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Article

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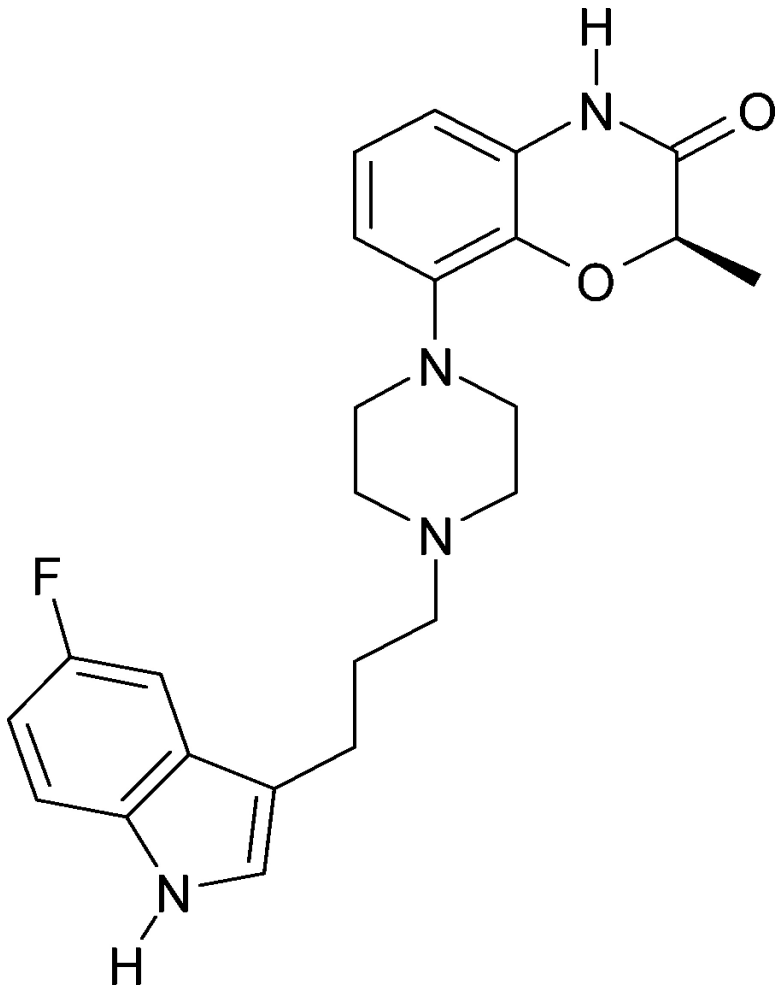

Synthesis, Structure−Activity Relationships, and Biological Properties of 1-Heteroaryl-4-[ω-(1*H*-indol-3-yl)alkyl]piperazines, Novel Potential Antipsychotics Combining Potent Dopamine D_2 Receptor Antagonism with Potent Serotonin Reuptake Inhibition

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A series of novel bicyclic 1-heteroaryl-4-[ω-(1*H*-indol-3-yl)alkyl]piperazines was synthesized and evaluated on binding to dopamine D_2 receptors and serotonin reuptake sites. This class of compounds proved to be potent in vitro dopamine D_2 receptor antagonists and in addition were highly active as serotonin reuptake inhibitors. Some key representatives showed potent pharmacological in vivo activities after oral dosing in both the antagonism of apomorphine-induced climbing and the potentiation of 5-HTP-induced behavior in mice. On the basis of the preclinical data, 8-{4-[3-(5-fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*R*)-2-methyl-3-one (**45c**, SLV314) was selected for clinical development. In vitro and in vivo studies revealed that **45c** has favorable pharmacokinetic properties and a high CNS−plasma ratio. Molecular modeling studies showed that the bifunctional activity of **45c** can be explained by its ability to adopt two different conformations fitting either the dopamine D_2 receptor pharmacophore or the serotonin transporter pharmacophore.

Introduction

Schizophrenia is a psychiatric disorder, which is characterized by a complex symptomatology. It expresses itself as a combination of positive (delusions, hallucinations, and conceptual disorganization) and negative (affective flattening, social withdrawal, anhedonia, and poverty of thought and content of speech) symptoms and cognitive impairment.[1] The co-occurrence of depressive symptoms is common in patients with schizophrenia, with estimates of the prevalence in clinical populations ranging from 25 to 60%.[2] Depressive symptoms are of great prognostic significance since they are associated with compromised quality of life and increased risk of psychotic relapse and suicide.[3] With the discovery of the dopaminergic system and demonstration that all antipsychotics have an action on this system, it has been proposed that antipsychotic drugs elicit their main clinical efficacy by blockade of dopamine D_2 receptors.[4] The binding affinity of the antipsychotic drugs at these receptors tends to be very strongly correlated to their clinical effect on positive symptoms. However, the occurrence of extrapyramidal side effects (EPS) has also been linked to the potency of antipsychotic drugs on the dopamine D_2 receptor.[5] Besides the EPS, a major complication with most antipsychotic drugs is that, although they are effective at reducing the positive effects of psychosis, the negative symptoms, comorbid depression, and cognitive deficits are not treated effectively.[3,6] Moreover, approximately 30% of patients do not respond to typical antipsychotics and EPS can become a treatment-limiting side effect.[7] Current theories have implicated the serotonergic system in the pathophysiology of anxiety, depression, and negative symptoms in schizophrenia. Evidence has accumulated concerning the interaction between the dopaminergic and the serotonergic system. It has been demonstrated that the combined use of a neuroleptic together with a SSRI (selective serotonin reuptake inhibitor) such as fluvoxamine,[8] fluoxetine,[9] or citalopram[10] gives an improvement in the negative symptoms of schizophrenia as well as a decrease in depression, without exacerbating EPS.[9] Further studies have demonstrated that this improvement of the negative symptoms is not due to a nonspecific action of the antidepressant but in fact to the SSRI characteristic, as maprotiline, an antidepressant drug acting via the noradrenergic system, did not improve negative symptoms.[11]

However, one of the main drawbacks of the administration of a combination of compounds is the potential for drug−drug interactions.[12] Hence, a single compound combining dopamine D_2 receptor antagonism with serotonin reuptake (SR) inhibition could improve on the presently used drugs for schizophrenia, since it would have the potential of treating positive, negative, and depressive symptoms in schizophrenia, without the disadvantages of potential pharmacokinetic interactions when combining two or more drugs.

In a recent publication,[13] we have shown that it is possible to combine dopamine D_2 receptor antagonism with SRI (serotonin reuptake inhibitor) effects in the same dose range in one molecule, i.e., SLV310 (**1**; see Figure 1). In this paper, we wish to demonstrate that

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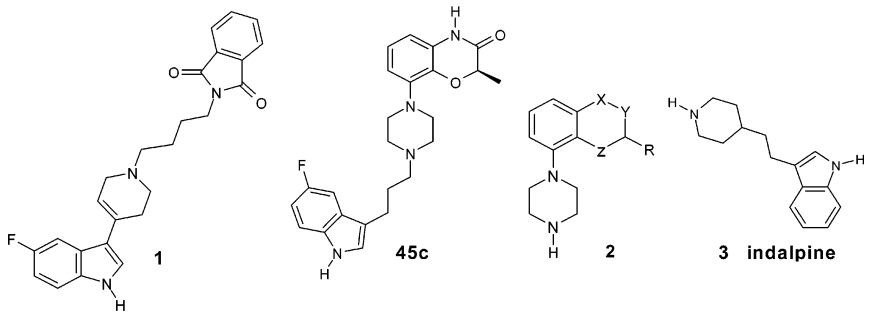


Figure 1.

compound **45c**, 8-{4-[3-(5-fluoro-1*H*-indol-3-yl)propyl]-piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*R*)-2-methyl-3-one, from a different structural class than compound **1**, has a favorable profile being the first example of a compound having a low nanomolar activity for the D_2 receptor and subnanomolar affinity for the SR site. Compound **45c** was built on the idea to combine a well-known dopamine D_2 pharmacophore such as the piperazine class **2** with a SRI. This paper describes the optimization program toward **45c** starting with the combination of eltoprazine[14] (**4**, X=Z=O, Y=CH_2, and R=H in **2**) and indalpine (**3**) to give compound class **5**, which was optimized with respect to (i) the length of the alkyl chain between the indole and the aryl piperazine moieties (i.e., **5a**−**e**), (ii) the substitution pattern of the indole moiety (i.e., **5f**−**p**), and (iii) the bicyclic heteroaryl part (i.e., compounds **15**, **19**, **20**, **25**, **31**, **38a**−**d**, **39**, and **45a**−**f**).

Chemistry

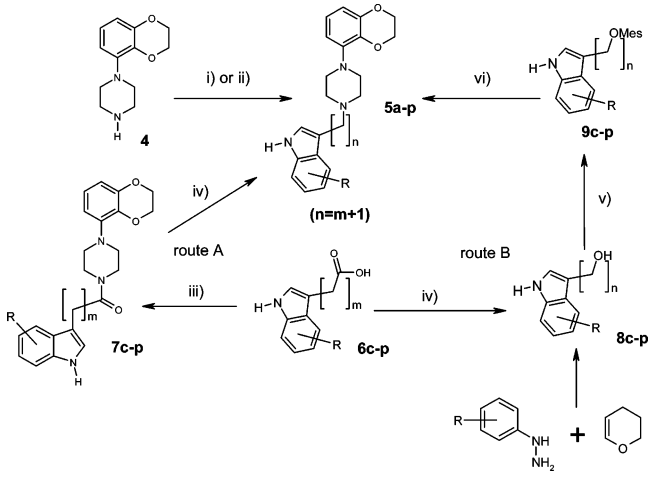
As depicted in Scheme 1, combination of indalpine (**3**) and **4** into one molecule was attempted by the synthesis of compound **5** (see Table 1). Compound **5a** (n = 1) was obtained via the Mannich reaction of **4** with indole in the presence of formaldehyde in a moderate yield of 33%. Compound **5b** (n = 2) was prepared via the alkylation of **4** with commercially available 3-(2-bromoethyl)indole in an excellent yield of 99%. For the synthesis of compounds **5c**−**p** (n = 3−5), two synthetic routes could be followed. Route A starts with the coupling of a (1*H*-indol-3-yl)alkanoic acid[15] derivative (**6**) with **4** in the presence of DCC, furnishing the amide derivatives **7**, which in turn were reduced with $LiAlH_4$ to give the corresponding compounds **5**. In route B, compounds **6** were reduced first to the alcohols **8**, which in turn were converted to the corresponding mesylate derivatives **9**. Alternatively, compounds **8c**,**f**−**p** (n = 3) could be prepared by the Fischer−Indole synthesis of an appropriately substituted phenylhydrazine with dihydropyran.[16] Compounds **9** were used in the alkylation of **4** to give **5** in a yield of 30−83% under relatively mild conditions, making route B more broadly applicable than route A. On the basis of the biological data of compounds **5** (vide infra), for optimization of the bicyclic heteroaryl moiety (see Table 2), derivative **9c** with the optimal spacer length (n = 3) and the unsubstituted indole was used.

Table 1. Synthesis of Benzdioxin Piperazine Derivatives (**5a**−**p**)

compd	n	R	salt[a]	route	yield based on **4** (%)
5a	1	H			33
5b	2	H			99
5c	3	H		B	77
5d	4	H	0.5 fum	B	25
5e	5	H	0.5 fum	A	35
5f	3	4-F	0.5 fum	B	30
5g	3	5-F	0.5 fum	B	70
5h	3	6-F	0.5 fum	B	56
5i	3	7-F	0.5 fum	B	68
5j	3	5-OMe	0.5 fum	B	83
5k	3	4-Cl	0.5 fum	B	69
5l	3	5-Cl	0.5 fum	B	62
5m	3	6-Cl	0.5 fum	B	61
5n	3	7-Cl	0.5 fum	B	73
5o	3	5-Me	0.5 fum	B	65
5p	3	7-Me	0.5 fum	B	78

[a] fum = fumarate.

Scheme 1[a]

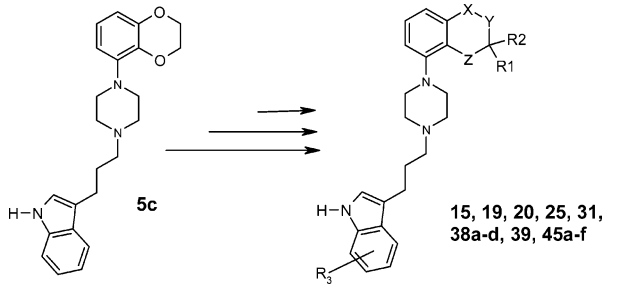


[a] Reagents and conditions: (i) n = 1: CH_2O, indole, ethanol, reflux, 18 h. (ii) n = 2: 3-(2-bromoethyl)indole, CH_3CN, KI, DIPEA, reflux, 18 h. (iii) Compound **4**, dry THF, DCC, RT, 18 h. (iv) $LiAlH_4$, reflux, 2 h. (v) Methanesulfonyl chloride, DIPEA, EtOAc, RT. (vi) Compound **4**, CH_3CN, KI, DIPEA, reflux, 18 h.

The synthesis of 3-[3-(4-chroman-5-yl-piperazin-1-yl)-propyl]-1*H*-indole **15** is depicted in Scheme 2. The starting material, 3-(4-benzyl-piperazin-1-yl)phenol (**10**),[17] was deprotonated with NaOMe in methanol and subsequently alkylated with propargyl bromide to furnish **11** in a yield of 60%. Compound **11** was heated at 220 °C in diethylaniline yielding the ring closed derivative **13** together with its region isomer **12** in a yield of 91% (ratio **13**/**12** of 3:1). The one-pot reduction of the double bond and the removal of the benzyl in **13** with H_2 and Pd/C furnished **14** in a yield of 85%. Subsequent alkylation of **14** with **9c** yielded compound **15** in a moderate yield of 50%.

The synthesis of compounds **19**, **20**, and **25** is outlined in Scheme 3. At first, compound **16**[14] was converted to **19** with **9c** according to route B in a yield of 50%. The

Table 2. Lead Optimization of **5c** by Exploration of the Bicyclic Heteroaryl Moiety



compd	X	Y	Z	R_1	R_2	R_3	synthesis
15	O	CH_2	CH_2	H	H	H	Scheme 2
19	NH	CH_2	CH_2	H	H	H	Scheme 3
20	NMe	CH_2	CH_2	H	H	H	Scheme 3
25	NH	CH_2	CH_2	Me	H	H	Scheme 3
31	NH	C(=O)	CH_2	H	H	H	Scheme 4
38a	NH	C(=O)	O	H	H	H	Scheme 5
38b	NH	C(=O)	O	Me (rac)[a]	H	H	Scheme 5
38c	NH	C(=O)	O	Me	Me	H	Scheme 5
38d	NMe	C(=O)	O	Me (rac)	H	H	Scheme 5
39	NH	CH_2	O	H	H	H	Scheme 5
45a,**c**,**e**	NH	C(=O)	O	(*R*)-Me	H	H, 5-F, 7-F	Scheme 6
45b,**d**,**f**	NH	C(=O)	O	(*S*)-Me	H	H, 5-F, 7-F	Scheme 6

[a] rac = racemic.

synthesis of **20** started with the acylation of **16** with **6c** in the presence of 2-chloro-1,3-dimethyl-2-imidazolinium tetrafluoroborate (CIP) giving **17** in a yield of 67%. Compound **17** was formylated[18] with formic acid in acetic anhydride to give **18**, and subsequent reduction of both amides in **18** with $LiAlH_4$ gave compound **20** in a yield of 70% based on **17**.

The racemic 3-methyl derivative of compound **19** was prepared starting from quinoline derivative **21**. Reduction of *21* to **22** was accomplished with H_2 and Pt/C under a pressure of 4 atmosphere. Crude **22** was converted to the corresponding piperazine derivative **23** with the *p*-tosyl-protected bis-chloroethylene amine (BCEA) in a yield of 50% based on **21**. Subsequent deprotection of **23** under strong acidic conditions gave **24**, which was converted to **25** following route B in a yield of 79% based on **23**.

The synthetic route toward compound **31** is shown in Scheme 4. Conversion of known **26** to key intermediate **28b** could be accomplished following two routes. According to the literature,[19] a Beckman rearrangement of **27b** (obtained in two steps from **26**) furnished a mixture of **28a** and **28b** in an unfavorable ratio of 3:1 but in a good combined yield of 84%. Alternatively, we found that a Schmidt rearrangement[20] of compound **26** with sodium azide and sulfuric acid in benzene gave a mixture of **28a** and the desired derivative **28b** in a ratio of 1/2 and in a yield of 67%. Reduction of the nitro moiety in **28b** (to **29**) and conversion of **29** into the piperazine derivative **30** with BCEA was accomplished in a yield of 35% based on **28b**. Finally, compound **30** was alkylated with **9c** to furnish compound **31** in a yield of 77%.

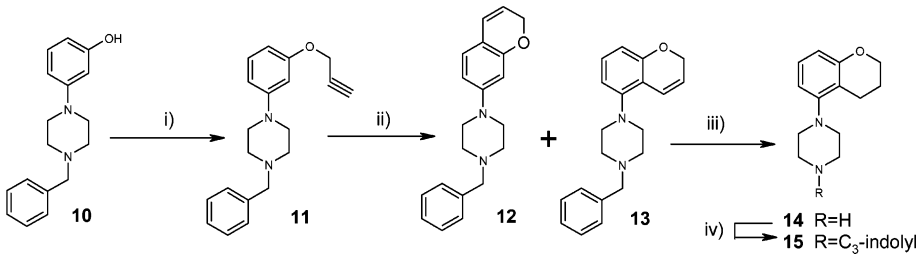
The synthetic route[21] of the last series of compounds described in this paper, compounds **38**, **39**, and **45**, is depicted in Schemes 5 and 6. The known starting material 2-amino-4-chlorophenol **32** was converted to **34a**−**c** with the chloroacetyl chloride derivatives **33a**,**b** and the bromoacetyl bromide derivative **33c** (37−79% yield). Subsequent nitration of **34a**−**c**, followed by K_2CO_3-mediated ring closure, furnished compounds **35a**−**c** in an overall yield of 40−70% based on **34**. Methylation of the amide moiety in **35b** (to **35d**) was accomplished with methyl iodide and KOH in a yield of 90%. Reduction of the nitro group and the 4-chloro function in **35a**−**d** (to **36a**−**d**) and subsequent reaction of the thus obtained aniline with BCEA·HCl yielded the bicyclic heteroarylpiperazine derivatives **37a**−**d** in an average yield of 40% over two steps. Compounds **37a**−**d** were converted to the C_3-indolyl derivatives **38a**−**d** via route B in a yield of 40−70%. The amide moiety in **38a** could be reduced with $LiAlH_4$ furnishing compound **39** in a yield of 80%.

On the basis of the biological properties of **38b**, it was decided to prepare from this compound both enantiomers (i.e., **45a** and **45b**) together with two pairs of indole-substituted analogues (**45c**−**f**). The synthesis of the enantiomers of **38b** is outlined in Scheme 6. Commercially available 2-amino-4-chloro-6-nitro-phenol **40** was converted with chirally pure lactate derivatives **41a**,**b** (to **42a**,**b**) under Mitsunobu conditions with inversion of configuration accompanied by a simultaneous ring closure. Reduction of the 6-nitro and 4-chloro group in **42a**,**b** (to **43a**,**b**) and subsequent transformation of the thus obtained aniline with BCEA·HCl yielded piperazine derivatives **44a**,**b** in a yield of 25−60% over two steps. The thus obtained piperazine derivatives were converted with the appropriate mesylate **9** (i.e., **9c**, **9g**, and **9i**) to give the end products **45a**−**f** in a yield of 50−80%. The enantiomeric purity of compound **45c** was determined via an HPLC method using a Chiracel OD-R column in a comparison experiment using the (*S*)-enantiomer **45d**. The experiments showed that the compounds had an enantiomeric purity of >95%.

Results and Discussion

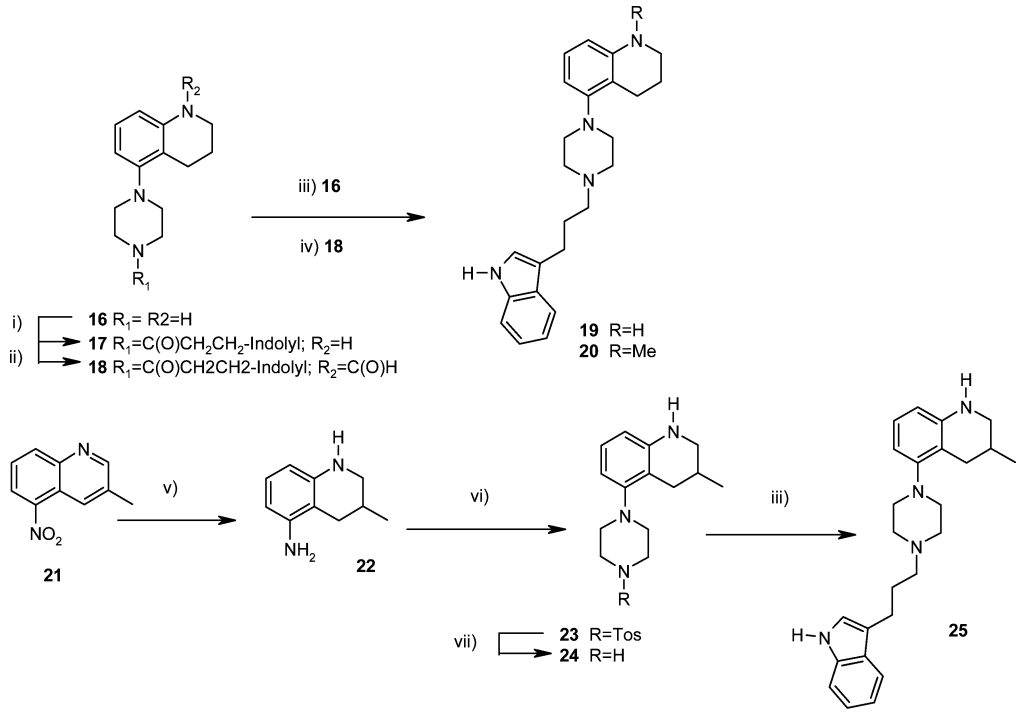
The affinity for dopamine D_2 receptors in a membrane preparation of CHO cells transfected with the human

Scheme 2[a]



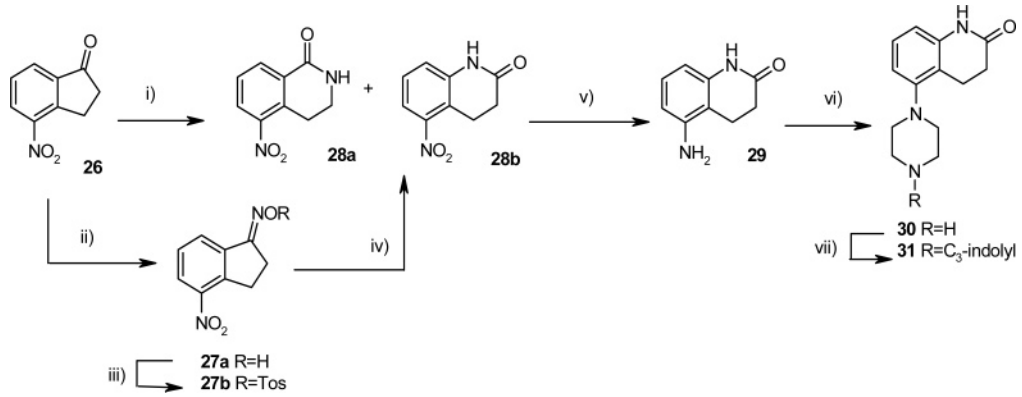
[a] Reagents and conditions: (i) NaOMe, MeOH, followed by propargyl bromide in DMF, RT. (ii) Heat at 220 °C, diethylaniline, 1 h. (iii) H_2, Pd/C, 2 mol equiv of HCl in EtOH, 2 h, RT. (iv) Compound **9c**, CH_3CN, KI, DIPEA, reflux, 16 h, THF, RT.

Scheme 3[a]



[a] Reagents and conditions: (i) CIP, DIPEA, DCM, RT, 16 h. (ii) HCOOH, $(Ac)_2O$, 55 °C, 1 h. (iii) Compound **9c**, CH_3CN, KI, DIPEA, reflux, 16 h. (iv) $LiAlH_4$, Et_2O, RT, 16 h. (v) H_2, Pt/C, EtOH, 6 h, 4 atm, 40 °C. (vi) $(Cl\text{-}CH_2CH_2)_2N$-Tos, chlorobenzene, PTS, 140 °C, 144 h. (vii) 6 N HCl, reflux, 18 h.

Scheme 4[a]



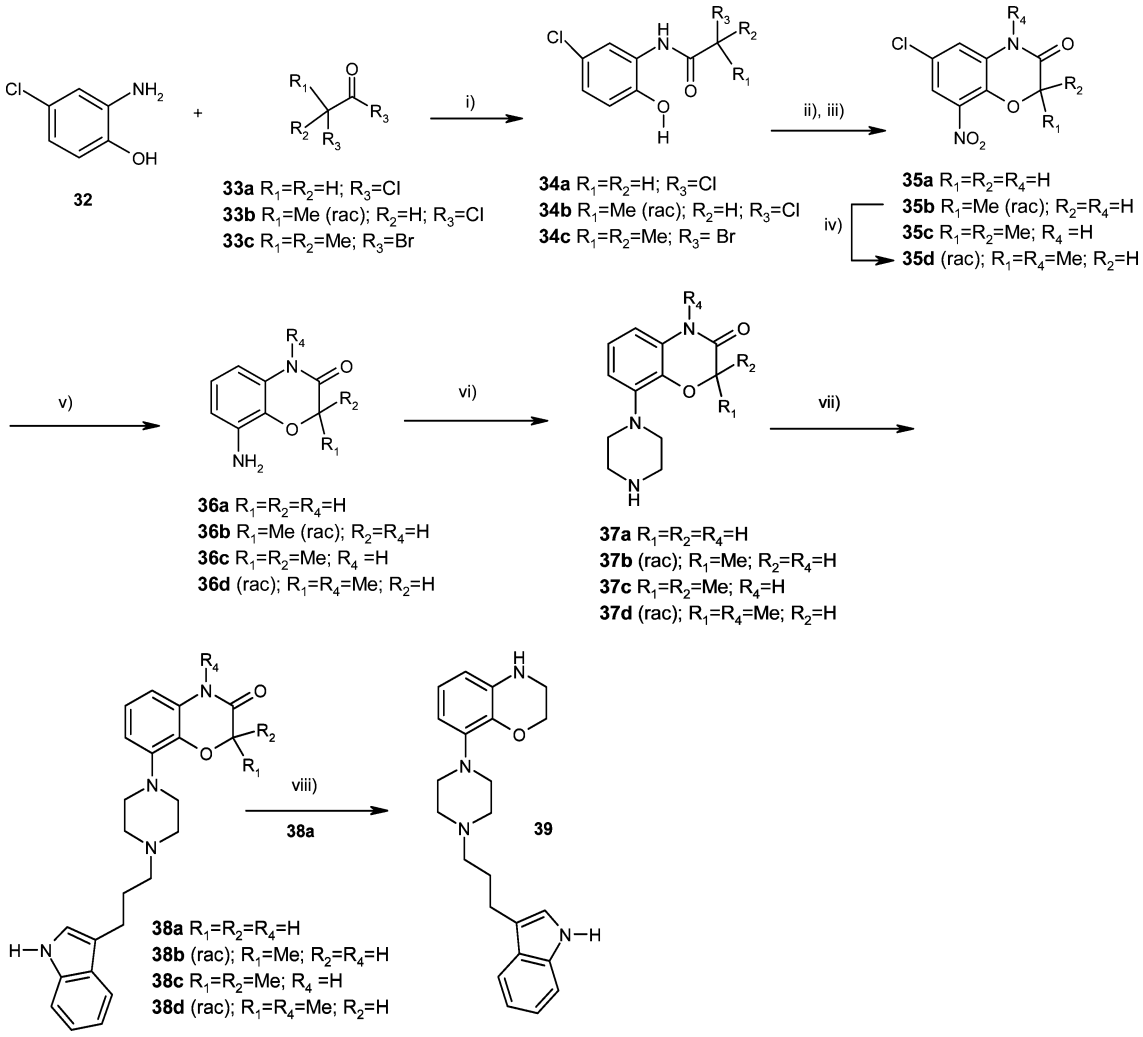
[a] Reagents and conditions: (i) Concentrated H_2SO_4, NaN_3, benzene, 70 °C, 10 min. (ii) $NH_2OH{\cdot}HCl$, 4 N NaOH, MeOH, −10 °C to RT. (iii) TosCl, 4 N NaOH, acetone, −10 °C to RT. (iv) $AlCl_3$, DCM, −10 °C to RT. (v) Pd/C, H_2, EtOH, 3 h. (vi) BCEA·HCl, chlorobenzene, reflux, 66 h. (vii) Compound **9c**, CH_3CN, KI, DIPEA, reflux, 16 h.

D_2L receptor was measured by binding studies using [^{3}H]spiperone as the ligand.[22] The affinity for SR sites in rat frontal cortex membranes was measured using [^{3}H]paroxetine.[23] The results on these receptors obtained with the compounds described in this paper are given in Tables 3 and 4. The affinities are expressed as K_i (nM) and are calculated from at least three independent experiments.

The dopaminergic antagonist and serotonin reuptake inhibitory activity were examined *in vivo* after oral (po) administration of the compounds by respectively antagonizing apomorphine induced climbing behavior[24] in mice (APO) and the potentiation of 5-hydroxytryptophan (5-HTP; the precursor of serotonin) induced serotinin syndrome[25] in mice.

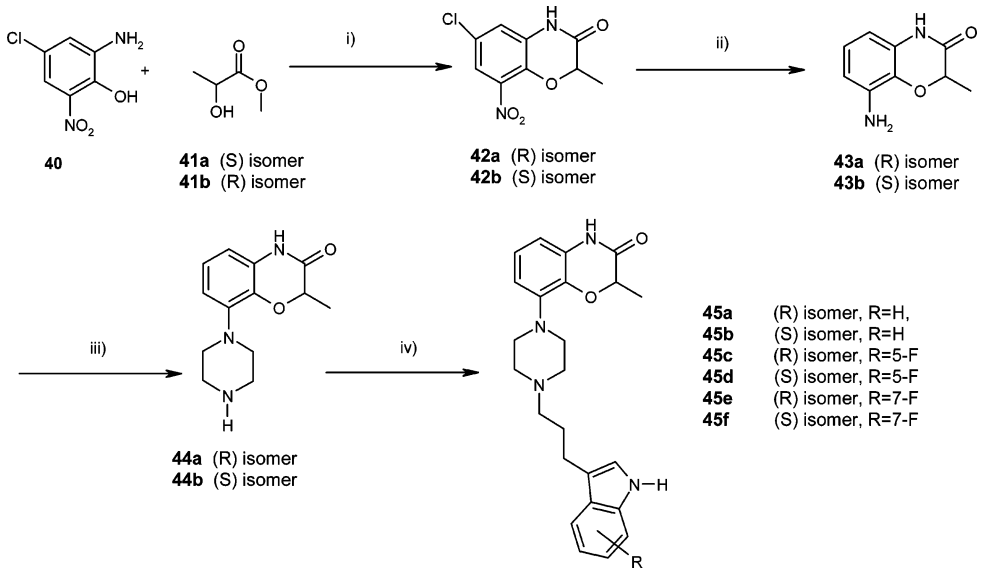
Table 3 shows that the combination of eltoprozine (**4**) with an indole moiety at a C_3 distance (i.e., compound **5c**) was promising, indeed, showing a D_2 receptor affinity of 21 nM and a SR site affinity of 0.4 nM. In addition, the APO and 5-HTP results of **5c** were rather encouraging with ED_{50} values of, respectively, 10 and 22 mg/kg (po). It is also clear from Table 3 that variation in the spacer length did not lead to better results if compared to compound **5c**. Shortening the spacer length to $n = 1$ or 2 (i.e., **5a** and **5b**) reduced the SR site affinity significantly and did not result in a higher D_2 receptor affinity. Enlarging the spacer length to $n = 4$ (i.e., **5d**) resulted in a better affinity for the D_2 receptor but also caused a 100-fold decrease of the SR site affinity. A spacer length of $n = 5$ (**5e**) did not improve this, leading to the conclusion that a preferred combination of activity on both of the receptors was obtained with a spacer length of $n = 3$. The next round of optimization was directed to the substitution pattern of the indole moiety in combination with the optimal spacer length of $n = 3$. Compounds **5f**−**i** having a fluorine atom at the indole

Scheme 5[a]



[a] Reagents and conditions: (i) Pyridine/DCM, RT. (ii) $HNO_3 \cdot H_2O$, 0 °C, 1 h. (iii) K_2CO_3, toluene, azeotropic distribution. (iv) MeI, KOH, DMF, 22 h, reflux. (v) H_2, Pd/C, 2 h, RT. (vi) BCEA·HCl, chlorobenzene, reflux, 72 h. (vii) Compound **9c**, CH_3CN, KI, DIPEA, reflux overnight. (viii) LiAlH4, THF, reflux, 3 h.

Scheme 6[a]



[a] Reagents and conditions: (i) $(Ph)_3P$, DIAD, dry THF, RT, 20 h. (ii) H_2, Pd/C, 2 h, RT. (iii) BCEA·HCl, chlorobenzene, reflux, 72 h. (iv) Compounds **9c/9g/9i**, CH_3CN, KI, DIPEA, reflux, 16 h.

Table 3. In Vitro and in Vivo Test Results on Dopamine D_2 Receptors (Receptor Binding and APO, Respectively) and SR Sites (Receptor Binding and 5-HTP, Respectively) for Compounds **3**−**5**

			in vitro[a]		in vivo	
compd	*n*	R	hD_2 (K_i nM)	rSRI (K_i nM)	APO[c] (ED_{50} mg/kg po)	5-HTP[d] (ED_{50} mg/kg po)
haloperidol			2.0 ± 0.1	NA[b]	0.1	
indalpine (**3**)			NA	2.0 ± 0.1		
5a	1	H	62.0 ± 17	176.0 ± 59		
5b	2	H	45.0 ± 17	12.0 ± 3.8		
5c	3	H	21.0 ± 9.9	0.4 ± 0.1	10	22
5d	4	H	5.1 ± 1.2	60.0 ± 12	3.8	>30
5e	5	H	9.1 ± 1.8	37.0 ± 3		
5f	3	4-F	8.1 ± 3.1	0.4 ± 0.1	13	32
5g	3	5-F	19.0 ± 3	0.3 ± 0.1	15	2.0
5h	3	6-F	14.6 ± 3.5	1.6 ± 0.2	9	30
5i	3	7-F	10.6 ± 4	0.6 ± 0.1	4.1	28.4
5j	3	5-OMe	15.0 ± 4	14.0 ± 4		
5k	3	4-Cl	24.0 ± 3	1.4 ± 0.4		
5l	3	5-Cl	31.6 ± 16	0.5 ± 0.7		
5m	3	6-Cl	2.1 ± 1	2.0 ± 0.7	4.5	86
5n	3	7-Cl	15.5 ± 5.4	7.9 ± 2.8		
5o	3	5-Me	10.7 ± 2.8	0.4 ± 0.9		
5p	3	7-Me	15.9 ± 4.7	12.0 ± 5		

[a] Calculated from three independent experiments. [b] NA = not active (>1 μM). [c] Antagonizing apomorphine induced climbing behavior in mice (po). [d] 5-HTP induced serotonin syndrome like behavior in mice (po).

Table 4. In Vitro and in Vivo Test Results on D_2 Receptors (Receptor Binding and APO, Respectively) and SR Sites (Receptor Binding and 5-HTP, Respectively) for Compounds **15**−**45f**

	in vitro[a]		in vivo	
compd	hD_2 (K_i nM)	rSRI (K_i nM)	APO[b] (ED_{50} mg/kg po)	5-HTP[c] (ED_{50} mg/kg po)
5c	21.0 ± 9.9	0.4 ± 0.1	10	22
15	20.3 ± 2.7	1.1 ± 0.3	15	100
19	11.3 ± 2.4	1.1 ± 0.2	6.9	15
20	90.0 ± 45	7.4 ± 3.1		
25	15.0 ± 6	2.7 ± 0.6	2.6	>100
31	11.4 ± 3	1.5 ± 0.9	2.6	9.0
38a	4.3 ± 1.2	0.6 ± 0.2	0.9	30
38b	4.5 ± 1.1	0.4 ± 0.1	0.13	3.0
38c	7.4 ± 0.5	2.8 ± 0.6	0.53	7.3
38d	35.7 ± 7.3	1.4 ± 0.4	1.2	5.6
39	17.9 ± 3.8	1.5 ± 0.4	>20	100
45a	8.7 ± 3.9	0.5 ± 0.3	0.13	3.0
45b	1.0 ± 0.3	1.0 ± 0.3	0.3	>10
45c	6.9 ± 1.8	0.2 ± 0.1	0.08	0.15
45d	4.7 ± 1.4	0.7 ± 0.2	0.6	0.7
45e	5.3 ± 1	2.4 ± 1.3	0.04	30
45f	1.0 ± 0.3	3.0 ± 1	0.6	10

[a] Calculated from three independent experiments. [b] Antagonizing apomorphine induced climbing behavior in mice (po). [c] 5-HTP induced serotonin syndrome like behavior in mice (po).

ring showed a comparable in vitro activity at the SR site as **5c**, but in addition, the D_2 affinity appeared to be slightly increased by this modification. In this respect, it is of interest to note that the in vivo activity of these compounds, when compared to **5c**, for the APO was improved by a factor of 2.5 with the 7-F derivative (i.e., **5i**) and for the 5-HTP was improved by a factor 11 with the 5-F derivative (i.e., **5g**). The 5-OMe derivative **5j** did not show any improvement in activity over **5c**. The series with a chlorine substituent at the indole ring (i.e., compounds **5k**−**n**) showed a significant improvement in D_2 affinity for the 6-Cl derivative (i.e., **5m**). The D_2 affinity was increased by a factor 10 (to 2 nM), and the compound also improved in the APO by a factor 2. Unfortunately, this was accompanied with a significant decrease on both the in vitro and the in vivo activity at the SR site. Finally, we prepared the 5- and 7-Me derivatives (i.e., **5o** and **5p**), which both did not improve the affinity for the D_2 receptor and the SR site if compared to **5c**. In conclusion, optimal results on the D_2 receptor and SR receptor affinity are obtained when the indole moiety is positioned at a C_3 distance from the phenyl piperazine. In compound **5c** also, in vivo activity was observed in both the APO and the 5-HTP models. The 5-F derivative of **5c** (i.e., **5g**) showed an increase in 5-HTP potency without a significant loss in APO activity, while the 7-F derivative of **5c** (i.e., **5i**) was beneficial for the APO activity. In the next stage, we turned our attention in the direction of modifying the benzdioxan moiety of **5c** with the intention to increase the D_2 receptor affinity without decreasing the affinity for the SR site. The novel bicyclic heteroarylpiperazine structures were at first alkylated with the unsubstituted indole propyl derivative **9c**. The chroman- and tetrahydroquinoline derivatives (i.e., **15** and **19**, **20** and **25**) resulted in a decrease of the affinity for the SR site without the desired increase in D_2 receptor affinity (see Table 4). The quinolinone derivative **31** showed better results, especially in vivo, in which the APO behavior was improved by a factor 4. Going from the quinolinone **31** to the benzo[1,4]oxazin-3-one series **38** appeared to be the key step in the lead optimization process. Compound **38a** showed that the D_2 receptor affinity increased by almost a factor 5, and in addition, the APO results were more than promising with 0.9 mg/kg. On the other hand, the 5-HTP result of **38a** was rather disappointing with 30 mg/kg. This was improved significantly by the introduction of a methyl at the 2-position of the oxazinone moiety (i.e., compound **38b**). The receptor binding results of **38b** were unchanged if compared to **38a**, but the in vivo results changed from 0.9 to 0.13 in the APO test and from 30 to 3 mg/kg in the 5-HTP test, an increase by a factor of 7−10-fold. Further methylation of **38b** to the 2,2-dimethyl derivative **38c** decreased both the APO and the 5-HTP component, whereas the N(Me) derivative **38d** resulted in a significant decrease of the D_2 component when compared to **38b**. In addition, it is clear from Table 4 that reduction of the 3-keto functionality in the benzoxazinone moiety of **38a** giving compound **39** leads to a dramatic loss of in vivo activity in both the APO and the 5-HTP tests. The two enantiomers of the preferred compound **38b** were separately prepared (i.e., **45a** and **45b**), and the receptor binding assays on these derivatives did not reveal a clear preference for one isomer. The same observation could be made by comparing the *R*- and *S*-enantiomers of its 5-F and 7-F indole derivatives (compounds **45c**, **45d**, **45e**, and **45f** respectively). On the other hand, the in vivo results of these chirally pure compounds show interesting differences in activity. For instance, from the in vivo results, it is clear that the *R*-(−)-derivatives **45a**,**c**,**e** are the better compounds by at least a factor 3 when compared to the *S*-(+)-derivatives **45b**,**d**,**f**. In addition, it is clear that the introduction of the 5-F in **45a** (to **45c**) even slightly improved the already very good APO activity (0.13 to 0.08 mg/kg), and on top of this, it also had a tremendous positive effect on the 5-HTP test, which improved by a factor 20 (3 to 0.15 mg/kg po), a similar effect as was

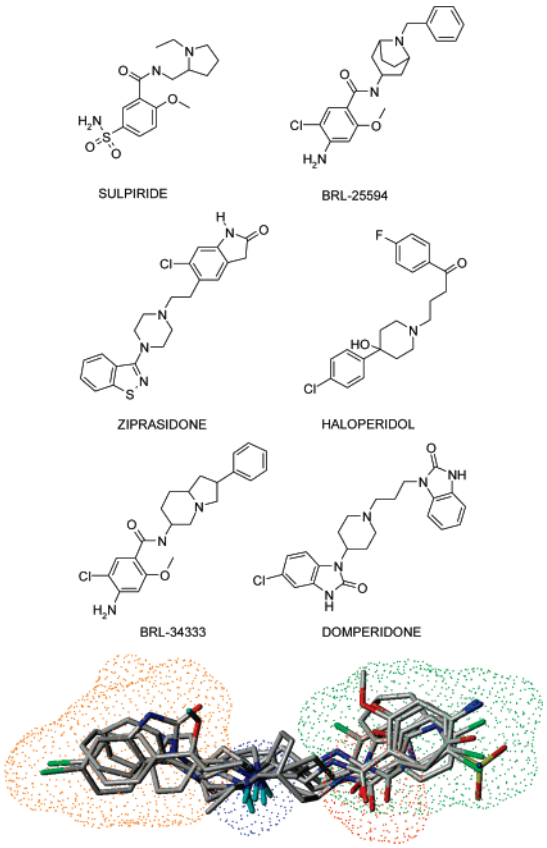


Figure 2. (a) Representative D_2 antagonists used for the building of the D_2 pharmacophore. (b) The D_2 antagonism pharmacophore.

observed for changing **5c** to **5g**. In this respect, it is of interest to note that the introduction of a 7-F substituent at the indole moiety of **45a** (to **45e**) improves the APO activity even by a factor 3 when compared to **45a** but also has a dramatic negative effect on the 5-HTP test in which the activity was diminished by a factor 10. In conclusion, several optimization steps led to **45c** as the most promising candidate for further development.

Molecular Modeling

A pharmacophoric model for D_2 antagonism was constructed from the well-known antagonists given in Figure 2a. It can be summarized (see Figure 2b) as a lipophilic aromatic area (orange) located about 6 Å from a basic nitrogen atom (blue). Further away (7.5 Å) from this center, there is a flat aromatic region with a lipophilic extension (green) within the vicinity of an H-bond accepting oxygen atom (red). This model is in line with other models described in the literature.[26]

We also reproduced the SRI pharmacophore reported recently[27] based on well-established SRIs (Figure 3a). It is characterized (see Figure 3b) by a basic nitrogen atom (blue), a lipophilic extended aromatic region (green) at 6.1 Å, and a lipophilic part (purple-blue). Additionally, it was found[28] that the space around the basic nitrogen atom is sterically restricted (violet). The presence of the same features in both pharmacophores may account for the possibility and existence of bifunctional molecules, although none of the features appeared to overlap properly in three-dimensional space. Apparently, **45c** can adopt different conformations to fit in

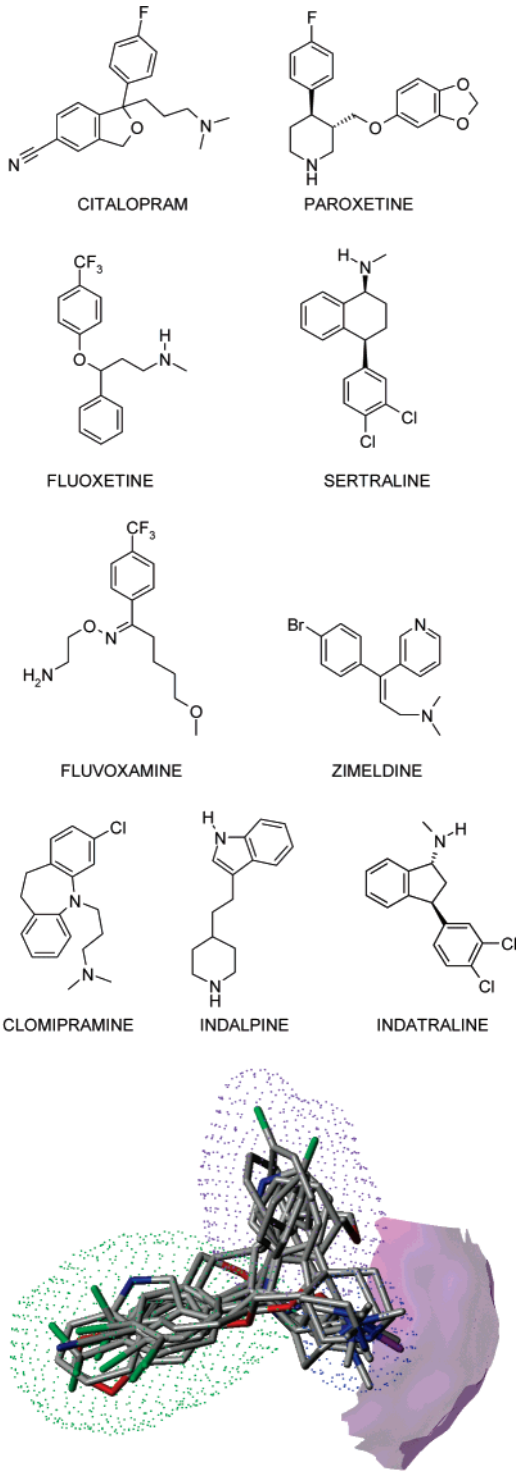


Figure 3. (a) Representative SRIs used for the building of the SRI pharmacophore. (b) The SRI pharmacophore.

both models. The flexibility of **45c** can be assigned to the aliphatic chain and the piperazine moiety. The conformational behavior of the latter functionality was further examined by semiempirical calculations on the protonated model compound **A** (see Figure 4). Phenylpiperazines tend to a planar orientation of the phenyl ring with respect to the piperazine ring, in which its π-system can conjugate with the nitrogen lone pair.[29] This can be influenced by steric and electronic effects of substituents on the aromatic ring. It was found that the protonated piperazine ring can adopt a chair or twisted boat conformation. In the chair conformation,

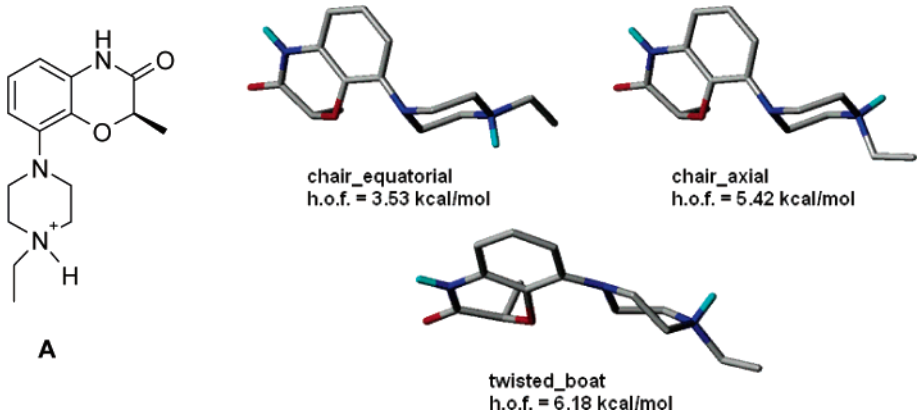


Figure 4. Low-energy conformations and their heats of formation (h.o.f.) of the chair (upper) and twisted boat conformation (lower) of model compound A.

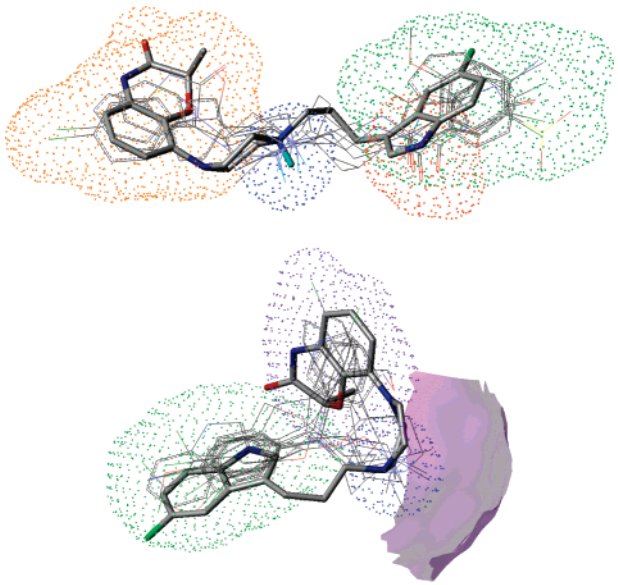


Figure 5. Compound **45c** fit into the D_2 antagonism pharmacophore (top) and into the SRI pharmacophore (bottom).

the alkyl substituent can have an axial or equatorial orientation with respect to the piperazine ring. Because of the symmetry of the twisted boat conformation, there is matter of only one orientation of the alkyl chain. The three concerning low-energy conformations of compound **A** and their heats of formation are given in Figure 4. The substitution around the anilinic nitrogen atom is almost planar due to the above-mentioned conjugation and the subsequent sp^2 character of the nitrogen atom. Nevertheless, in the chair conformations, a "pseudo"-axial conformation of the aromatic moiety is preferred, while in the twisted boat conformation this ring takes the "pseudo"-equatorial orientation. As expected, the equatorial orientation of the alkyl chain in the chair conformation is preferred above the axial orientation. All conformations are within an energy range so that they are accessible at room temperature, although the chair conformations have a lower energy than the twisted boat conformation. In line with these findings, two different low-energy conformations of **45c** were found to fit in the D_2 and SRI pharmacophore, having h.o.f.s of 13.7 and 17.1 kcal/mol, respectively.[30] In Figure 5, these conformations are shown in their pharmacophores. In the D_2 pharmacophore, **45c** has adopted the chair equatorial conformation, while for the SRI pharmacophore the molecule has taken the twisted boat conformation. Very recently, Morphy et al.[31] described their concept of "multiple" ligands that act on different targets. They differentiate between "conjugates", in which two pharmacophores are connected by a (cleavable) linker and (partially) overlapping pharmacophores referring to ligands of which different features in one molecule, overlapping to a varying extent, are responsible for activity on different targets. In fact, **45c** can be considered to be from another type. The molecule as a whole meets two different pharmacophores by its ability to adopt two different conformations.

Further in Vivo and in Vitro Profiling of 45c. The kinetics of **45c** was studied in both in vitro and in vivo experiments. Compound **45c** has a log *P* of 3, which is considered to be optimal for orally dosed drugs targeting the CNS. The aqueous solubility of **45c** (at both pH 4 and pH 7.4) exceeded 100 μg/mL, which was the highest concentration tested. Membrane passage was tested using LLC PK1 MDR cells in a two compartment cell culture system described.[32] After 3 h of incubation with 1 μg/mL of **45c**, more than 28% of the compound was transported over this cellular membrane. This brings **45c** in the category of well membrane permeable drugs. In addition, it was determined that **45c** is a poor substrate for P-glycoprotein.[32] In vivo pharmacokinetic studies in rats show that **45c** has an oral bioavailability of about 20%. The exposure to **45c** both in plasma and in brains appears to be proportional with a dose between 3 and 30 mg/kg. No drug accumulation occurs after repeated dosing. From iv studies in rats, it was calculated that **45c** is a high clearance drug, with a clearance of 120 mL/min/kg body weight. Because of its high volume of distribution of about 7 L/kg, its plasma half-life of about 3 h after oral dosing is in the range of 1−8 h, which is usually observed for preclinical drug candidates for the central nervous system. Compound **45c** easily penetrates the brain since high brain/plasma values of 3−6 are found in pharmacokinetic studies in rats. Because this ratio is similar in value to that of the volume of distribution of **45c** in iv studies in rats, this indicates that the compound has free access to the brain. These favorable in vitro and in vivo pharmacokinetic data showed their value in in vivo profiling tests. For example, the antipsychotic potency of **45c** was demonstrated by the fact that **45c** significantly disrupted avoidance behavior in a conditioned avoidance response

paradigm (CAR)[33] in three independent groups of trained rats (ED_{50} = 2.5 mg/kg po, based on the free base of **45c**). Thus, it can be concluded that **45c** is a promising novel antipsychotic indeed, combining strong dopamine D_2 receptor antagonism[34] with SRI effects in the same dose range.

Conclusion

A series of novel bicyclic heteroaryl-4-[3-(1*H*-indol-3-yl)propyl]piperazines proved to be potent in vitro dopamine D_2 receptor and SR site ligands. Some key representatives showed potent pharmacological in vivo activities after oral dosing in both the antagonism of apomorphine-induced climbing and the potentiation of 5-HTP-induced behavior in mice. In particular, 8-{4-[3-(5-fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]-oxazin-(*R*)-2-methyl-3-one (**45c**) was very potent both in vitro and in vivo. Molecular modeling studies showed that the bifunctional activity of **45c** can be explained by its ability to adopt two different conformations fitting either the dopamine D_2 receptor pharmacophore or the SR pharmacophore. In vitro and in vivo studies revealed that **45c** has favorable pharmacokinetic properties. The antipsychotic potency of **45c** was demonstrated in the CAR paradigm. Thus, it can be concluded that **45c** is a promising novel antipsychotic indeed, combining strong dopamine D_2 receptor antagonism with SRI effects in the same dose range, and **45c** was selected for clinical development under the acronym SLV314.

Experimental Section

^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance DRX600 instrument (600 MHz), a Varian UN400 instrument (400 MHz), or a Varian VXR200 instrument (200 MHz) using DMSO-d_6 or $CDCl_3$ with $(CH_3)_4Si$ as an internal standard, as solvents. Chemical shifts are given in ppm (δ scale). Thin-layer chromatography was performed on Merck precoated 60 F_{254} plates, and spots were visualized with UV light. Column chromatography was performed using silica gel 60 (0.040−0.063 mm, Merck). Melting points were recorded on a Büchi B-545 melting point apparatus and are uncorrected. Mass spectra were recorded on a Micromass QTOF-2 instrument with MassLynx application software for acquisition and reconstruction of the data. Exact mass measurement was done of the quasimolecular ion (MH^+). Optical rotations ($[\alpha]_d$) were measured on an Optical Activity polarimeter. Specific rotations are given as deg/dm, and the concentration values are reported as g/100 mL of the specified solvent and were recorded at 23 °C. Elemental analyses were performed on a Vario EL elemental analyzer by Solvay Pharmaceuticals (Hanover, Germany). Yields refer to isolated pure products and were not maximized. All test compounds have a chemical purity of at least 95% unless stated otherwise.

3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-ylmethyl]-1*H*-indole (5a). A solution of compound **4** (2.2 g, 8.5 mmol),[14] indole (1 g, 8.5 mmol), and formaldehyde (37%, 0.7 mL) in ethanol (30 mL) was refluxed for 18 h. The mixture was allowed to cool to room temperature and was concentrated in vacuo to give crude **5a** as a brown oil, which was purified by silica gel column chromatography (EtOAc/methanol, 95/5, v/v). Compound **5a** was obtained as a white solid (850 mg, 33%); mp 85−86 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H, NH-indole); 7.65 (d, 1H, J = 8 Hz, H-arom); 7.35 (d, 1H, J = 8 Hz, H-arom); 7.18 (d, 1H, J = 2 Hz, H2-indole); 7.07 (t, 1H, J = 7 Hz, H-arom); 6.98 (t, 1H, J = 7 Hz, H-arom); 6.67 (t, 1H, J = 7 Hz, H-arom); 6.4−6.48 (2 × d, 2H, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.7 (bs, 2H, CH_2); 3.0, 2.55 (2 × bs, 8H, piperazine). HRMS ($C_{21}H_{24}N_3O_2$) $[M + H]^+$: found *m/z*, 350.1899; calcd, 350.1869. Anal. ($C_{21}H_{23}N_3O_2$) C, H, N.

3-{2-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]ethyl}-1*H*-indole (5b). To a solution of compound **4** (1.1 g, 4.5 mmol) in dry acetonitrile (40 mL) was added DIPEA (2.3 mL, 13.5 mmol), commercially available 3-(2-bromo-ethyl)-1*H*-indole (1.0 g, 4.5 mmol), and potassium iodide (0.74 g, 4.5 mmol). The mixture was refluxed overnight, after which time TLC analysis revealed complete conversion of the starting material **4** (DMA 0.25 = DCM/MeOH/NH_4OH, 96/3.73/0.25, v/v/v). The mixture was concentrated in vacuo, and the crude product was purified by silica gel column chromatography (DMA 0.25) to give pure **5b** (1.6 g, 99%) as a white solid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.7 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.12 (d, 1H, J = 2 Hz, H2-indole); 7.05 (t, 1H, J = 7 Hz, H-arom); 6.95 (t, 1H, J = 7 Hz, H-arom); 6.70 (t, 1H, J = 7 Hz, H-arom); 6.44−6.5 (dd, 2H, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.03 (bs, 4H, piperazine); 2.9 (bt, 2H, CH_2); 2.65 (m, 6H, CH_2 and 4H piperazine). Anal. ($C_{22}H_{25}N_3O_2$) C, H, N.

General Procedure for the Synthesis of Compounds 5c−p. Route A. To a solution of compound **4** in dry THF (5 mL/mmol) was added 3-(ω-alkyl-carboxylic acid)-1*H*-indole **6**,[15] dicyclohexylcarbodiimide (DCC, 1 equiv), and the mixture was stirred overnight under a blanket of nitrogen. The reaction mixture was filtered and concentrated in vacuo. The residue was purified by silica gel column chromatography to give compound **7**. Compound **7** was dissolved in dry THF (5 mL/mmol) and cooled to 0 °C, and to this mixture a solution of $LiAlH_4$ (1.5 equiv) in dry THF (10 mL/mmol) was added. The reaction mixture was refluxed for 2 h and allowed to cool to room temperature. To the cooled mixture was added 1 N NaOH solution (5 mL/mmol), and the mixture was stirred for 1 h. The mixture was extracted with DCM (2×), and the combined organic layers were washed with water and dried on $MgSO_4$. The crude residue was purified by silica gel column chromatography to give compound **5**. The compounds were converted to the fumaric acid salts by addition of 0.5 equiv of fumaric acid, unless stated otherwise.

Route B. To a solution of compound **4** in dry acetonitrile (10 mL/mmol) was added methanesulfonic acid (1*H*-indole-3-yl)alkanoic ester (**9**)[16] (1 equiv), potassium iodide (1 equiv), and DIPEA (3 equiv). The reaction mixture was refluxed for 18 h, after which time TLC analysis revealed complete conversion of **4**. The mixture was concentrated in vacuo, and the crude residue was purified by silica gel column chromatography to give compound **5**. The compounds were converted to the fumaric acid salts by addition of 0.5 equiv of fumaric acid, unless stated otherwise.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-1*H*-indole (5c). Compound **5c** was prepared via route B and isolated as a white solid as the free base in a yield of 77%. TLC analysis and silica gel column chromatography: DMA 0.25, R_f 0.4; mp 150−152 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.7 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.06 (d, 1H, J = 2 Hz, H2-indole); 7.04 (t, 1H, J = 7 Hz, H-arom); 6.95 (t, 1H, J = 7 Hz, H-arom); 6.7 (t, 1H, J = 8 Hz, H-arom); 6.4−6.5 (2 × dd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0 (bs, 4H, piperazine); 2.72 (t, 2H, CH_2); 2.55 (bs, 4H, piperazine); 2.4 (t, 2H, CH_2); 1.85 (q, 2H, CH_2). ^{13}C NMR (DMSO-d_6): 144.1, 141.9, 136.6, 136.4, 127.5, 114.8 (6 × C-quart), 122.7, 121.0, 120.5, 118.6, 118.3, 111.6, 111.3, 110.4 (8 × CH-arom), 64.1, 64.0 (2 × C−O), 50.5, 53.4 (C-piperazin), 58.0, 27.5, 22.8 (3 × CH_2-propyl). Anal. ($C_{23}H_{27}N_3O_2$) C, H, N.

3-{4-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]butyl}-1*H*-indole (5d) Fumaric Acid Salt. Compound **5d** was prepared via route B in a yield of 25%. TLC analysis and silica gel column chromatography: eluent DMA 0.25, R_f 0.5. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.6 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.3 (d, 1H, J = 8 Hz, H-arom); 7.07 (d, 1H, J = 2 Hz, H2-indole); 7.06 (t, 1H, J = 7 Hz, H-arom); 6.95 (t, 1H, J = 7 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (0.5 mol equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2

× bs, 8H, piperazine); 2.72 (t, 2H, CH_2); 2.45 (t, 2H, CH_2); 1.7 (q, 2H, CH_2); 1.56 (q, 2H, CH_2). Anal. ($C_{24}H_{29}N_3O_2$) C, H, N.

3-{5-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]pentyl}-1*H*-indole (5e) 2.5 Fumaric Acid Salt. Compound **5e** was prepared via route A. Compound **4** was converted to **7e** with known[15] 1*H*-indole-3-pentanoic acid (**6e**) in a yield of 80%. TLC analysis: eluent DCM/MeOH, 95/5, v/v, R_f 0.6; mp 70−72 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (s, 1H, NH-indole); 7.6 (d, 1H, H-arom); 7.36 (d, 1H, H-arom); 7.16 (t, 1H, H-arom); 7.1 (t, 1H, H-arom); 6.96 (s, 1H, H2-indole); 6.78 (dt, 1H, H-arom); 6.62 (d, 1H, H-arom); 6.46 (d, 1H, H-arom); 4.22−4.34 (dm, 4H, OCH_2CH_2O); 3.8, 3.6, 3.0 (m, 8H, piperazine); 2.8 (t, 2H, CH_2); 2.4 (t, 2H, CH_2); 1.8 (m, 4H, CH_2). Compound **7e** was converted to **5e** in a yield of 45%. TLC analysis and silica gel column chromatography: eluent DMA 0.5, R_f 0.5. Compound **5e** gave a white solid with 3 equiv of fumaric acid. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.6 (s, 1H, NH-indole); 7.48 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.04 (m, 2H, H2-indole, H-arom); 6.95 (t, 1H, J = 7 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (3 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.7 (2 × bs, 8H, piperazine); 2.7 (t, 2H, CH_2); 2.5 (m, 2H, CH_2); 1.7 (m, 2H, CH_2); 1.58 (m, 2H, CH_2); 1.4 (m, 2H, CH_2). Anal. ($C_{25}H_{31}N_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-4-fluoro-1*H*-indole (5f) 0.5 Fumaric Acid. Compound **5f** was prepared via route B as a 0.5 fumaric acid salt in an unoptimized yield of 30%. TLC analysis: eluent EtOAc, R_f 0.1; mp 207−208 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.0 (s, 1H, NH-indole); 7.15 (d, 1H, J = 8 Hz, H-arom); 7.07 (d, 1H, J = 2 Hz, H2-indole); 7.0 (m, 1H, H-arom); 6.62−6.72 (m, 2H, H-arom); 6.6 (s, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.8 (t, 2H, J = 7 Hz, CH_2); 2.5 (m, 2H, CH_2); 1.9 (m, 2H, CH_2). Anal. ($C_{23}H_{26}FN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-5-fluoro-1*H*-indole (5g) 0.5 Fumaric Acid. Compound **5g** was prepared via route B as a 0.5 fumaric acid salt in a yield of 70%. TLC analysis: eluent EtOAc, R_f 0.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H, NH-indole); 7.3 (dd, 1H, J = 5 Hz, J = 8 Hz, H-arom); 7.2 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 7.15 (d, 1H, J = 2 Hz, H2-indole); 6.85 (dt, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × d, 2H, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × d, 8H, piperazine); 2.7 (t, 2H, J = 7 Hz, CH_2); 2.44 (t, 2H, J = 7 Hz, CH_2); 1.84 (m, 2H, CH_2). Anal. ($C_{23}H_{26}FN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-6-fluoro-1*H*-indole (5h) 0.5 Fumaric Acid Salt. Compound **5h** was prepared via route B in a yield of 56%. TLC analysis and silica gel column chromatography: eluent EtOAc, R_f 0.3; mp 205−206 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H, NH-indole); 7.5 (dd 1H, J = 5 Hz, J = 8 Hz, H-arom); 7.08 (m, 2H, H2-indole, H-arom); 6.8 (m, 1H, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.7 (t, 2H, CH_2); 2.47 (t, 2H, CH_2); 1.85 (m, 2H, CH_2). Anal. ($C_{23}H_{26}FN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-7-fluoro-1*H*-indole (5i) 0.5 Fumaric Acid Salt. Compound **5i** was prepared via route B in a yield of 68%. TLC analysis and silica gel chromatography: eluent EtOAc, R_f 0.25. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.2 (s, 1H, NH-indole); 7.32 (d 1H, J = 8 Hz, H-arom); 7.14 (d,1H, J = 2 Hz, H2-indole); 6.9−6.96 (m, 1H, H-arom); 6.82 (dd, 1H, J = 8 Hz, J = 11 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.73 (t, 2H, J = 7 Hz, CH_2); 2.48 (t, 2H, J = 7 Hz, CH_2); 1.87 (m, 2H, CH_2). Anal. ($C_{23}H_{26}FN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-5-methoxy-1*H*-indole (5j) Fumaric Acid Salt. Compound **5j** was prepared via route B in a yield of 83%. TLC analysis and silica gel chromatography: eluent diethyl ether, R_f 0.15. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.5 (s, 1H, NH-indole); 7.22 (d,1H, J = 9 Hz, H-arom); 7.04 (d, 1H, J = 2 Hz, H2-indole); 6.96 (d, 1H, J = 2 Hz, H-arom); 6.7 (m, 2H, H-arom); 6.6 (s, 2H, fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.78 (s, 3H, OMe); 3.04, 2.63 (2 × bs, 8H, piperazine); 2.7 (t, 2H, J = 7 Hz, CH_2); 2.5 (t, 2H, CH_2); 1.87 (q, 2H, CH_2). HRMS ($C_{24}H_{30}N_3O_3$) $[M + H]^+$: found *m/z*, 408.2292; calcd, 408.2292. Anal. ($C_{24}H_{29}N_3O_3$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-4-chloro-1*H*-indole (5k) 0.5 Fumaric Acid. Compound **5k** was prepared via route B as a 0.5 fumaric acid salt in a yield of 69%. TLC analysis and silica gel column chromatography: eluent EtOAc, R_f 0.2. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.1 (s, 1H, NH-indole); 7.29 (d, 1H, J = 8 Hz, H-arom); 7.14 (d,1H, J = 2 Hz, H2-indole); 7.0 (t, 1H, J = 7 Hz, H-arom); 6.94 (d, 1H, J = 8 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 1H, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.92 (t, 2H, J = 7 Hz, CH_2); 2.5 (t, 2H, J = 7 Hz, CH_2); 1.87 (m, 2H, CH_2). Anal. ($C_{23}H_{26}ClN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-5-chloro-1*H*-indole (5l) 0.5 Fumaric Acid Salt. Compound **5l** was prepared via route B in a yield of 62%; mp 61−63 °C (free base); mp 220−222 °C (dec) of the 0.5 equiv of fumaric acid. ^{1}H NMR (400 MHz, DMSO-d_6): δ11.0 (s, 1H, NH-indole); 7.54 (d, 1H, J = 2 Hz, H-arom); 7.34 (d, 1H, J = 8 Hz, H-arom); 7.14 (d, 1H, J = 2 Hz, H2-indole); 7.03 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.7 (t, 1H, J = 8 Hz, H-arom); 6.6 (s, 1H, fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.06, 2.7 (2 × m, 10H, 8H piperazine, CH_2); 2.5 (m, 2H, CH_2); 1.87 (m, 2H, CH_2). HRMS ($C_{23}H_{27}ClN_3O_2$) $[M + H]^+$: found *m/z*, 412.1798; calcd, 412.1792. Anal. ($C_{23}H_{26}ClN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-6-chloro-1*H*-indole (5m) 0.5 Fumaric Acid. Compound **5m** was prepared via route B as a 0.5 fumaric acid salt in a yield of 61%. Silica gel column chromatography: eluent EtOAc, R_f 0.25. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.35 (d, 1H, J = 1.5 Hz, H-arom); 7.14 (d,1H, J = 2 Hz, H2-indole); 6.96 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 1H, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.72 (t, 2H, J = 7 Hz, CH_2); 2.46 (t, 2H, J = 7 Hz, CH_2); 1.85 (m, 2H, CH_2). Anal. ($C_{23}H_{26}ClN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-7-chloro-1*H*-indole (5n) 0.5 Fumaric Acid Salt. Compound **5n** was prepared via route B in a yield of 73%. Silica gel column chromatography: eluent diethyl ether, R_f 0.1. ^{1}H NMR (400 MHz, DMSO-d_6): δ 11.1 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.17 (d, 1H, J = 2 Hz, H2-indole); 7.12 (d, 1H, J = 8 Hz, H-arom); 6.96 (t, 1H, J = 7 Hz, H-arom); 6.7 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 1H, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.72 (t, 2H, J = 7 Hz, CH_2); 2.48 (t, 2H, J = 7 Hz, CH_2); 1.86 (m, 2H, CH_2). Anal. ($C_{23}H_{26}ClN_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-5-methyl-1*H*-indole (5o) 0.5 Fumaric Acid Salt. Compound **5o** was prepared via route B in a yield of 65%; mp free base, 65−67 °C; fumaric acid salt: mp 215−217 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ10.6 (s, 1H, NH-indole); 7.31 (bs, 1H, H-arom); 7.23 (d,1H, J = 8 Hz, H-arom); 7.04 (d, 1H, J = 2 Hz, H2-indole); 6.90 (dd, 1H, J = 1.5 Hz, J = 8 Hz, H-arom); 6.74 (t, 1H, J = 8 Hz, H-arom); 6.6 (s, 1H, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.2 (bm, 4H, OCH_2CH_2O); 3.06, 2.7 (2 × m, 10H, CH_2,

8H-piperazine); 2.57 (bm, 2H, CH_2); 2.40 (s, 3H, Me); 1.90 (m, 2H, CH_2). HRMS ($C_{24}H_{30}N_3O_2$) $[M + H]^+$: found *m/z*, 392.2356; calcd, 392.2338. Anal. ($C_{24}H_{29}N_3O_2$) C, H, N.

3-{3-[4-(2,3-Dihydro-benzo[1,4]dioxin-5-yl)piperazin-1-yl]propyl}-7-methyl-1*H*-indole (5p) 0.5 Fumaric Acid Salt. Compound **5p** was prepared via route B in a yield of 78%. TLC analysis and silica gel column chromatography: eluent EtOAc, R_f 0.3. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.65 (s, 1H, NH-indole); 7.32 (d, 1H, $J = 8$ Hz, H-arom); 7.06 (d,1H, $J = 2$ Hz, H2-indole); 6.82−6.92 (m, 2H, H-arom); 6.7 (t, 1H, $J = 7$ Hz, H-arom); 6.6 (s, 1H, 0.5 equiv of fumaric acid); 6.4−6.5 (2 × dd, 2H, $J = 1.5$ Hz, $J = 8$ Hz, H-arom); 4.2 (bm, 4H, OCH_2-CH_2O); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.72 (t, 2H, $J = 7$ Hz, CH_2); 2.48 (t, 2H, $J = 7$ Hz, CH_2); 2.44 (s, 3H, Me); 1.86 (q, 2H, CH_2). HRMS ($C_{24}H_{30}N_3O_2$) $[M + H]^+$: found *m/z*, 392.2362; calcd, 392.2338. Anal. ($C_{24}H_{29}N_3O_2$) C, H, N.

1-Benzyl-4-(3-prop-2-ynyloxy-phenyl)piperazine (11). To a solution of compound **10** (27 g, 90 mmol)[17] in MeOH (200 mL) was added a solution of sodium (4.15 g, 180 mmol) in MeOH (200 mL). The mixture was stirred for 30 min at RT and subsequently concentrated in vacuo. The residue was dissolved in DMF (200 mL), and a solution of propargyl bromide (11.3 g, 95 mmol) in DMF (50 mL) was added. The mixture was stirred overnight at room temperature. The reaction mixture was quenched with water, and the resulting mixture was extracted with DCM (2 × 300 mL). The combined organic layers were washed with water, dried ($MgSO_4$), and concentrated to give crude **11** as a black oil, which was purified by silica gel column chromatography (DCM/MeOH, 98/2, v/v) to give **11** (20 g, 60%) as a colorless oil. ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.0−7.4 (m, 6H, H-arom); 6.4−6.6 (m, 3H, H-arom); 4.7 (d, 2H, $J = 2$ Hz, O−CH_2); 3.5 (s, 2H, N−CH_2); 3.1, 2.5 (2 × m, 8H, piperazine); 1.98 (s, H, CH).

1-Benzyl-4-(2*H*-chromen-5-yl)piperazine (13). Compound **11** was dissolved in diethylaniline (45 mL), and the solution was heated at 220 °C for 1 h, after which time TLC analysis revealed complete conversion of **11** into two products. The reaction mixture was allowed to cool to room temperature and concentrated in vacuo to give a brown oil, which was purified by silica gel column chromatography to give pure **13** (10.6 g, 69%) and **12** (3.4 g, 22%) as colorless oils. Compound **12**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.3−7.4 (m, 5H, phenyl); 6.84 (d, 1H, $J = 8$ Hz, H-arom); 6.42 (dd, 1H, $J = 2$ Hz, $J = 8$ Hz, H-arom); 6.32−6.38 (m, 2H, H-4, H-arom); 5.6 (m, 1H, H3); 4.76 (dd, 2H, H-2); 3.54 (s, 2H, CH_2 Bn); 3.0, 2.6 (2 × m, 8H, piperazine). Compound **13**: ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.24−7.4 (m, 5H, phenyl); 7.06 (t, 1H, $J = 8$ Hz, H-arom); 6.7 (m, 1H, $J = 2$ Hz, $J = 8$ Hz, H-4); 6.55 (d, 2H, $J = 8$ Hz, H-arom); 5.7−5.8 (dt, 1H, $J = 3$ Hz, $J = 8$ Hz, H-3); 4.66 (dd, 2H, $J = 2$ Hz, $J = 4$ Hz, H-2); 3.6 (s, 2H, CH_2 Bn); 3.0, 2.6 (2 × m, 8H, piperazine).

1-Chroman-5-yl-piperazine (14). Compound **13** (2.4 g, 8 mmol) was dissolved in ethanol containing hydrochloric acid (2 mol equiv), and the catalyst Pd on charcoal (100 mg) was added. The mixture was shaken for 2 h under an atmosphere of hydrogen. The mixture was filtered and concentrated in vacuo to give crude **14** as an oil, which was purified by silica gel column chromatography to give pure **14** (2 g, 85%) as the hydrochloric acid salt. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.2 (t, 1H, $J = 8$ Hz, H-arom); 6.7−6.8 (2 × d, 2H, $J = 8$ Hz, H-arom); 4.2 (t, 2H, $J = 5$ Hz, H2); 3.4, 3.2 (2 × m, 8H, piperazine); 2.8 (t, 2H, H4); 2.0 (m, 2H, H3).

3-[3-(4-Chroman-5-yl-piperazine-1-yl)propyl]-1*H*-indole (15) 0.5 Fumaric Acid Salt. Compound **14** (1.75 g, 6 mmol) was converted with **9c** via route B to give compound **15** (1.4 g, 50%) as a white solid. TLC analysis and silica gel column chromatography: eluent: DMA 0.5 R_f 0.7. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.7 (s, 1H, NH-indole); 7.5 (d, 1H, $J = 8$ Hz, H-arom); 7.32 (d, 1H, $J = 8$ Hz, H-arom); 7.06 (d, 1H, $J = 2$ Hz, H2-indole); 7.04 (t, 1H, $J = 7$ Hz, H-arom); 6.9−7.0 (m, 2H, H-arom); 6.6 (s, 1H, 0.5 fumaric acid); 6.5 (d, 1H, $J = 8$ Hz, H-arom); 6.44 (d, 1H, $J = 8$ Hz, H-arom); 4.1 (t, 2H, OCH_2); 2.9, 2.6 (2 × bs, 8H, piperazine); 2.72 (t, 2H, CH_2); 2.64, 2.5 (2 × t, 4H, CH_2); 1.9 (m, 4H, H-2, CH_2). Anal. ($C_{24}H_{29}N_3O$) C, H, N.

5-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-1,2,3,4-tetrahydroquinoline (19) Hydrochloric Acid Salt. 5-Piperazin-1-yl-1,2,3,4-tetrahydroquinoline[14] (**16**) was converted to **19** with **9c** following route B. Compound **19** was isolated as the hydrochloric acid salt in a yield of 50%; mp 236−239 °C (dec). ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.7 (s, 1H, NH-indole); 7.54 (bd, 1H, $J = 8$ Hz, H-arom); 7.34 (bd, 1H, $J = 8$ Hz, H-arom); 7.24 (bt, 1H, $J = 7$ Hz, H-arom); 7.18 (d, 1H, $J = 1.5$ Hz, H2-indole); 7.08 (bt, 1H, $J = 7$ Hz, H-arom); 6.9−7.0 (m, 3H, H-arom); 3.2−3.6 (m, 12H, 8 × H-piperazine, 2 × CH_2); 2.82 (t, 2H, CH_2); 2.74 (t, 2H, CH_2); 2.2 (m, 2H, CH_2); 1.7 (m, 2H, CH_2). HRMS ($C_{24}H_{31}N_4$) $[M + H]^+$: found *m/z*, 375.2562; calcd, 375.2549. Anal. ($C_{24}H_{30}N_4$) C, H, N.

3-(1*H*-Indol-3-yl)-1-[4-(1,2,3,4-tetrahydroquinolin-5-yl)-piperazin-1-yl]propan-1-one (17). To a cooled solution of **16** (3 g, 14 mmol), **6c** (R=H, *m*=2, 2.3 g, 12 mmol), and 2-chloro-1,3-dimethyl-2-imidazolinium tetrafluoroborate (CIP, 4.2 g, 15 mmol) in DCM (60 mL) was added DIPEA (10 mL), and the mixture was stirred at room temperature for 16 h after which time TLC analysis (EtOAc/hexane, 2/1, v/v) showed complete conversion of **6c**. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography (R_f 0.25, EtOAc/hexane, 2/1, v/v) to furnish **17** (3.1 g, 67%) as a colorless oil. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.33 (s, 1H, NH-indole); 7.62 (d, 1H, $J = 8$ Hz, H-arom); 7.36 (d, 1H, $J = 8$ Hz, H-arom); 7.18 (t, 1H, $J = 7$ Hz, H-arom); 7.1 (t, 1H, $J = 7$ Hz, H-arom); 7.04 (bs, 1H, $J = 2$ Hz, H2-indole); 6.92 (t, 1H, $J = 7$ Hz, H-arom); 6.24 (t, 2H, $J = 7$ Hz, H-arom); 3.26, 2.82 (2 × s, 8H, H-piperazine); 3.24 (t, 2H, CH_2); 3.16 (t, 2H, $J = 7$ Hz, CH_2); 2.76 (t, 2H, $J = 7$ Hz, CH_2); 2.7 (t, 2H, $J = 7$ Hz, CH_2); 1.86 (m, 2H, CH_2).

5-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-1-methyl-1,2,3,4-tetrahydroquinoline (20) Hydrochloric Acid Salt. A mixture of acetic anhydride (0.46 mL) and formic acid (0.24 mL) was stirred at 55 °C for 1 h. The mixture was allowed to reach room temperature, and a solution compound **17** (1 g, 2.6 mmol) in dry THF was added slowly. The reaction mixture was stirred overnight at room temperature after which time TLC analysis (EtOAc) showed complete conversion of **17**. The mixture was concentrated in vacuo to give crude **18** as an oil, which was used in the next step without further purification. To a cooled (0 °C) solution of crude **18** (0.95 g, 2.5 mmol) in dry diethyl ether (20 mL) was added a suspension of $LiAlH_4$ (0.27 g, 7 mmol) in diethyl ether (10 mL). The reaction mixture was stirred overnight at room temperature, cooled again to 0 °C, and water (1 mL), 2 N NaOH (2 mL), and water (1 mL) were added. The mixture was filtered, and the filtrate was concentrated in vacuo. The oily residue was purified by silica gel chromatography (eluent: DCM/MeOH, 95/5, v/v; R_f 0.3) to give **20** (0.7 g) in a yield of 75% based on **17**. Compound **20** was isolated as a white solid after treatment with a solution of HCl (1 equiv) in EtOH; free base of **20**: mp 78−80 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.08 (s, 1H, NH-indole); 7.6 (d, 1H, $J = 8$ Hz, H-arom); 7.34 (d, 1H, $J = 8$ Hz, H-arom); 7.22 (t, 1H, $J = 7$ Hz, H-arom); 7.14 (t, 1H, $J = 7$ Hz, H-arom); 7.08 (t, 1H, $J = 7$ Hz, H-arom); 7.02 (d, 1H, $J = 2$ Hz, H2-indole); 6.4−6.5 (2 × d, 2H, $J = 8$ Hz, H-arom); 3.2 (t, 2H, $J = 6$ Hz, CH_2); 2.94 (m, 4H, H-piperazine); 2.9 (s, 3H, Me); 2.84 (t, 2H, $J = 6$ Hz, CH_2); 2.70 (m, 6H, H-piperazin, CH_2); 2.6 (m, 2H, CH_2); 2.0 (m, 2H, CH_2); 1.90 (m, 2H, CH_2). HRMS ($C_{25}H_{33}N_4$) $[M + H]^+$: found *m/z*, 389.2726; calcd, 389.2705. Anal. ($C_{25}H_{32}N_4$) C, H, N.

3-Methyl-5-(tosyl-piperazin-1-yl)-1,2,3,4-tetrahydroquinoline (23). To a suspension of commercially available 3-methyl-5-nitroquinoline (**21**, 27 g, 143 mmol) in ethanol (1000 mL) was added platinum on charcoal (5 wt. %, 12 g). The mixture was stirred for 6 h under a hydrogen pressure of 4 atm at a temperature of 40 °C. The mixture was filtered, and the filtrate was concentrated in vacuo to give crude **22** as a brown oil. To a mixture of crude **22** (14 g, 86 mmol) and the tosyl-protected methanesulfonic acid 2-(2-methanesulfonyloxy-

ethylamino)ethyl ester (36 g, 86 mmol) was added DIPEA (30 mL), and the mixture was heated at 140 °C for 4 h, after which time TLC analysis (MTBE, R_f 0.5) showed complete conversion of the starting material. The mixture was allowed to cool to room temperature, dissolved in dichloromethane, and washed with 2 N NaOH. The organic layer was concentrated, and the residue was purified by silica gel column chromatography (TLC eluent: MTBE/PA, 1/2, v/v) to give **23** as a brown solid (16.6 g, 50% yield); mp 169−170 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.7 (d, 2H, tosyl); 7.4 (d, 2H, tosyl); 6.9 (t, 1H, H-arom); 6.3 (2 × dd, 2H, H-arom); 2.4 (s, 3H, Me-tosyl); 1.6−3.4 (13H, H-piperazine, H-quinoline); 1.0 (d, 3H, J = 6 Hz, CH_3).

3-Methyl-5-[piperazin-1-yl]-1,2,3,4-tetrahydroquinoline (24). Compound **23** (2.06 g, 5.35 mmol) was suspended in concentrated HCl (40 mL). The mixture was refluxed overnight after which time TLC analysis (EtOAc) showed complete conversion of the starting material. The reaction mixture was diluted with 50 mL of ice water and 50 mL of 2 N NaOH and extracted with dichloromethane (3 × 100 mL). The combined organic layers were washed with brine (2 × 100 mL) and dried on $MgSO_4$. Filtration, followed by concentration in vacuo, gave crude **24** as a yellow solid, which was used in the next step without further purification.

5-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-3-methyl-1,2,3,4-tetrahydroquinoline (25) 0.5 Fumaric Acid Salt. 3-Methyl-5-(piperazin-1-yl)-1,2,3,4-tetrahydroquinoline (**24**) was converted to **25** with mesylate **9c** following route B. Compound **25** was isolated as the fumaric acid salt in a yield of 79%; mp 210−212 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.7 (s, 1H, NH-arom); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.08 (d, 1H, J = 2 Hz, H2-indole); 7.04 (t, 1H, J = 7 Hz, H-arom); 6.96 (t, 1H, J = 7 Hz, H-arom); 6.78 (t, 1H, J = 7 Hz, H-arom); 6.6 (s, 1H, 1/2 fumerate); 6.2 (t, 2H, H-arom); 1.7−3.4 (19H, H-piperazine, H-quinoline, 3 × CH_2 propyl); 1.0 (d, 3H, J = 6 Hz, Me). Anal. ($C_{25}H_{32}N_4$) C, H, N.

5-Nitro-3,4-dihydro-1*H*-quinolin-2-one (28b). The starting material, 4-nitro-indan-1-one (**26**), was prepared as described in the literature.[20] To a solution of **26** (14.7 g, 83 mmol) in benzene (150 mL) were added H_2SO_4 (95−97%, 44 mL) and sodium azide (5.4 g in portions of 540 mg) resulting in an exothermic reaction, and the reaction mixture was allowed to stir for 10 min at 70 °C. The reaction mixture was allowed to reach room temperature, the benzene layer was separated, and to the residue suspension was added water (200 mL). The suspension was stirred for 30 min and extracted with DCM (4 × 200 mL). The combined organic layers were washed with 1 N $NaHCO_3$ (3 × 100 mL), dried on $MgSO_4$, and filtered to give a crude mixture of compounds **28a** and **28b**. Pure compound **28b** (6.8 g, 45%) was isolated from the mixture by silica gel chromatography (eluent: EtOAc/hexane, 1/1, v/v) and separated from the other isomer **28a** (3.9 g, 22%). The ^{1}H NMR data of both compounds were in complete accordance with the data reported in the literature.[20]

5-Amino-3,4-dihydro-1*H*-quinolin-2-one (29). Compound **28b** (6.2 g, 32 mmol) was dissolved in EtOH (400 mL). To the solution was added palladium on charcoal (10%, 500 mg), and the mixture was stirred under a blanket of hydrogen for 4 h. Filtration over Hyflo and subsequent concentration in vacuo yielded crude **29** in a yield of 95%, which was used in the next step without further purification.

5-Piperazin-1-yl-3,4-dihydro-1*H*-quinolin-2-one (30). To a solution of compound **29** (4.95 g, 30.5 mmol) in chlorobenzene (125 mL) was added BCEA HCl salt (bis{chloroethylene}-amine, 5.7 g, 32.1 mmol), and the mixture was refluxed for 66 h. The mixture was concentrated in vacuo, and the resulting oil was purified by silica gel chromatography (DMA 0.5−1.0) to give **30** as a white solid in a yield of 72%. HRMS ($C_{13}H_{17}N_3O$) $[M + H]^+$: found m/z, 232.3; calcd, 232.3.

5-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-3,4-dihydro-1*H*-quinolin-2-one (31). Compound **30** (1.1 g, 4.8 mmol) was converted to **31** with mesylate **9c** following route B. Compound **31** was isolated as the free base in a yield of 45%; mp 181−182 °C. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.8 (s, 1H, NH-arom); 7.55 (d, 1H, J = 8 Hz, H-arom); 7.38 (d, 1H, J = 8 Hz, H-arom); 7.0−7.14 (m, 4H, H-arom, H2-indole); 6.76 (d, 1H, J = 8 Hz, H-arom); 6.64 (d, 1H, J = 8 Hz, H-arom); 1.9−2.9 (18H, H-piperazine, H-quinoline, 3 × CH_2). Anal. ($C_{24}H_{28}N_4O$) C, H, N.

2-Chloro-N-(5-chloro-2-hydroxyphenyl)acetamide (34a). To a cooled (0 °C) solution of 2-amino-4-chloro-phenol (**32**, 100 g, 700 mmol) in DCM (400 mL) and pyridine (56 mL) was added a solution of chloroacetyl chloride in DCM (**33a**, 700 mmol in 75 mL). The mixture was allowed to reach room temperature slowly and was subsequently stirred for 18 h. The precipitation was filtered, washed with DCM, and dried overnight at 50 °C to give crude **34a** as a brown solid (57 g, 37%), which was used in the next step without further purification.

2-Chloro-N-(5-chloro-2-hydroxyphenyl)propionamide (34b). Compound **34b** was prepared in a similar fashion as **34a** starting from **32** and **33b**. Compound **34b** was isolated as a purple solid in a yield of 61%, which could be used in the next step without further purification.

2-Bromo-N-(5-chloro-2-hydroxyphenyl)-2-methyl-propionamide (34c). Compound **34c** was prepared in a similar fashion as **34a** starting from **32** and **33c**. Compound **34c** was isolated as a beige solid in a yield of 79%, which could be used in the next step without further purification; mp 172 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.45 (d, 1H, H-arom); 7.08 (dd, 1H, H-arom); 6.9 (d, 1H, H-arom); 2.08 (s, 6H, 2 × Me).

6-Chloro-8-nitro-4*H*-benzo[1,4]oxazin-3-one (35a). Compound **34a** (57 g, 260 mmol) was suspended in water (240 mL) at a temperature of 0 °C. To the suspension was added HNO_3 (1.5 equiv, 387 mmol) over a period of 0.75 h. The resulting red solution was allowed to reach RT after 1 h, and water was added (250 mL) giving a dark brown solid, which was isolated by filtration. The resulting filtrate was washed with cold water (3 × 200 mL) and dried at 50 °C to give the nitrated derivative of **34a** as a yellow solid in a yield of 90%. Ring closure to **35a** was established by refluxing this intermediate with potassium carbonate in toluene/water, 50/1, v/v (51 mL) for 2 h. The reaction mixture was allowed to reach RT, which resulted in the precipitation of a brown solid, which was purified by silica gel chromatography (EtOAc/PA, 1/1, v/v to 1/0, v/v) to give compound **35a** as a white solid in a yield of 70%.

6-Chloro-8-nitro-4*H*-benzo[1,4]oxazin-2-methyl-3-one (35b). Compound **35b** was prepared in a similar fashion as **35a** starting from **34b**. Compound **35b** was isolated as a yellow solid in a yield of 40%.

6-Chloro-8-nitro-4*H*-benzo[1,4]oxazin-2,2-dimethyl-3-one (35c). Compound **35c** was prepared in a similar fashion as **35a** starting from **34c**. Compound **35c** was isolated as a yellow solid in a yield of 62%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.8 (bs, 1H, NH); 7.6 (d, 1H, J = 2 Hz, H-arom); 7.1 (d, 1H, J = 2 Hz, H-arom); 1.6 (s, 6H, 2 × Me).

6-Chloro-8-nitro-4*H*-benzo[1,4]oxazin-2,4-dimethyl-3-one (35d). To a cooled (0 °C) solution of compound **35b** (8.2 g, 34 mmol) in DMF (75 mL) were added powdered KOH (2 g) and methyl iodide (2.32 mL). A yellow precipitation was formed. After stirring for 22 h, water (10 mL) was added and the mixture was concentrated in vacuo. The residue was applied to silica gel chromatography (DCM/MeOH, 99/1, v/v; R_f 0.5) resulting in the isolation of **35d** as a yellow powder in a yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.6 (d, 1H, J = 2 Hz, H-arom); 7.15 (d, 1H, J = 2 Hz, H-arom); 4.8 (q, 1H, J = 7 Hz, CH); 3.4 (s, 3H, NMe); 1.6 (d, 3H, J = 7 Hz, Me).

8-Amino-4*H*-benzo[1,4]oxazin-3-one (36a). Compound **35a** (10 g, 43.7 mmol) was dissolved in 96% EtOH (400 mL), and Pd/C (0.5 g) was added. The mixture was hydrogenated at a pressure of 3 bar of hydrogen for 4 h at a temperature of 50 °C. The reaction mixture was filtered over Hyflo, and the filtrate was concentrated in vacuo to give crude **36a** in a yield of 80% as a brown solid, which was used in the next step without further purification.

8-Amino-4*H*-benzo[1,4]oxazin-2-methyl-3-one (36b). Compound **36b** was prepared in a similar fashion as **36a** starting from **35b**. Compound **36b** was isolated as a yellow

solid in a yield of 90%, which was used in the next step without further purification.

8-Amino-4*H*-benzo[1,4]oxazin-2,2-dimethyl-3-one (36c). Compound **36c** was prepared in a similar fashion as **36a** starting from **35c**. Compound **36c** was isolated as a yellow solid in a yield of 81%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 10.8 (s, 1H, NH); 6.8−7.1 (m, 3H, H-arom); 1.45 (s, 6H, 2 × Me).

8-Amino-4*H*-benzo[1,4]oxazin-2,4-dimethyl-3-one (36d). Compound **36d** was prepared in a similar fashion as **36a** starting from **35d**. Compound **36d** was isolated as a white solid in a yield of 85%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 6.85 (t, 1H, J = 8 Hz, H-arom); 6.4−6.55 (ddd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.7 (q, 1H, J = 7 Hz, CH); 3.35 (s, 3H, Me); 1.6 (d, 3H, J = 7 Hz, Me).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-3-one (37a). To a solution of compound **36a** (5.7 g, 34.8 mmol) in chlorobenzene (125 mL) was added BCEA hydrochloric acid (6.5 g, 36 mmol), and the mixture was refluxed for 69 h. The reaction mixture was concentrated in vacuo, and the residue was stirred in EtOAc for 2 h. The resulting brown solid was filtered and purified by silica gel chromatography (DMA 0.5−1.0) to give pure **37a** (2.44 g, 30%).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-2-methyl-3-one (37b). Compound **37b** was prepared in a similar fashion as **37a** starting from **36b**. Compound **37b** was isolated as a yellow solid in a yield of 50%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 (t, 1H, H-arom); 6.7 (m, 2H, H-arom); 4.6 (q, 1H, CH); 2.95−3.1 (m, 8H, piperazine); 1.6 (d, 3H, Me).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-2,2-dimethyl-3-one (37c). Compound **37c** was prepared in a similar fashion as **37a** starting from **36c**. Compound **37c** was isolated as a beige solid in a yield of 89%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.5 (bs, 1H, NH); 6.8 (m, 1H, H-arom); 6.5 (d, 2H, J = 8 Hz, H-arom); 3.4 (bs, 2H, NH_2^+); 2.8−3.0 (m, 8H, piperazine); 1.4 (s, 6H, 2 × Me).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-2,4-dimethyl-3-one (37d). Compound **37d** was prepared in a similar fashion as **37a** starting from **36d**. Compound **37d** was isolated as an oil in a yield of 90%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.0 (t, 1H, J = 7 Hz, H-arom); 6.7 (m, 2H, H-arom); 4.6 (q, 1H, J = 7 Hz, CH); 3.4 (s, 3H, Me); 2.95−3.1 (m, 8H, piperazine); 1.6 (d, 3H, J = 7 Hz, Me).

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-3-one (38a). To a solution of compound **37a** (2.6 g, 9.6 mmol) in acetonitrile (100 mL) were added mesylate **9c** (2.5 g, 9.7 mmol), KI (1.6 g, 9.7 mmol), and DIPEA (5.1 mL, 29 mmol), and the mixture was refluxed for 18 h. The reaction mixture was concentrated in vacuo, and the residue was purified by silica gel chromatography (DMA 0.25−0.5) to give pure **38a** as a beige foam in a yield of 67%. ^{1}H NMR (400 MHz, DMSO-d_6): δ 10.5 (s, 1H, NH-indole); 7.5 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.07 (d, 1H, J = 2 Hz, H-2 indole); 7.04 (t, 1H, J = 7 Hz, H-arom); 6.96 (t, 1H, J = 7 Hz, H-arom); 6.83 (t, 1H, J = 8 Hz, H-arom); 6.56 (d, 2H, J = 8 Hz, H-arom); 4.51 (s, 2H, CH_2); 3.0, 2.6 (2 × bs, 8H, piperazine); 2.72 (bt, 2H, CH_2); 2.4 (bt, 2H, CH_2); 1.84 (m, 2H, CH_2). Anal. ($C_{23}H_{26}N_4O_2$), C, H, N.

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-2-methyl-3-one (38b). Compound **38b** was prepared in the same way as described for **38a** starting from **37b**. Compound **38b** was obtained as a white solid in a yield of 50%; mp 196−197 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96, 7.76 (2 × s, 2H, 2 × NH); 7.63 (d,1H, J = 8 Hz, H-arom); 7.36 (d, 1H, J = 8 Hz, H-arom); 7.18 (t, 1H, J = 7 Hz, H-arom); 7.12 (t, 1H, J = 7 Hz, H-arom); 7.0 (d, 1H, J = 2 Hz, H-2 indole); 6.9 (t, 1H, J = 8 Hz, H-arom); 6.64 (d, 1H, J = 8 Hz, H-arom); 6.44 (d, 1H, J = 8 Hz, H-arom); 4.64 (q, 1H, CH); 3.15, 2.6 (2 × m, 8H, piperazine); 2.8 (bt, 2H, J = 7 Hz, CH_2); 2.5 (bm, 2H, CH_2); 1.94 (m, 2H, CH_2); 1.6 (d, 3H, CH_3). Anal. ($C_{24}H_{28}N_4O_2$), C, H, N.

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-2,2-dimethyl-3-one (38c). Compound **38c** was prepared in the same way as described for **38a** starting from **37c**. Compound **38c** was obtained as a white foam in a yield of 29%; ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.9 (s, 1H, NH); 7.56 (s, 1H, NH-arom); 7.62 (d, 1H, J = 8 Hz, H-arom); 7.34 (d, 1H, J = 8 Hz, H-arom); 7.06−7.18 (m, 2H, H-arom); 7.0 (d, 1H, J = 2 Hz, H2-indole); 6.86 (t, 1H, J = 8 Hz, H-arom); 6.6 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.38 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 3.17, 2.66 (2 × m, 8H, piperazine); 2.82 (t, 2H, J = 7 Hz, CH_2); 2.5 (t, 2H, J = 7 Hz, CH_2); 1.96 (m, 2H, CH_2); 1.58 (s, 6H, 2 × Me). HRMS ($C_{25}H_{30}N_4O_2$) $[M + H]^+$: found m/z, 419.2467; calcd, 419.2447. Anal. ($C_{25}H_{30}N_4O_2$), C, H, N.

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-2,4-dimethyl-3-one (38d). Compound **38d** was prepared in the same way as described for **38a** starting from **37d**. Compound **38d** was obtained as a white foam in an yield of 46%. ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.92 (s, 1H, NH-arom); 7.62 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 8 Hz, H-arom); 7.04−7.2 (m, 2H, H-arom); 6.98 (d, 1H, J = 2 Hz, H2-indole); 6.92 (t, 1H, J = 7 Hz, H-arom); 6.6−6.7 (2 × dd, 2H, J = 2 Hz, J = 8 Hz, H-arom); 4.58 (q, 1H, J = 7 Hz, CH); 3.34 (s, 3H, Me); 3.0−3.2, 2.65 (2 × bm, 8H, piperazine); 2.8 (t, 2H, J = 7 Hz, CH_2); 2.5 (t, 2H, J = 7 Hz, CH_2); 2.0 (q, 2H, CH_2); 1.6 (d, 3H, J = 7 Hz, Me). Anal. ($C_{25}H_{30}N_4O_2$), C, H, N.

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-3,4-dihydro-2*H*-benzo[1,4]oxazine (39) Fumaric Acid Salt. To a suspension of lithium aluminum hydride (0.97 g, 25.5 mmol) in dry THF (25 mL) was slowly added a solution of compound **38a** (0.96 g, 2.5 mmol) in dry THF (25 mL), and the mixture was refluxed for 3 h under a nitrogen atmosphere. The reaction was cautiously quenched with water (1 mL) and 2 N NaOH (2 mL), and the resulting mixture was filtered over Hyflo. The filtrate was concentrated in vacuo to give **39** as a brown solid in a yield of 99%. Crude **39** was dissolved in EtOH (50 mL), and fumaric acid (1 mol equiv, 286 mg) was added. The solution was concentrated in vacuo, and the residue was dissolved in dry ether from which it crystallized. The crystals were isolated by filtration and dried to give pure **39** as a beige solid in an yield of 80%; mp 200−201 °C. ^{1}H NMR (400 MHz, DMSO): δ 10.8 (s, 1H, NH-arom); 8.2 (s, 1H, NH); 7.51 (d, 1H, J = 8 Hz, H-arom); 7.32 (d, 1H, J = 7 Hz, H-arom); 6.94−7.1 (m, 3H, H-arom); 6.6 (s, 0.5 fum); 6.56 (t, 1H, J = 7 Hz, H-arom); 6.18−6.26 (2 × d, 2H, J = 8 Hz, H-arom); 4.14, 3.28 (2 × m, 4H, 2 × CH_2); 3.0−3.2, 2.7 (2 × bm, 8H, piperazine); 2.78 (t, 2H, CH_2); 2.58 (t, 2H, CH_2); 1.9 (q, 2H, CH_2). HRMS ($C_{23}H_{38}N_4O$) $[M + H]^+$: found m/z, 377. 2365; calcd, 377.2487.

6-Chloro-(*R*)-2-methyl-8-nitro-4*H*-benzo[1,4]oxazin-3-one (42a). To a cooled (0 °C) solution of commercially available **40** (37.3 g, 200 mmol), methyl (*S*)-(−)-lactate **41a** (20 mL, 200 mmol), and triphenyl phosphine (58 g, 220 mmol) in dry THF (2 L) was slowly added a solution of diisopropyl azodicarboxylate (DIAD, 43 mL, 220 mmol) in dry THF (400 mL). The mixture was stirred for 4 days at room temperature after which time TLC analysis (MTBE, R_f 0.5) showed complete conversion of compound **40** into **42a**. The mixture was concentrated in vacuo to give a red oil. The oil was dissolved in EtOH, from which compound **42a** crystallized as a brown solid (38 g, 79% yield). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.8 (s, 1H, NH); 7.6 (d, 1H, J = 2 Hz, H-arom); 7.06 (d, 1H, H-arom); 4.85 (q, 1H, J = 7 Hz, CH); 1.7 (d, 3H, J = 7 Hz, CH_3).

6-Chloro-(*S*)-2-methyl-8-nitro-4*H*-benzo[1,4]oxazin-3-one (42b). Compound **42b** was obtained in a similar fashion as **42a** starting from **40** and methyl (*R*)-(+)-lactate **41b.** Compound **42b** was obtained as a brown solid in a yield of 80%. $[\alpha]_d$ −8 (MeOH).

(*R*)-2-Methyl-8-amino-4*H*-benzo[1,4]oxazin-3-one (43a). To a solution of compound **42a** (15 g, 62 mmol) in EtOH/EtOAc, 1/1, v/v (400 mL) was added Pd/C (0.4 g), and the reaction was stirred under a blanket of hydrogen for 24 h. The mixture was filtered, and the filtrate was concentrated in vacuo to give crude **43a** as a beige solid in an yield of 86%, which was used in the next step without further purification; $[\alpha]_d$ −42 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.2 (bs, 1H, NH); 6.76 (t, 1H, J = 7 Hz, H-arom); 6.44 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.24 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.68 (q, 1H, J = 7 Hz, CH); 3.8 (bs, 2H, NH_2^+); 1.6 (d, 3H, J = 7 Hz, CH_3).

(*S*)-2-Methyl-8-amino-4*H*-benzo[1,4]oxazin-3-one (43b). Compound **43b** was obtained in a similar fashion as **43a** starting from **42b**. Compound **43b** was obtained as a brown solid in a yield of 50%, which was used in the next step without further purification; $[\alpha]_d$ +43 (MeOH).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-(*R*)-2-methyl-3-one (44a). Compound **44a** was prepared as described for the synthesis of **37a**. Pure compound **44a** was obtained after silica gel column chromatography (EtOAc/MeOH/NH4OH, 90/5/5, v/v/v; R_f 0.1) in a yield of 80%; $[\alpha]_d$ −42 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 9.0 (bs, 1H, NH); 6.9 (t, 1H, J = 7 Hz, H-arom); 6.5−6.6 (2 × d, 2H, J = 8 Hz H-arom); 4.65 (q, 1H, J = 7 Hz, CH); 3.1 (m, 8H, piperazine); 1.65 (d, 3H, J = 8 Hz, CH_3).

8-Piperazin-1-yl-4*H*-benzo[1,4]oxazin-(*S*)-2-methyl-3-one (44b). Compound **44b** was prepared as described for the synthesis of **37a**. Pure compound **44b** was obtained after silica gel column chromatography (EtOAc/MeOH/NH4OH, 90/5/5, v/v/v; R_f 0.1) in a yield of 40%; $[\alpha]_d$ +37 (MeOH).

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-(*R*)-2-methyl-3-one (45a). Compound **45a** was obtained from **44a** and **9c** via method B. Compound **45a** was obtained as a white solid in a yield of 55%; mp 178−180 °C; $[\alpha]_d$ −26 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96, 7.84 (2 × bs, 2H, 2 × NH); 7.62 (d, 1H, J = 8 Hz, H-arom); 7.36 (d, 1H, J = 8 Hz, H-arom); 7.1−7.2 (m, 2H, H-arom); 7.0 (d, 1H, J = 2 Hz, H2-indole); 6.9 (t, 1H, J = 8 Hz, H-arom); 6.64 (dd, 1H, J = 1.5 Hz, J = 8 Hz, H-arom); 6.44 (dd, 1H, J = 1.5 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.8 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.6 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{28}N_4O_2$) $[M + H]^+$: found *m/z*, 405.2291; calcd, 405.2302. Anal. ($C_{24}H_{28}N_4O_2$) C, H, N.

8-{4-[3-(1*H*-Indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo-[1,4]oxazin-(*S*)-2-methyl-3-one (45b). Compound **45b** was obtained from **44b** and **9c** via method B in a yield of 60%; $[\alpha]_d$ +27 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.9−8.0 (bs, 2H, 2 × NH); 7.62 (d, 1H, J = 8 Hz, H-arom); 7.36 (d, 1H, J = 8 Hz, H-arom); 7.1−7.2 (m, 2H, H-arom); 7.0 (d, 1H, J = 2 Hz, H2-indole); 6.9 (t, 1H, J = 7 Hz, H-arom); 6.64 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.44 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.8 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.6 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{29}N_4O_2$) $[M + H]^+$: found *m/z*, 405.2330; calcd, 405.2291. Anal. ($C_{24}H_{28}N_4O_2$) C, H, N.

8-{4-[3-(5-Fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*R*)-2-methyl-3-one (45c). Compound **45c** was obtained from **44a** and **9g** via method B in a yield of 58%; $[\alpha]_d$ −24 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.5, 8.0 (2 × bs, 2H, 2 × NH); 7.22−7.28 (m, 2H, H-arom); 7.04 (d, 1H, J = 1.5 Hz, H2-indole); 6.84−6.96 (m, 2H, H-arom); 6.64 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.44 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.8 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.6 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{27}FN_4O_2$) $[M + H]^+$: found *m/z*, 423.2211; calcd, 423.2196. Anal. ($C_{24}H_{27}FN_4O_2$) C, H, N.

8-{4-[3-(5-Fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*S*)-2-methyl-3-one (45d). Compound **45d** was obtained from **44b** and **9g** via method B in a yield of 56%; $[\alpha]_d$ +24 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.96, 7.9 (2 × bs, 2H, 2 × NH); 7.22−7.28 (m, 2H, H-arom); 7.04 (d, 1H, J = 1.5 Hz, H2-indole); 6.84−6.96 (m, 2H, H-arom); 6.64 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.44 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.76 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.62 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{28}FN_4O_2$) $[M + H]^+$: found *m/z*, 423.2184; calcd, 423.2196. Anal. ($C_{24}H_{27}FN_4O_2$) C, H, N.

8-{4-[3-(7-Fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*R*)-2-methyl-3-one (45e). Compound **45e** was obtained from **44a** and **9i** via method B in a yield of 78%; $[\alpha]_d$ −25 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18, 8.02 (2 × bs, 2H, 2 × NH); 7.38 (d, 1H, J = 8 Hz, H-arom); 6.98−7.04 (m, 2H, H-arom); 6.86−6.94 (m, 2H, H-arom); 6.64 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.46 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.80 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.62 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{28}FN_4O_2$) $[M + H]^+$: found *m/z*, 423.2234; calcd, 423.2196. Anal. ($C_{24}H_{27}FN_4O_2$) C, H, N.

8-{4-[3-(7-Fluoro-1*H*-indol-3-yl)propyl]piperazin-1-yl}-4*H*-benzo[1,4]oxazin-(*S*)-2-methyl-3-one (45f). Compound **45f** was obtained from **44b** and **9i** via method B in a yield of 84%; $[\alpha]_d$ +25 (MeOH). ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.18, 8.02 (2 × bs, 2H, 2 × NH); 7.38 (d, 1H, J = 8 Hz, H-arom); 6.98−7.04 (m, 2H, H-arom); 6.86−6.94 (m, 2H, H-arom); 6.64 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 6.46 (dd, 1H, J = 2 Hz, J = 8 Hz, H-arom); 4.64 (q, 1H, J = 7 Hz, CH); 3.1−3.2 (m, 4H, H-piperazine); 2.80 (t, 2H, J = 7 Hz, CH_2); 2.65 (m, 4H, H-piperazine); 2.5 (m, 2H, CH_2); 1.94−2.0 (m, 2H, CH_2); 1.62 (d, 3H, J = 7 Hz, CH_3). HRMS ($C_{24}H_{28}FN_4O_2$) $[M + H]^+$: found *m/z*, 423.2217; calcd, 423.2196. Anal. ($C_{24}H_{27}FN_4O_2$) C, H, N.

In Vitro Kinetic Studies. The capability of the human MDR1 P-glycoprotein pump to translocate compounds over a cellular monolayer of PK1 LLC MDR cells was assessed. The transport method essentially described in the literature[32] was used. Compounds were added at the start of the experiment at 1 μg/mL to one side of the cellular layer. The bottom to top transport was measured as well as the top to bottom transport. The p-glycoprotein (Pgp) factor was expressed as the ratio of the bottom to top transport and top to bottom transport. The membrane passage was expressed as the mean percentage of compound transported from bottom to top and from top to bottom at 3 h after adding the compound. Compound detection was performed using a LC/MS method.

The aqueous solubility of compounds was determined by dissolving compounds in 10 mg/mL in DMSO. Hereafter, serial dilutions were made in DMSO. Finally, a 1:100 dilution was made in Episerf (Gibco) tissue culture medium. The first concentration, which did not precipitate in this series, was defined as the aqueous solubility of the compounds.

In Vivo Kinetic Studies of Compound 45c. In pharmacokinetic experiments, six male rats were daily dosed with doses of **45c** ranging from 3 to 30 mg/kg for 14 days for multiple dose kinetics and once for single dose kinetics. For single dose kinetics, the same animals were used for iv and po dosing. Po dosing and blood sampling were done 1 week after the iv dosing and blood sampling. From each animal, two blood samples were taken per dosing session. This resulted in six time points (0.5, 1, 2, 4, 8, and 24 h) with duplicate samples per time point. Compound **45c** concentrations in plasma were determined by HPLC-MS.

The following parameters were obtained/calculated. Prepeak concentrations below the limit of quantification were taken as zero. If no sample analysis was available at a given time point, that time point was omitted from the analysis. The validated pharmacokinetic program Win Nonlin Professional, version 2.1, was used for data evaluation.

Molecular Modeling Studies. Modeling studies were carried out on Silicon Graphics Octane workstations running Sybyl V6.9.2[35] Structures were first minimized by MM calculations using the Tripos Force Field with Gasteiger−Hückel charges prior to MOPAC minimization using the AM1 method. Pharmacophores were obtained by manual fitting of the structures.

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Supporting Information Available: Elemental analysis data of the test compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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