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Pd(0) Amination of Benzimidazoles as an Efficient Method towards New (Benzimidazolyl)piperazines with High Affinity for the 5-HT_{1A} Receptor

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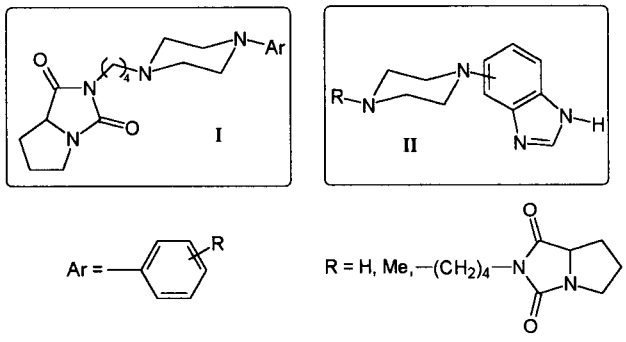
Abstract—New (benzimidazolyl)amines have been synthesized from 4- and 6-bromobenzimidazole derivatives via palladium-mediated amination reactions. Among them, (benzimidazol-4(7)-yl)piperazine derivatives have been shown to be a new family of high affinity 5-HT_{1A} receptor ligands.

Introduction

Serotonin 5-HT_{1A} receptors have been intensively studied[1] because of their implication in several physiological processes and psychiatric disorders such as anxiety and depression. In addition to these therapeutic uses, serotonergic 5-HT_{1A} agonists have been proposed recently to be employed as neuroprotective agents[2] and the effect of these drugs may be therapeutically relevant. For these reasons, the discovery of new 5-HT_{1A} receptor ligands is an area of active research in Medicinal Chemistry. Within this field, we have found that arylpiperazines **I** (Scheme 1) are potent 5-HT_{1A} ligands.[3] 3D-QSAR studies[4] suggested that increasing the size of the substituent of the aromatic ring could enhance the affinity for 5-HT_{1A} receptors. These results led us to design a new family of arylpiperazines where the substituted phenyl ring (Ar) has been replaced by a bicyclic aromatic ring. Among the considered moieties, we found particularly interesting arylpiperazines **II** (Scheme 1), which include a benzimidazole ring attached to the piperazine through carbon 4(7) or 5(6) and this required an efficient entry to 1-(benzimidazol-4(7)- and -5(6)-yl)piperazines.

Benzimidazole derivatives are becoming increasingly important since they are present in naturally occurring cyanocobalamine, serine protease inhibitors and a number of different therapeutic agents.[5] They are also applied as cyanine dyes in photographic emulsions and as high temperature resistive polymers.[6] Nevertheless, there are few methods available to prepare benzimidazole derivatives bearing substituents attached to the homocycle, since most of the known routes are directed to functionalize carbon-2 and nitrogens (N-1, N-3).[7] On the other hand, most methods to obtain arylpiperazines involve cyclization of aromatic amines and bis(haloethyl)amines.[8] However, these procedures present some problems such as the use of toxic reagents and the difficult isolation of the products. Moreover, in our hands treatment of 4-amino-1-tritylbenzimidazole with bis(chloroethyl)amine under a number of different conditions did not yield the expected 1-(1-tritylbenzimidazol-4-yl)piperazine, but complex crude mixtures with extensive decomposition. These disappointing results prompted us to explore alternative routes to reach our target compounds.

The metal-mediated coupling of aromatic halides and triflates with amines has become a powerful tool to synthesize



Scheme 1.

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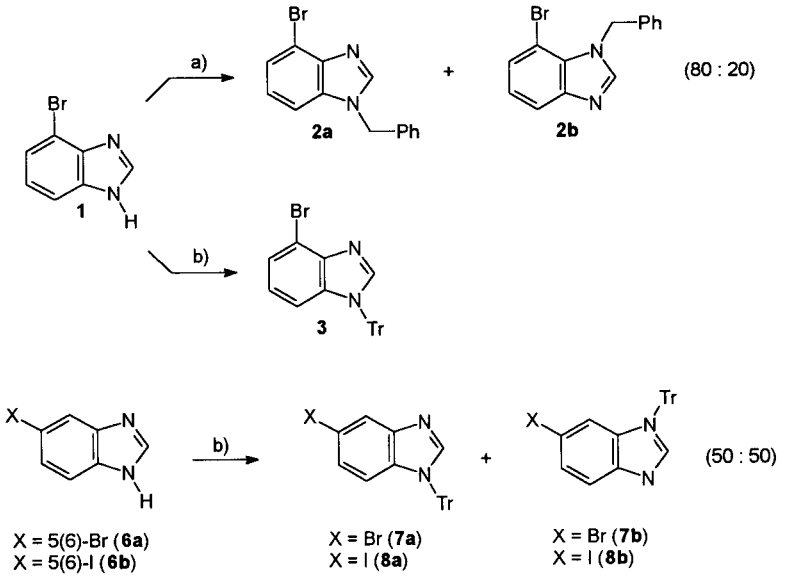


Scheme 2. (a) NaH, BnCl, Bu_4Ni, THF, 48% for **2a**; 20% for **2b**; (b) NaH, TrCl, Bu_4Ni, 90% for **3**; 45% for **7a**; 40% for **7b**; 46% for **8a**.

aromatic amines, especially since Buchwald and Hartwig independently studied the process from a synthetic and mechanistic standpoint.[9] Because of the broad scope of the amination reaction, we considered it suitable for our purposes.[10] In this paper, we would like to report our results on the coupling of 4(7)- and 5(6)-halobenzimidazoles with different aliphatic and aromatic amines. Among the coupled compounds, (benzimidazol-4(7)-yl)piperazine derivatives have shown to be a new family of high affinity 5-HT_{1A} receptor ligands.

Results and Discussion

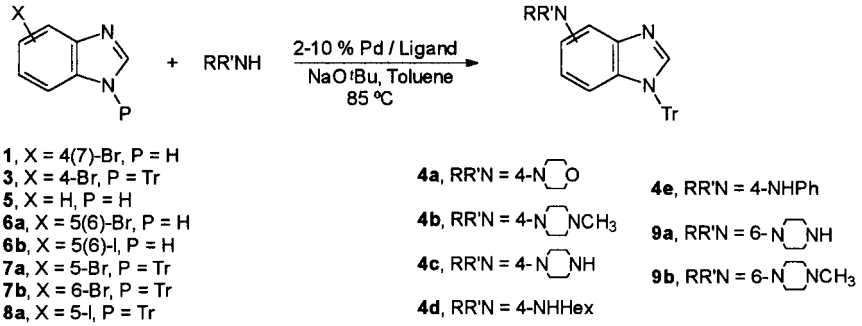
The synthesis of 4(7)-bromobenzimidazole **1** was carried out starting from 4-bromoaniline following a described procedure in five steps.[11] 5(6)-Bromobenzimidazole **6a** was obtained by treating benzimidazole with *N*-bromosuccinimide in the presence of silica gel.[12] This reaction, employing *N*-iodosuccinimide instead of the bromine analogue, did not allow us the attainment of 5(6)-iodobenzimidazole **6b**, finally obtained by iodation, reduction and cyclization of *o*-nitroaniline.[13]

Substrates **1**, **6a** and **6b** were *N*-protected before the amination procedure (Scheme 2), because no amination reaction was observed for the unprotected halobenzimidazoles (Scheme 3, Table 1, entry 4). Initially, a benzyl group was selected as the protective group, but the treatment of **1** with benzyl chloride yielded an 80/20 mixture of the *anti*/*syn* isomers (**2a**, **2b**) (the relative percentage was determined by integration of the ^{1}H NMR spectrum of the crude mixture, and the identification of each isomer, using steady state 1D-NOE experiments).[14] In order to avoid this lack of regioselectivity, we considered the introduction of a bulkier trityl group, obtaining then a single *anti* *N*-alkylated product, identified as 4-bromo-1-tritylbenzimidazole **3**. In contrast, reaction of **6a** and **6b** with trityl chloride was a non-selective process, producing a 50/50 mixture of 5-halo-1-trityl- and 6-halo-1-tritylbenzimidazoles, subsequently separated by column chromatography.

The following step in our synthetic plan was the amination of the protected halobenzimidazoles (Scheme 3). Starting from **3**, a wide variety of amine/catalyst/ligand systems have been tested to optimize this procedure for our substrates. Treatment of **3** with morpholine (1.4 equiv.) in the presence of $Pd_2dba_3{\cdot}CHCl_3$ (2–10%), dppp (4–10%) and NaO^tBu (1.4 equiv.) in toluene rendered 4-(benzimidazol-4-yl)morpholine **4a** in 65% yield, and we did not observe the corresponding reduction product (Scheme 3, Table 1, entry 1). In a similar way, 1-methylpiperazine reacted with **3** giving an excellent yield of **4b** even when $Pd_2dba_3{\cdot}CHCl_3$ was changed to $Pd(OAc)_2$ as the palladium source (Scheme 3, Table 1, entries 2–3).

When piperazine was used as amine, a higher excess (4 equiv.) was employed to avoid an undesired double coupling. Formation of the corresponding (benzimidazolyl)-piperazine **4c** was carried out under slightly different conditions than used for morpholine and 1-methylpiperazine, because the use of $Pd_2dba_3{\cdot}CHCl_3$/dppp did not yield the expected product but a 75/25 mixture of starting material **3** and reduction product **5** after 24 h under these reaction conditions, probably due to a competitive β-elimination process. Moreover, changing the catalyst system to $Pd(OAc)_2$/dppp gave a small amount of **4c** in the crude mixture (25/50/25, **3/4c/5**). The best result was obtained with $Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP, with 87% yield of **4c** (Scheme 3, Table 1, entries 5–7). Under these conditions, neither the corresponding dimer nor the reduction product **5** were observed, even in the presence of an excess of **3** and after prolonged reaction times (48 h).

Other amines submitted to the coupling reaction showed a lower reactivity.[15] Thus, hexylamine (Scheme 3, Table 1, entry 8) led to only 28% conversion after 48 h. In contrast, $PhNH_2$ afforded *N*-(benzimidazol-4-yl)aniline **4e**, which was isolated pure in 54% yield (Scheme 3, Table 1, entry 9).



Scheme 3.

Table 1. Pd(0) amination of bromobenzimidazoles

Entry	Substrate	RR′NH	Catalyst/Ligand	Product (yield %)[a]
1	**3**	Morpholine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	**4a** (65)
2	**3**	1-Methylpiperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	**4b** (97)
3	**3**	1-Methylpiperazine	$Pd(OAc)_2$/dppp	**4b** (97)
4	**1**	1-Methylpiperazine	$Pd(OAc)_2$/dppp	–[b]
5	**3**	Piperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	–[c]
6	**3**	Piperazine	$Pd(OAc)_2$/dppp	**4c**[d]
7	**3**	Piperazine	$Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP	**4c** (87)
8	**3**	Hexylamine	$Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP	**4d**[e]
9	**3**	Aniline	$Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP	**4e**[f] (54)
10	**7a**	Piperazine	$Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP	–[g]
11	**8a**	1-Methylpiperazine	$Pd_2dba_3{\cdot}CHCl_3$/dppp	–[g]
12	**7b**	Piperazine	$Pd(OAc)_2$/(±)-BINAP	–[h]
13	**7b**	Piperazine	$Pd(OAc)_2$/(±)-BINAP	**9a** (60)[i]
14	**7b**	1-Methylpiperazine	$Pd(OAc)_2$/(±)-BINAP	**9b** (55)[i]

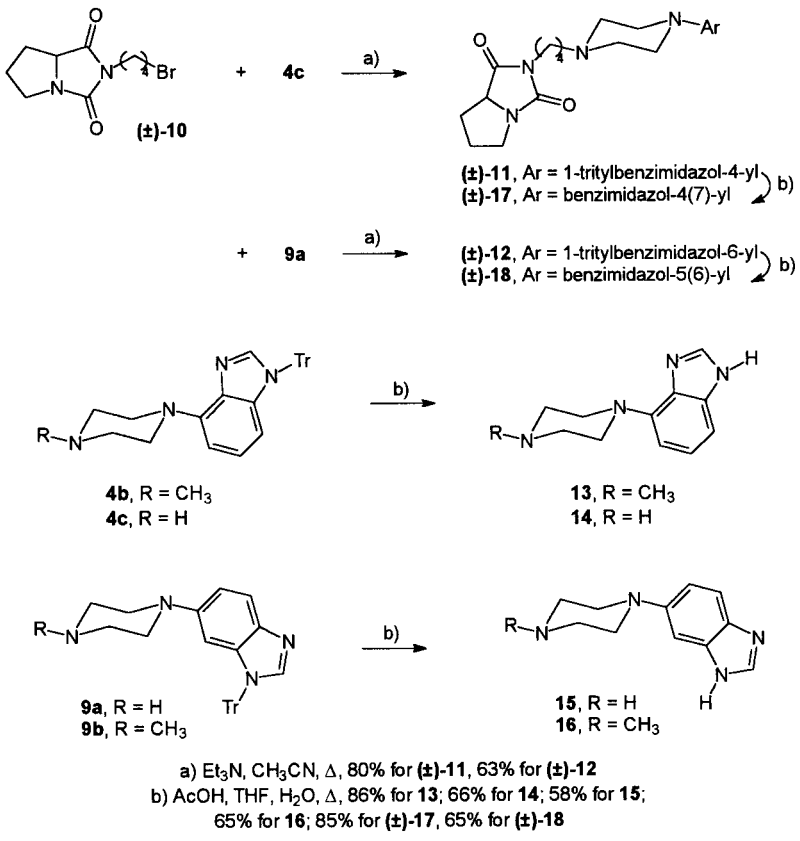
[a] Yield of isolated pure compounds.
[b] No reaction was observed.
[c] A 75/25 mixture of **3** and **5** was observed in the reaction crude (^{1}H NMR, 300 MHz).
[d] A 25/50/25 mixture of **3**, **4c** and **5** was observed in the reaction crude (^{1}H NMR, 300 MHz).
[e] A 72/28 mixture of **3** and **4d** was observed in the reaction crude (^{1}H NMR, 300 MHz); **4d** was not isolated from this mixture.
[f] 60% conversion after 20 h of reaction.
[g] A 50/50 mixture of starting material and **5** was observed in the reaction crude (^{1}H NMR, 300 MHz).
[h] A 30/40/30 mixture of **7b**, **5** and **9a** was observed in the reaction crude (^{1}H NMR, 300 MHz).
[i] A 15% of **5** was also obtained; Cs_2CO_3 instead of NaO^{t}Bu was employed.

With regard to *N*-trityl derivatives **7a** and **7b**, an unexpectedly very different reactivity of these regioisomers was found towards the Pd(0) catalyzed amination. Thus, 5-bromo-1-tritylbenzimidazole **7a** was not a suitable substrate for the coupling process, yielding the starting material along with variable amounts of reduction product **5**, independently of the reaction conditions employed, $Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP/NaO^{t}Bu/toluene (Scheme 3, Table 1, entry 10), $Pd_2dba_3{\cdot}CHCl_3$/(±)-BINAP/Cs_2CO_3/toluene or $Pd(OAc)_2$/(±)-BINAP/NaO^{t}Bu/toluene. Even when aniline was used to prevent β-elimination, the coupling product could not be detected upon examination of the crude reaction mixture. The use of 5-iodo-1-tritylbenzimidazole **8a** gave again a mixture of the starting material and reduction product (Table 1, entry 11). On the other hand, 6-bromo-1-tritylbenzimidazole **7b** reacted more readily than its isomer **7a** (Table 1, entries 12–13), although a low conversion to the corresponding (benzimidazolyl)piperazine **9a** (30%) along with an important amount of reduction product **5** (40%) were produced after treatment of **7b** with an excess of piperazine and $Pd(OAc)_2$/(±)-BINAP/NaO^{t}Bu. The use of Cs_2CO_3 instead of NaO^{t}Bu allowed the isolation of the desired product **9a** in a moderate yield (60%). Following the same procedure, the *N*-methyl analogue **9b** was obtained from **7b** (Table 1, entry 14).

Once afforded 1-(1-tritylbenzimidazol-4-yl)piperazine **4c** and 1-(1-tritylbenzimidazol-6-yl)piperazine **9a**, the next step was the incorporation of a bicyclohydantoin moiety. Reaction of **4c** or **9a** with bromoderivative (±)-**10**[3a] gave, in good yields, the mixed hydantoin–arylpiperazine derivatives (±)-**11** and (±)-**12**, susceptible to be tested as new ligands for serotonin 5-HT_{1A} receptors (Scheme 4).

Finally, standard acidic conditions[16] (AcOH/H_2O/THF) allowed for the smooth removal of the trityl group for (±)-**11** and (±)-**12** derivatives, obtaining (±)-**17** and (±)-**18**, respectively. Similarly, simple arylpiperazines **4b**, **4c**, **9a** and **9b** were converted into **13**, **14**, **15** and **16**, respectively. All these compounds were obtained in very good yields (Scheme 4).

Target compounds were evaluated for in vitro affinity at central 5-HT_{1A} receptors by radioligand binding assays, using [^{3}H]-8-OH-DPAT in rat cerebral cortex membranes.[17] The binding data of the tested compounds are presented in



Scheme 4.

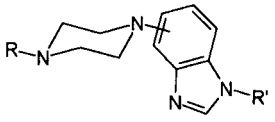
Table 2, as the inhibition constant K_i, defined from the IC_{50} using the Cheng–Prusoff equation.[18]

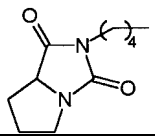
Interestingly, benzimidazol-4(7)-yl derivatives exhibit high affinity (nanomolar range) for the 5-HT_{1A} receptor (i.e. K_i (**13**)=4.72±0.50 nM, K_i (**17**)=1.21±0.02 nM), whereas benzimidazol-5(6)-yl analogues are inactive (K_i>1000 nM). These results indicate that these arylpiperazines are new potent 5-HT_{1A} receptor ligands. Thus, the fragment 1-(benzimidazol-4-yl)piperazine represents a novel and readily accessible pharmacophoric moiety in the research for new potent 5-HT_{1A} ligands.

Conclusion

The synthesis of target (benzimidazolyl)piperazines exemplifies a new approach to (benzimidazolyl)amines via Pd(0) amination of bromobenzimidazole derivatives. Among the prepared compounds, we have identified some

Table 2. In vitro binding affinity of (benzimidazolyl)piperazines at 5-HT_{1A} receptors (K_i values are means ± SEM of two to four assays, performed in triplicate. Inhibition curves were analyzed by a computer-assisted-curve-fitting program (Prism GraphPad) and K_i values were determined from Cheng–Prusoff equation)



Compound	R	Position of piperazine	R′	K_i (nM)±SEM
4b	CH_3	4	Tr	>1000
4c	H	4	Tr	>1000
13	CH_3	4(7)	H	4.72±0.50
14	H	4(7)	H	27.0±1.7
9a	H	6	Tr	>1000
9b	CH_3	6	Tr	>1000
15	H	5(6)	H	>1000
16	CH_3	5(6)	H	>1000
(±)-**11**		4	Tr	36.7±4.6
(±)-**12**		6	Tr	>1000
(±)-**17**		4(7)	H	1.21±0.02
(±)-**18**		5(6)	H	>1000

(benzimidazol-4(7)-yl)piperazines as novel and potent 5-HT_{1A} receptor ligands. The synthesis of new analogues bearing this innovative pharmacophoric moiety, assessment for 5-HT_{1A} receptor affinity and further pharmacological characterization of selected products are in progress in our laboratory, and the results will be published in due course.

Experimental

Synthesis

All reagents were the commercial products purchased from Aldrich, Fluka or Strem Chemicals. All solvents were distilled prior to use. Anhydrous toluene was obtained by distillation over CaH_2. Analytical TLC was carried out on Merck (Kieselgel 60F-254) silica gel plates with detection by UV light, iodine and acidic vanillin solution. Melting points were determined on a Gallenkamp apparatus and are uncorrected. Infrared spectra (IR) were obtained on an FTIR-8300 Shimadzu spectrophotometer. Nuclear magnetic resonance spectra were recorded on a Varian VXR-300S, Bruker AM-300 and Bruker AM-200. Low resolution mass spectra were recorded by direct injection on an HP5989A EI (70 eV). Elemental analyses were carried out on a Perkin–Elmer 2400 apparatus at the Facultad de Farmacia, UCM.

1-Benzyl-4-bromobenzimidazole, 2a and 1-benzyl-1-bromobenzimidazole, 2b. To a solution of **1** (175 mg, 0.9 mmol) in anhydrous THF (2.6 mL) at 0°C, 60% NaH in mineral oil (40.5 mg, 0.99 mmol) was added under an argon atmosphere. After 30 min stirring, benzyl chloride (0.11 mL, 0.99 mmol) and a catalytic amount of *n*-Bu_4NI were added, and the mixture was refluxed for 5 h. The mixture was then cooled down, hydrolyzed with H_2O (2 mL/mmol) and extracted with $CHCl_3$ (3×50 mL). The extracts were dried over Na_2SO_4 and evaporated to dryness in vacuo. Purification of the crude by column chromatography on silica gel, using mixtures of CH_2Cl_2/EtOAc as eluent, rendered an 80/20 mixture of **2a** (white solid, yield: 48%) and **2b** (white solid, yield: 20%). Data of **2a**; R_f=0.6 (CH_2Cl_2/EtOAc, 8/1). mp: 114–116°C ($CHCl_3$/hexane). IR (KBr, cm^{-1}): 3060–3000, 1495, 1450, 1430, 1270, 1195, 780. ^1H NMR ($CDCl_3$-δ): 7.91 (s, 1H, H_2), 7.38 (d, 1H, H_5, J=7.5 Hz), 7.26–7.23 (m, 3H, benzyl), 7.12 (d, 1H, H_7, J=7.5 Hz), 7.09–7.06 (m, 2H, benzyl), 7.05 (t, 1H, H_6, J=7.5 Hz), 5.23 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$-δ): 143.6 (C_2), 142.5 (C_{3a}), 134.9 (benzyl/C_{7a}), 134.4 (C_{7a}/benzyl), 128.8 (benzyl), 128.2 (benzyl), 126.8 (benzyl), 125.3 (C_5/C_6), 124.0 (C_6/C_5), 113.8 (C_4), 109.6 (C_7), 49.2 (CH_2). Data of **2b**; R_f=0.5 (CH_2Cl_2/EtOAc, 8/1). IR (KBr, cm^{-1}): 2990–2910, 1560, 1500, 1440, 1280, 1170, 725. ^1H NMR ($CDCl_3$-δ): 7.83 (s, 1H, H_2), 7.72 (d, 1H, H_4, J=7.8 Hz), 7.36 (d, 1H, H_6, J=7.8 Hz), 7.31–7.27 (m, 3H, benzyl), 7.08 (t, 1H, H_5, J=7.8 Hz), 7.08–7.02 (m, 2H, benzyl), 5.72 (s, 2H, CH_2). ^{13}C NMR ($CDCl_3$-δ): 145.7 (C_2), 142.9 (C_{3a}), 137.5 (C_{7a}), 128.8 (benzyl), 127.9 (C_6), 126.9 (benzyl), 126.4 (benzyl), 123.5 (C_5), 120.0 (C_4), 109.3 (C_7), 49.8 (CH_2).

4-Bromo-1-tritylbenzimidazole, 3. To a solution of **1** (1 g, 5.1 mmol) in anhydrous THF (25 mL) at 0°C, 60% NaH in mineral oil (252 mg, 6.1 mmol) was added under an argon atmosphere. After 30 min stirring, TrCl (1.9 g, 6.6 mmol) and a catalytic amount of *n*-Bu_4NI were added, and the mixture was refluxed for 5 h. The mixture was then cooled down, hydrolyzed with H_2O (2 mL/mmol) and extracted with $CHCl_3$ (3×50 mL). The extracts were dried over Na_2SO_4 and evaporated to dryness in vacuo. Purification of the crude by column chromatography on silica gel rendered **3** (90%) as a white solid. R_f=0.2 ($CHCl_3$). mp: 225–227°C (EtOAc). IR ($CHCl_3$, cm^{-1}): 3030–3080, 1440, 1420, 1300, 1210, 700. ^1H NMR ($CDCl_3$-δ): 7.94 (s, 1H, H_2), 7.36–7.28 (m, 10H, trityl), 7.19–7.13 (m, 6H, trityl, H_5), 6.76 (t, 1H, H_6, J=8.1 Hz), 6,42 (d, 1H, H_7, J=8.1 Hz). ^{13}C NMR ($CDCl_3$-δ): 144.5 (C_2), 143.2 (C_{3a}), 140.9 (trityl), 135.3 (C_{7a}), 130.0 (trityl), 128.3 (trityl), 128.2 (trityl), 125.2 (C_5/C_6), 123.3 (C_6/C_5), 114.8 (C_7), 113.6 (C_4), 75.9 (trityl). MS (*m*/*z*): 243 (100%), 228, 215, 198, 165, 117, 90, 63.

5-Bromo-1-tritylbenzimidazole, 7a and 6-bromo-1-tritylbenzimidazole, 7b. From **6a** (6 g, 30 mmol), NaH (1.4 g, 36 mmol) and TrCl (11.2 g, 39 mmol), following the procedure reported for **3**, a 50/50 mixture of **7a** and **7b** (white solids) was obtained. Separation was performed by column chromatography (silica gel) using mixtures of hexane/EtOAc as eluent. Yield: **7a** (45%), **7b** (40%). Data of **7a**; R_f=0.6 (hexane/EtOAc, 1/1). mp: 232–234°C (toluene/hexane). IR (KBr, cm^{-1}): 3440, 1490, 1475, 1450, 1220, 700. ^1H NMR ($CDCl_3$-δ): 7.93 (d, 1H, H_4, J=1.8 Hz), 7.88 (s, 1H, H_2), 7.36–7.28 (m, 10H, trityl), 7.22–7.12 (m, 5H, trityl), 7.00 (dd, 1H, H_6, J=8.8, 1.8 Hz), 6.34 (d, 1H, H_7, J=8.8 Hz). ^{13}C RMN ($CDCl_3$-δ): 146.0 (C_{3a}), 145.1 (C_2), 141.0 (trityl), 133.8 (C_{7a}), 129.9 (trityl), 128.3 (trityl), 128.2 (trityl), 125.5 (C_4/C_6), 123.1 (C_6/C_4), 116.5 (C_7), 115.3 (C_5), 75.5 (trityl). Data of **7b**; R_f=0.4 (hexane/EtOAc, 1/1). mp: 234–236°C (toluene/hexane). IR (KBr, cm^{-1}): 3060, 1600, 1490, 1450, 1280, 700. ^1H NMR ($CDCl_3$-δ): 7.87 (s, 1H, H_2), 7.60 (d, 1H, H_4, J=8.8 Hz), 7.37–7.31 (m, 10H, trityl), 7.25 (dd, 1H, H_5, J=8.8, 2.5 Hz), 7.19–7.11 (m, 5H, trityl), 6.58 (d, 1H, H_7, J=2.5 Hz). ^{13}C NMR ($CDCl_3$-δ): 144.7 (C_2), 143.6 (C_{3a}), 140.9 (trityl), 135.8 (C_{7a}), 129.9 (trityl), 128.3 (trityl), 128.2 (trityl), 125.6 (C_4/C_5), 121.5 (C_5/C_4), 118.0 (C_7), 115.7 (C_6), 75.7 (trityl). MS (*m*/*z*): 243 (100%), 228, 215, 198, 165, 120, 90, 63.

5-Iodo-1-tritylbenzimidazole, 8a. From **6b** (470 mg, 1.9 mmol), NaH (95 mg, 2,3 mmol) and TrCl (663 mg, 2.3 mmol), following the procedure reported for **3**, a 50/50 mixture of **8a** (46%, white solid) and its isomer 6-iodo-1-tritylbenzimidazole (**8b**) was obtained. Separation was performed by column chromatography (silica gel) using mixtures of hexane/EtOAc as eluent. Data of **8a**; R_f=0.4 (hexane/EtOAc, 3/1). mp: 242–244°C (MeOH/Et_2O). IR ($CHCl_3$, cm^{-1}): 3020, 2400, 1605, 1490, 1480, 1450, 1280, 1035, 865, 850, 650, 630. ^1H NMR ($CDCl_3$-δ): 8.14 (s, 1H, H_2), 7.84 (s, 1H, H_4), 7.35–7.27 (m, 10H, trityl), 7.18–7.14 (m, 6H, trityl, H_6), 6.23 (d, 1H, H_7, J=8.7 Hz). ^{13}C NMR ($CDCl_3$-δ): 146.4 (C_{3a}), 144.6 (C_2), 140.9 (trityl), 134.3 (C_{7a}), 130.9 (C_4/C_6), 129.8 (trityl), 129.3 (C_6/C_4), 128.2 (trityl), 128.1 (trityl), 117.0 (C_7), 85.7 (C_5), 75.6 (trityl). MS (*m*/*z*): 243 (100%), 228, 215, 198, 165, 139, 115, 91, 63, 51. Partial data of **8b** (from crude mixture):[19] R_f=0.3 (hexane/EtOAc, 3/1).^1H NMR ($CDCl_3$-δ): 7.82 (s, 1H, H_2), 7.53 (d, 1H, H_4, J=8.5 Hz), 7.44 (dd, 1H, H_5,

J=8.5, 1.2 Hz), 7.37–7.32. (m, 10H, trityl), 7.17–7.13 (m, 5H, trityl), 6.76 (d, 1H, H_7, J=1.2 Hz). ^{13}C NMR ($CDCl_3$-δ): 141.0 (C_2), 131.2 (C_{3a}/C_{7a}), 129.9 (trityl), 129.3 (C_{7a}/C_{3a}), 128.3 (trityl), 128.2 (trityl), 127.3 (C_5/C_7), 124.1 (C_7/C_5), 122.0 (C_4), 86.3 (C_6), 75.7 (trityl).

General procedure for the palladium catalyzed amination of halobenzimidazoles

To a solution of 1 equiv. of the corresponding bromobenzimidazole in toluene (10 mL×mmol), under an argon atmosphere, amine (1.2–6 equiv.), base (1.4–2 equiv.), palladium catalyst (0.02–0.1 equiv.) and phosphine (0.04–0.15 equiv.) were added. The mixture was heated at 85°C (2–10 h), and when TLC showed complete disappearance of the starting material the mixture was cooled down and filtered through a short column of Celite. The resulting solution was evaporated to dryness under vacuum. The crude mixture was purified by column chromatography on silica gel using the appropriate eluent.

1-(1-Tritylbenzimidazol-4-yl)morpholine, 4a. From **3** (50 mg, 0.12 mmol), morpholine (0.012 mL, 0.14 mmol), NaO^{t}Bu (15.8 mg, 0.16 mmol), Pd_2dba_3·$CHCl_3$ (2.4 mg, 0.0023 mmol), dppp (2 mg, 0.0046 mmol) and toluene (1.2 mL) was obtained **4a** (yield: 65%, white solid) after chromatography using mixtures of hexane/EtOAc as eluent. R_f=0.3 (hexane/EtOAc, 3/1). mp: 196–198°C ($CHCl_3$/hexane). IR (KBr, cm^{-1}): 3060–3010, 1590, 1495, 1445, 1250, 1200. ^{1}H NMR ($CDCl_3$-δ): 7.79 (s, 1H, H_2), 7.25–7.19 (m, 10H, trityl), 7.13–7.08 (m, 5H, trityl), 6.80 (t, 1H, H_6, J=8.0 Hz), 6.52 (d, 1H, H_5, J=8.4 Hz), 6.08 (d, 1H, H_7, J=7.5 Hz), 3.98 (m, 4H, $2CH_2$-O), 3.54 (m, 4H, $2CH_2$-N). ^{13}C NMR ($CDCl_3$-δ): 143.5 (C_4), 141.7 (C_2), 141.2 (trityl), 136.7 (C_{3a}/C_{7a}), 136.0 (C_{7a}/C_{3a}), 129.9 (trityl), 128.0 (trityl), 127.9 (trityl), 122.8 (C_6), 108.9 (C_5/C_7), 107.1 (C_7/C_5), 75.4 (trityl), 67.2 ($2CH_2$-O), 50.6 ($2CH_2$-N). MS (m/z): 445 (M), 243 (100%), 228, 203, 172, 165, 145, 118, 105, 91, 63.

1-(1-Tritylbenzimidazol-4-yl)-4-methylpiperazine, 4b. From **3** (150 mg, 0.34 mmol), 1-methylpiperazine (0.05 mL, 0.41 mmol), NaO^{t}Bu (47.5 mg, 0.48 mmol), Pd_2dba_3·$CHCl_3$ (36 mg, 0.034 mmol) or $Pd(OAc)_2$ (7.63 mg, 0.034 mmol), dppp (22 mg, 0.05 mmol) and toluene (4 mL) was obtained **4b** (yield: 97%, pale yellow solid) after chromatography using mixtures of $CHCl_3$/EtOH as eluent. R_f=0.3 ($CHCl_3$). mp: 217–219°C (CH_2Cl_2/hexane). IR (KBr, cm^{-1}): 3050–3000, 1590, 1500, 1485, 1240, 1000, 700. ^{1}H NMR ($CDCl_3$-δ): 7.71 (s, 1H, H_2), 7.23–7.19 (m, 10H, trityl), 7.12–7.09 (m, 5H, trityl), 6.70 (t, 1H, H_6, J=8.0 Hz), 6.46 (d, 1H, H_5, J=7.8 Hz), 5.99 (d, 1H, H_7, J=8.3 Hz), 3.51 (m, 4H, $2CH_2$-N), 2.63 (m, 4H, $2CH_2$-N), 2.26 (s, 3H, CH_3-N). ^{13}C NMR ($CDCl_3$-δ): 143.5 (C_4), 141.5 (C_2), 141.2 (trityl), 136.5 (C_{3a}/C_{7a}), 135.9 (C_{7a}/C_{3a}), 129.9 (trityl), 127.9 (trityl), 127.8 (trityl), 122.7 (C_6), 108.6 (C_5/C_7), 107.3 (C_7/C_5), 75.2 (trityl), 55.3 ($2CH_2$-N), 50.0 ($2CH_2$-N), 46.2 (CH_3-N). Anal. calculated for $C_{31}H_{30}N_4$: C, 81.19%; H, 6.59%; N, 12.22%. Found: C, 80.92%; H, 6.75%; N, 12.08%.

1-(1-Tritylbenzimidazol-4-yl)piperazine, 4c. From **3** (1.0 g, 2.28 mmol), piperazine (1.2 g, 13.7 mmol), NaO^{t}Bu (316 mg, 3.2 mmol), Pd_2dba_3·$CHCl_3$ (47 mg, 0.046 mmol), (±)-BINAP (82 mg, 0.136 mmol) and toluene (22 mL) was obtained **4c** (yield: 87%, pale yellow solid) after chromatography using mixtures of toluene/EtOH as eluent. R_f=0.3 (toluene/EtOH/NH_3, 9/1/0.1). mp: 104–108°C. IR (KBr, cm^{-1}): 3650–3340, 1590, 1490, 1445, 1235, 1090. ^{1}H NMR ($CDCl_3$-δ): 7.79 (s, 1H, H_2), 7.34–7.25 (m, 10H, trityl), 7.21–7.17 (m, 5H, trityl), 6.77 (t, 1H, H_6, J=7.8 Hz), 6.51 (d, 1H, H_5, J=7.8 Hz), 6.08 (d, 1H, H_7, J=8.4 Hz), 3.50 (m, 4H, $2CH_2$-N), 3.14 (m, 4H, $2CH_2$-N). ^{13}C NMR ($CDCl_3$-δ): 143.8 (C_4), 141.2 (C_2), 141.0 (trityl), 136.5 (C_{3a}/C_{7a}), 135.7 (C_{7a}/C_{3a}), 129.7 (trityl), 127.7 (trityl), 127.6 (trityl), 122.5 (C_6), 108.3 (C_5/C_7), 107.0 (C_7/C_5), 75.0 (trityl), 51.1 ($2CH_2$-N), 46.0 ($2CH_2$-N). Anal. calculated for $C_{30}H_{28}N_4$: C, 81.05%; H, 6.35%; N, 12.60%. Found: C, 81.31%; H, 6.68%; N, 12.40%.

***N*-(1-Tritylbenzimidazol-4-yl)aniline, 4e.** From **3** (44 mg, 0.1 mmol), aniline (53 mg, 0.12 mmol), NaO^{t}Bu (13.4 mg, 0.14 mmol), Pd_2dba_3·$CHCl_3$ (2 mg, 0.002 mmol), (±)-BINAP (4 mg, 0.006 mmol) and toluene (1 mL) was obtained **4e** (yield: 54%, yellow oil) after chromatography using mixtures of $CHCl_3$/EtOAc as eluent. R_f=0.4 ($CHCl_3$/EtOAc, 9.5/1). IR (KBr, cm^{-1}): 3410, 3020, 2925, 1615, 1590, 1495, 1370, 1215, 755. ^{1}H NMR ($CDCl_3$-δ): 7.71 (s, 1H, H_2), 7.34–7.27 (m, 10H, trityl), 7.25–7.19 (m, 7H, trityl, $2H_{3'}$), 7.02 (d, 1H, H_5, J=7.3 Hz), 6.93–6.86 (m, 3H, $2H_{2'}$, $H_{4'}$), 6.75 (t, 1H, H_6, J=8.1 Hz), 5.93 (d, 1H, H_7, J=8.1 Hz). ^{13}C NMR ($CDCl_3$-δ): 142.1 ($C_{1'}$, C_4), 142.0 (C_2), 141.4 (trityl), 135.4 (C_{3a}/C_{7a}), 135.0 (C_{7a}/C_{3a}), 130.4 ($C_{3'}$), 129.2 (trityl), 128.1 (trityl), 128.0 (trityl), 123.1 (C_6), 121.4 ($C_{4'}$), 119.0 ($C_{2'}$), 106.8 (C_5/C_7), 104.1 (C_7/C_5), 75.6 (trityl). MS (m/z): 451 (M), 351, 282, 243 (100%), 228, 209, 165, 141, 119, 84, 57.

1-(1-Tritylbenzimidazol-6-yl)piperazine, 9a. From **7b** (550 mg, 1.25 mmol), piperazine (441 mg, 5.01 mmol), Cs_2CO_3 (572 mg, 1.75 mmol), $Pd(OAc)_2$ (28 mg, 0.12 mmol), (±)-BINAP (241 mg, 0.38 mmol) and toluene (12 mL) was obtained **9a** (yield: 60%, white solid) after chromatography using mixtures of toluene/EtOH/NH_3 as eluent. R_f=0.3 (toluene/EtOH/NH_3, 9/1/0.1). mp: 136–139°C. IR ($CHCl_3$, cm^{-1}): 3400–3200, 3060, 2950, 1670, 1600, 1490, 1230. ^{1}H NMR ($CDCl_3$-δ): 7.74 (s, 1H, H_2), 7.61 (d, 1H, H_4, J=8.7 Hz), 7.29–7.26 (m, 10H, trityl), 7.16–7.13 (m, 5H, trityl), 6.85 (dd, 1H, H_5, J=8.7, 1.8 Hz), 5.83 (d, 1H, H_7, J=1.8 Hz), 3.67 (br s, 1H, NH), 2.89 (m, 4H, $2CH_2$-N), 2.72 (m, 4H, $2CH_2$-N). ^{13}C NMR ($CDCl_3$-δ): 147.5 (C_6), 143.2 (C_2), 141.3 (trityl), 139.1 (C_{3a}), 135.4 (C_{7a}), 130.1 (trityl), 128.1 (trityl), 128.0 (trityl), 120.1 (C_4), 116.2 (C_5/C_7), 114.6 (C_7/C_5), 77.2 (trityl), 50.8 ($2CH_2$-N), 45.3 ($2CH_2$-N). MS (m/z): 444 (M), 243 (100%), 228, 202, 165, 146, 120, 85, 71, 57.

1-(1-Tritylbenzimidazol-6-yl)-4-methylpiperazine, 9b. From **7b** (300 mg, 0.68 mmol), 1-methylpiperazine (82 mg, 0.82 mmol), Cs_2CO_3 (312 mg, 0.95 mmol), $Pd(OAc)_2$ (2 mg, 0.01 mmol), (±)-BINAP (25 mg, 0.04 mmol) and toluene (4 mL) was obtained **9b** (yield: 55%, white solid) after chromatography using mixtures of toluene/EtOH/NH_3 as eluent. R_f=0.3 (toluene/EtOH/NH_3, 10/1/0.1). mp: 228–230°C. IR ($CHCl_3$, cm^{-1}): 3020, 2940, 2810, 1620, 1600, 1490, 1480, 1290, 1260. ^{1}H NMR ($CDCl_3$-δ): 7.72 (s, 1H, H_2), 7.60 (d, 1H, H_4, J=9.0 Hz), 7.30–7.26 (m, 10H, trityl), 7.17–7.14 (m, 5H, trityl), 6.86 (dd, 1H, H_5, J=9.0, 2.1 Hz),

5.83 (d, 1H, H_7, J=2.1 Hz), 3.20 (t, 4H, $2CH_2$-N, J=5.1 Hz), 2.57 (t, 4H, $2CH_2$-N, J=5.1 Hz), 2.34 (s, 3H, CH_3-N). ^{13}C NMR ($CDCl_3$-δ): 147.3 (C_6), 143.1 (C_2), 141.3 (trityl), 138.9 (C_{3a}), 135.3 (C_{7a}), 130.0 (trityl), 129.8 (trityl), 128.0 (trityl), 120.0 (C_4), 114.6 (C_7), 77.2 (trityl), 54.7 ($2CH_2$-N), 50.2 ($2CH_2$-N), 45.8 (CH_3-N).

2-[4-[4-(1-Tritylbenzimidazol-4-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (±)-11. To a solution of (±)-**10** (62 mg, 0.23 mmol) and NEt_3 (0.2 mL) in acetonitrile (2 mL, 10 mL×mmol) was added 100 mg of **4c** (0.23 mmol). The mixture was stirred at 60°C during 24 h, and when TLC (toluene/EtOH/NH_3, 9/1/0.1) showed complete disappearance of the starting materials the solvent was removed under vacuum. The resulting crude mixture was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. (±)-**11** (white solid) was obtained in 80% yield after purification by chromatography on silica gel using mixtures of $CHCl_3$/MeOH as eluent. R_f=0.3 ($CHCl_3$/MeOH, 9/1). mp: 98–100°C. IR (KBr, cm^{-1}): 3600–3400, 1775, 1710, 1590, 1490, 1440, 1410, 1235. ^{1}H NMR ($CDCl_3$-δ): 7.71 (s, 1H, $H_{2'}$), 7.25–7.13 (m, 10H, trityl), 7.12–7.08 (m, 5H, trityl), 6.70 (t, 1H, $H_{6'}$, J=8.0 Hz), 6.45 (d, 1H, $H_{5'}$, J=7.6 Hz), 5.99 (d, 1H, $H_{7'}$, J=8.0 Hz), 4.01 (dd, 1H, H_{7a}, J=9.0, 7.4 Hz), 3.8–3.5 (m, 7H, $1H_5$, CH_2-N, $2CH_2$-pip), 3.24–3.11 (m, 1H, $1H_5$), 2.65 (br s, 4H, $2CH_2$-pip), 2.38 (t, 2H, CH_2-N, J=7.4 Hz), 2.20–2.11 (m, 1H, $1H_7$), 2.07–1.98 (m, 2H, $2H_6$), 1.71–1.56 (m, 5H, $1H_7$, $2CH_2$). ^{13}C NMR ($CDCl_3$-δ): 173.3 (C_1), 160.2 (C_3), 143.0 ($C_{4'}$), 141.0 ($C_{2'}$), 140.7 (trityl), 136.1 ($C_{3'a}$/$C_{7'a}$), 135.3 ($C_{7'a}$/$C_{3'a}$), 129.4 (trityl), 127.4 (trityl), 127.3 (trityl), 122.3 ($C_{6'}$), 108.1 ($C_{5'}$/$C_{7'}$), 106.8 ($C_{7'}$/$C_{5'}$), 76.4 (trityl), 62.7 (C_{7a}), 57.5 (CH_2-N), 52.8 ($2CH_2$-pip), 44.9 ($2CH_2$-pip), 44.9 (C_5), 38.2 (CH_2-N), 27.0 (C_7), 26.4 (C_6), 25.5 (CH_2), 23.3 (CH_2). Anal. calculated for $C_{40}H_{42}N_6O_2$: C, 75.21%; H, 6.63%; N, 13.16%. Found: C, 75.47%; H, 6.62%; N, 13.32%.

2-[4-[4-(1-Tritylbenzimidazol-6-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (±)-12. To a solution of (±)-**10** (160 mg, 0.56 mmol) and NEt_3 (0.6 mL) in acetonitrile (5 mL, 10 mL×mmol) was added 100 mg of **9c** (0.23 mmol). The mixture was stirred at 60°C during 19 h, and when TLC (EtOH) showed complete disappearance of the starting materials the solvent was removed under vacuum. The resulting crude mixture was dissolved in CH_2Cl_2 and washed with H_2O. The organic layer was dried over anhydrous Na_2SO_4, filtered and the solvent was evaporated. (±)-**12** (white solid) was obtained in 63% yield after purification by chromatography on silica gel using mixtures of EtOH/EtOAc as eluent. R_f=0.3 ($CHCl_3$/MeOH, 9/1). mp: 126–128°C (toluene). IR ($CHCl_3$, cm^{-1}): 3670–3500, 3060, 2950, 1770, 1710, 1600, 1495, 1450, 1275. ^{1}H NMR ($CDCl_3$-δ): 7.72 (s, 1H, $H_{2'}$), 7.59 (d, 1H, $H_{4'}$, J=8.8 Hz), 7.24–7.17 (m, 10H, trityl), 7.12–7.07 (m, 5H, trityl), 6.82 (dd, 1H, $H_{5'}$, J=8.8, 2.0 Hz), 5.82 (d, 1H, $H_{7'}$, J=2.0 Hz), 4.03 (dd, 1H, H_{7a}, J=9.1, 7.3 Hz), 3.70–3.56 (m, 1H, $1H_5$), 3.50–3.40 (m, 2H, CH_2-N), 3.24–3.11 (m, 1H, $1H_5$), 2.76–2.71 (m, 4H, $2CH_2$-pip), 2.43–2.40 (m, 4H, $2CH_2$-pip), 2.35–2.26 (m, 2H, CH_2-N), 2.22–2.12 (m, 1H, $1H_7$), 2.10–1.98 (m, 2H, $2H_6$), 1.70–1.40 (m, 5H, $1H_7$, $2CH_2$). ^{13}C NMR ($CDCl_3$-δ): 173.9 (C_1), 160.8 (C_3), 147.4 ($C_{6'}$), 143.1 ($C_{2'}$), 141.3 (trityl), 139.0 ($C_{3'a}$), 135.4 ($C_{7'a}$), 130.2 (trityl), 129.0 (trityl), 127.9 (trityl), 120.1 ($C_{4'}$), 116.0 ($C_{5'}$/$C_{7'}$), 114.6 ($C_{7'}$/$C_{5'}$), 75.2 (trityl), 63.3 (C_{7a}), 57.9 (CH_2-N), 53.1 ($2CH_2$-pip), 50.3 ($2CH_2$-pip), 45.5 (C_5), 38.8 (CH_2-N), 27.5 (C_7), 26.9 (C_6), 26.0 (CH_2), 23.9 (CH_2). MS (m/z): 639 (M), 396, 243 (100%), 215, 175, 165, 125, 86, 70, 56. Anal. calculated for $C_{40}H_{42}N_6O_2$: C, 75.21%; H, 6.63%; N, 13.16%. Found: C, 75.47%; H, 6.89%; N, 13.02%.

General procedure for trityl group removal

A solution of the corresponding (1-tritylbenzimidazolyl)-piperazine (1 equiv.) in THF (7.5 mL×mmol), H_2O (7.5 mL×mmol) and AcOH (7.5 mL×mmol) was refluxed for 3 h (TLC). After cooling, the mixture was brought to pH=1–2 by addition of 1 M HCl, and then extracted with EtOAc. The aqueous layer was basified to pH=9–10 by addition of solid K_2CO_3 and extracted with CH_2Cl_2. The organic extracts were dried (Na_2SO_4) and the solvent was evaporated under vacuum. Purification of the crude was performed by column chromatography using the appropriate eluent.

1-(Benzimidazol-4(7)-yl)-4-methylpiperazine, 13. From **4b** (155 mg, 0.34 mmol) in THF (2.5 mL), H_2O (2.5 mL) and AcOH (2.5 mL) was obtained **13** (yield: 86%, yellow solid) after chromatography using MeOH as eluent. R_f=0.3 (MeOH). mp: 71–73°C (EtOAc/hexane). IR ($CHCl_3$, cm^{-1}): 3500–3100, 1610, 1590, 1450, 1250, 1140, 1000. ^{1}H NMR ($CDCl_3$-δ): 10.20 (br s, NH), 7.95 (s, 1H, H_2), 7.20–6.90 (m, 2H, H_5, H_7), 6.67 (d, 1H, H_6, J=7.4 Hz), 3.51 (s, 4H, $2CH_2$-N), 2.62 (s, 4H, $2CH_2$-N), 2.31 (s, 3H, CH_3-N). ^{13}C NMR ($CDCl_3$-δ): 142.9 (C_4), 138.9 (C_2), 135.9 (C_{3a}/C_{7a}), 134.1 (C_{7a}/C_{3a}), 123.5 (C_6), 55.0 ($2CH_2$-N), 50.1 ($2CH_2$-N), 45.9 (CH_3-N). MS (m/z): 216 (M, 100%), 201, 173, 160, 146, 132, 118, 90, 85, 70, 56. Anal. calculated for $C_{12}H_{16}N_4$: C, 66.64%; H, 7.46%; N, 25.90%; Found: C, 66.46%; H, 7.34 %; N, 25.79%.

1-(Benzimidazol-4(7)-yl)piperazine, 14. From **4c** (200 mg, 0.45 mmol) in THF (3.5 mL), H_2O (3.5 mL) and AcOH (3.5 mL) was obtained **14** (yield: 66%, yellow solid) after chromatography using MeOH as eluent. R_f=0.2 ($CHCl_3$/MeOH/NH_3, 3/3/0.1). mp: 132–135°C (EtOH/Et_2O). IR (KBr, cm^{-1}): 3600–3300, 3080, 2920, 1590, 1510, 1450, 1300. ^{1}H NMR ($CDCl_3$-δ): 7.94 (s, 1H, H_2), 7.18–7.08 (m, 2H, H_5, H_7), 6.66–6.60 (m, 1H, H_6), 3.34 (m, 4H, $2CH_2$-N), 2.98 (m, 4H $2CH_2$-N). ^{13}C NMR ($CDCl_3$-δ): 142.8 (C_4), 138.8 (C_2), 136.0 (C_{3a}/C_{7a}), 133.3 (C_{7a}/C_{3a}), 123.4 (C_6), 108.2 (C_5/C_7), 106.5 (C_7/C_5), 51.3 ($2CH_2$-N), 45.7 ($2CH_2$-N). Anal. calculated for $C_{11}H_{14}N_4$: C, 65.32%; H, 6.98%; N, 27.70%; Found: C, 65.02%; H, 7.05 %; N, 27.62%.

1-(Benzimidazol-5(6)-yl)piperazine, 15. From **9a** (138 mg, 0.31 mmol) in THF (2.3 mL), H_2O (2.3 mL) and AcOH (2.3 mL) was obtained **15** (yield: 58%, white solid) after chromatography using mixtures of $CHCl_3$/MeOH/NH_3 as eluent. R_f=0.2 ($CHCl_3$/MeOH/NH_3, 5/5/0.1). mp: 126–128°C. IR (KBr, cm^{-1}): 3020–2960, 1710, 1640, 1600, 1570, 1520, 1450, 1260, 1220. ^{1}H NMR ($CDCl_3$-δ): 7.92 (s, 1H, H_2), 7.55 (d, 1H, H_4, J=9.2 Hz), 7.04 (d, 1H, H_7, J=2.4 Hz), 6.98 (dd, 1H, H_5, J=9.2, 2.4 Hz), 3.15 (m, 4H, $2CH_2$-N), 2.99 (m, 4H, $2CH_2$-N), 1.64 (br s, 1H, NH). ^{13}C

NMR ($CDCl_3$-δ): 146.5 (C_6), 144.8 (C_2), 141.4 (C_{3a}), 134.8 (C_{7a}), 116.1 (C_5/C_7), 113.1 (C_7/C_5), 100.8 (C_4), 56.3 ($2CH_2$-N), 50.5 ($2CH_2$-N). Anal. calculated for $C_{11}H_{14}N_4$: C, 65.32%; H, 6.98%; N, 27.70%; Found: C, 65.30%; H, 7.16 %; N, 27.66%.

1-(Benzimidazol-5(6)-yl)-4-methylpiperazine, 16. From **9b** (90 mg, 0.20 mmol) in THF (1.5 mL), H_2O (1.5 mL) and AcOH (1.5 mL) was obtained **16** (yield: 65%, white solid) after chromatography using mixtures of $CHCl_3$/MeOH as eluent. R_f=0.2 ($CHCl_3$/MeOH, 1/1). mp: 82–84°C. IR (KBr, cm^{-1}): 3020–2950, 1710, 1670, 1630, 1590, 1510, 1450, 1220. ^1H NMR ($CDCl_3$-δ): 7.92 (s, 1H, H_2), 7.53 (d, 1H, H_4, J=8.8 Hz), 7.05 (d, 1H, H_7, J=2.1 Hz), 7.01 (dd, 1H, H_5, J=8.8, 2.1 Hz), 3.17 (m, 4H, $2CH_2$-N), 2.61 (m, 4H, $2CH_2$-N), 2.35 (s, 3H, CH_3-N). ^{13}C NMR ($CDCl_3$-δ): 148.5 (C_6), 146.1 (C_2), 140.1 (C_{3a}), 135.1 (C_{7a}), 116.3 (C_5/C_7), 115.3 (C_7/C_5), 103.1 (C_4), 55.1 ($2CH_2$-N), 50.7 ($2CH_2$-N), 45.9 (CH_3-N). Anal. calculated for $C_{12}H_{16}N_4$: C, 66.64%; H, 7.46%; N, 25.90%; Found: C, 66.81%; H, 7.28 %; N, 26.00%.

2-[4-[4-(Benzimidazol-4(7)-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (±)-17. From (±)-**11** (110 mg, 0.24 mmol) in THF (1.8 mL), H_2O (1.8 mL) and AcOH (1.8 mL) was obtained (±)-**17** (yield: 85%, white solid) after chromatography using mixtures of $CHCl_3$/MeOH as eluent. R_f=0.2 ($CHCl_3$/EtOH, 9/1). mp: 160–163°C (acetone/hexane). IR ($CHCl_3$, cm^{-1}): 3450–3100, 1770, 1705, 1610, 1485, 1350, 1300. ^1H NMR ($CDCl_3$-δ): 7.96 (s, 1H, $H_{2'}$), 7.20–7.08 (m, 2H, $H_{5'}$, $H_{7'}$), 6.66 (d, 1H, $H_{6'}$, J=6.9 Hz), 4.05 (t, 1H, H_{7a}, J=8.4 Hz), 3.70–3.61 (m, 1H, $1H_5$), 3.47 (m, 6H, CH_2-N, $2CH_2$-pip), 3.24–3.18 (m, 1H, $1H_5$), 2.70 (br s, 4H, $2CH_2$-pip), 2.44 (t, 2H, CH_2-N, J=7.5 Hz), 2.24–2.19 (m, 1H, $1H_7$), 2.10–2.01 (m, 2H, $2H_6$), 1.70–1.50 (m, 5H, $1H_7$, $2CH_2$). ^{13}C NMR ($CDCl_3$-δ): 174.0 (C_1), 160.8 (C_3), 142.6 ($C_{4'}$), 138.5 ($C_{2'}$), 135.9 ($C_{3'a}$/$C_{7'a}$), 133.5 ($C_{7'a}$/$C_{3'a}$), 120.6 ($C_{6'}$), 108.7 ($C_{5'}$/$C_{7'}$), 106.5 ($C_{7'}$/$C_{5'}$), 63.3 (C_{7a}), 57.9 (CH_2-N), 53.1 ($2CH_2$-pip), 50.0 ($2CH_2$-pip), 45.5 (C_5), 38.8 (CH_2-N), 27.5 (C_7), 27.0 (C_6), 26.0 (CH_2), 23.6 (CH_2). MS (*m*/*z*): 396 (M), 379, 250, 237, 215, 200, 187, 173, 146, 132, 118, 98, 83, 70, 55. Anal. calculated for $C_{21}H_{28}N_6O_2$: C, 63.62%; H, 7.12%; N, 21.20%; Found: C, 63.59%; H, 7.15%; N, 21.10%.

2-[4-[4-(Benzimidazol-5(6)-yl)piperazin-1-yl]butyl]-1,3-dioxoperhydropyrrolo[1,2-*c*]imidazole, (±)-18. From (±)-**12** (54 mg, 0.086 mmol) in THF (0.7 mL), H_2O (0.7 mL) and AcOH (0.7 mL) was obtained (±)-**18** (yield: 65%, white solid) after chromatography using mixtures of $CHCl_3$/EtOH as eluent. R_f=0.2 ($CHCl_3$/EtOH, 9/1). mp: 138–140°C (toluene). IR (KBr, cm^{-1}): 3400–3200, 1770, 1710, 1590, 1450, 1420. ^1H NMR ($CDCl_3$-δ): 7.94 (s, 1H, $H_{2'}$) 7.51 (d, 1H, $H_{4'}$, J=8.7 Hz), 7.00 (m, 1H, $H_{5'}$), 6.95 (d, 1H, $H_{7'}$, J=1.8 Hz), 4.12–4.02 (m, 1H, H_{7a}), 3.69–3.58 (m, 1H, $1H_5$), 3.50–3.46 (m, 2H, CH_2-N), 3.27–3.17 (m, 1H, $1H_5$), 3.16–3.10 (m, 4H, $2CH_2$-pip), 2.60–2.55 (m, 4H, $2CH_2$-pip), 2.43–2.37 (m, 2H, CH_2-N), 2.28–2.17 (m, 1H, $1H_7$), 2.09–2.00 (m, 2H, $2H_6$), 1.68–1.48 (m, 5H, $1H_7$, $2CH_2$). ^{13}C NMR ($CDCl_3$-δ): 174.0 (C_1), 160.8 (C_3), 148.4 ($C_{6'}$), 140.1 ($C_{2'}$), 139.5 ($C_{3'a}$), 135.5 ($C_{7'a}$), 116.8 ($C_{5'}$/$C_{7'}$), 115.3 ($C_{7'}$/$C_{5'}$), 101.3 ($C_{4'}$), 63.3 (C_{7a}), 57.8 (CH_2-N), 53.2 ($2CH_2$-pip), 50.7 ($2CH_2$-pip), 45.5 (C_5), 38.7 (CH_2-N), 27.5 (C_7), 27.0 (C_6), 25.9 (CH_2), 23.7 (CH_2). MS (*m*/*z*): 396 (M), 381, 250 (100%), 200, 172, 160, 145, 117, 98, 83, 70, 56. Anal. calculated for $C_{21}H_{28}N_6O_2$: C, 63.62%; H, 7.12%; N, 21.20%; Found: C, 63.75%; H, 7.03%; N, 21.22%.

Radioligand binding assays at 5-HT_{1A} receptor

Male Sprague-Dawley rats (*Rattus norvegicus albinus*), weighing 180–200 g, were killed by decapitation and the brains rapidly removed and dissected. Tissues were stored at −80°C for subsequent use. Membrane suspensions were centrifugated on a Beckman XL-90.

Binding assays were performed by a modification of the procedure previously described by Clark et al.[17] The cerebral cortex was homogenized in 10 volumes of ice-cold 50 mM Tris–HCl buffer (pH 7.7 at 25°C) and centrifuged at 28000 *g* for 15 min. The membrane pellet was washed once by resuspension and centrifugation. The resuspended pellet was incubated at 37°C for 10 min. Membranes were then collected by centrifugation, and the final pellet was resuspended in 50 mM Tris–HCl, 5 mM $MgSO_4$, and 0.5 mM EDTA buffer (pH 7.4 at 25°C). Fractions of 100 μL of the final membrane suspension (about 5 mg/mL of protein) were incubated at 37°C for 15 min with 0.6 nM [^{3}H]-8-OH-DPAT (8-hydroxy-2-(di-*n*-propylamino)tetralin) (133 C_i/mmol), in the presence or absence of several concentrations (10^{-5}–10^{-10} M) of the competing drug, in a final volume of 1.1 mL of assay buffer (50 mM Tris–HCl, 10 nM clonidine, 30 nM prazosin, pH 7.4 at 25°C). Nonspecific binding was determined with 10 μM 5-HT and represented less than 15% of the total binding. Competing drug, nonspecific, total and radioligand bindings were defined in triplicate. Incubation was terminated by rapid vacuum filtration through Whatman GF/C filters, using a Brandel harvester, and the filters were washed twice with 4 mL of ice-cold 50 mM Tris–HCl (pH 7.4 at 25°C). The filters were placed in poly(ethylene) vials to which were added 4 mL of a scintillation cocktail (Ecolite), and the radioactivity bound to the filters was measured by liquid scintillation spectrometry on a Packard 2500 TR instrument. The data were analyzed by using an iterative curve-fitting procedure (program Prism, Graphpad), which provided IC_{50}, K_i and r^2 values for test compounds, K_i values being calculated from the Cheng and Prusoff equation.[18] The protein concentrations of the rat cerebral cortex were determined by the method of Lowry[20] with bovine serum albumin as the standard.

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