Synthesis and Structure−Affinity Relationship Investigations of 5-Heteroaryl-Substituted Analogues of the Antipsychotic Sertindole. A New Class of Highly Selective α_1 Adrenoceptor Antagonists

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A new class of 5-heteroaryl-substituted 1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indoles as highly selective and potentially CNS-active α_1-adrenoceptor antagonists is described. The compounds are derived from the antipsychotic sertindole. The structure−affinity relationships of the 5-heteroaryl substituents, and the substituents on the piperidine nitrogen atom were optimized with respect to affinity for α_1 adrenoceptors and selectivity in respect to dopamine (D_{1-4}) and serotonin (5-HT_{1A-1B} and 5-$HT_{2A,2C}$) receptors. The most selective compound obtained, 3-{4-[1-(4-fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}propionitrile (**15c**), has affinities of 0.99, 3.2, and 9.0 nM for the α_{1a}, α_{1b}, and α_{1d} adrenoceptor subtypes, respectively, and a selectivity for adrenergic α_{1a} receptors in respect to dopamine D_2, D_3, and D_4 and serotonin 5-HT_{2A} and 5-HT_{2C} higher than 900, comparable to the selectivity of prazosin. In addition, the compound is more than 150-fold selective in respect to serotonin 5-HT_{1A} and 5-HT_{1B} receptors. A new basic pharmacophore for α_1-adrenoceptor antagonists based on a previously reported pharmacophore model for dopamine D_2 antagonist is suggested.

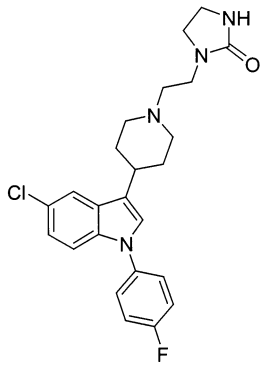
Introduction

Interest in the development of selective α_1-adrenoceptor antagonists has primarily focused on therapeutics for the treatment of cardiovascular diseases and benign prostatic hyperplasia.[1−3] However, modulation of α_1-adrenoceptor activity in the central nervous system (CNS) might also be of interest in regard to treatment of CNS-related diseases.[4,5]

In human brain, all three adrenoceptor subtypes α_{1A}, α_{1B}, and α_{1D} are present at the mRNA level.[6] At the protein level, radioligand-binding experiments have confirmed the existence of α_{1A}[7] and α_{1D} adrenoceptors.[8] The functional role, tissue distribution and density of the different α_1 adrenoceptor subtypes, are not yet completely understood,[9] but results indicate that functional roles of the different adrenergic α_1 receptor subtypes may vary between species.[10]

A common feature of atypical antipsychotics such as clozapine, sertindole (**1**, Chart 1), olanzapine, and seroquel is nanomolar affinity for α_1-adrenoceptors in addition to their affinities for dopamine D_2 and serotonin 5-HT_{2A} receptors.[11] The proper balanced affinities for these receptors might underlie the improved profile of these drugs (improved ratio between doses inducing antipsychotic activity and extrapyramidal side effects) as compared to classical antipsychotic drugs, such as haloperidol.[11]

Chart 1. Structure of Sertindole (**1**)



1 Sertindole

The contribution of the α_1-component to the therapeutic value of these antipsychotic agents has been studied intensively. Repeated coadministration of the α_1-adrenoceptor antagonist prazosin and the classical antipsychotic haloperidol was found to selectively inhibit the firing of dopaminergic neurones in the ventral tegmental area in rats, suggesting that the combination would be effective as antipsychotic treatment without producing extrapyramidal side effects.[12] Coadministration of subthreshold doses of the dopamine D_2 antagonist raclopride and the α_1-adrenoceptor antagonist prazosin caused significantly enhanced suppression of conditioned avoidance behavior in rats without inducing catalepsy.[13] It was suggested that α_1 adrenoceptor blockade in the presence of a low D_2 receptor occupancy might improve antipsychotic efficacy and thereby improve the therapeutic window with regard to extrapyramidal side effects. Drug combination studies in the

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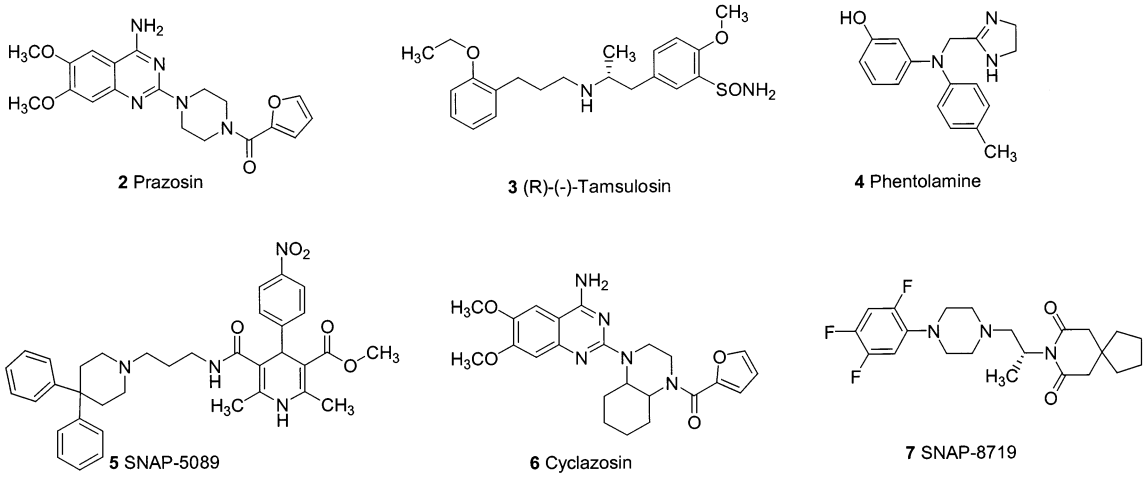
Chart 2. Selected Selective α_1 Adrenoceptor Antagonists Belonging to Different Chemical Classes



paw test in rats indicate a central role of the α_1-component for the atypical profile of clozapine.[14]

Several lines of evidence indicate that blockade of α_1-adrenoceptor neurotransmission alone could be beneficial in the treatment of schizophrenia. Metabolic and postmortem studies indicate hyperactivity of the noradrenergic system in psychotic patients.[4] The firing pattern of midbrain dopamine neurons in rats is modulated by prazosin administration[15] and by electrical stimulation of noradrenergic neurons in the locus coeruleus.[16] In addition, prazosin reversed the disruption of prepulse inhibition of acoustic startle response in rats induced by phencyclidine (PCP),[17,18] indicating that α_1 antagonists would be beneficial in the treatment of at least subpopulations of schizophrenic patients. In contrast to these pharmacological observations, prazosin has been tested in a small placebo controlled trial on schizophrenic patients without promising results.[19]

Furthermore, centrally acting α_1-adrenergic antagonists might have a potential as therapeutics for the treatment of CNS-related diseases characterized by noradrenergic overactivity such as mania[5] and post-traumatic stress disorder.[20]

Numerous selective adrenergic α_1 antagonists have been discovered[3] belonging to a variety of different chemical classes exemplified by compounds as diverse as prazosin (**2**), (R)-(−)-tamsulosin (**3**), phentolamine (**4**), SNAP-5089 (**5**), cyclazosin (**6**), and SNAP-8719 (**7**) (Chart 2). Whereas prazosin (**2**) is subtype unselective, (−)-SNAP-5089 ((−)-**5**),[21] (+)-cyclazosin ((+)-**6**),[22] and SNAP-8719 (**7**)[23] represent examples of compounds selective for the α_{1a}, α_{1b}, and α_{1d} receptor subtypes, respectively. Based on site-directed mutagenesis studies on the adrenergic α_{1a} receptor, it is suggested that a selection of chemically highly diverse antagonists have a conserved pharmacophore that recognize a common site on the receptor.[24]

In the present investigation, sertindole (**1**, Chart 1) was selected as a lead compound for development of a new class of centrally acting α_1 adrenoceptor antagonists. Sertindole (**1**) has nanomolar affinity for adrenergic (α_1), dopaminergic (D_1, D_2, D_3, D_4), and serotonergic (5-HT_{2A}, 5-HT_{2C}) receptors[12] and moderate affinity for serotonin 5-HT_{1A} and 5-HT_{1B} receptors.[25,26] In addition, it has been reported that sertindole (**1**) is a specific inhibitor of the α_{1A} adrenoceptor subtype in rat small arteries[27] and binds with sub-nanomolar affinity for the α_1 adrenoceptor subtypes α_{1a}, α_{1b}, and α_{1d}[25,28] The phenylindole skeleton of sertindole has previously been used as template for the development of selective antagonists of serotonin 5-HT_2[29−31]and dopamine D_2[31] receptors.

We have recently described that the phenylindole skeleton of sertindole (**1**) is a promising template for the development of centrally acting α_1 antagonists. Replacement of the 5-chloro atom in sertindole (**1**) with polar substituents such as substituted carbamoyl and aminomethyl groups afforded a new class of selective α_1 adrenoceptor antagonists.[25] The investigation revealed that 5-substituents combining hydrogen bond acceptor properties with steric bulk in the plane of the indole nucleus are essential to obtain high affinity for adrenergic α_1 receptors combined with high selectivity in respect to dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors. In this paper, we describe the replacement of the 5-chloro atom in sertindole (**1**) with heteroaromatic substituents such as azoles, pyridines, and pyrimidines full-filling these requirements. Subsequently, optimization of the substituent on the piperidinyl nitrogen atom with focus on selectivity for α_1-adrenergic receptors is described.

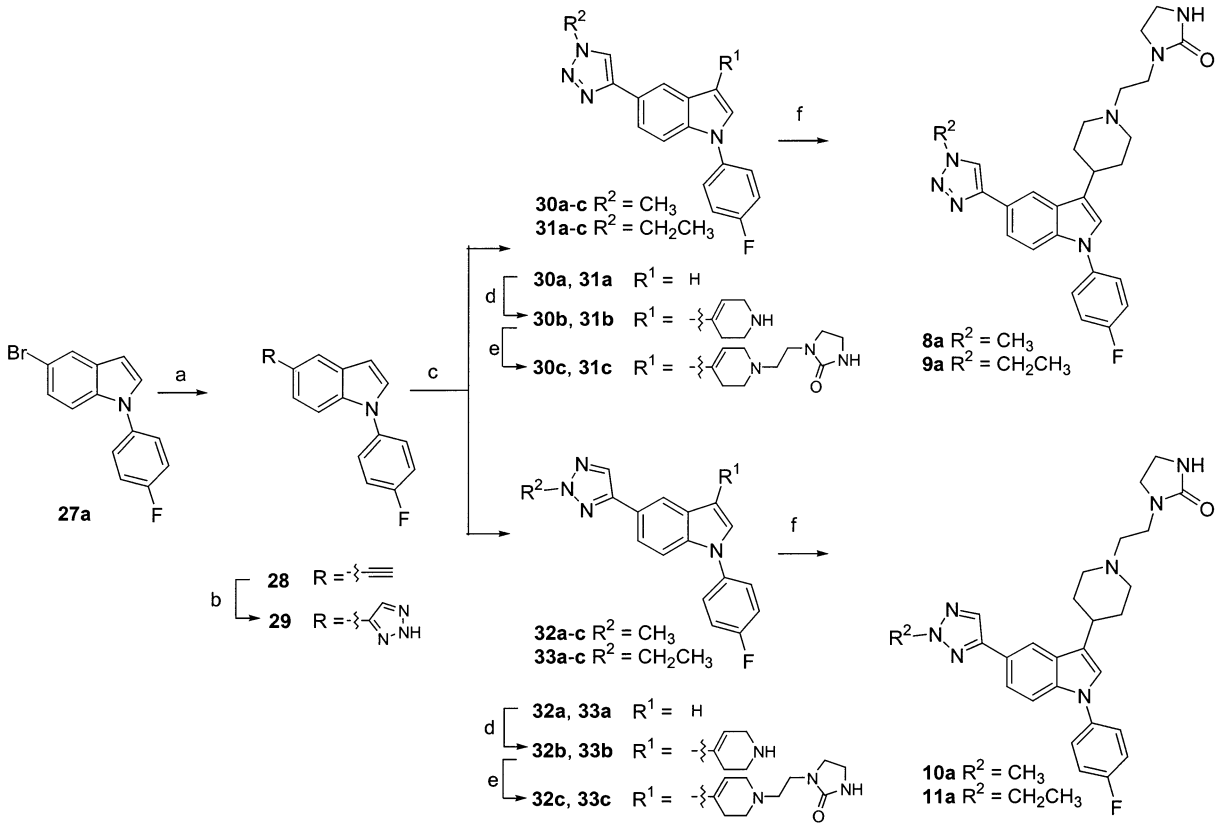
Chemistry

The preparation of 1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indoles substituted in the 5- and 6-positions of the indole nucleus have previously been described by Perregaard et al.[29,32]

Introduction of aromatic substituents in the indole 5-position has previously been reported in the literature. Most procedures involve palladium-catalyzed cross-coupling of substituted 5-bromo-1*H*-indole with aryl boronic acids,[33] aryl stannanes,[34] or an arylzinc halide.[35] For the reverse procedure where aryl halides are reacted with indole-5-boronic acid derivatives only a few examples have been reported.[36−38]

We reported recently an efficient one-pot Negishi cross-coupling procedure for the preparation of 5-heteroaryl-substituted 1-(4-fluorophenyl)-1*H*-indoles from the corresponding 5-bromo-1-(4-fluorophenyl)-1*H*-indole via halogen−metal exchange, transmetalation to the

Scheme 1[a]



[a] Reagents: (a) (*i*) $HCCSi(CH_3)_3$, $Pd(PPh_3)_2Cl_2$, CuI, $N(Et)_3$, CH_3CN, reflux, 8 h (*ii*) KOH, $MeOH/H_2O$, reflux, 3 h; (b) (*i*) $(CH_3)_3SiN_3$, sealed tube, 170 °C, 24 h (*ii*) CH_2Cl_2, 2 N NaOH, 2 h; (c) K_2CO_3, R^2I ($R^2 = CH_3$ or CH_3CH_2), acetone, reflux, 18 h, column chromatography; (d) 4-piperidone hydrochloride hydrate, TFA/AcOH, reflux, 90 min; (e) 1-(2-chloroethyl)imidazolidin-2-one, K_2CO_3, KI, 4-methyl-2-pentanone, reflux, 8 h; (f) H_2, PtO_2, AcOH, 5 h.

corresponding zinc chloride derivative and subsequent palladium-catalyzed cross-coupling with heteroaryl halides.[39]

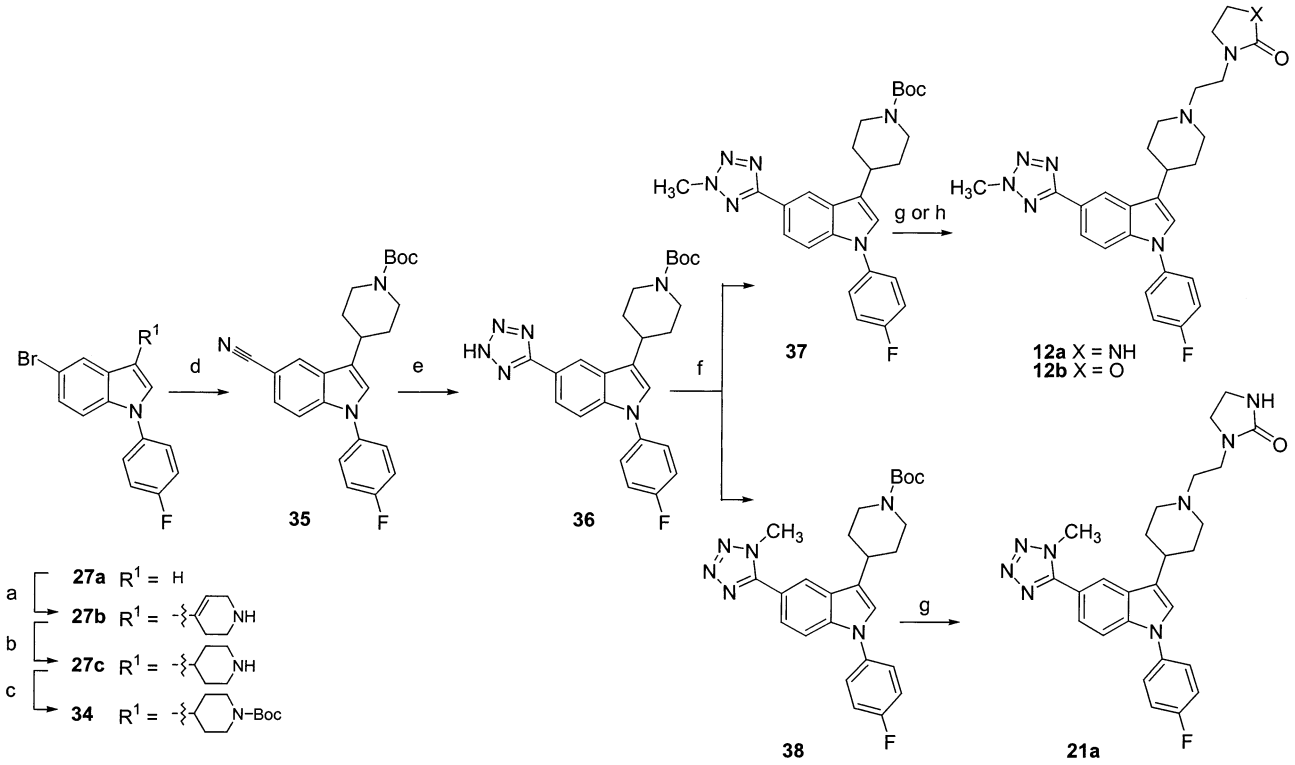
The 1,2,3-triazole analogues of sertindole (**8a**−**11a**) were prepared as depicted in Scheme 1 using 5-bromo-1-(4-fluorophenyl)-1*H*-indole (**27a**)[32] as starting material. Bis(triphenylphosphine)palladium(II) chloride and cupper(I) iodide catalyzed Sonogashira coupling[40,41] with (trimethylsilyl)acetylene and hydrolysis of the carbon−silicon bond gave the acetylene **28**. Subsequent 1,3-dipolar cycloaddition of azidotrimethylsilane to the triple bond in **28** and hydrolysis of the nitrogen−silicon bond afforded the 1,2,3-triazole **29**. Methylation of compound **29** gave, after chromatographic separation of the isomers, the 1-methyl-1,2,3-triazol-4-yl derivative **30a** and the 2-methyl-1,2,3-triazol-4-yl derivative **32a**. The corresponding ethyl derivatives **31a** and **33a** were prepared accordingly. The 1-methyl- and 1-ethyl-substituted 1,2,3-triazol-5-yl derivatives (not shown) were not isolated since only traces of these isomers were formed. Reaction of intermediates **30a**−**33a** with 4-piperidone hydrochloride hydrate using acidic conditions gave the substituted 5-(1,2,3-triazol-4-yl)-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles **30b**−**33b**. Alkylation with 1-(2-chloroethyl)imidazolidin-2-one gave the corresponding imidazolidin-2-one derivatives **30c**−**33c**, and finally catalytic hydrogenation using platinum as catalyst gave the final piperidinyl derivatives **8a**−**11a**. The position of the alkyl group in the 1,2,3-triazole moiety in the final analogues **8a**−**11a** were determined by 1D-NOESY experiments.[42] A significant NOE (2%) was observed on the proton in the 4-position of the 1,2,3-triazole moiety of **8a** by irradiation of the methyl group whereas no significant NOE was observed by irradiation of the methyl group in the 2-methyl-1,2,3-triazole derivative **10a**. In none of the cases, significant NOEs on the protons in the indole nucleus were observed. The structures of the ethyl derivatives **9a** and **11a** were confirmed accordingly.

The remaining 5-heteroaryl-substituted 1-(4-fluorophenyl)-1*H*-indoles in the present paper were prepared as outlined in Schemes 2 and 3 using *N*-Boc-protected 5-bromo-piperidinyl-1*H*-indole **34** as key intermediate. The key intermediate **34** was prepared in three steps from 5-bromo-1-(4-fluorophenyl)-1*H*-indole (**27a**) as outlined in Scheme 2. Reaction of 4-piperidinone hydrochloride hydrate with 5-bromo-1-(4-fluorophenyl)-1*H*-indole (**27a**) using acidic conditions followed by catalytic hydrogenation analogously to published procedures[32] gave the unsubstituted piperidyl compound **27c**. Finally, reaction with Boc-anhydride afforded the *N*-Boc-protected 5-bromo-3-piperidinyl-1*H*-indole **34**.

Replacement of the bromine atom in **34** with heteroaromatic substituents was either performed by reaction with zinc cyanide and subsequent tetrazole ring synthesis as depicted in Scheme 2 or by Negishi cross-coupling reactions[43] as depicted in Scheme 3.

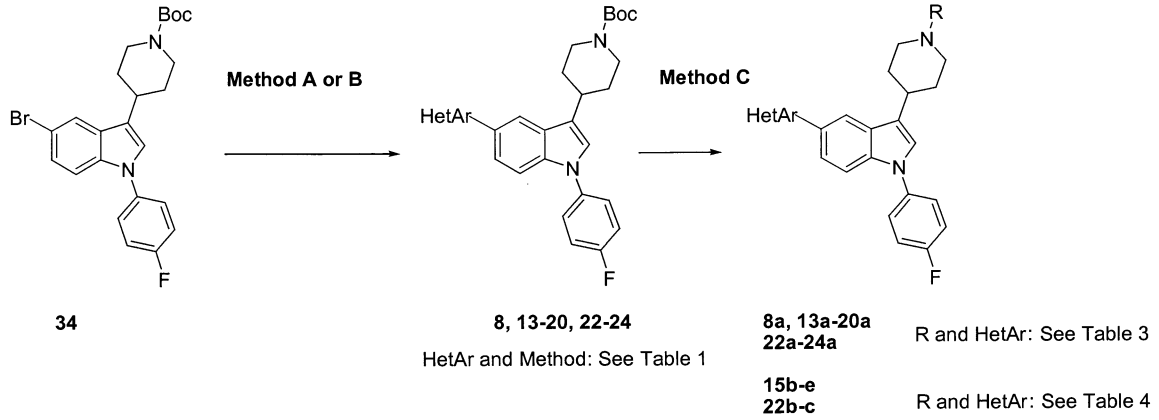
The tetrazole analogues **12a**,**b** and **21a** were prepared by ring synthesis as shown in Scheme 2. Reaction of the *N*-Boc-protected 5-bromopiperidinyl-1*H*-indole **34** with zinc cyanide in DMF under tetrakis(triphenylphosphine)palladium(0) catalysis using the conditions

Scheme 2[a]



[a] Reagents: (a) 4-piperidone hydrochloride hydrate, TFA/AcOH, reflux, 90 min; (b) H_2, PtO_2, AcOH, 5 h; (c) $(Boc)_2O$, THF/water, 60 °C, 8 h; (d) $Zn(CN)_2$, $Pd(PPh_3)_4$, DMF, 80 °C, 8 h; (e) NaN_3, toluene, reflux, 8 h; (f) K_2CO_3, CH_3I, acetone, reflux, 18 h, column chromatography; (g) (*i*) HCl, MeOH, rt, 4 h (*ii*) 1-(2-chloroethyl)-2-imidazolidinone, K_2CO_3, KI, 4-methyl-2-pentanone, reflux, 8 h; (h) HCl, MeOH, rt, 1 h, then 1-(2-chloroethyl)-2-oxazolidinone, K_2CO_3, KI, 4-methyl-2-pentanone, reflux, 8 h.

Scheme 3[a]



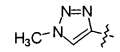
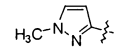
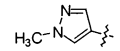
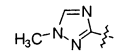
[a] Reagents: method A: (*i*) n-BuLi (reversed addition), THF, −78 °C, 3 min (*ii*) $ZnCl_2$/THF (1 M), −78 °C, 30 min; (*iii*) HetAr-X, $Pd(PPh_3)_4$, DMF, 80 °C, 8 h; method B: HetAr−ZnCl/THF, $Pd(PPh_3)_4$, DMF, 80 °C, 8 h; method C: (*i*) HCl/MeOH, rt, 4 h (*ii*) R−Y (Y = Cl, Br), K_2CO_3, KI, 4-methyl-2-pentanone (CH_3CN for **20e**), reflux 8 h.

described by Tschaen et al.[44] gave the nitrile **35** in 90% yield. Subsequent 1,3-dipolar cycloaddition with sodium azide gave the tetrazole **36**, and alkylation of this intermediate with methyl iodide followed by chromatographic separation of the formed isomers gave the 1- and 2-methyl-substituted tetrazoles **37** and **38**. The position of the methyl group in the two isomers was determined by 2-D NOESY experiments.[42] The methyl group of the 1-methyltetrazole isomer **38** showed NOE cross-peaks to the indole 4- and 6-protons, whereas no NOE cross-peaks were observed between the methyl group in the 2-methyltetrazole isomer **37** and the protons in the indole nucleus. Deprotection of the Boc-group and alkylation at the piperidine nitrogen atom was performed in a one-pot procedure (method C). The Boc-protected intermediates **37** and **38** were treated with a saturated solution of hydrochloric acid in methanol followed by evaporation of the solvent. Subsequent treatment with the appropriate alkylating agent, potassium iodide, and an excess of base gave the imidazolidin-2-one derivatives **12a** and **21a**. The oxazolidin-2-one substituted derivative **12b** was prepared accordingly.

Replacement of the bromine atom in key intermediate **34** by means of Negishi cross-couplings as depicted in Scheme 3 were performed by two complementary methods (methods A and B).

In method A, the *N*-Boc-protected 5-bromo-piperidinyl-1*H*-indole **34** was treated with *n*-butyllithium fol-

Table 1. Methods and Reagents Used for the Preparation of Intermediates **8**, **13**−**20**, and **22**−**24**

Compd	HetAr	X =	Method
8		Br	A
13		I	A
14		Br	A
15		Br	A
16		Br	A
17		Br	A
18		H	B
19		H	B
20		H	B
22		Br	A
23		Br	A
24		Br	B

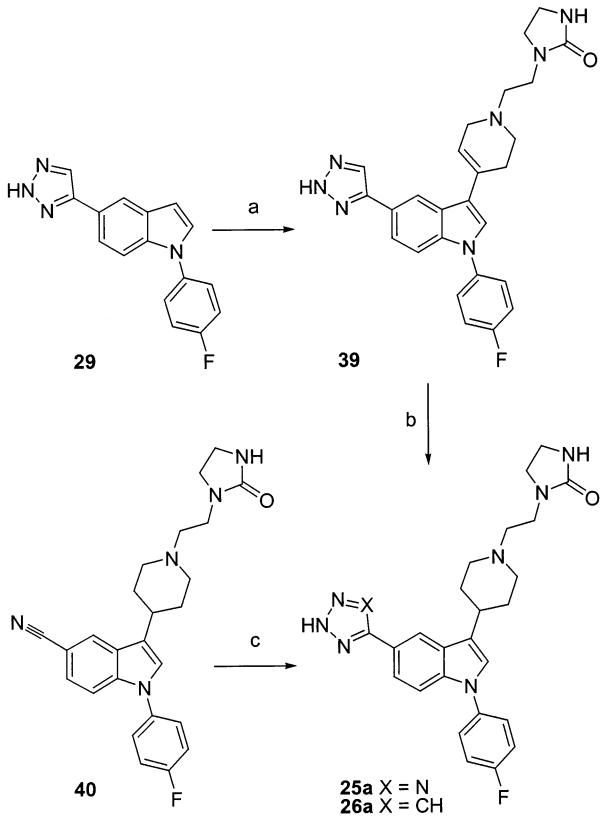
lowed by transmetalation with zinc chloride in analogy to procedures reported by us recently.[39] Reversed addition of the substrate **34** to an excess of *n*-butyllithium and short reaction time before addition of a solution of 3 equiv of zinc chloride in THF were found to give the best results. Addition of the appropriate heteroaryl halide and 5 mol % tetrakis(triphenylphosphine)-palladium(0) afforded the heteroaryl substituted intermediates **8**, **13**−**17**, **22**, and **23** (Table 1) in yields varying from 28% to 67%.

The heteroaryl-substituted intermediates **18**−**20** and **24** (Table 1) were prepared by the reverse method B (Scheme 3). Deprotonation of the heteroaryl derivative or halogen/metal exchange of heteroaryl halides followed by transmetalation to the corresponding zinc chlorides and tetrakis(triphenylphosphine)palladium-(0) catalyzed cross-coupling with the *N*-Boc-protected 5-bromo-piperidinyl-1*H*-indole **34** gave the 5-heteroaryl-indoles **18**−**20** and **24** (Table 1) in yields varying from 28−80%.

The Boc-protected derivatives obtained by methods A and B were easily transformed into the final compounds shown in the Tables 3 and 4 by method C as described for the preparation of the tetrazole analogues **12a**,**b** and **21a**. Preparation of 1-methyl-1,2,3-triazol-4-yl derivative **8a** by this method confirmed the structure of **8a** obtained by ring closure as described above (Scheme 1).

The *N*-unsubstituted tetrazole **25a** and 1,2,3-triazole **26a** were prepared as outlined in Scheme 4. Reaction of the 1,2,3-triazole **29** with 1-[2-(1,5-dioxa-9-azaspiro-[5,5]undecane-9-yl)ethyl]imidazolidin-2-one using acidic conditions gave the tetrahydropyridine **39**. Subsequent catalytic hydrogenation gave the *N*-unsubstituted 1,2,3-

Scheme 4[a]



[a] Reagents: (a) 1-[2-(1,5-dioxa-9-azaspiro[5,5]undecane-9-yl)-ethyl]imidazolidin-2-one, AcOH/TFA, reflux, 50 min; (b) H_2, PtO_2, AcOH, 14 h; (c) NaN_3, NEt_3·HCl, DME, reflux, 16 h.

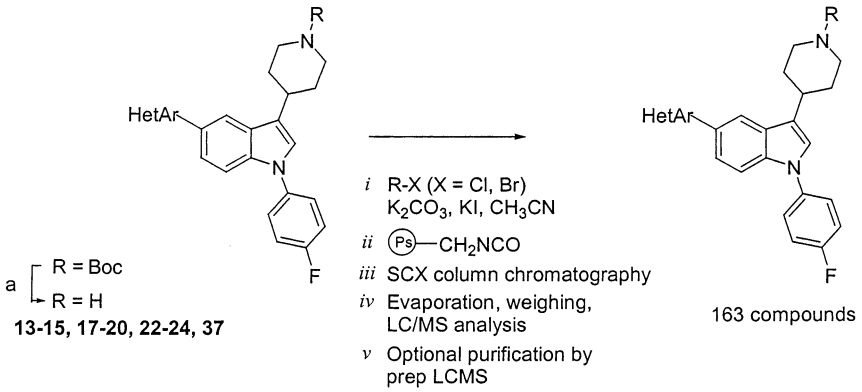
triazole **26a**. The *N*-unsubstituted tetrazole **25a** was prepared from the corresponding nitrile **40**[32] by reaction with sodium azide.

Parallel organic synthesis in 96-well format was performed as depicted in Scheme 5. *N*-Unsubstituted piperidine derivatives resulting from deprotection of the intermediates **13**−**15**, **17**−**20**, **22**−**24**, and **37** were alkylated with 24 different alkyl halides in the presence of potassium iodide and an excess of base in a Multi-synthech Microchem multichamber block[45] containing 96 reactors using a rotating oven. The unreacted piperidinyl derivatives were removed by reaction with resin-bound isocyanate.[46] Filtration and cation ion exchange chromatography afforded the final products. The purity of all samples was analyzed by HPLC/MS with UV and ELSD detection. Compounds were optionally purified by preparative HPLC/MS if the purity did not exceed 70%. Of 264 possible compounds 163 were obtained in sufficient yield and purity to allow for pharmacological characterization were obtained. Selected representative examples of yields and purity of the products obtained by this method are reported in Table 6.

Results and Discussion

The receptor-binding assays are described in Table 1 and in detail in the Experimental Section. Receptor-binding affinities (adrenergic α_1, dopamine D_2, and serotonin 5-HT_{1A}, 5HT_{1B}, 5HT_{2A}, and 5-HT_{2C} receptors) for sertindole and compounds prepared in the present study are reported in the Tables 3−5. In addition, receptor-binding affinities for the α_1-adrenergic receptor

Scheme 5[a]



[a] Reagents: (a) HCl, MeOH, rt., 4 h.

Table 2. Receptor-Binding Assays Used and Receptor-Binding Affinities for Reference Compounds[a]

receptor	species	membrane source	radioligand (concn) (nM)	ref compd	K_i, nM
α_1	rat	whole brain	[^{3}H]prazosin (0.25)	prazosin	0.29
α_{1a}	bovine[b]	BHK cells	[^{3}H]prazosin (0.3)	prazosin	0.93
α_{1b}	hamster[b]	Rat-1cells	[^{3}H]prazosin (0.5)	(±)-cyclazosin	0.46
α_{1d}	rat[b]	CHO cells	[^{3}H]prazosin (0.3)	SNAP-8719	1.4
D_1	rat	corpus striatum	[^{3}H]SCH 23390 (0.2)	haloperidol	29
D_2	rat	corpus striatum	[^{3}H]spiperone (0.5)	haloperidol	1.9
D_3	human[b]	CHO cells	[^{3}H]spiperone (0.3)	haloperidol	2.7
D_4	human[b]	CHO cells	[^{3}H]YM-09151-2 (0.06)	clozapine	30
5-HT$_{1A}$	human[b]	HeLa cells	[^{3}H]5-CT (2.0)	metitepine	2.2
5-HT$_{1B}$	human[b]	HeLa cells	[^{3}H]5-CT (1.5)	serotonin	4.8
5-HT$_{2A}$	rat	cerebral cortex	[^{3}H]ketanserin (0.5)	mianserine	2.5
5-HT$_{2C}$	rat[b]	SR-3T3 cells	[^{3}H]mesulergine (0.5)	mesulergine	0.37
h-5-HT$_{2C\ (VSV)}$	human[b]	CHO cells	[^{3}H]mesulergine (0.5)	mesulergine	0.92

[a] For detailed description af assays, see Experimental Section. [b] Cloned receptors.

subtypes α_{1a}, α_{1b}, and α_{1d} and dopamine D_1, D_3, and D_4 receptors are reported in Table 5 for selected compounds and reference compounds. Good correlation between receptor-binding affinities observed for the cloned α_{1a} (bovine), α_{1b} (hamster), α_{1d} (rat) receptors and the corresponding human clones all expressed in LTK cells has been documented.[47]

Replacement of the chlorine atom in sertindole (**1**) with 1-methyl- or 1-ethyl-1,2,3-triazol-4-yl (**8a**, **9a**), 1-methylpyrazol-4-yl (**14a**), and *N*-unsubstituted tetrazole **25a** (Table 3) resulted in 6−45-fold reduced affinity for α_1-adrenoceptors. The remaining heteroaryl-substituted derivatives **10a**−**13a**, **15a**−**24a**, and **26a** (Table 3) have essentially equipotent affinity for α_1-adrenoceptors compared to sertindole (**1**). All compounds have significantly reduced affinities for dopamine D_2 receptors by factors of 35−1500 and for serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors by factors of 30−1100 and 72−5700, respectively. The structure−affinity relationships for dopamine D_2 receptors and serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors seem to be essentially parallel. The serotonin 5-HT$_{2C}$ receptors seem most sensitive to the replacement of the chlorine atom in sertindole as apparent by comparing the binding affinites of the 1,2,4-triazole **15a** with sertindole. The affinity for serotonin 5-HT$_{2C}$ receptors is reduced by a factor of 5700, whereas the affinities for 5-HT$_{2A}$ and dopamine D_2 receptors are reduced by factors of 700 and 1500, respectively.

The effect of replacement of the methyl group of the 2-methyl-1,2,3-triazole **10a** with an ethyl group (**11a**) or a hydrogen (**26a**) on affinity for the receptors studied is negligible, indicating that the receptor-binding affinities for the receptors studied are essentially uninfluenced by steric factors in this area. In the corresponding tetrazole series, replacement of the methyl group of **12a** with a hydrogen (**25a**) leads to a 35-fold decrease in affinity for α_1-adrenoceptors. Apparently, the acidic nature of the *N*-unsubstituted tetrazole[48] leads to repulsion between the tetrazole anion and the receptor.

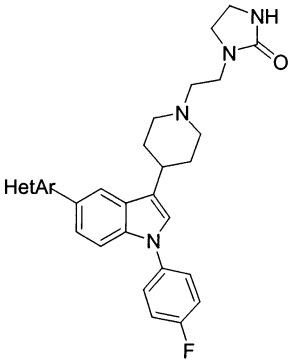
Sertindole has moderate affinity for serotonin 5-HT$_{1A}$ (K_i = 33 nM) and 5-HT$_{1B}$ (K_i = 56 nM) receptors as apparent from Table 3.[25]

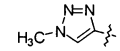
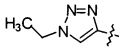
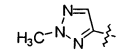
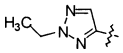
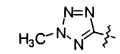
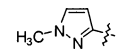
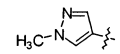
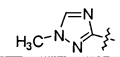
The effect of replacement of the chlorine atom in sertindole with five-membered heterocycles on binding affinity for serotonin 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors is variable. The most pronounced effects are observed for the imidazole derivative **19a** having affinities enhanced by factors of 10 and 5, respectively, and for the 2-ethyl-1,2,3-triazol-4-yl derivative **11a** having affinities reduced by factors of 8 and 3, respectively.

The optimal compounds with respect to affinity for α_1-adrenoceptors and selectivity in respect to dopamine D_2 and serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$ receptors are the 1,2,4-triazole **15a**, the pyrazole **13a**, the *N*-unsubstituted 1,2,3-triazole **26a**, and the tetrazole **12a** having selectivity in respect to these receptors higher than 30. These compounds have unchanged affinity for serotonin 5-HT$_{1A}$ receptors compared to sertindole (**1**), except for the tetrazole **12a** having 4-fold reduced affinity. Compounds combining high affinity for adrenergic α_1 receptors with low affinity for both dopamine D_2 and serotonin 5-HT$_{2A}$ and 5-HT$_{2C}$, and low affinity for serotonin 5-HT$_{1A}$ and 5-HT$_{1B}$ receptors were not identified in the present series.

In an attempt to further improve the selectivity for α_1-adrenergic receptors, the substituent on the piperi-

Table 3. Receptor-binding Affinities of 2-(2-Oxoimidazolidinyl)ethyl-Substituted 5-Heteroarylindole Derivatives **8a**−**24a** and Sertindole **1**

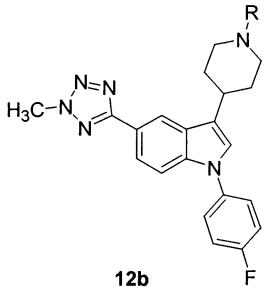


		K_i (nM)[a]					
Compd	HetAr	α_1	D_2	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2C}
1	Sertindole	1.4[b]	0.45[b]	33	56	0.20[b]	0.51[b]
8a		9.5	310	29	36	110	1500
9a		11	43	236	28	60	500
10a		1.7	86	290	67	43	73
11a		4.4	86	273	208	21	37
12a		1.8	140	130	48	60	330
13a		3.7	490	33	110	140	330
14a		22	570	49	45	130	1000
15a		2.5	660	24	68	140	2900
16a		6.8	430	40	20	160	1100
17a		0.45	60	11	6.5	9.0	190
18a		2.9	29	5.8	5.9	6.0	45
19a		1.2	200	3.3	11	22	130
20a		1.2	20	18	2.8	12	140
21a		1.3	16	51	20	11	180
22a		2.0	230	12	76	37	1200
23a		3.2	91	35	4.2	55	120
24a		5.3	140	13	14	41	50
25a		63	140	NT	NT	210	NT
26a		1.0	80	45	31	30	150

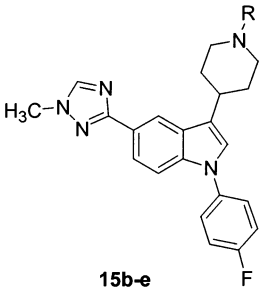
[a] For description of assays see Table 2. [b] Reference 11.

dine nitrogen atom was optimized. The intermediates **13**−**15**, **17**−**20**, **22**−**24**, and **37** were alkylated in a parallel fashion using 24 different alkylating agents. Low molecular weight alkylating agents ($M_{\text{side chain}} <$ 210 g/mol) were chosen in order to keep the average molecular weight of the final products below 500 g/mol.

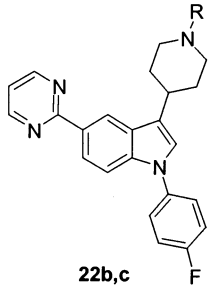
Table 4. Receptor-Binding Affinities for 5-(2-Methyltetrazol-5-yl)indole Derivatives **12b**, 5-(2-Methyl-1,2,4-triazol-3-yl)indole Derivatives **15b−e**, and 5-(Pyrimid-2-yl)indole Derivatives **22b,c**



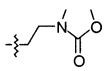
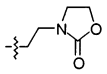
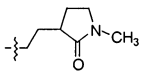
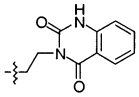
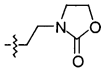
12b



15b-e



22b,c

Compd	R	K_i (nM)[a] α_1	D_2	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	h-5-HT_{2C}
12b		2.6	190	49	220	65	410
15b		5.3	2300	25	480	500	>4200
15c		6.3	>2900	160	340	1200	>4200
15d		6.3	540	64	100	320	>4200
15e		13	370	55	560	60	1100
22b		14	400	47	360	260	>4200
22c		5.8	490	67	200	500	>4200

[a] For detailed description of assays, see Table 2.

Of 264 possible products, 163 were obtained in sufficient purity (>70%) and yield to allow for determination of affinity by single concentration-binding studies to adrenergic α_1, dopamine D_2, and serotonin 5-HT_{2A} receptors. For the most potent compounds, K_i values were determined. In general, the effect of the different piperidine N-substituents were independent of the indole 5-substituent. Representative examples of data obtained by this method are given in Table 6. The most promising compounds obtained were the 1-methyl-1,2,4-triazol-3-yl, pyrimidin-2-yl, and 2-methyltetrazol-5-yl derivatives **15b−e**, **22b**,**c**, and **12b**. These compounds were resynthesized, and the receptor binding affinities are presented in Table 4.

The affinities of the prepared compounds for adrenergic α_1 receptors were essentially unchanged by replacement of the imidazolidinone side chain with the side chains listed in Table 4, except for the 3-ethyl-1*H*-quinazoline-2,4-dione **15e** and the oxazolidinone **22b** where the affinities were reduced by factors of 5 and 14, respectively.

The 3-ethyl-1-methylpyrrolidin-2-one derivative **15d** (racemate) showed a receptor-binding profile similar to the corresponding imidazolidinone **15a**, indicating that the N−H in the imidazolidinone 3-position has no specific interaction contributing to the receptor-binding affinity.

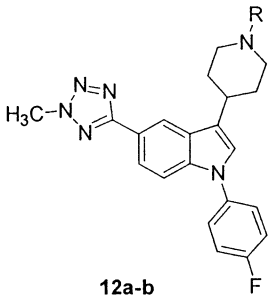
Replacement of the imidazolidinone side chain with an oxazolidinone side chain as in compounds **15b** and **22b** resulted in reduced affinity for dopamine D_2 and serotonin 5-HT_{1B} and 5-HT_{2A} receptors. The effect was most pronounced for 5-HT_{1B} receptors, where the affinity was reduced 4- to 7-fold. In contrast, no improvement in selectivity in respect to dopamine D_2 and serotonin 5-HT_{2A} receptors was observed with similar replacement in the tetrazole series, as apparent by comparison of **12a** and **12b**.

As apparent by comparing the propionitriles **15c** and **22c** (Table 4) with the corresponding imidazolidinones **15a** and **22a** (Table 3), this replacement resulted in significantly reduced affinities for dopamine D_2, as well as serotonin 5-HT_{1A}, 5-HT_{1B} and 5-HT_{2A} receptors. Despite the slightly reduced affinity for α_1 adrenergic receptors, the overall selectivity of these compounds is enhanced significantly.

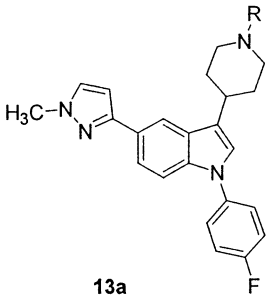
The affinity of the most selective compounds and selected compounds from Tables 3 and 4 are listed in Table 5 together with additional receptor-binding affinities at α_1 adrenergic subtypes (α_{1a}, α_{1b}, α_{1d}) and dopamine D_1, D_3, and D_4 receptors.

All compounds have low affinity for the dopamine D_1, D_3, and D_4 receptors. The receptor-binding affinity of the 1,2,4-triazole (**15a**) was reduced by a factor of 340,

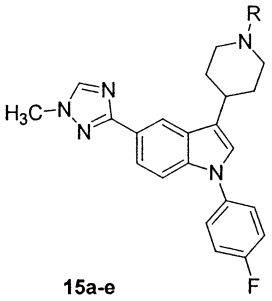
Table 5. Receptor-Binding Profiles for the Most Selective 5-Heteroarylindole Derivatives and for Reference Compounds



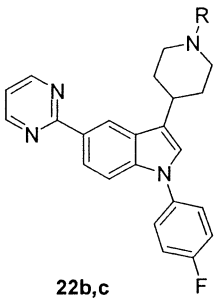
12a-b



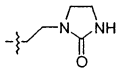
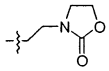
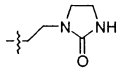
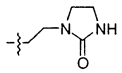
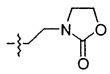
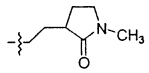
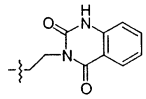
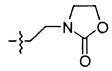
13a



15a-e



22b,c

Compd	R	K_i (nM)[a] α_1	α_{1a}	α_{1b}	α_{1d}	D_1	D_2	D_3	D_4	5-HT_{1A}	5-HT_{1B}	5-HT_{2A}	5-HT_{2C}
1	Sertindole	1.4[c]	0.37	0.33	0.66	12[c]	0.45[c]	2.6[c]	11[c]	33	56	0.20[c]	0.51[c]
2	Prazosin	0.29	0.93	0.83	0.26	>5600	NT	>7100	8300	>1800	>7700	1500	>4200[b]
4	Phentolamine	90	6.8	220	45	NT	NT	NT	NT	NT	NT	NT	NT
6	(±)-Cyclazosin	1.2	5.1	0.46	0.86	NT	NT	NT	NT	NT	NT	NT	NT
7	SNAP8719	840	5900	170	1.4	NT	970	59	49	490	7700	120	2600
	(R)-octoclothepin	1.4[d]	1.4	0.93	0.47	1.2[d]	6.6[d]	NT	4.5[e]	NT	NT	0.48[d]	NT
42	(S)-octoclothepin	0.45[d]	0.56	0.22	0.15	2.2[d]	1.3[d]	NT	1.5[e]	NT	NT	0.48[d]	NT
12a		1.8	0.23	1.1	2.0	>100	140	1200	4300	130	48	60	330
12b		2.6	0.35	0.69	2.7	2600	190	1400	5700	49	220	65	410[b]
13a		3.7	0.49	4.0	4.8	NT	490	2100	6400	33	110	140	330
15a		2.5	0.80	6.9	5.9	4100	660	2900	3000	24	68	140	2900
15b		5.3	0.62	3.2	7.9	4500	2300	3100	4900	25	480	500	>4200[b]
15c		6.3	0.99	3.2	9.0	NT	>2900	1200	920	160	340	1200	>4200[b]
15d		6.3	2.2	8.8	15	5600	540	>7100	7200	64	100	320	>4200[b]
15e		13	1.3	0.39	3.1	1600	370	590	3600	55	560	60	1100[b]
22b		14	0.56	1.8	52	1800	400	2800	7500	47	360	260	>4200[b]
22c		5.8	3.9	4.6	20	3000	490	680	7000	67	200	600	>4200[b]

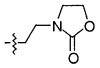
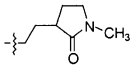
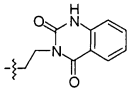
[a] For description of assays, see Table 2. [b] h-5-HT_{2C}. [c] Reference 11. [d] IC_{50} value.[55] [e] Reference 55.

1100 and 272, respectively, for these receptors compared to sertindole (**1**).

Sertindole (**1**) binds with sub-nanomolar affinity for the three α_1-adrenergic subtypes (α_{1a}, α_{1b}, α_{1d}) as shown in Table 5.[25] The affinity of the compounds of the present investigation listed in Table 5 for the recombinant α_{1a} receptor subtype was generally higher with a factor of 3−25 compared to the data obtained in the α_1 assay (rat brain homogenate). All compounds have the highest affinity for the α_{1a} receptor subtype, except the quinazoline-2,4-dione **15e** which has higher affinity for the α_{1b} receptor.

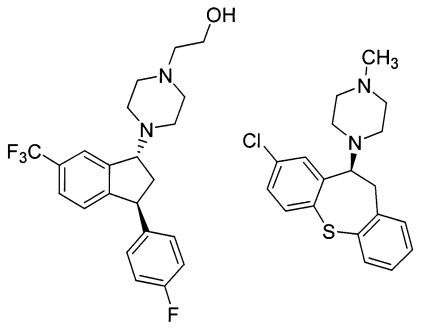
The imidazolidinone derivatives **12a**, **13a**, and **15a** all showed some degree of subtype selectivity. The affinities for the adrenergic α_{1b} and α_{1d} receptor subtypes were lower by a factor of 5−10 compared to the α_{1a} receptor subtype. The same trend was observed with the oxazolidinones **12b** and **15b**, with the propionitrile

Table 6. Examples of Yields, Purity, and Pharmacological Data Obtained from Parallel Synthesis Library

		Yield	Purity		% Inhibition (100 nM)		
Compd	R	%	UV (%)	ELSD (%)	α_1	D_2	5-HT_{2A}
15b		27	98	100	93	60	9
15c		16	90	100	88	81	9
15d		27	78	99	88	48	15
15e		6	92	99	105	3	49

[a] For detailed description of assays, see Table 2.

Chart 3. Structure (1*R*,3*S*)-Tefludazine (**41**) and (*S*)-Octeclothepin (**42**)



41 (1*R*,3*S*)-Tefludazine **42** (*S*)-Octoclothepin

15c and with the 3-ethyl-1-methylpyrrolidin-2-one **15d**. In contrast, the oxazolidinone-substituted pyrimidine derivative **22b** bound with 100 times lower affinity for the α_{1d} receptor subtypes compared to α_{1a} This indicates that further exploration of the area around the indole 5-position may hold a potential for development of subtype-selective ligands.

The 3-ethyl-1*H*-quinazoline-2,4-dione **15e** displayed subnanomolar affinity for the adrenergic α_{1b} receptor (0.39 nM). Compared to the imidazolidinone **15a**, the affinity for this receptor subtype was enhanced 17 times without significantly affecting the affinity for the α_{1a} and α_{1d} receptor subtypes. This could indicate an additional binding site for aromatic substituents in the α_{1b} receptor.

Sertindole (**1**) has been shown to antagonize the response to the α_1-agonist phenylephrine in rat small arteries[27] and to inhibit the pressor response of phenylephrine after iv dosing in pithed rats ($ED_{50} = 0.65$ μmol/kg).[49] Similarly, compound **12a** inhibits the pressor response of phenylephrine after iv dosing in pithed rats ($ED_{50} = 1.5$ μmol/kg),[50] suggesting that this compound is an α_1-adrenoceptor antagonist like sertindole. This is further supported by the inhibition of isoniazide-induced convulsions in mice[51] by the compounds **8a** ($ED_{50} = 3.6$ μmol/kg) and **12a** ($ED_{50} = 1.1$ μmol/kg),[50] indicating that these compounds are centrally acting α_1-adrenoceptor antagonists.

The Liljefors−Bøgesø pharmacophore model for dopamine D_2 receptor antagonists[52] is based on superimposition of the two potent dopamine D_2 anatagonists (*S*)-octoclothepin (**42**, Chart 3) and (1*R*,3*S*)-tefludazine (**41**, Chart 3) and was validated by studies on phenylindoles including sertindole (**1**). The basic features of this model, consisting of two aromatic rings and one basic nitrogen atom, were later used to develop receptor interaction models for antagonists of serotonin 5-HT_2[53,54] and dopamine D_4[55] receptors. Both (1*R*,3*S*)-tefludazine and (*S*)-octoclothepin, used as basis for the model, are potent adrenergic α_1 antagonists,[56] suggesting that the model can be used to rationalize the binding of adrenergic α_1 antagonists. This is further supported by a study of the enantiomers of octoclothepin.[56] The (*S*)-enantiomer displays 2.5 times higher affinity for the dopamine D_2 receptor compared to the (*R*)-enantiomer. It was shown that conformations exist where the two enantiomers adopt very similar 3-D shapes and are well accommodated into the model. The conformational energies for the compounds in these conformations agreed well with the displayed eudismic ratio.[56] The eudismic ratio of the two octoclothepin enantiomers with respect to α_1 adrenoceptor affinity is comparable to the eudismic ratio reported for dopamine D_2 receptor affinity.[56] As apparent from the results in Table 5, (*R*)- and (*S*)-octoclothepin showed a similar subtype profile with decreasing affinity from α_{1a} over α_{1b} to α_{1d} and eudismic ratios in the range of 2.5−4.3, the *S*-enantiomer being consistently more potent compared to the *R*-enantiomer. These results indicate that the D_2 pharmacophore also can be extended to a pharmacophore for the adrenergic α_1 subtypes, α_{1a} α_{1b}, and α_{1d}. Accordingly it can be assumed that the phenylindoles of the present investigation bind to the α_1 receptors in a conformation similar to that reported for phenylindoles on the D_2, D_4, and 5-HT_2 receptors.[53−55] The selectivities obtained may be explained by interactions between the substituents in the 5-position in the indole nucleus and the receptors studied as discussed in the following.

We recently hypothesised that steric bulk of large substituents in the plane of the indole nucleus in the area corresponding to the indole 5-position reduced the affinity for dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors and that compensatory electrostatic interactions explained the high affinity for adrenergic α_1 receptors despite the repulsive steric interactions.[25]

The present results seem to support this hypothesis. The derivatives having "ortho" methyl-substituted 5-heteroaryl groups (**16a**−**21a**) may adopt conformations where the 5-heteroaryl group and the indole moiety are not coplanar due to repulsion between the methyl group and the protons in the indole 4- and 6-position. In

contrast, the derivatives unsubstituted in the "ortho" position of the 5-heteroaryl group (**8a**−**15a**) may adopt conformations where the two ring systems are coplanar. The most selective compounds in the present study are identified within the group of compounds unsubstituted in the "ortho" position (e.g. **8a** and **15a**) where coplanar conformations are expected to be of low conformational energy. Accordingly, this group of compounds **8a**−**15a** (Table 3) tends to have lower affinity for dopamine D_2 and serotonin 5-HT_{2A} and 5-HT_{2C} receptors compared to the "ortho" substituted compounds **16a**−**21a**.

The importance of favorable electrostatic interaction between the receptor and the 5-heteroaryl moieties in the present compounds for the affinity for adrenergic α_1 receptors is difficult to address by qualitative means. However, comparison of the least potent of the compounds listed in Table 3, the 1-methylpyrazol-4-yl derivative **14a**, with any of the compounds in Table 3 indicates the importance of a hydrogen-bond acceptor in the position "ortho" to the point of attachment to the indole nucleus.

We are currently investigating the structure-affinity relationships of the present 5-heteroaryl-substituted phenylindoles together with previously reported 5- and 6-substituted phenylindoles by a 3D-QSAR approach in order to address the importance of the proper balance between unfavorable steric interactions and favorable electrostatic interactions for the affinity for adrenergic α_1 receptors of phenylindoles.

In the present study, several highly selective α_1-adrenoceptor antagonists were obtained. The optimal compounds with respect to overall selectivity are the tetrazoles **12a** and **12b**. The selectivity of these compounds is limited by affinity for serotonin 5-HT_{1A}, 5-HT_{1B}, 5-HT_{2A} and dopamine D_2 receptors. Considering selectivity for α_{1a} receptors in respect to dopamine D_2, D_3, and D_4 and serotonin 5-HT_{2A} and 5-HT_{2C}, the optimal compound is the 1-methyl-1,2,4-triazol-3-yl-substituted propionitrile **15c**. This compound has affinities of 0.99, 3.2, and 9.0 nM for the α_{1a}, α_{1b}, and α_{1d} adrenoceptor subtypes, respectively, and a selectivity for adrenergic α_{1a} receptors in respect to dopamine D_2, D_3, and D_4 and serotonin 5-HT_{2A} and 5-HT_{2C} higher than 900, comparable to the selectivity of prazosin. In addition, the compound is more than 150-fold selective in respect to serotonin 5-HT_{1A} and 5-HT_{1B} receptors.

The 5-heteroaryl-substituted 1-(4-flurophenyl)indoles presented in this paper represent a novel class of selective adrenergic α_1 receptor ligands. The potential of the most selective compounds for the treatment of CNS-related diseases is currently under investigation. Furthermore, the compounds may have a potential as PET ligands for imaging of central adrenergic α_1 receptors.

Experimental Section

General. All reactions were carried out under a positive pressure of nitrogen or argon. Glassware for water-sensitive reactions was dried in an oven at 150 °C overnight. THF was freshly distilled from sodium/benzophenone. DMF was sequentially dried and stored over 3 Å molecular sieves. $ZnCl_2$ was flame-dried in vacuo and dissolved to 1.0 M in dry THF after cooling to room temperature. Acetone and CH_3CN for alkylation reactions were HPLC grade. Saturated HCl/MeOH solutions were prepared by saturation of MeOH with HCl gas. For flash chromatography either silica gel of type Kiesel gel 60, 230−400 mesh ASTM or Biotage Flash40 (50 or 100 g columns) were used. ^{1}H NMR spectra were recorded of all novel compounds at 250 MHz on a Bruker AC 250 or at 500 MHz on a Bruker Avance DRX500 instrument. Deuterated chloroform (99.8%D) or DMSO-d_6 (99.9%D) were used as solvents. TMS was used as internal reference standard. Chemical shift values are expressed in ppm-values. The following abbreviations are used for multiplicity of NMR signals: s = singlet, d = doublet, t = triplet, q = quartet, dd = double doublet, dt = double triplet, tt = triplet of triplets, m = multiplet. NMR signals corresponding to acidic protons are generally omitted. Melting points are reported uncorrected. Solvent residuals in elemental analysis samples were measured by Karl Fisher titration (H_2O) or by Thermo Gravimetric Analysis (TGA) on a TA-instruments TGA 2950 with heating rate 10 °C per min. The identity of the solvent was determined by ^{1}H NMR. Solvent residuals are not reported in the NMR data. LC-MS data (Liquid Chromatography Mass Spectroscopy) were obtained on a PE Sciex API150EX equipped with a Heated Nebulizer source operating at 425 °C. The LC-MS pumps were Shimadzu 8A series running with a Waters C-18 4.6 × 50 mm, 3.5 μm column. Solvent A: 100% H_2O + 0.05% trifluoroacetic acid, solvent B: 95% CH_3CN, 5% H_2O + 0.035% trifluoroacetic acid. Gradient (2 mL/min): 10% B-100% B in 4 min, 10% B for 1 min. Total time including equilibration 5 min. Injection volume 10 μL from a Gilson 215 Liquid Handler. Preparative HPLC-MS was run with 190 μL injections on a YMC RP18 (50 × 20 mm) column with a gradient of A/B 80/20 → 0/100 during 7 min, then isocratic 80/20 during one minute. The flow was 22.7 mL/min throughout and detection was performed using the MS (TIC) signal in a split system. The reported purities are based on integration of the peaks in the UV and ELSD spectrum.

Reagents. The following reagents were prepared according to published procedures: 1-(2-chloroethyl)imidazolidin-2-one,[32,57] 3-(2-chloroethyl)oxazolidin-2-one,[58] 3-(2-chloroethyl)-1-methyl-2-pyrrolidin-2-one,[59] 1-methyl-1,2,3-triazole,[60] 4-bromo-1-methyl-1,2,3-triazole,[61] 2-bromo-1-methyl-1,3,4-triazole,[62] 5-bromo-1-methyl-1,2,4-triazole,[62] 3-bromo-1-methyl-1,2,4-triazole,[62] 3-iodo-1-methylpyrazole.[39] The reference compound, SNAP 8719 (**7**), was prepared as described in a patent application.[63]

5-Bromo-1-(4-fluorophenyl)-1*H*-indole (27a). 5-Bromo-1*H*-indole (250 g, 1.28 mol), 1-fluoro-4-iodobenzene (510 g, 2.30 mol), K_2CO_3 (530 g, 3.84 mol), CuI (90 g, 0.47 mol), and ZnO (30 g, 0.37 mol) were heated at 100 °C in NMP (3 L) with mechanical stirring for 24 h. Additional K_2CO_3 (53 g, 0.39 mol), CuI (9 g, 0.05 mol), and ZnO (3 g, 0.04 mol) were added, and the mixture was stirred for further 24 h. After filtration, H_2O (2 L) and aqueous NH_4OH (25%, 100 mL) were added, and the aqueous phase was extracted with EtOAc (3 × 2 L). The combined organic phases were washed with brine (500 mL) and dried over $MgSO_4$. After evaporation of the solvent in vacuo, the crude product (473 g) was purified by flash chromatography (EtOAc/heptane 5/95). Recrystallization from EtOAc/heptane 5/95 gave 229 g (55%) of **27**: Mp 104−105 °C (EtOAc/heptane 5/95) (lit.[32] 101 °C (cyclohexane)); ^{1}H NMR ($CDCl_3$) δ: 6.70 (d, 1H), 7.30 (d, 1H), 7.40−7.45 (m, 3H), 7.60−7.65 (m, 2H). 7.70 (d, 1H), 7.80 (d, 1H).

5-Ethynyl-1-(4-fluorophenyl)-1*H*-indole (28). A mixture of **27a** (40.0 g, 0.14 mol), (trimethylsilyl)acetylene (21.4 g, 0.22 mol), $Pd(PPh_3)_2Cl_2$ (2.9 g, 3 mol %), CuI (1.3 g, 5 mol %), NEt_3 (40 mL), and CH_3CN (150 mL) was boiled under reflux for 8 h. After the mixture was cooled to room temperature, H_2O (100 mL) was added and the resulting mixture was extracted with EtOAc (4 × 300 mL). The combined organic phases were washed with brine (2 × 800 mL) and dried (Na_2SO_4), and the solvents were evaporated in vacuo. A solution of the remaining oil and KOH (12.1 g, 0.22 mol) in a mixture of MeOH (500 mL) and H_2O (200 mL) was boiled under reflux for 3 h. The volatile solvents were evaporated in vacuo, and a mixture of H_2O (200 mL) and EtOAc (1000 mL) was added. The phases were separated, and the aqueous phase was extracted with EtOAc (250 mL). The combined organic phases were dried

(Na_2SO_4) and the volatile solvents evaporated in vacuo. Purification of the remaining oil by column chromatography on silica gel (CH_2Cl_2/heptane 1:6) afforded 11.4 g (35%) of the crystalline pure title compound (**28**): Mp 99−100 °C; ^{1}H NMR ($CDCl_3$) δ: 3.00 (s, 1H), 6.55 (d, 1H), 7.20 (t, 2H), 7.25 (d, 1H), 7.35 (m, 2H), 7.40 (dd, 2H), 7.85 (broad s, 1H).

1-(4-Fluorophenyl)-5-(1,2,3-triazol-4-yl)-1*H*-indole (29). A mixture of **28** (9.6 g, 41 mmol) and neat azidotrimethylsilane (21.7 g, 0.19 mol) was heated in a sealed tube at 170 °C for 24 h. The reaction mixture was cooled to 0 °C, and CH_2Cl_2 (150 mL) and 2 N aqueous NaOH (20 mL) were added. After the mixture was stirred at room temperature for 2 h, H_2O (200 mL) was added and the solution acidified by addition of concentrated aqueous HCl. The phases were separated, and the aqueous phase was extracted with CH_2Cl_2 (2 × 200 mL). The combined organic phases were washed with brine (200 mL), dried ($MgSO_4$) and the volatile solvents evaporated in vacuo affording 11.8 g (100%) of **29** as an oil: ^{1}H NMR ($CDCl_3$) δ: 6.80 (d, 1H), 7.25 (t, 2H), 7.40 (d, 1H), 7.55 (dd, 2H), 7.60 (d, 1H), 7.75 (broad d, 1H), 8.05 (s, 1H), 8.20 (broad s, 1H).

1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-1*H*-indole (30a) and 1-(4-fluorophenyl)-5-(2-methyl-1,2,3-triazol-4-yl)-1*H*-indole (32a). A mixture of **29** (6.0 g, 21.6 mmol), CH_3I (6.7 mL, 0.11 mol), K_2CO_3 (6.0 g, 43.2 mmol), and acetone (100 mL) was boiled under weak reflux for 18 h. The solids were filtered off, and the solvent was evaporated in vacuo. The mixture of **30a** and **32a** was separated by flash chromatography (EtOAc/heptane 1:1). Evaporation of the solvent from the fractions containing the fastest eluting compound afforded 2.1 g (33%) pure **32a** as an oil: ^{1}H NMR ($CDCl_3$) δ: 4.25 (s, 3H), 6.70 (d, 1H), 7.20 (t, 2H), 7.30 (d, 1H), 7.40−7.55 (m, 3H), 7.65 (broad d, 1H), 7.85 (s, 1H), 8.10 (broad s, 1H). Evaporation of the solvent from the fractions containing the slowest eluting compound afforded 0.80 g (13%) pure **30a** as an oil: ^{1}H NMR ($CDCl_3$) δ: 4.15 (s, 3H), 6.70 (d, 1H), 7.20 (t, 2H), 7.30 (d, 1H), 7.50 (dd, 2H), 7.55 (d, 1H), 7.70 (broad d, 1H), 7.75 (s, 1H), 8.10 (broad s, 1H).

The following derivatives were prepared accordingly using ethyl iodide:

5-(1-Ethyl-1,2,3-triazol-4-yl)-1-(4-fluorophenyl)-1*H*-indole (31a): Oil (1.5 g, 20%): ^{1}H NMR ($CDCl_3$) δ: 1.60 (t, 3H), 4.45 (q, 2H), 6.70 (d, 1H), 7.20 (t, 2H), 7.30 (d, 1H), 7.40−7.55 (m, 3H), 7.70 (broad d, 1H), 7.75 (s, 1H), 8.15 (broad s, 1H).

5-(2-Ethyl-1,2,3-triazol-4-yl)-1-(4-fluorophenyl)-1*H*-indole (33a): Oil (2.6 g, 43%): ^{1}H NMR ($CDCl_3$) δ: 1.60 (t, 3H), 4.50 (q, 2H), 6.70 (d, 1H), 7.20 (t, 2H), 7.30 (d, 1H), 7.45 (dd, 2H), 7.45 (d, 1H), 7.65 (broad d, 1H), 7.80 (s, 1H), 8.10 (broad s, 1H).

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyltriazol-4-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (8a). A mixture of 4-piperidone hydrochloride hydrate (2.5 g, 16.4 mmol), glacial acetic acid (20 mL), and trifluoroacetic acid (20 mL) was boiled under reflux. During 20 min, **30a** (0.80 g, 2.7 mmol) in glacial acetic acid (10 mL) was added in small portions. The mixture was boiled under reflux for another 1.5 h. After the mixture was cooled, the solvents were evaporated in vacuo and H_2O (100 mL) was added. The aqueous phase was made alkaline by the addition of concentrated aqueous NaOH and subsequently extracted with EtOAc (3 × 100 mL). The combined organic phases were dried (Na_2SO_4), and the solvents evaporated in vacuo to give 0.90 g (91%) of 1-(4-fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**30b**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 2.50−2.60 (m, 2H), 2.60−2.70 (broad s, 1H), 3.15 (t, 2H), 3.60−3.70 (m, 2H), 4.15 (s, 3H), 6.30−6.40 (m, 1H), 7.15−7.25 (m, 3H), 7.35−7.50 (m, 3H), 7.65 (broad d, 1H), 7.75 (s, 1H), 8.40 (broad s, 1H). A solution of **30b** (0.90 g, 2.0 mmol) and 1-(2-chloroethyl)imidazolidin-2-one (0.30 g, 2.2 mmol) in 4-methyl-2-pentanone (50 mL) was boiled under reflux with K_2CO_3 (0.40 g, 3.0 mmol) and KI (0.10 g, 0.6 mmol) for 8 h. After the mixture was cooled to room temperature, water (25 mL) was added and the aqueous phase extracted with EtOAc (3 × 50 mL). Evaporation of the solvents and flash chromatography (EtOAc/EtOH/NEt_3 50/50/2) afforded 0.70 g (64%) of 1-(2-{4-[1-(4-fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl)imidazolidin-2-one (**30c**) as an oil: ^{1}H NMR ($CDCl_3$) δ: 2.60−2.75 (m, 4H), 2.80 (t, 2H), 3.25−3.35 (m, 2H), 3.35−3.50 (m, 4H), 3.50−3.60 (m, 2H), 4.15 (s, 3H), 4.70 (broad s, 1H), 6.25−6.35 (broad s, 1H), 7.20 (t, 2H), 7.25 (s, 1H), 7.40−7.50 (m, 3H), 7.70 (broad d, 1H), 7.80 (s, 1H), 8.40 (broad s, 1H). A solution of **30c** (0.70 g, 1.4 mmol) in glacial acetic acid (100 mL) and PtO_2 (70 mg) was reacted in a Parr apparatus with H_2 at 2−3 ato for 24 h. After filtration and evaporation of the solvent, ice (50 mL) and 10% aqueous NH_4OH were added to pH 10, and extraction with EtOAc (3 × 50 mL) was performed. The solution was dried over $MgSO_4$, and the solvent was removed in vacuo to yield 0.50 g of crude product that was purified by flash chromatography (EtOAc/EtOH/NEt_3 50/50/2) to yield a foam (0.30 g). Addition of Et_2O and filtration afforded 0.24 g (34%) of the title compound **8a**: Mp 116−118 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ: 1.70−1.90 (m, 2H), 2.05−2.30 (m, 4H), 2.60 (t, 2H), 2.95 (tt, 1H), 3.00−3.15 (m, 2H), 3.30−3.45 (m, 4H), 3.50−3.60 (m, 2H), 4.15 (s, 3H), 4.40 (broad s, 1H), 7.05 (s, 1H), 7.20 (t, 2H), 7.45 (dd, 2H), 7.50 (d, 1H), 7.60 (broad d, 1H), 7.75 (s, 1H), 8.20 (broad s, 1H); 1D-NOE: 2% on δ = 8.20 (1,2,3-triazole H4) by irradiation of δ = 4.15 (*N*-CH_3); MS *m*/*z*: 488 (MH^+, 29%), 194 (28%), 168 (23%), 113 (100%); Anal. ($C_{27}H_{30}FN_7O$·1.80% H_2O): C, H, N.

The following derivatives were prepared accordingly:

1-(2-{4-[5-(1-Ethyl-1,2,3-triazol-4-yl)-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (9a). The material obtained after chromatography was stirred with EtOH. Filtration afforded 0.20 g (12%) of **9a**. Mp 132−134 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.60 (t, 3H), 1.70−1.95 (m, 2H), 2.05−2.30 (m, 4H), 2.55 (t, 2H), 2.90 (tt, 1H), 3.00−3.15 (m, 2H), 3.30−3.45 (m, 4H), 3.45−3.60 (m, 2H), 4.30 (broad s, 1H), 4.45 (q, 2H), 7.05 (s, 1H), 7.10 (t, 2H), 7.35−7.50 (m, 3H), 7.60 (broad d, 1H), 7.75 (s, 1H), 8.15 (broad s, 1H); 1D-NOE: 2% on δ = 8.15 (1,2,3-triazole H4) by irradiation of δ = 4.45 (*N*-CH_2); MS *m*/*z*: 502 (MH^+, 100%), 113 (86%); Anal. ($C_{28}H_{32}FN_7O$·2.67% H_2O): C, H; N: calcd 19.02, found: 18.22.

1-(2-{4-[1-(4-Fluorophenyl)-5-(2-methyl-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (10a). The material obtained after chromatography was recrystallized from EtOH to give 0.60 g (50%) of **10a**. Mp 203−204 °C (EtOH); ^{1}H NMR ($CDCl_3$) δ: 1.70−1.90 (m, 2H), 2.05−2.15 (m, 2H), 2.20−2.30 (m, 2H), 2.60 (t, 2H), 2.90 (tt, 1H), 3.05−3.15 (m, 2H), 3.35−3.50 (m, 4H), 3.50−3.60 (m, 2H), 4.25 (s, 3H), 4.40 (broad s, 1H), 7.05 (s, 1H), 7.20 (t, 2H), 7.45 (dd, 2H), 7.50 (d, 1H), 7.60 (broad d, 1H), 7.85 (s, 1H), 8.05 (broad s, 1H); 1D-NOE: No significant NOEs observed by irradiation of δ = 4.25 (*N*-CH_3); MS *m*/*z*: 488 (MH^+, 49%), 196 (35%), 113 (100%); Anal. ($C_{27}H_{30}FN_7O$): C, H, N.

1-(2-{4-[5-(2-Ethyl-1,2,3-triazol-4-yl)-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (11a). The material obtained after chromatography was recrystallized from EtOAc to give 1.1 g (69%) of **11a**. Mp 173−175 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ: 1.60 (t, 3H), 1.75−1.95 (m, 2H), 2.05−2.15 (m, 2H), 2.20−2.35 (m, 2H), 2.60 (t, 2H), 2.95 (tt, 1H), 3.05−3.15 (m, 2H), 3.35−3.50 (m, 4H), 3.50−3.60 (m, 2H), 4.30 (broad s, 1H), 4.55 (q, 2H), 7.10 (s, 1H), 7.20 (t, 2H), 7.35−7.50 (m, 3H), 7.60 (broad d, 1H), 7.85 (s, 1H), 8.05 (broad s, 1H); 1D-NOE: No significant NOEs observed by irradiation of δ = 4.55 (*N*-CH_2); MS *m*/*z*: 502 (MH^+, 47%), 196 (28%), 113 (100%); Anal. ($C_{28}H_{32}FN_7O$): C, H; N: calcd 19.55, found: 18.69.

4-[5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (34). A solution of **27a** (172 g, 0.59 mol) and 4-piperidone hydrochloride hydrate (550 g, 3.6 mol) in glacial acetic acid (0.63 L) and trifluoro acetic acid (1.2 L) was reacted in analogy to the method described in the reference[32] to yield 220 g (100%) of crude 5-bromo-1-(4-fluorophenyl)-3-(1,2,3,6-tetrahydro-4-pyridyl)-1*H*-indole (**27b**) (free base) as white solid: ^{1}H NMR ($CDCl_3$) δ: 2.40−2.55 (m, 2H), 3.15 (t, 2H), 3.55−3.65 (m, 2H), 6.25 (s, broad, 1H), 7.12−7.30 (m, 5H), 7.35−7.45 (m, 2H), 8.03 (s, 1H). A solution of crude **27b** (220 g, 0.59 mol) in glacial acetic acid (1.5 L) and PtO_2 (5 g) was treated with H_2 in a Parr apparatus at 2−3 ato

for 24 h. Additional PtO_2 (4 g) was added, and the reaction was continued for 24 h. Solids were filtered off, and the solvents were evaporated in vacuo. evaporation of the solvent, 10% aqueous NH_4OH (600 mL) was added and the resulting slurry was extracted with EtOAc (3 × 400 mL). The combined organic phases were dried ($MgSO_4$) and the solvent removed in vacuo to yield 125 g (57%) of crude 5-bromo-1-(4-fluorophenyl)-3-(4-piperidinyl)-1*H*-indole (**27c**) as an oil: ^{1}H NMR (DMSO-d_6) δ: 1.78 (qd, 2H), 2.05 (d, 2H), 2.90 (td, 2H), 3.05 (m, 1H), 3.25 (d, 2H), 7.30 (d, 1H), 7.35−7.45 (m, 3H), 7.49 (s, 1H), 7.56−7.63 (m, 2H), 7.93 (d, 1H). A solution of crude **27c** (125 g, 0.33 mol) and di-*tert*-butyl dicarbonate (260 g, 1.2 mol) in 1:1 THF/H_2O mixture (1 L) was stirred overnight with K_2CO_3 (300 g, 2.2 mol) at 60 °C. EtOAc (1 L) was added. After separation of the two phases, the aqueous phase was extracted with EtOAc (3 × 0.5 L). The combined organic phases were washed with brine (300 mL) and dried ($MgSO_4$), and the solvent was removed in vacuo. The crude product (115 g) was washed with cold MeOH to yield 97 g of the title compound **34** (35% from **27a**) as a white solid: Mp 160−162 °C (heptane); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.65 (q, 2H), 2.04 (d, 2H), 2.85−3.00 (m, 3H), 4.25 (d, 2H), 7.03 (s, 1H), 7.15−7.35 (m, 4H), 7.39−7.43 (m, 2H), 7.78 (s, 1H); MS *m*/*z*: 473 + 475 (MH^+, 1%), 417+419 (40%), 373+375(100%); Anal. ($C_{24}H_{26}BrFN_2O_2$): C, H, N.

4-[5-Cyano-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (35). A solution of **34** (26.2 g, 55.4 mmol) and $Zn(CN)_2$ (6.5 g, 55.4 mmol) in DMF (300 mL) was stirred at room temperature for 20 min under argon. $Pd(PPh_3)_4$ (3.0 g, 5 mol %) was added, and the solution was stirred for 8 h at 80 °C. After the mixture was cooled to room temperature, DMF was removed in vacuo, EtOAc (500 mL) was added, and the solution was extracted with H_2O (2 × 300 mL) and brine (300 mL). Evaporation of the solvent in vacuo and flash chromatography (EtOAc/heptane 1/4 → 1/1) gave 21.0 g (90%) of the title compound (**35**): Mp 85−87 °C (EtOAc/heptane 1/4); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.70 (qd, 2H), 2.05 (d, 2H), 2.90 (t, 2H), 2.99−3.06 (m, 1H), 4.27 (d, broad, 2H), 7.15 (s, 1H), 7.20−7.27 (m, 2H), 7.40−7.48 (m, 4H), 8.03 (s, 1H); Anal. ($C_{25}H_{26}FN_3O_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1*H*-tetrazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (36). A solution of **35** (10.2 g, 24.3 mmol), NaN_3 (4.9 g, 75 mmol), and NEt_3·HCl (10.0 g, 72 mmol) in toluene (75 mL) was boiled under reflux for 8 h. After the mixture was cooled to room temperature, H_2O (100 mL) was added and the pH-value was adjusted to 8−9. The phases were separated, and the aqueous phase was extracted with EtOAc (3 × 200 mL). The combined organic phases were washed with H_2O (3 × 100 mL) and brine (50 mL) and dried ($MgSO_4$), and the solvents were removed in vacuo. The crude product was recrystallized from acetone to yield 8.0 g (71%) of **36**: ^{1}H NMR ($CDCl_3$) δ: 1.45 (s, 9H), 1.65 (qd, 2H), 2.05 (d, 2H), 2.96 (s, broad, 2H), 3.05−3.15 (m, 1H), 4.13 (s, broad, 2H), 7.40.7.48 (m, 2H), 7.62 (s, 1H), 7.65−7.70 (m, 3H), 7.88 (d, 1H), 8.42 (s, 1H); Anal. ($C_{25}H_{27}FN_6O_2$): C, H; N: calcd 18.17 found 17.29.

4-[1-(4-Fluorophenyl)-5-(2-methyl-tetrazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (37) and 4-[1-(4-Fluorophenyl)-5-(1-methyl-tetrazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (38). A suspension of **36** (5.9 g, 12.7 mmol), K_2CO_3 (8.7 g, 63 mmol) and CH_3I (1.6 mL, 25 mmol) in acetone (200 mL) was stirred at 0 °C for 10 min. The temperature was raised to 35 °C during 1 h, and stirring was continued at this temperature for 30 min. The solids were filtered off, and the solvent removed in vacuo. H_2O (200 mL) was added, and the aqueous phase was extracted with EtOAc (3 × 150 mL). The combined organic phases were washed with brine and evaporated on kiesel gel. Flash chromatography (EtOAc/heptane 30/70) afforded 3.9 g (57%, white solid) of **37**: Mp 164−165 °C (EtOAc/heptane 1/4); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.72 (qd, 2H), 2.10 (d, 2H), 2.93 (s, broad, 2H), 3.04−3.14 (m, 1H), 4.22 (s, 3H), 4.27 (s, broad, 2H), 7.20 (s, 1H), 7.23−7.25 (m, 2H), 7.45−7.49 (m, 2H), 7.50 (d, 1H), 7.59 (d, 1H), 8.13 (s, 1H). 2D-NOE cross-peak between δ = 4.22 (tetrazole N-CH_3) and δ = 8.13 (indole H4) and δ = 7.59 (indole H6) present; Anal. ($C_{26}H_{29}FN_6O_2$): C, H, N. The column was eluted further to give 1.2 g (20%, white foam) of **38**: Mp 129−130 °C (EtOAc/heptane 1/4); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.72 (qd, 2H), 2.13 (d, 2H), 2.92 (t, 2H), 3.06−3.16 (m, 1H), 4.28 (s. broad, 2H), 4.42 (s, 3H), 7.10 (s, 1H), 7.18−7.25 (m, 2H), 7.42−7.48(m, 2H), 7.52 (d, 1H), 7.99 (d, 1H), 8.49 (s, 1H). 2D-NOE cross-peak between δ = 4.42 (tetrazole N-CH_3) and δ = 8.49 (indole 4H) and δ = 7.99 (indole 6H) absent; Anal. ($C_{26}H_{29}FN_6O_2$): C, H, N.

Cross-Coupling of 4-[5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (34) with Heteroaryl Halides (Method A). A solution of **34** (10.0 g, 21.1 mmol) in THF (20 mL) was added during 2 min to a solution of *n*-butyllithium (39.6 mL, 63.4 mmol) in THF (210 mL) at −78 °C. After the mixture was stirred for 3 min, $ZnCl_2$ in THF (105.6 mL, 105.6 mmol) was added. The solution was stirred for further 30 min at −78 °C. The heteroaryl halide (amount specified below) was added together with $Pd(PPh_3)_4$ (1.2 g, 5 mol %) and DMF (60 mL). The reaction mixture was stirred at 80 °C for 8 h. After the mixture was cooled to room temperature, H_2O (300 mL) and EtOAc (500 mL) were added and the phases were separated. The organic phase was washed with H_2O (200 mL) and a saturated aqueous $CaCl_2$ solution (3 × 100 mL) and dried over $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified by flash chromatography. The amount of reagents and solvents were scaled according to the actual amount of **34** used.

The following derivatives were prepared according to method A.

4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (8). A solution of **34** (4.7 g, 10 mmol) in THF was reacted with 4-bromo-1-methyl-1,2,3-triazole (1.1 g, 6.8 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 100/0) to yield 0.90 g (28%) of **8** as a white foam: ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.69 (q, 2H), 2.12 (d, 2H), 2.94 (t, 2H), 3.09 (t, 1H), 4.18 (s, 3H), 4.28 (s, broad, 1H), 7.06 (s, 1H), 7.17−7.24 (m, 2H), 7.40−7.55 (m, 3H), 7.61 (d, 1H), 7.78 (s, 1H), 8.23 (s, 1H); MS *m*/*z*: 476 (MH^+, 4%), 420 (46%), 376 (100%); Anal. ($C_{27}H_{30}N_5FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-3-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (13). A solution of **34** (6.8 g, 14.4 mmol) in THF was reacted with 1-methyl-3-iodopyrazole (3.0 g, 14.4 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 50/50) to yield 4.31 g (63%) of **13** as white crystals: Mp 145−146 °C (EtOAc/heptane); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.68 (q, 2H), 2.10 (d, 2H), 2.93 (t, 2H), 3.11 (t, 1H), 3.98 (s, 3H), 4.26 (s, broad, 2H), 6.57 (d, J = 2.0 Hz, 1H), 7.04 (s, 1H), 7.17−7.24 (m, 2H), 7.39 (d, J = 2.1 Hz, 1H), 7.42−7.52 (m, 3H), 7.65 (d, J = 8.6 Hz, 1H), 8.08 (s, 1H); MS *m*/*z*: 475 (MH^+, 7%), 419 (100%), 375 (73%); Anal. ($C_{28}H_{31}N_4FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-4-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (14). A solution of **34** (10.0 g, 21.1 mmol) in THF was reacted with 1-methyl-4-bromopyrazole (4.2 g, 31.7 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 20/80 → 30/70) to yield 2.8 g (28%) of **14** as white crystals: Mp 133−136 °C (EtOAc/heptane); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.71 (q, 2H), 2.10 (d, 2H), 2.94 (t, 2H), 3.05 (t, 1H), 3.96 (s, 3H), 4.27 (s, broad, 2H), 7.04 (s, 1H), 7.20−7.25 (m, 2H), 7.34 (d, 1H), 7.41−7.50 (m, 3H), 7.63 (s, 1H), 7.71 (s, 1H), 7.79 (s, 1H); MS *m*/*z*: 475 (MH^+, 5%), 419 (86%), 375 (100%); Anal. ($C_{28}H_{31}N_4FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (15). A solution of **34** (20.0 g, 42 mmol) in THF was reacted with 3-bromo-1-methyl-1,2,4-triazole (8.8 g, 55 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 50/50/0 → 100/0/0 → 90/0/10) and crystallized from Et_2O to yield 8.0 g (40%) of **15** as white crystals: Mp 189−191 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s,

9H), 1.70 (q, 2H), 2.12 (d, 2H), 2.95 (t, 2H), 3.13 (t, 1H), 4.00 (s, 3H), 4.28 (s, broad, 2H), 7.06 (s, 1H), 7.15−7.28 (m, 2H), 7.40−7.52 (m, 3H), 8.00 (d, 1H), 8.08 (s, 1H), 8.42 (s, 1H); MS *m*/*z*: 476 (MH^+, 72%), 420 (66%), 376 (100%); Anal. ($C_{27}H_{30}N_5FO_2$·2.17% Et_2O): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methyl-1,3,4-triazol-2-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (16). A solution of **34** (10.0 g, 21.1 mmol) in THF was reacted with 2-bromo-1-methyl-1,3,4-triazole (2.8 g, 17.3 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 30/70/0 → 100/0/0 → 90/0/10) to yield 2.5 g (31%) of **16** as white crystals: Mp 156−158 °C (toluene/heptane 1:1); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.70 (q, 2H), 2.08 (d, 2H), 2.90 (t, 2H), 3.07 (t, 1H), 3.78 (s, 3H), 4.26 (s, broad, 2H), 7.13 (s, 1H), 7.20−7.28 (m, 2H), 7.41−7.50 (m, 3H), 7.53 (d, 1H), 8.05 (s, 1H), 8.21 (s, 1H); MS *m*/*z*: 476 (MH^+, 100%), 420 (51%), 376 (83%); Anal. ($C_{27}H_{30}N_5FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (17). A solution of **34** (7.5 g, 15.8 mmol) in THF was reacted with 5-bromo-1-methyl-1,2,4-triazole (2.1 g, 13 mmol). The crude product was purified by flash chromatography (EtOAc/heptane/MeOH 30/70/0 → 100/0/0 → 90/0/10) to yield 2.8 g (45%) of **17** as a pale yellow foam: ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.70 (q, 2H), 2.09 (d, 2H), 2.91 (t, 2H), 3.07 (t, 1H), 4.03 (s, 3H), 4.28 (s, broad, 2H), 7.13 (s, 1H), 7.20−7.30 (m, 2H), 7.42−7.50 (m, 3H), 7.52 (d, 1H), 7.96 (s, 1H), 8.02 (s, 1H); MS *m*/*z*: 476 (MH^+, 100%), 420 (33%), 376 (41%); Anal. ($C_{27}H_{30}N_5FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (22). A solution of **34** (18.0 g, 38 mmol) in THF was reacted with 2-bromopyrimidine (10.0 g, 75 mmol). The crude product was purified by flash chromatography (EtOAc/heptane 10/90 → EtOAc/MeOH 90/10) and crystallized from Et_2O to yield 12.0 g (67%) of **22** as white crystals: Mp 164−166 °C (Et_2O); ^{1}H NMR ($CDCl_3$) δ: 1.50 (s, 9H), 1.71 (q, 2H), 2.14 (d, 2H), 2.96 (t, 2H), 3.16 (t, 1H), 4.27 (s, broad, 2H), 7.08 (s, 1H), 7.13 (t, 1H), 7.20−7.25 (m, 2H), 7.43−7.49 (m, 2H), 7.51 (d, 1H), 8.36 (d, 1H), 8.77−8.81 (m, 3H); MS *m*/*z*: 473 (MH^+, 11%), 417 (100%), 373 (84%); Anal. ($C_{28}H_{29}N_4FO_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(pyrimidin-5-yl)-1*H*-indol-3-yl]-piperidine-1-carboxylic Acid *tert*-Butyl Ester (23). A solution of **34** (10.0 g, 21.1 mmol) in THF was reacted with 5-bromopyrimidine (5.0 g, 31.6 mmol). Flash chromatography (EtOAc/heptane/NEt_3 30/70/4 → 70/30/4) gave 8.2 g which was recrystallized from toluene/heptane 1:1 to yield 5.0 g (50%) of **23**: Mp 144−146 °C (toluene/heptane 1:1); MS *m*/*z*: 473 (MH^+, 3%), 417 (100%), 373 (33%); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.75 (q, 2H), 2.13 (d, 2H), 2.95 (t, 2H), 3.08 (t, 1H), 4.28 (s, broad, 2H), 7.13 (s, 1H), 7.20−7.30 (m, 2H), 7.42 (dd, 1H), 7.43−7.50 (m, 2H) 7.57 (d, 1H), 7.85 (d, 1H), 9.02 (s, 2H), 9.19 (s, 1H); Anal. ($C_{28}H_{29}FN_4O_2$): C, H, N.

Cross-Coupling of a Heteroarylzinc Chloride with 4-[5-Bromo-1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (34) (Method B). A solution of **34** (8.3 g, 16.9 mmol) in DMF (20 mL) was added to a solution of heteroarylzinc chloride in THF (amount and preparation specified below) with $Pd(PPh_3)_4$ (5 mol %) and DMF (30% of the total amount of THF). The solution was stirred at 80 °C for 8 h. Workup was performed as described in method A. The amounts of reagents and solvents were scaled according to the actual amount of **34** used.

The following derivatives were prepared according to method B:

4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (18). 1-Methylpyrazole (3.2 g, 39 mmol) in THF (200 mL) was cooled to −78 °C. *n*-Butyllithium (43 mL, 26.9 mmol) was added during 5 min. The solution was heated slowly to room temperature during 15 min and cooled again to −78 °C. $ZnCl_2$ in THF (120 mL, 120 mmol) was added, and the solution was stirred at −78 °C for 30 min. Reaction with **34** (14.2 g, 30 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/5 → 50/50/5) and recrystallization from CH_2Cl_2 afforded 11.5 g (80%) of **18**: Mp 166−168 °C (CH_2Cl_2); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.72 (q, 2H), 2.07 (d, 2H), 2.93 (t, 2H), 3.05 (t, 1H), 3.90 (s, 3H), 4.26 (s, broad, 2H), 6.32 (s, 1H), 7.10 (s, 1H), 7.20−7.30 (m, 3H), 7.40−7.47 (m, 2H), 7.50 (d, 1H), 7.54 (s, 1H), 7.69 (s, 1H); Anal. ($C_{28}H_{31}FN_4O_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methylimidazol-2-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (19). 1-Methylimidazole (1.39 g, 16.9 mmol) in THF (195 mL) was cooled to −78 °C. *n*-Butyllithium (14.7 mL, 23.5 mmol) was added during 2 min. The solution was stirred for 5 min at −78 °C, and $ZnCl_2$ in THF (60 mL, 60 mmol) was added. After the mixture was stirred at −78 °C for 1 h, reaction with **34** (8.30 g, 16.9 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/4 → 70/30/4) afforded 6.77 g which was recrystallized from toluene/heptane 1:1 to give 4.73 g (59%): Mp 189−191 °C (toluene/heptane 1:1); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 7.69 (q, 2H), 2.10 (d, 2H), 2.89 (t, 2H), 3.05 (t, 1H), 3.77 (s, 3H), 4.25 (s, broad, 2H), 6.99 (s, 1H), 7.09 (s, 1H), 7.15 (s, 1H), 7.15−7.25 (m, 2H), 7.4−7.55 (m, 4H), 7.97 (s, 1H); Anal. ($C_{28}H_{31}FN_4O_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-5-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (20). 1-Methyl-1,2,3-triazole (1.71 g, 20.6 mmol) was dissolved in THF (200 mL) and cooled to −78 °C. *n*-Butyllithium (15.4 mL, 24.7 mmol) was added during 2 min, and the solution was stirred for further 5 min before $ZnCl_2$ in THF (61.8 mL, 61.8 mmol) was added. After 30 min at −78 °C reaction with **34** (9.75 g, 20.6 mmol) was performed following method B. Purification by flash chromatography (EtOAc/heptane/EtOH 30/70/2) gave 6.8 g which was recrystallized from toluene/heptane 1:2 to yield 4.3 g (44%) of **20**: Mp 137−141 °C (toluene/heptane 1:2); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.70 (q, 2H), 22.08 (d, 2H), 2.93 (t, 2H), 3.05 (t, 1H), 4.09 (s, 3H), 4.30 (s, broad, 2H), 7.15 (s, 1H), 7.20−7.30 (m, 3H), 7.40−7.50 (m, 2H), 7.45 (d, 1H), 7.69 (s, 1H), 7.74 (s, 1H); Anal. ($C_{27}H_{30}FN_5O_2$): C, H, N.

4-[1-(4-Fluorophenyl)-5-(pyridin-3-yl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Ester (24). 3-Bromopyridine was lithiated as described by Furneaux et al.[61] THF (200 mL) was cooled to −100 °C (Et_2O/liquid N_2), and *n*-butyllithium (19 mL, 30.4 mmol) was added. 3-Bromopyridine (4.0 g, 25.3 mmol) was added during 2 min. After 20 min at −100 °C, $ZnCl_2$ in THF (60 mL, 60 mmol) was added. Hereby, a white precipitate was formed. The temperature was shortly raised to −30 °C to dissolve the precipitate. The solution was thereafter stirred at −78 °C for 30 min. Reaction with **34** (10.0 g, 21.1 mmol) was performed following method B. Flash chromatography (EtOAc/heptane/NEt_3 30/70/5) afforded 8.3 g which was recrystallized from EtOAc/heptane 1:1 to yield 6.0 g (60%) of **24**: Mp 160−162 °C (EtOAc/heptane 1:1); MS *m*/*z*: 472 (MH^+, 3%), 416 (100%), 372 (37%); ^{1}H NMR ($CDCl_3$) δ: 1.49 (s, 9H), 1.74 (q, 2H), 2.14 (d, 2H), 2.93 (t, 2H), 3.10 (t, 1H), 4.29 (s, broad, 2H), 7.11 (s, 1H), 7.20−7.30 (m, 2H), 7.36 (dd, 1H), 7.40−7.50 (m, 3H), 7.55 (d, 1H), 7.85 (d, 1H), 7.95 (dt, 1H), 8.57 (dd, 1H), 8.91 (d, 1H); Anal. ($C_{29}H_{30}FN_3O_2$): C, H, N.

Deprotection and Alkylation of 5-Heteroaryl-Substituted 4-[1-(4-Fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic Acid *tert*-Butyl Esters (8, 13−20, 22−24, and 37−38) (Method C). The 5-heteroaryl-substituted 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester (6.3 mmol) was dissolved in THF (20 mL), and HCl/MeOH (30 mL) was added. The solution was stirred for 4 h, and the solvents were removed in vacuo. 4-Methyl-2-pentanone (30 mL) was added, and the solvent was again removed in vacuo. K_2CO_3 (5 g, 36 mmol), KI (0.5 g, 3 mmol), 4-methyl-2-pentanone (100 mL), and an alkyl halide (R−Y) (9.5 mmol if nothing else stated) were added, and the solution was stirred under reflux for 8 h. The amounts of reagents and solvents were scaled according to the actual amount of 5-heteroaryl-

substituted 4-[1-(4-fluorophenyl)-1*H*-indol-3-yl]piperidine-1-carboxylic acid *tert*-butyl ester used.

Workup: H_2O (50 mL) was added to the warm mixture, and the phases were separated. The aqueous phase was extracted with CH_2Cl_2 (100 mL). Kiesel gel was added to the combined organic phases, and the solvents were removed in vacuo. The resulting compound adsorbed to kiesel gel was purified using Biotage flash 40 equipped with an FZIM-0035 solid injection module.

The following derivatives **8a** and **12a**−**24a** were prepared by method C using **8** and **12**−**24** as starting material and 1-(2-chloroethyl)imidazolidin-2-one as alkylating agent:

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-1piperidinyl}ethyl)imidazolidin-2-one (8a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 90/10/4 → 80/20/4) to yield 0.30 g (33%) of **8a,** identical to the material described above.

1-(2-{4-[1-(4-Fluorophenyl)-5-(2-methyltetrazol-5-yl)-1*H*-indol-3-yl]-1piperidinyl}ethyl)imidazolidin-2-one (12a). The crude product was purified by flash chromatography (EtOAc/heptane 50/50 → EtOAc/MeOH/NEt_3 90/10/2) to yield 1.0 g (75%) of **12a**: Mp 182−184 °C (CH_3CN); ^{1}H NMR (DMSO-d_6) δ: 1.78 (qd, 2H), 2.05 (d, 2H), 2.16 (t, 2H), 2.46 (t, 2H), 2.85−2.95 (m, 1H), 3.02 (d, 2H), 3.15−3.28 (m, 4H), 3.41 (t, 2H), 4.43 (s, 3H), 6.24 (s, broad, 1H), 7.38−7.48 (m, 2H), 7.54 (s, 1H), 7.62 (d, 1H), 7.64−7.68 (m, 2H), 7.91 (d, 1H), 8.36 (s, 1H); Anal. ($C_{26}H_{29}FN_8O$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (13a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 90/10/4 → 80/20/4) to yield 0.67 g of pure material as well as 0.90 g containing impurities. The pure material was washed on a filter with EtOAc to give 0.25 g (9.8%) of **13a**: Mp 203−204 °C; ^{1}H NMR ($CDCl_3$) δ: 1.82 (q, 2H), 2.10 (d, 2H), 2.24 (t, 2H), 2.59 (t, 2H), 2.95 (t, 1H), 3.08 (d, 2H), 3.36−3.50 (m, 4H), 3.56 (t, 2H), 3.98 (s, 3H), 4.23 (s, 1H), 6.56 (d, J = 2 Hz, 1H), 7.05 (s, 1H), 7.15−7.24 (m, 2H), 7.39 (d, J = 2.2 Hz, 1H), 7.42−7.48 (m, 3H), 7.65 (dd, ^1J = 8,6 Hz, ^3J = 1.7 Hz, 1H) 8.08 (d, J = 1.4 Hz, 1H); MS *m*/*z*: 487 (MH^+, 100%), 369 (17%), 292 (3%); Anal. ($C_{28}H_{31}N_6FO$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-4-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (14a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 95/5/4 → 90/10/4) to yield 1.0 g as white foam. The compound crystallized upon addition of EtOAc to give 0.36 g (29%) of **14a**: Mp 221−223 °C; ^{1}H NMR (DMSO-d_6) δ: 1.73 (q, 2H), 2.03 (d, 2H), 2,16 (t, 2H), 2.48 (t, 2H), 2.85 (t, 1H), 3.04 (d, 2H), 3.23 (q, 4H), 3.40 (t, 2H), 3.84 (s, 3H), 6.20 (s, broad, 1H), 7.35−7.42 (m, 4H), 7.46 (d, 1H), 7.59−7.67 (m, 2H), 7.81 (s, 1H), 7.87 (s, 1H), 8.13 (s, 1H); MS *m*/*z*: 487 (MH^+, 100%), 369 (3%); Anal. ($C_{28}H_{31}N_6FO$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (15a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 95/5/4 → 90/10/4) and crystallized from EtOAc to yield 1.2 g (65%) of **15a**: Mp 204−206 °C (EtOAc); ^{1}H NMR ($CDCl_3$) δ: 1.83 (q, 2H), 2.21 (d, 2H), 2.25 (t, 2H), 2.58 (t, 2H), 2.97 (t, 1H), 3.08 (d, 2H), 3.35−3.45 (m, 4H), 3.54 (t, 2H), 3.98 (s, 3H), 4.58 (s, broad, 1H), 7.07 (s, 1H), 7.15−7.25 (m, 2H), 7.42−7.50 (m, 3H), 7.97 (d, 1H), 8.06 (s, 1H), 8.42 (S, 1H); MS *m*/*z*: 488 (MH^+, 100%) 370 (19%), 293 (3%); Anal. ($C_{27}H_{30}N_7FO$·1.25% EtOAc): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,3,4-triazol-2-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (16a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 95/5/4 → 90/10/4) to yield 60 mg (5%) of **16a** as a white solid: Mp 122−126 °C; ^{1}H NMR ($CDCl_3$) δ: 1.85 (q, 2H), 2.09 (d, 2H), 2.12 (t, 2H), 2.58 (t, 2H), 2.90 (t, 1H), 3.08 (d, 2H), 3.34−3.42 (m, 4H), 3.55 (t, 2H), 3.78 (s, 3H), 4,18 (s, broad, 1H), 7.14 (s, 1H), 7.20−7.25 (m, 2H), 7.41−7−49 (m, 3H), 7.53 (d, 1H), 8.05 (s, 1H), 8.21 (s, 1H); MS *m*/*z*: 488 (MH^+, 100%) 314 (24%), 241 (10%); Anal. ($C_{27}H_{30}N_7FO$· 4.32% EtOAc and 1.64% H_2O): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (17a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 95/5/4 → 90/10/4) to yield 1.2 g as white foam. The compound crystallized from EtOAc to give 0.90 g (49%) of the title compound (**17a**): Mp 209−211 °C (EtOAc). ^{1}H NMR ($CDCl_3$) δ: 1.84 (q, 2H), 2.09 (d, 2H), 2.12 (t, 2H), 2.58 (t, 2H), 2.92 (t, 1H), 3.08 (d, 2H), 3.35−3.50 (m, 4H), 3.54 (t, 2H), 4.03 (s, 3H), 4.33 (s, broad, 1H), 7.14 (s, 1H), 2.20−2.25 (m, 2H), 7.42−7.48 (m, 3H), 7.53 (d, 1H), 7.95 (s, 1H), 8.02 (s, 1H); MS *m*/*z*: 488 (MH^+, 100%) 370 (7%), 314 (3%); Anal. ($C_{27}H_{30}N_7FO$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methylpyrazol-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (18a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/20/5). The resulting compound was recrystallized from CH_2Cl_2 to yield 0.80 g (26%) of **18a**: Mp 248−251 °C (CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ: 1.75 (q, 2H), 2.03 (d, 2H), 2.18 (t, 2H), 2.45 (t, 2H), 2.90 (t, 1H), 3.03 (d, 2H), 3.15−3.30 (m, 4H), 3.42 (t, 2H), 3.90 (s, 3H), 6.25 (s, 1H), 6.40 (s, 1H), 7.31 (d, 1H), 7.43 (t, 2H), 7.48 (d, 1H), 7.50 (s, 1H), 7.58 (d, 1H), 7.60−7.70 (m, 2H), 7.80 (s, 1H); Anal. ($C_{28}H_{31}FN_6O$·1.70% CH_2Cl_2): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methylimidazol-2-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (19a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 90/10/5 → 85/15/5). The resulting compound (1.6 g) was recrystallized from 2-propanol to yield 0.33 g (16%) of **19a**: Mp 215−217 °C (2-propanol); ^{1}H NMR (DMSO-d_6) δ: 1.82 (q, 2H), 2.10 (d, 2H), 2.18 (t, 2H), 2.56 (t, 2H), 2.90 (t, 1H), 3.08 (d, 2H), 3.30−3.45 (m, 4H), 3.55 (t, 2H), 3.77 (s, 3H), 4.30 (s, 1H), 7.00 (s, 1H), 7.10 (s, 1H), 7.17 (s, 1H), 7.20 (t, 2H), 7.40−7.55 (m, 4H), 7.96 (s, 1H); Anal. ($C_{28}H_{31}FN_6O$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,3-triazol-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (20a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/20/4) resulting in 2.0 g which was recrystallized twice from EtOAc/heptane 1:4 to yield 0.70 g (22%) of **20a**: Mp 236−238 °C; ^{1}H NMR ($CDCl_3$) δ: 1.85 (qd, 2H), 2.10 (d, 2H), 2.25 (t, 2H), 2.58 (t, 2H), 2.85−2.95 (m, 1H), 3.10 (d, 2H), 3.36−3.47 (m, 4H), 3.54 (t, 2H), 4.09 (s, 3H), 4.30 (s, broad, 1H) 7.15 (s, 1H), 7.19−7.30 (m, 3H), 7.40−7.49 (m, 2H), 7.53 (d, 1H), 7.70 (d, 1H), 7.73 (s, 1H); Anal. ($C_{27}H_{30}FN_7O$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyltetrazol-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (21a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/20/4) to give 0.60 g which was recrystallized from toluene to give 0.30 g (41%) of **21a**: Mp 203−205 °C (toluene); ^{1}H NMR (DMSO-d_6) δ: 1.75 (qd, 2H), 2.01 (d, 2H), 2.14 (t, 2H), 2.84−2.94 (m,1H), 3.02 (d, 2H), 3.10−3.25 (m, 4H), 3.35−3.45 (t, 2H), 4.20 (s, 3H), 6.23 (s, broad, 1H), 7.40−7.49 (m, 2H), 7.59 (s, 1H), 7.61 (d, 1H), 7.62−7.72 (m, 4H), 8.18 (s, 1H); Anal. ($C_{26}H_{29}FN_8O$·2.21% toluene): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (22a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 90/10/4 → 80/20/4). The resulting material was washed on a filter with EtOAc to yield 1.8 g (62%) of **22a**: Mp 217−219 °C; ^{1}H NMR ($CDCl_3$) δ: 1.85 (q, 2H), 2.15 (d, 2H), 2.26 (t, 2H), 2.59 (t, 2H), 2.02 (t, 1H), 3.09 (d, 2H), 3.30−3.50 (m, 4H), 3.55 (t, 2H), 4.59 (s, 1H), 7.09 (s, 1H), 7.13 (t, 1H), 7.15−7.24 (m, 2H),7.44−7.48 (m, 2H), 7.50 (d, 1H), 8.35 (d, 1H), 8.78−8.82 (m, 3H); MS *m*/*z*: 485 (MH^+, 100%), 367 (10%), 290 (7%); Anal. ($C_{28}H_{29}N_6FO$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(pyrimidin-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (23a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 90/10/5 → 50/50/5) and washed on a filter with EtOAc to yield 1.2 g (59%). Mp 228−230 °C; ^{1}H NMR (DMSO-d_6) δ: 1.75 (q, 2H), 2.07 (d, 2H), 2.18 (t, 2H), 2.44 (t, 2H), 2.95 (t, 1H), 3.05 (d, 2H), 3.22 (q, 4H), 3.41 (t, 2H), 6.19 (s, broad,

1H), 7.37−7.47 (m, 2H), 7.50 (s, 1H), 7.60−7.62 (m, 2H), 7.64−7.69 (m, 2H), 8.16 (s, 1H), 9.15 (s, 1H), 9.19 (s, 2H); MS *m/z*: 485 (MH^+, 100%), 367 (17%), 290 (3%); Anal. ($C_{28}H_{29}N_6FO$): C, H, N.

1-(2-{4-[1-(4-Fluorophenyl)-5-(pyridin-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one (24a). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 75/25/5). The remaining compound (2.0 g) was recrystallized from 2-propanol to yield 0.30 g (7%) of **24a**: Mp 200−203 °C (2-propanol); ^{1}H NMR (DMSO-d_6) δ: 1.75 (q, 2H), 2.04 (d, 2H), 2.16 (t, 2H), 2.45 (t, 2H), 2.94 (t, 1H), 3.03 (d, 2H), 3.15−3.25 (m, 4H), 3.42 (t, 2H), 6.25 (s, 1H), 7.42 (t, 2H), 7.40−7.45 (m, 2H), 7.46−7.50 (m, 2H), 7.54 (d, 1H), 7.58 (d, 1H), 7.62−7.68 (m, 2H), 8.02 (s, 1H), 8,13 (d, 1H), 8.54 (d, 1H), 8.95 (s, 1H); Anal. ($C_{29}H_{30}FN_5O$) H, N; C: calcd, 72.03, found 71.46.

The following derivatives **12b**, **15b**, and **22b** were prepared by method C using **37**, **15** and **22** as starting material and 3-(2-chloroethyl)oxazolidin-2-one as alkylating agent:

3-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyltetrazol-5-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)oxazolidin-2-one Oxalate (12b). The crude product was purified by flash chromatography (EtOAc/heptane/NEt_3 80/20/4 → 75/25/4) to give 0.70 g that was precipitated with oxalic acid from EtOH to give 0.50 g (54%) of the oxalate of **12b**: Mp 212−215 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 1.99 (q, 2H), 2.19 (d, 2H), 3.00 (m, 2H), 3.17 (m, 3H), 3.54 (m, 4H), 3.62 (t, 2H), 4.30 (t, 2H), 4.43 (s, 3H), 7.41−7.45 (m, 2H), 7.60−7.68 (m, 4H), 7.92 (d, 1H), 8.43 (s, 1H); MS *m/z*: 490 (MH^+, 100%); Anal. ($C_{26}H_{28}FN_7O_2 \cdot C_2H_2O_4$): C, H, N.

3-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)oxazolidin-2-one 1.1Oxalate (15b). The crude product was purified by flash chromatography (EtOAc/MeOH/NEt_3 80/20/4 → 75/25/4) giving 1.0 g containing impurities. Precipitation with oxalic acid from EtOAc/heptane/EtOH 20/30/50 gave 0.5 g (38%) of the oxalate **15b**: Mp 225−226 °C; ^{1}H NMR (DMSO-d_6) δ: 2.04 (q, 2H), 2.21 (d, 2H), 3.03 (t, 2H), 3.12−3.22 (m, 3H), 3.50−3.60 (m, 4H), 3.60−3.68 (t, 2H), 3.92 (s, 3H), 4.30 (t, 2H), 7.38−7.48 (m, 2H), 7.52 (s, 1H), 7.54 (d, 1H), 7.60−7.68 (m, 2H), 7.88 (d, 1H), 8.35 (s, 1H), 8.49 (s, 1H); MS *m/z*: 489 (MH^+, 100%), 448 (6%), 370 (4%); Anal. ($C_{27}H_{29}FN_6O_2 \cdot 1.1C_2H_2O_4$): C, H, N.

3-(2-{4-[1-(4-Fluorophenyl)-5-(pyrimidin-2-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)oxazolidin-2-one (22b). The crude product was purified by flash chromatography (EtOAc/heptane 70/30 → EtOAc/MeOH/NEt_3 90/10/4) to give 1.1 g which was recrystallized from EtOAc/CH_2Cl_2 to give 0.90 g (67%) of **22b** (free base): Mp 175−176 °C (EtOAc/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ: 1.79 (qd, 2H), 2.03 (d, 2H), 2.18 (t, 2H), 2.87−2.97 (m, 1H), 3.06 (d, 2H), 3.30−3.40 (m, 4H), 3.63 (t, 2H), 4.30 (t, 2H), 7.38 (t, 1H), 7.40−7.47 (m, 2H), 7.50 (s, 1H), 7.58 (d, 1H), 7.63−7.70 (m, 2H), 8.30 (d, 1H), 8.77 (s, 1H), 8.88 (d, 2H); MS *m/z*: 486 (MH^+, 100%), 367 (6%), 271 (3%); Anal. ($C_{28}H_{28}FN_5O_2$): C, H, N.

The following derivatives **15c** and **22c** were prepared by method C using **15** and **22** as starting material and 3-bromopropionitrile as alkylating agent:

3-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}propionitrile Oxalate (15c). The crude product was purified by flash chromatography (EtOAc/heptane 50/50 → EtOAc/MeOH 90/10) and precipitated with oxalic acid from EtOH to give 0.45 g (34%) of the oxalate of **15c**: Mp 216−217 °C (EtOH); ^{1}H NMR (DMSO-d_6) δ: 1.95 (qd, 2H), 2.12 (d, 2H), 2.76 (t, 2H), 2.93 (t, 2H), 3.02−3.15 (m, 3H), 3.32 (d, 2H), 3.93 (s, 3H), 7.40−7.47 (m, 2H), 7.48 (s, 1H), 7.54 (d, 1H), 7.60−7.68 (m, 2H), 7.89 (d, 1H), 8.32 (s, 1H), 8.48 (s, 1H); MS *m/z*: 429 (MH^+, 100%), 388 (12%), 241 (3%); Anal. ($C_{25}H_{25}FN_6 \cdot C_2H_2O_4 \cdot 0.55\%\ H_2O$): C, H, N.

3-{4-[1-(4-Fluorophenyl)-5-pyrimidin-2-yl-1*H*-indol-3-yl]-1-piperidinyl}propionitrile (22c). The free base was recrystallized from EtOAc/CH_2Cl_2 90/10 to give 0.96 g (63%) of **22c**: Mp 182−183 °C (EtOAc/CH_2Cl_2); ^{1}H NMR (DMSO-d_6) δ: 1.81 (q, 2H), 2.03 (d, 2H), 2.25 (t, 2H), 2.60−2.70 (s, broad, 2H), 2.70−2.80 (m, 2H), 2.83−2.95 (m, 1H), 3.02 (d, 2H), 3.33 (s, 3H), 7.38 (t, 1H), 7.41−7.48 (m, 2H), 7.52 (s, 1H), 7.58 (d, 1H), 7.62−7.70 (m, 2H) 8.31 (d, 1H), 8.77 (s, 1H), 8.89 (d, 2H); MS *m/z*: 426 (MH^+, 100%), 384 (95%), 373 (95%); Anal. ($C_{26}H_{24}FN_5$): C, H, N.

The following derivative **15d** was prepared by method C using **15** as starting material and 3-(2-chloroethyl)-1-methylpyrrolidin-2-on as alkylating agent:

3-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-1-methylpyrrolidin-2-one Oxalate (15d). The crude product was purified by flash chromatography (EtOAc/heptane 50/50 → EtOAc/MeOH 90/10) and precipitated with oxalic acid from EtOH to give 0.40 g (26%) of the oxalate of **15d**: Mp 174−177 °C (EtOH, dec); ^{1}H NMR (DMSO-d_6) δ: 1.65 (q, 1H), 1.70−1.78 (m, 1H), 1.95−2.12 (m, 3H), 2.12−2.27 (m, 3H), 2.38−2.49 (m, 1H), 2.76 (s, 3H), 3.02−3.19 (m, 3H), 3.19−3.30 (m, 2H), 3.30−3.35 (t, 2H), 3.45−3.65 (m, 2H, 3.95 (s, 3H), 7.40−7.46 (m, 2H), 7.53 (s, 1H), 7.55 (d, 1H), 7.60−7.70 (m, 2H), 7.89 (d, 1H), 8.35 (s, 1H), 8.50 (s, 1H); MS *m/z*: 501 (MH^+, 100%), 370 (50%), 293 (5%); Anal. ($C_{29}H_{33}FN_6O \cdot 1.1C_2H_2O_4$): C, H, N.

The following derivative **15e** was prepared by method C (except CH_3CN was used as solvent) using **15** as starting material and 3-(2-chloroethyl)-1*H*-quinazoline-2,4-dione as alkylating agent:

3-(2-{4-[1-(4-Fluorophenyl)-5-(1-methyl-1,2,4-triazol-3-yl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-1*H*-quinazoline-2,4-dione (15e). The crude product was purified by flash chromatography (EtOAc/heptane 30/70 → EtOAc/MeOH/NEt_3 90/10/2) followed by recrystallization from EtOAc to yield 0.16 g (14%) of **15e**: Mp 241−244 °C (EtOAc); ^{1}H NMR (DMSO-d_6) δ: 1.75 (qd, 2H), 2.00 (d, 2H), 2.18 (t, 2H), 2.60 (t, 2H), 2.80−2.90 (m, 1H), 3.10 (s, broad, 2H), 3.90 (s, 3H), 4.10 (s, broad, 2H), 7.15−7.25 (m, 2H), 7.38−7.43 (m, 2H), 7.45 (s, broad, 1H), 7.52 (d, 1H) 7.60−7.70 (m, 3H, 7.85 (d, 1H), 7.95 (d, 1H), 8.30 (s, 1H), 8.50 (s, 1H); MS *m/z*: 464 (MH^+, 100%), 370 (30%), 293 (3%); Anal. ($C_{32}H_{30}FN_7O_2$): C, H; N: calcd 17.40 found 16.74.

1-(2-{4-[5-(Tetrazol-5-yl)-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)imidazolidin-2-one Hydrochloride (25a). A suspension of 1-(2-{4-[5-cyano-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl}ethyl)-2-imidazolidinone (**40**) (7.0 g, 16.2 mmol) (prepared according to the method described in Perregaard et al.[32]), $NEt_3 \cdot HCl$ (7.5 g, 55 mmol), and sodium azide (4.2 g, 64 mmol) in DME (100 mL) was boiled under reflux for 16 h. After the mixture was cooled to room temperature, H_2O (500 mL), NEt_3 (5 mL), and EtOAc (500 mL) were added. The phases were separated and the organic solvents evaporated in vacuo. The remaining viscous oil was stirred with methanol (25 mL), and solids were filtered off. Methanol was evaporated, and the remaining crystalline product was washed successively with acetone and H_2O. The hydrochloride of the title compound (**25a**) precipitated from ethanol by adding HCl/ether. The crystalline product was stirred with H_2O and finally filtered off and dried to yield 1.3 g (16%): Mp 193−197 °C; ^{1}H NMR (DMSO-d_6) δ: 2.20−2.40 (m, 4H), 3.20−3.80 (m, 13H), 6.60 (s, 1H), 7.40 (t, 2H), 7.60−7.70 (m, 4H), 7.95 (d, 1H), 8.75 (s, 1H); MS *m/z*: 475 (MH^+, 100%), 113 (75%); Anal. ($C_{25}H_{27}FN_8O \cdot HCl \cdot 1.80\%\ H_2O$): C, H, N.

1-[2-[4-[1-(4-Fluorophenyl)-5-(1,2,3-triazol-4-yl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]imidazolidin-2-one (26a). 1-[2-(1,5-Dioxa-9-azaspiro[5.5]undecan-9-yl)ethyl]imidazolidin-2-one (17.0 g, 63 mmol) (prepared by boiling 1,5-dioxa-9-azaspiro[5.5]undecane with 1-(2-chloroethyl)imidazolidin-2-one and K_2CO_3 in 4-methyl-2-pentanone under reflux) was dissolved in AcOH (30 mL) and TFA (12 mL) and added during 30 min to a refluxing solution of **29** (5.8 g, 21 mmol) in AcOH (30 mL) and TFA (12 mL). The solution was boiled under reflux for 50 min. After the mixture was cooled to room temperature, the solvents were removed in vacuo. H_2O (50 mL) was added and pH adjusted to 4−5 using 2 N aqueous NaOH. The aqueous phase was extracted with EtOAc (3 × 50 mL), washed with brine (50 mL), and dried over $MgSO_4$. The product was purified by flash chromatography (EtOAc/EtOH/NEt_3 50/60/4) to yield 2.0 g of 1-(2-{4-[1-(4-fluorophenyl)-5-(1,2,3-

triazol-4-yl)-1*H*-indol-3-yl]-1,2,3,6-tetrahydropyridin-1-yl}ethyl-9-imidazolidin-2-one (**39**) as an oil: ^{1}H NMR (DMSO-d_6) δ: 2.55−2.68 (m, 4H) 2.70−2.80 (t, 2H), 3.17−3.35 (m, 6H), 3.40−3.60 (m, 3H), 6.25 (s, 1H), 6.35 (broad, s, 1H), 7.45 (t, 3H), 7.68 (d, 1H), 7.70 (d, 1H), 7.72 (s, 1H), 7.78 (d, 1H), 8.37 (s, 1H) 8.40 (s, 1H). A solution of crude **39** (2.0 g, 4.2 mmol) was treated with H_2 as described in the preparation of **8a**. Solids were filtered off, and the solvent was evaporated in vacuo. The crude product was purified by preparative HPLC and freeze-dried to give 0.30 g (20%) of the trifluoroacetate salt of the title compound: ^{1}H NMR (DMSO-d_6) δ: 1.95−2.15 (m, 4H), 2.15−2.25 (m, 2H), 2.30 (d, 2H), 3.15−3.25 (m, 1H), 3.25−3.35 (m, 2H), 3.35−3.55 (m, 4H), 3.75 (d, 2H), 6.65 (s, broad, 1H), 7.40 (m, 3H), 7.55 (m, 2H), 7.65 (m, 2H), 7.70 (d, 1H), 8.25 (s, 1H), 8.32 (s, broad, 1H), 9.85 (s, broad, 1H). Liberation of the free base by addition of aqueous NH_4OH and extraction with EtOAc afforded the title compound **26a** as a pale yellow oil: Anal. ($C_{26}H_{28}FN_7O$): C, H, N.

Parallel Synthesis. Each of the intermediates **13**−**15, 17**−**20, 22**−**24**, and **37** (1.0 mmol) were dissolved in THF (30 mL) and reacted overnight with a saturated solution of HCl in MeOH (15 mL) at room temperature. The solvents were removed in vacuo, H_2O (50 mL) was added, and pH was adjusted to 10 by addition of 25% aqueous ammonium hydroxide. The aqueous phase was extracted with CH_2Cl_2 (3 × 30 mL), and the combined organic phases were dried over $MgSO_4$. After evaporation of the solvent in vacuo, stock solutions of the piperidinyl derivatives were prepared by dissolving to 0.2 M by addition of DMSO. Stock solutions of alkyl halides were prepared by dissolving the halides in as little DMF as possible. Solutions were subsequently diluted to 0.2 M by addition of CH_3CN. Blocks (Multisyntech Microchem Blocks[45]) containing 96 1.2 mL reactors fitted with frits were loaded with K_2CO_3 (40 mg, 0.3 mmol) and KI (10 mg, 0.06 mmol). From the stock solutions, the piperidinyl derivatives (0.15 mL, 0.03 mmol), the alkyl halide (0.225 mL, 0.045 mmol), and CH_3CN (0.3 mL) were added, and the reactors were closed and rotated in an oven at 70 °C for 14 h. After the mixture was cooled to 50 °C, isocyanate resin (30 mg, 1 mmol/g) was added, and the reactors were again closed and rotated at 50 °C for 2 h. After the mixture was cooled to room temperature, solids were filtered off and washed with CH_3CN (2 × 0.3 mL). The combined organic phases were purified using SCX ion exchange chromatography as follows: Columns (Varian Bond Elut-SCX 500 mg/3 mL) were conditioned with acetic acid in methanol (10%, 3 mL). The combined organic phases from the sample was added and washed with MeOH (3 mL) and CH_3CN (3 mL). Finally, the sample was eluted with 4 M ammonia in MeOH (3 mL). Between each step a slight air pressure was applied. The solvents were evaporated in vacuo, and the solutions diluted to 2 mM with DMSO. The identity and purity of the compounds was determined by HPLC/MS analysis with UV and ELSD detection. Compounds with purity of 70% or above were submitted for biological evaluation. The remaining compounds were purified by preparative LC/MS.[65] The following alkylating agents were used for the preparation of the examples given in Table 6: 3-bromo-propionitrile, 3-(2-chloroethyl)oxazolidin-2-one, 3-(2-chloroethyl)-1*H*-quinazoline-2,4-dione, 3-(2-chloroethyl)-1-methylpyrolidin-2-one.

Pharmacology. Cell Lines and Animals. CHO cell lines expressing the rat $\alpha_{1d,}$ human D_3, and human D_4 receptors and BHK cells expressing bovine α_{1a} receptors were generated in-house at H. Lundbeck using standard stable transfection techniques. The Rat-1 cell line expressing the hamster α_{1B} receptor was obtained from the University of Utah, Salt Lake City, UT. The HeLa cells expressing the 5-HT_{1A} receptor were obtained from Dr. Hamblin (Duke University, Durham, NC) and those expressing the 5-HT_{1b} receptor from Medical Center University, Seattle, WA. The SR-3T3 cells expressing the rat 5-HT_{2C} receptors were purchased from the American Type Culture Collection. The CHO cell line expressing the human 5-$HT_{2C\ (VSV)}$ receptors was purchased from Euroscreen (Brussels, Belgium) and grown according to their instructions. Brain preparations were generated from male Sprague Dawley rats weighing approximately 220 g. The animals were decapitated prior to brain extraction.

In Vitro Binding Assays. α_1 and Serotonin Receptors. The tissues were homogenized in ice-cold 50 mM Tris, pH 7.7, using an Ultra-Turrax and the homogenates either kept on ice or stored at −80 °C until used. The assay buffer subsequently used contained 50 mM Tris, pH 7.7. Nonspecific binding for the α_1 assays was defined as the binding in the presence of prazosin (1 μM) for the α_1 (rat brain) and of WB-4101 (1 μM) for the cloned α_{1a}, α_{1b}, and α_{1d} assays. For the serotonin assays, the nonspecific binding was defined using metergoline (1 μM) for the 5-HT_{1A} assay, 5-HT (10 μM) for the 5-HT_{1B} assay and mianserine (1 μM) for both the 5-HT_{2A} and 5-HT_{2C} assays. In all the α_1 assays, samples were incubated at 25 °C for 20 min. The 5-HT_{1A} and 5-HT_{1B} assays were incubated for 15 min at 37 °C whereas the 5-HT_{2A} and 5-HT_{2C} assays were incubated for 30 min at 37 °C. In all assays bound and free radioactivity were separated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux).

Dopamine Receptors. The $D_1$and D_2 tissues were homogenized in ice-cold 50 mM phosphate buffer, pH 7.4, using an Ultra-Turrax and the homogenates were kept on ice or stored at −80 °C until used. The homogenization buffer was also used as assay buffer. For the D_3 receptor, 25 mM Tris containing 6.0 mM $MgCl_2$ and 1.0 mM EDTA, pH 7.4, was used as homogenization and assay buffer. The D_4 receptor was homogenized and tested in 50 mM Tris containing 5 mM $MgCl_2$, 5 mM EDTA, 5 mM KCl, 1.5 mM $CaCl_2$, pH 7.4. To define nonspecific binding, Z-glupentizol (1 μM) was used for the D_1 assay, ADTN (10 μM) for the D_2 assay, haloperidol (10 μM) for the D_3 assay, and clozapine (10 μM) for the D_4 assay. Incubation times and temperatures were 60 min at 30 °C for the D_1 assay, 15 min at 37 °C for the D_2 assay, and 60 min at 25 °C for both the D_3 and D_4 assays. All assays were terminated by vacuum filtration on GF/B filters and counted in a scintillation counter (Wallac Trilux).

For details regarding the membrane source, radioligand, and radioligand concentration, refer to Table 2. Data shown in tables are means from a minimum of two full concentration−response curves using 10 concentrations of drugs (covering 3 decades). The results are given as K_i values (nM) derived from computer fitted IC_{50} values converted to K_i values using the Cheng−Prusoff equation. Standard errors for pK_i values were within 0.3 for all reported compounds.

Note Added after ASAP Posting. This manuscript was posted ASAP on 12/11/2002 with an error in a compound number in the abstract. The correct version was posted 12/13/2002.

References

(1) Ruffolo, R. R. J.; Bondinell, W.; Hieble, J. P. α- and β-Adrenoceptors: From the Gene to the Clinic. 2. Structure−Activity Relationships and Therapeutic Applications. *J. Med. Chem.* **1995**, *38*, 3681−3716.

(2) Lagu, B. Identification of α_{1A}-Adrenoceptor Selective Antagonists for the Treatment of Benign Prostatic Hyperplasia. *Drugs Future* **2001**, *26*, 757−765.

(3) Kenny, B.; Ballard, S.; Blagg, J.; Fox, D. Pharmacological Options in the Treatment of Benign Prostatic Hyperplasia. *J. Med. Chem.* **1997**, *40*, 1293−1315.

(4) Baldessarini, R. J.; Huston-Lyons, D.; Campbell, A.; Marsh, E.; Cohen, B. M. Do Central Antiadrenergic Actions Contribute to the Atypical Properties of Clozapine? *Br. J. Psychiatry.* **1992**, *Suppl*, 12−16.

(5) Lipinski, J. F. J.; Cohen, B. M.; Zubenko, G. S.; Waternaux, C. M. Adrenoceptors and the Pharmacology of Affective Illness: a Unifying Theory. *Life Sci.* **1987**, *40*, 1947−1963.

(6) Price, D. T.; Lefkowitz, R. J.; Caron, M. G.; Berkowitz, D.; Schwinn, D. A. Localization of mRNA for Three Distinct α_1-Adrenergic Receptor Subtypes in Human Tissues: Implications for Human α-Adrenergic Physiology. *Mol. Pharmacol.* **1994**, *45*, 171−175.

(7) O'Malley, S. S.; Chen, T. B.; Francis, B. E.; Gibson, R. E.; Burns, H. D.; DiSalvo, J.; Bayne, M. L.; Wetzel, J. M.; Nagarathnam, D.; Marzabadi, M.; Gluchowski, C.; Chang, R. S. L. Characterization of Specific Binding of (^{125}I)L-762, 459, a Selective α_{1A}-Adrenoceptor Radioligand to Rat and Human Tissues. *Eur. J. Pharmacol.* **1998**, *348*, 287−295.

(8) De Paermentier, F.; Mauger, J. M.; Lowther, S.; Crompton, M. R.; Katona, C. L.; Horton, R. W. Brain α-Adrenoceptors in Depressed Suicides. *Brain Res.* **1997**, *757*, 60−68.

(9) Garcia-Sainz, J. A.; Vazquez-Prado, J.; Villalobos-Molina, R. α_1-Adrenoceptors: Subtypes, Signaling, and Roles in Health and Disease. *Arch. Med. Res.* **1999**, *30*, 449−458.

(10) Vargas, H. M.; Gorman, A. J. Vascular Alpha-1 Adrenergic Receptor Subtypes in the Regulation of Arterial Pressure. *Life Sci.* **1995**, *57*, 2291−2308.

(11) Arnt, J.; Skarsfeldt, T. Do Novel Antipsychotics Have Similar Pharmacological Characteristics? A Review of the Evidence. *Neuropsychopharmacology* **1998**, *18*, 63−101.

(12) Chiodo, L. A.; Bunney, B. S. Possible Mechanisms by Which Repeated Clozapine Administration Differentially Affects the Activity of Two Subpopulations of Midbrain Dopamine Neurons. *J. Neurosci.* **1985**, *5*, 2539−2544.

(13) Wadenberg, M. L.; Hertel, P.; Fernholm, R.; Hygge, B. K.; Ahlenius, S.; Svensson, T. H. Enhancement of Antipsychotic-Like Effects by Combined Treatment With the α_1-Adrenoceptor Antagonist Prazosin and the Dopamine D_2 Receptor Antagonist Raclopride in Rats. *J. Neural Transm.* **2000**, *107*, 1229−1238.

(14) Prinssen, E. P.; Ellenbroek, B. A.; Cools, A. R. Combined Antagonism of Adrenoceptors and Dopamine and 5-HT Receptors Underlies the Atypical Profile of Clozapine. *Eur. J. Pharmacol.* **1994**, *262*, 167−170.

(15) Grenhoff, J.; Svensson, T. H. Prazosin Modulates the Firing Pattern of Dopamine Neurons in Rat Ventral Tegmental Area. *Eur. J. Pharmacol.* **1993**, *233*, 79−84.

(16) Grenhoff, J.; Nisell, M.; Ferre, S.; Aston-Jones, G.; Svensson, T. H. Noradrenergic Modulation of Midbrain Dopamine Cell Firing Elicited by Stimulation of the Locus Coeruleus in the Rat. *J. Neural Transm. Gen. Sect.* **1993**, *93*, 11−25.

(17) Bakshi, V. P.; Geyer, M. A. Phencyclidine-Induced Deficits in Prepulse Inhibition of Startle are Blocked by Prazosin, an Alpha-1 Noradrenergic Antagonist. *J. Pharmacol. Exp. Ther.* **1997**, *283*, 666−674.

(18) Carasso, B. S.; Bakshi, V. P.; Geyer, M. A. Disruption in Prepulse Inhibition After Alpha-1 Adrenoceptor Stimulation in Rats. *Neuropharmacology* **1998**, *37*, 401−404.

(19) Hommer, D. W.; Zahn, T. P.; Pickar, D.; van Kammen, D. P. Prazosin, a Specific Alpha$_1$−Noradrenergic Receptor Antagonist, Has No Effect on Symptoms but Increases Autonomic Arousal in Schizophrenic Patients. *Psych. Res.* **1984**, *11*, 193−204.

(20) Raskind, M. A.; Dobie, D. J.; Kanter, E. D.; Petrie, E. C.; Thompson, C. E.; Peskind, E. R. The α_1-Adrenergic Antagonist Prazosin Ameliorates Combat Trauma Nightmares in Veterans With Posttraumatic Stress Disorder: a Report of 4 Cases. *J. Clin. Psych.* **2000**, *61*, 129−133.

(21) Wetzel, J. M.; Miao, S. W.; Forray, C.; Borden, L. A.; Branchek, T. A.; Gluchowski, C. Discovery of α_{1a}-Adrenergic Receptor Antagonists Based on the L-Type Ca^{2+} Channel Antagonist Niguldipine. *J. Med. Chem.* **1995**, *38*, 1579−1581.

(22) Giardina, D.; Crucianelli, M.; Romanelli, R.; Leonardi, A.; Poggesi, E.; Melchiorre, C. Synthesis and Biological Profile of the Enantiomers of [4-(4-Amino-6,7-dimethoxyquinazolin-2-yl)-*cis*-octahydroquinoxalin-1-yl]furan-2-ylmethanone (Cyclazosin), a Potent Competitive α_{1B}-Adrenoceptor Antagonist. *J. Med. Chem.* **1996**, *39*, 4602−4607.

(23) Konkel, M. J.; Wetzel, J. M.; Cahir, M.; Craig, D.; Noble, S. A.; Gluchowski, C. Discovery of Antagonists Selective for the Alpha-1D-Adrenoceptor. Presented at the 216th American Chemical Society National Meeting, Boston, Aug 23−27, 1998 (poster).

(24) Piascik, M. T.; Perez, D. M. α_1-Adrenergic Receptors: New Insights and Directions. *J. Pharmacol. Exp. Ther.* **2001**, *298*, 403−410.

(25) Balle, T.; Perregaard, J.; Larsen, S.; Ramirez, M. T.; Søby, K. K.; Liljefors, T.; Andersen, K. Synthesis and Structure-Affinity Relationship Investigations of 5-Aminomethyl and 5-Carbamoyl Analogues of the Antipsychotic Sertindole. A New Class of Selective α_1 Adrenoceptor Antagonists. *Bioorg. Med. Chem.*, in press.

(26) These data are in contrast to previously published receptor-binding affinity for 5-HT_{1A} receptors of 2200[11] and 1050 nM.[63] However, the data presented in Table 3 is obtained from an assay of human recombinant 5-HT_{1A} receptors expressed in HeLa-cells using [^{3}H]5-CT as radioligand, whereas the previously published value was obtained in an assay of human and rat brain membranes using [^{3}H]8-OH-DPAT as radioligand.[25]

(27) Ipsen, M.; Zhang, Y.; Dragsted, N.; Han, C.; Mulvany, M. J. The Antipsychotic Drug Sertindole is a Specific Inhibitor of α_{1A}-Adrenoceptors in Rat Mesenteric Small Arteries. *Eur. J. Pharmacol.* **1997**, *336*, 29−35.

(28) These data are in contrast to previously published values by Ipsen et al.[27] Ipsen et al. found that the affinity of sertindole (**1**) for adrenergeic α_{1b} and α_{1d} was lower by a factor of 64 and 125 compared to binding at adrenergic α_{1a} receptors (K_i = 1.3 nM) measured by inhibition of [^{125}I]IBE-2254 at cloned adrenergic bovine (α_{1a}), rat (α_{1b}), and hamster (α_{1d}) receptors expressed in HEK293 cell lines. We used similar cloned receptors expressed in the cell lines listed in Table 2 together with a different radioligand, [^{3}H]prazosin (see Experimental Section for details). These differences might account for the observed discrepancy.[25]

(29) Perregaard, J.; Andersen, K.; Hyttel, J.; Sánchez, C. Selective, Centrally Acting Serotonin 5-HT_2 Antagonists. 1. 2- and 6-Substituted 1-Phenyl-3-(4-piperidinyl)-1*H*-indoles. *J. Med. Chem.* **1992**, *35*, 4813−4822.

(30) Andersen, K.; Perregaard, J.; Arnt, J.; Nielsen, J. B.; Begtrup, M. Selective, Centrally Acting Serotonin 5-HT_2 Antagonists. 2. Substituted 3-(4-Fluorophenyl)-1*H*-indoles. *J. Med. Chem.* **1992**, *35*, 4823−4831.

(31) Andersen, K.; Liljefors, T.; Hyttel, J.; Perregaard, J. Serotonin 5-HT_2 Receptor, Dopamine D2 Receptor, and α_1 Adrenoceptor Antagonists. Conformationally Flexible Analogues of the Atypical Antipsychotic Sertindole. *J. Med. Chem.* **1996**, *39*, 3723−3738.

(32) Perregaard, J.; Arnt, J.; Bøgesø, K. P.; Hyttel, J.; Sánchez, C. Noncataleptogenic, Centrally Acting Dopamine D-2 and Serotonin 5-HT2 Antagonists within a Series of 3-Substituted 1-(4-Fluorophenyl)-1*H*-Indoles. *J. Med. Chem.* **1992**, *35*, 1092−1101.

(33) Yang, Y.; Martin, A. R. Tandem Coupling of 5-Bromo-3-iodo-1-tosyl-indole With Trimethylarylstannanes and Aryl Boronic Acids. *Synth. Commun.* **1992**, *22*, 1757−1762.

(34) Pearce, B. C. 2-Trialkylstannyl-5-*tert*-butoxyfurans: Convenient 5-Substituted-2-(3*H*)-furanone Synthons. *Synth. Commun.* **1992**, *22*, 1627−1643.

(35) Jensen, J.; Skjærbæk, N.; Vedsø, P. Preparation of 2- and 5-Aryl Substituted Thiazoles via Palladium-Catalyzed Negishi Cross-Coupling. *Synthesis* **2001**, 128−134.

(36) Yang, Y.; Martin, A. R. Synthesis of 5-Arylated Indoles via Palladium-Catalyzed Cross-Coupling Reaction of 5-Indolylboronic acid with Aryl and Heteroaryl Halides. *Heterocycles* **1992**, *34*, 1395−1398.

(37) Yang, Y.; Martin, A. R.; Nelson, D. L.; Regan, J. Synthesis of Some 5-Substituted Indoles. *Heterocycles* **1992**, *34*, 1169−1175.

(38) Carbonnelle, A.-C.; Zamora, E. G.; Beugelmans, R.; Roussi, G. Indole Arylation Studies Directed Towards the Synthesis of Simplified Eastern Subunits of Chloropeptin and Kistamycin. *Tetrahedron Lett.* **1998**, *39*, 4467−4470.

(39) Balle, T.; Andersen, K.; Vedsø, P. Preparation of 5-Heteroaryl Substituted 1-(4-Fluorophenyl)-1*H*-Indoles via Palladium Catalyzed Negishi and Stille Cross-Coupling Reactions. *Synthesis* **2002**, 1509−1512.

(40) Sonogashira, K.; Tohda, Y.; Hagihara, N. Convenient Synthesis of Acetylenes. Catalytic Substitution of Acetylenic Hydrogen with Bromo Alkenes, Iodo Arenes and Bromopyridines. *Tetrahedron Lett.* **1975**, *50*, 4467−4470.

(41) Thorand, S.; Krause, N. Improved Procedure for the Palladium Catalyzed Coupling of Terminal Alkynes With Aryl Bromides (Sonogashira Coupling). *J. Org. Chem.* **1998**, *63*, 8551−8553.

(42) Neuhaus, D.; Williamson, M. *The Nuclear Overhauser Effect in Structural and Conformational Analysis*; VCH Publishers: New York, Weinheim, Cambridge, 1989.

(43) Negishi, E.; King, a. O.; Okukado, N. Selective Carbon−Carbon Bond Formation via Transition Metal Catalysis. 3. A Highly Selective Synthesis of Unsymmetrical Biaryls and Diarylmethanes by Nickel- or Palladium-Catalyzed Reaction of Aryl- and Benzylzinc Derivatives with Aryl Halides. *J. Org. Chem.* **1977**, *42*, 1821−1823.

(44) Tschaen, D. M.; Desmond, R.; King, a. O.; Fortin, M. C.; Pipik, B.; King, S.; Verhoeven, T. R. An Improved Procedure for Aromatic Cyanation. *Synth. Commun.* **1994**, *24*, 887−890.

(45) MultiSynTech GmbH. www.multisyntech.com.

(46) Kaldor, S. W.; Siegel, M. G.; Fritz, J. E.; Dressman, B. A.; Hahn, P. J. Use of Solid Supported Nucleophiles and Electrophiles for the Purification of Non-Peptide Small Molecule Libraries. *Tetrahedron Lett.* **1996**, *37*, 7193−7196.

(47) Hancock, A. A. α_1 Adrenoceptor Subtypes: A Synopsis of Their Pharmacology and Molecular Biology. *Drug Dev. Res.* **1996**, *39*, 54−107.

(48) Costantino, G.; Maltoni, K.; Marinozzi, M.; Camaiono, E.; Prezeau, L.; Pin, J.-P.; Pellicciari, R. Synthesis and Biological Evaluation of 1-(3′-(1H-Tetrazol-5-yl)bicyclo[1.1.1]pent-1-yl)glycine (S-TBPG), a Novel mGLU1 Receptor Antagonist. *Bioorg. Med. Chem.* **2001**, *9*, 221−227.

(49) Sánchez, C.; Arnt, J.; Dragsted, N.; Hyttel, J.; Lembøl, H. L.; Meier, E.; Perregaard, J.; Skarsfeldt, T. Neurochemical and in Vivo Pharmacological Profile of Sertindole, a Limbic-Selective Neuroleptic Compound. *Drug Dev. Res.* **1991**, *22*, 239−250.

(50) Sánchez, C. (2002) H. Lundbeck A/S, unpublished observations. Experiments were performed according to published procedures: Inhibition of phenylephrine induced pressor response.[49] Inhibition of isoniazide-induced convulsions.[67]
(51) Isoniazide is an inhibitor of glutamic acid decarboxylase (GAD), the enzyme responsible for synthesis of GABA, and is as such a test for anticonvulsive effects of GABA stimulants and benzodiazepines. No direct evidence supports that α_1-adrenoceptors are involved, but results from our laboratories have indicated a good correlation between affinities for α_1-adrenoceptors in vitro and anticonvulsant potencies against isoniazide, as long as affinity for GABA and benzodiazepine can be excluded. Such compounds would be false positives.[11] Both compounds **8a** and **12a** binds at GABA and benzodiazepine receptors with IC_{50} values larger than 1000 nM (H. Lundbeck A/S, unpublished results, 2001), suggesting that the observed effect is mediated via blockade of central α_1 adrenoceptors.
(52) Liljefors, T.; Bøgesø, K. P. Conformational Analysis and Structural Comparisons of (1*R*,3*S*)-(+)- and (1*S*,3*R*)-(−)-Tefludazine, (*S*)-(+)- and (*R*)-(−)-Octoclothepin, and (+)-Dexclamol in Relation to Dopamine Receptor Antagonism and Amine-Uptake Inhibition. *J. Med. Chem.* **1988**, *31*, 306−312.
(53) Andersen, K.; Liljefors, T.; Gundertofte, K.; Perregaard, J.; Bøgesø, K. P. Development of a Receptor-Interaction Model for Serotonin 5-HT_2 Receptor Antagonists. Predicting Selectivity with Respect to Dopamine D_2 Receptors. *J. Med. Chem.* **1994**, *37*, 950−962.
(54) Palm, J.; Bøgesø, K. P.; Liljefors, T. A Structure−Activity Study of Four Dopamine D-1 and D-2 Receptor Antagonists, Representing the Phenylindan, −Indene, and −Indole Structural Classes of Compounds. *J. Med. Chem.* **1993**, *36*, 2878−2885.
(55) Boström, J.; Gundertofte, K.; Liljefors, T. A Pharmacophore Model for Dopamine D_4 Receptor Antagonists. *J. Comput.-Aided Mol. Des.* **2000**, *14*, 769−786.
(56) Bøgesø, K. P.; Liljefors, T.; Arnt, J.; Hyttel, J.; Pedersen, H. Octoclothepin Enantiomers. A Reinvestigation of Their Biochemical and Pharmacological Activity in Relation to a New Receptor-Interaction Model for Dopamine D-2 Receptor Antagonists. *J. Med. Chem.* **1991**, *34*, 2023−2030.
(57) Johnston, T. P.; McCaleb, G. S.; Montgomery, J. A. The Synthesis of Antineoplastic Agents. XXXII. N-Nitrosureas. *J. Med. Chem.* **1963**, *6*, 669−681.
(58) Robinson, C. B.; Herbrandson, H. F. Kinetics and Mechanism of the Reaction of 2,2′-Dichlorodiethylamine with Aqueous Carbon Dioxide. *J. Am. Chem. Soc.* **1972**, *94*, 7883−7887.
(59) Sucrow, W.; Slopianka, M.; Winkler, D. Hydroxyalkylierung von Carbonsäure-dialkylamiden mit Epoxiden. *Chem. Ber.* **1972**, *105*, 1621−1633.
(60) Begtrup, M.; Larsen, P. Alkylation, Acylation and Silylation of Azoles. *Acta Chem. Scand.* **1990**, *44*, 1050−1057.
(61) Hüttel, R.; Welzel, G. Die Halogenierung der 1,2,3-Triazole. *Liebigs Ann. Chem.* **1955**, *593*, 207−218.
(62) Bernardini, A.; Viallefont, P.; Daunis, J.; Roumestant, M.-L.; Soulami, A. B. Synthèses D'Halogéno-Triazoles-1,2,4 Substitués en Position 1 ou 4. *Soc. Chim.* **1975**, *5*, 647−653.
(63) Konkel, M.; Wetzel, J. M.; Noble, S.; Gluchowski, C.; Craig, D. A. Compounds Specific for the Human α_{1d} Adrenergic Receptor and Uses Thereof. Patent Application WO 00/04012, 2000; *Chem. Abstr.* **2000**, *132*, 107961.
(64) Furneaux, R. H.; Limberg, G.; Tyler, P. C. Synthesis of Transitionstate Inhibitors for N-Riboside Hydrolases and Transferases. *Tetrahedron* **1997**, *53*, 2915−2930.
(65) Zeng, L.; Burton, L.; Yung, K.; Shushan, B.; Kassel, D. B. Automated Analytical/Preparative High-Performance Liquid Chromatography−Mass Spectrometry System for the Rapid Characterization and Purification of Compound Libraries. *J. Chromatogr. A.* **1998**, *794*, 3−13.
(66) Richelson, E.; Souder, T. Binding of Antipsychotic Drugs to Human Brain Receptors. Focus on Newer Generation Compounds. *Life Sci.* **2000**, *68*, 29−39.
(67) Christensen, A. V.; Larsen, J. J. Antinociceptive and Anticonvulsive Effect of THIP, a Pure GABA Agonist. *Pol. J. Pharmacol. Pharm.* **1982**, *34*, 127−134.

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