7.33–7.39 (m, 2H), 7.47–7.50 (m, 1H), 7.60–7.62 (m, 1H), 7.68–7.72 (m, 1H), 8.15 (s, 1H), 8.85–8.89 (m, 2H), 11.34 (br, 1H). Anal. Calcd for $C_{27}H_{28}N_6H_2O$: C, 71.34; H, 6.65; N, 18.49. Found: C, 71.65; H, 6.11; N, 18.18.

5.1.75. 3-[(1,4-*trans*)-4-(4-Quinoxalin-5-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole-5-carbonitrile (*trans*-23)

The *trans* isomer was isolated at the same time as the *cis*-**23** isomer affording 0.24 g (29%) of a pale yellow *cis*-**23** isomer solid: mp 257–259 °C; MS (ESI) *m/z* 437 [(M+H]$^+$); ^{1}H NMR (MHz, DMSO-d_6) δ 1.53–1.59 (m, 4H), 1.97–2.07 (m, 4H), 2.80–2.82 (m, 4H), 3.34–3.44 (m, 6H), 7.19–7.21 (m, 1H), 7.29 (m, 1H), 7.37–7.39 (m, 1H), 7.47–7.49 (m, 1H), 7.61–7.63 (m, 1H), 7.69–7.73 (m, 1H), 8.14 (s, 1H), 8.87–8.90 (m, 2H), 11.36 (br, 1H). Anal. Calcd for $C_{27}H_{28}N_6{\cdot}0.75H_2O$: C, 72.05; H, 6.61; N, 18.67. Found: C, 72.32; H, 6.14; N, 18.25.

5.1.76. 5-Fluoro-3-[(1,4-*cis*)-4-(4-naphthalen-1-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole (*cis*-24)

This compound was prepared by the manner shown in *cis*-**19** by replacing 5-(1-piperazinyl)-quinoline with 1-(1-naphthyl)piperazine (0.41 g, 1.9 mmol). 0.24 g (29%) of the title product was obtained as a white solid: mp 195–197 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.55–1.66 (m, 4H), 1.93–2.01 (m, 4H), 2.26–2.29 (m, 1H), 2.62–2.78 (m, 4H), 2.83–2.94 (m, 1H), 2.96–3.10 (m, 4H), 6.83 (m, 1H), 7.09 (d, *J* = 6.73 Hz, 1H), 7.16 (d, *J* = 2.2 Hz, 1H), 7.27 (dd *J* = 8.80, 4.63 Hz, 1H), 7.32 (dd, *J* = 10.32, 2.55 Hz, 1H), 7.38(t, *J* = 7.54 Hz, 1H), 7.42–7.47 (m, 2H), 7.51 (m, 1H), 7.84 (m, 1H), 8.09 (m, 1H). Anal. Calcd for $C_{28}H_{30}FN_3$: C, 78.66; H, 7.07; N, 9.83. Found: C, 78.24; H, 7.06; N, 9.59.

5.1.77. 5-Fluoro-3-[(1,4-*trans*)-4-(4-naphthalen-1-yl-piperazin-1-yl)-cyclohexyl]-1*H*-indole (*trans*-24)

The *trans* isomer was isolated at the same time as the *cis*-**25** affording 70 mg (9%) of the title compound as a white solid: mp 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.58–1.70 (m, 4H), 1.96–2.04 (m, 4H), 2.37 (m, 1H), 2.74 (m, 3H), 2.93–2.97 (m, 1H), 3.07 (m, 3H), 6.86 (m, 1H), 7.11 (d, *J* = 7.04 Hz, 1H), 7.19 (d, *J* = 2.2 Hz, 1H), 7.30 (dd *J* = 8.76, 4.60 Hz, 1H), 7.36 (dd, *J* = 10.32, 2.40 Hz, 1H), 7.41(t, *J* = 7.72 Hz, 1H), 7.46–7.49 (m, 2H), 7.51 (d, *J* = 5.04 Hz, 1H), 7.57 (d, *J* = 8.12 Hz, 1H), 7.86–7.88 (m, 1H), 8.11–8.13 (m, 1H), 10.83 (br, 1H). Anal. Calcd for $C_{28}H_{30}FN_3$: C, 78.66; H, 7.07; N, 9.83. Found: C, 78.28; H, 7.05; N, 9.79.

5.1.78. 4-(1*H*-3-Pyrrolo[2,3-*b*]pyridyl)-cyclohexanone (41)

This compound was prepared in a similar fashion as described above (**28c**) by replacing 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-6-fluoro-1*H*-indole with 3-(1,4-dioxa-spiro[4,5]dec-8-yl)-1*H*-azaindole (2.48 g). 1.96 g (95%) of the title compound was obtained as a white solid: mp 162–164 °C; MS (EI) *m/z* 214 (M$^+$); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.83–1.94 (m, 2H), 2.22–2.29 (m, 4H), 2.56–2.65 (m, 2H), 3.26–3.30 (m, 1H), 7.00–7.03 (m, 1H), 7.24 (s, 1H), 8.02–8.05 (m, 1H), 8.16–8.18 (m, 1H), 11.36 (s, 1H).

5.1.79. 3-{(1,4-*cis*)-4-[(1*H*-Indole-4-yl)-piperazin-1-yl]-cyclohexyl}-1*H*-pyrrolo[2,3-*b*]pyridine (*cis*-25)

This compound was prepared in a similar fashion as described above (*cis*-**4**) by replacing 4-(1*H*-indol-3-yl)-cyclohexanone with 4-(1*H*-3-pyrrolo[2,3-*b*]-pyridyl)cyclohexanone (**41**) (1.52 g, 7.1 mmol). 0.79 g (27%) of the title product was obtained. Its hydrochloride salt was prepared in ethanol. mp 250 °C (dec); ^{1}H NMR (MHz, DMSO-d_6) δ 1.82–1.96 (m, 4H), 2.03–2.06 (m, 2H), 2.27–2.28 (m, 2H), 3.33–3.60 (m, 6H), 3.64–3.70 (m, 4H), 6.54 (m, 1H), 6.61(d, *J* = 6.80 Hz, 1H), 7.00 (t, *J* = 7.72 Hz, 1H), 7.13 (d, *J* = 8.12 Hz, 1H), 7.29–7.31 (m, 1H), 7.42–7.46 (m, 1H), 7.76 (m, 1H), 8.42 (d, *J* = 5.08 Hz, 1H), 8.68 (d, *J* = 7.92 Hz, 1H), 11.16 (br, 1H), 11.25 (s, 1H), 12.78 (s, 1H). Anal. Calcd for $C_{25}H_{29}N_5{\cdot}3HCl$: C, 58.49; H, 6.38; N, 13.64. Found: C, 58.47; H, 6.52; N, 12.91.

5.1.80. 3-{(1,4-*trans*)-4-[4-(1*H*-Indole-4-yl)-piperazin-1-yl]-cyclohexyl}-1*H*-pyrrolo[2,3-*b*]pyridine (*trans*-25)

The *trans* compound was isolated at the same time as the *cis*-**25** isomer in 9% yield (0.26 g) as a white solid: mp >228 °C. Its hydrochloride salt was prepared in ethanol: mp >250 °C (dec); ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.57–1.67 (m, 2H), 1.74–1.84 (m, 2H), 2.14–2.17 (m, 2H), 2.34–2.37 (m, 2H), 2.86–2.92 (m, 1H), 3.36–3.45 (m, 5H), 3.58–3.63 (m, 2H), 3.72–3.74 (m, 2H), 6.55 (m, 1H), 6.61–6.63 (m, 1H), 7.01 (t, *J* = 7.68 Hz, 1H), 7.14 (d, *J* = 8.12 Hz, 1H), 7.31 (m, 1H), 7.41–7.44 (m, 1H), 7.50 (m, 1H), 8.40–8.42 (m, 1H), 8.67–8.68 (m, 1H), 11.24 (s, 1H), 11.38 (br, 1H), 12.58 (s, 1H). Anal. Calcd for $C_{25}H_{29}N_5{\cdot}3HCl$: C, 56.50; H, 6.54; N, 13.18. Found: C, 56.45; H, 6.63; N, 12.98.

Acknowledgments

The authors thank the Discovery Analytical Chemistry-Chemical and Screening Sciences at Wyeth Research for providing ^{1}H NMR, MS, and CHN elemental analysis data reported here in the experimental section.

References and notes

1. Blier, P.; Bergerpm, R. *J. Clin. Psychiatry* **1998**, 16–23.
2. Kreiss, D. S.; Lucki, I. *J. Pharmacol. Exp. Ther.* **1995**, *274*, 219–225.
3. Hjorth, S.; Auerbach, S. B. *Behav. Brain Res.* **1996**, *73*, 281–283.
4. Romero, L.; Bel, N.; Casanovas, J. M.; Artigas, F. *Int. Clin. Psychopharm.* **1996**, *11*, 1–8.
5. Dawson, L. A.; Nguyen, H. Q. *Eur. J. Pharmacol.* **1998**, *345*, 41–46.
6. Dawson, L. A.; Nguyen, D. L.; Schechter, L. E. *J. Psychopharacol.* **2002**, *16*, 145–152.
7. Hjorth, S.; Westlin, D.; Bengtsson, H. J. *Neuropharmacology* **1997**, *36*, 461–465.
8. Artigas, F.; Perez, V.; Alvarez, E. *Arch. Gen. Psychiatry* **1994**, *51*, 248–251.
9. Blier, P.; Bergeron, R. *J. Clin. Psycho-pharmacol.* **1995**, *15*, 217–222.
10. Meagher, K. L.; Mewshaw, R. E.; Evrard, D. A.; Zhou, P.; Smith, D.; Scerni, R.; Spangler, T.; Abulhawa, S.; Shi, X.; Schechter, L.; Andree, T. H. *Bioorg. Med. Chem. Lett.* **2001**, *11*, 1885–1888.
11. Martinez-Esparza, J.; Oficialdegui, A.; Perez-Silanes, S.; Heras, B.; Orus, L.; Palop, J.; Lasheras, B.; Roca, J.; Mourelle, M.; Bosch, A.; Del Castillo, J.; Tordera, R.; Del Rio, J.; Monge, A. *J. Med. Chem.* **2001**, *44*, 418–428.
12. Page, M. E.; Cryan, J. F.; Sullivan, A.; Dalvi, A.; Saucy, B.; Manning, D. R.; Lucki, I. *J. Pharmacol. Exp. Ther.* **2002**, *302*, 1220–1228.
13. (a) Takeuchi, K.; kohn, T. J.; Honigschmidt, N. A.; Rocco, V. P.; Spinazze, P. G.; Koch, D. J.; Nelson, D. L.; Wainscott, D. B.; Ahmad, L. J.; Shaw, J.; Threlkeld, P. G.; Wong, D. T. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 1903–1905; (b) Rocco, V. P.; Spinazze, P. G.; Kohn, T. J.; Honigschmidt, N. A.; Nelson, D. L.; Wainscott, D. B.; Ahmad, L. J.; Shaw, J.; Threlkeld, P. G.; Wong, D. T.; Takeuchi, K. *Bioorg. Med. Chem. Lett.* **2004**, *14*, 2653–2656.
14. (a) Atkinson, P. J.; Bromidge, S. M.; Duxon, M. S.; Gaster, L. M.; Hadley, M. S.; Hammond, B.; Johnson, C. N.; Middlemiss, D. N.; North, S. E.; Price, G. W.; Rami, H. K.; Riley, G. J.; Scott, C. M.; Shaw, T. E.; Starr, K. R.; Stemp, G.; Thewlis, K. M.; Thomas, D. R.; Thompson, M.; Vong, A. K. K.; Watson, J. M. *Bioorg. Med. Chem. Lett.* **2005**, *153*, 737–741; (b) Lovell, P. J.; Blaney, F. E.; Goodacre, C. J.; Scott, C. M.; Smith, P. W.; Starr, K. R.; Thewlis, K. M.; Vong, A. K. K.; Ward, S. E.; Watson, J. M. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 1033–1036.
15. Evrard, D. A.; Zhou, P.; Yi, S.-Y.; Zhou, D.; Smith, D.; Sullivan, K. M.; Hornby, G. A.; Schechter, L. E.; Andree, T. H.; Mewshaw, R. E. *Bioorg. Med. Chem. Lett.* **2005**, *11*, 1885–1888.
16. (a) Wustrow, D. J.; Smith, W. J., III; Corbin, A. E.; Davis, M. D.; Georgic, L. M.; Pugsley, T. A.; Whetzel, S. Z.; Heffner, T. G.; Wise, L. D. *J. Med. Chem.* **1997**, *40*, 250–259; (b) Mewshaw; R. E.; Zhou; P.; Zhou; D.; Meagher; K. L.; Asselin; M.; Evrard; D. A.; Gilbert; A. M. U.S. Patent US 6,465,482.
17. Lopez-Rodriguez, M. L. ; Benhamu, B. ; Ayala, D. ; Rominguera, J. L. ; Murcia, M. ; Ramos, J. A. ; Viso, A. *Tetrahedron* **2000**, *56*, 3245–3253.
18. Guerret, P.; Tisne-Versailles, J.; Ancher, J. F.; Langlois, M. Brit. UK Pat. Appl. 1982, GB 2097790.

19. (a) Guram, A. S.; Rennels, R. A.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1995**, *34*, 1348; (b) Sadighi, J. P.; Singer, R. A.; Buchwald, S. L. *J Am. Chem. Soc.* **1998**, *120*, 4960; (c) Singer, R. A.; Buchwald, S. L. *Tetrahedron Lett.* **1999**, *40*, 1095; (d) Louie, J.; Hartwig, J. F. *Tetrahedron Lett.* **1995**, *36*, 3609.
20. Kerrigan, F.; Martin, C.; Thomas, G. H. *Tetrahedron Lett.* **1998**, *39*, 2219–2222.
21. Cheng, Y.-C. ; Preusoff, W. H. *Biochem. Pharmacol.* **1973**, *23*, 3099.
22. Cheetham, S. C.; Viggers, J. A.; Slater, N. A.; Heal, D. J.; Buckett, W. R. *Neuropharmacology* **1993**, *32*, 737–743.
23. Dunlop, J.; Zhang, Y.; Smith, D. L.; Schechter, L. E. *J. Pharmacol. Toxicol. Methods* **1998**, *40*, 47.
24. Larenzo, S.; Birdsall, N. J. *Br. J. Pharmacol.* **1993**, *109*, 1120–1127.
25. Morrow, A.; Creese, I. *Mol. Pharmacol.* **1986**, *29*, 321.