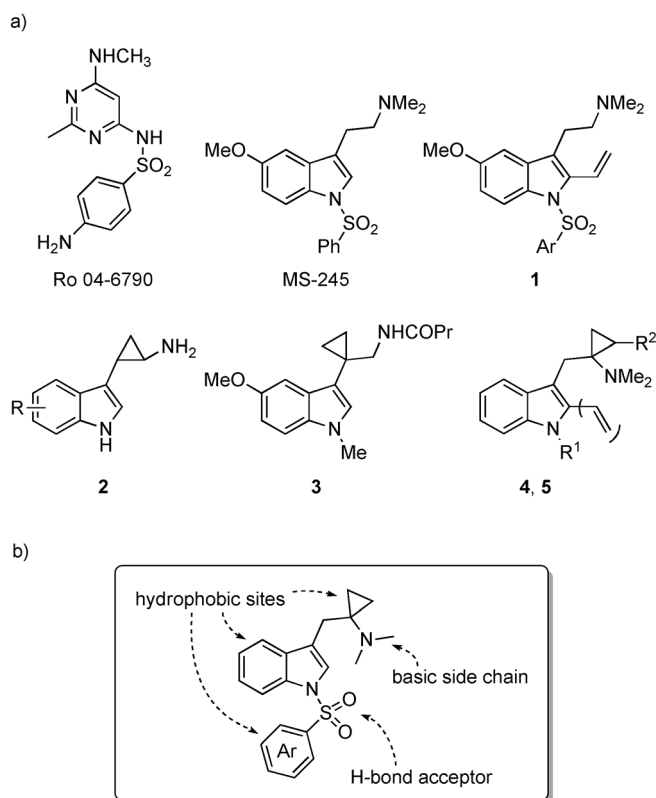# Cyclopropyl-tryptamine Analogues: Synthesis and Biological Evaluation as 5-HT6 Receptor Ligands

Claude Szalata,[a] Jan Szymoniak,[a] Frédéric Fabis,[b] Sabrina Butt-Gueulle,[b] Sylvain Rault,[b] Philippe Bertus,*[c] Stéphane Gérard,*[a] and Janos Sapi[a]

Serotonin (5-hydroxytryptamine, 5-HT) is an important neurotransmitter that produces its effects via interaction with 5-HT receptors and serotonin the transporter (SERT). At least seven distinct serotonin receptor subclasses are expressed in the mammalian central nervous system (CNS).[1] Among these families, 5-HT6 is the most recently discovered and cloned member. Rat and mouse 5-HT6 receptors were described in 1993 and 1994, respectively,[2,3] while the human 5-HT6 receptor (h5-HT6) was firstly reported in 1996.[4] This subtype was then identified as member of the G-protein-coupled receptor superfamily, positively coupled to an adenylate cyclase second messenger system, and mainly localized in the CNS. On account of its possible implication in serious CNS disorders, including depression, anxiety and schizophrenia, this receptor represents an interesting therapeutic target.

In recent years, several 5-HT6-selective ligands have been reported.[5] For example, the bismethylaminopyrimidinyl sulfonamide Ro 04-6790[6] and the N_1-benzenesulfonyltryptamine derivative MS-245[7] were identified as the first 5-HT6 antagonists (Figure 1a). Subsequently, a series of piperazinyl-benzenesulfonamide-derived antagonists SB-271046, SB-258585 and SB-357134 were disclosed,[8] and the first non-sulfonamide antagonist was reported by Riemer et al.[9] In continuation of our preliminary work on the synthesis of N-arylsulfonyl-2-vinyltryptamines (1) possessing promising 5-HT6 binding activity,[10] we chose to introduce conformational restrictions on the structure to try to increase the potency and/or selectivity. Cyclopropyl rings are commonly used in drug design for this purpose,[11,12] and some examples of serotonin analogues incorporating a cyclopropyl moiety are known. For instance, compounds 2 were tested for their affinity against 5-HT1A and 5-HT2 receptors,[13] while more recently, melatonin analogue 3 was used to investi-

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Supporting information for this article is available on the WWW under
http://dx.doi.org/10.1002/cmdc.201200396.

Figure 1. a) Structure of known serotonin receptor ligands and the proposed tryptamine analogues. b) Design of cyclopropyl-tryptamine analogues as 5-HT6 receptor ligands.

gate the nature of the binding site of the melatonin receptor (Figure 1a).[14]

Herein, we describe the synthesis of the first representatives of a new class of tryptamine derivatives 4 and 5 bearing a cyclopropyl ring on the α-position of the tryptamine side chain. This design, summarized in Figure 1b, reflects the main components of a 5-HT6 ligand, that is, the presence of a protonatable nitrogen (the tertiary cyclopropyl amine) in addition to two hydrophobic areas (indole and aryl moieties) separated by a hydrogen-bond acceptor (sulfonamide moiety).[15] We expected that the presence of a three-membered ring would increase both the hydrophobic area and the conformational restriction around the tertiary nitrogen leading to improved efficacy and/or subtype selectivity.
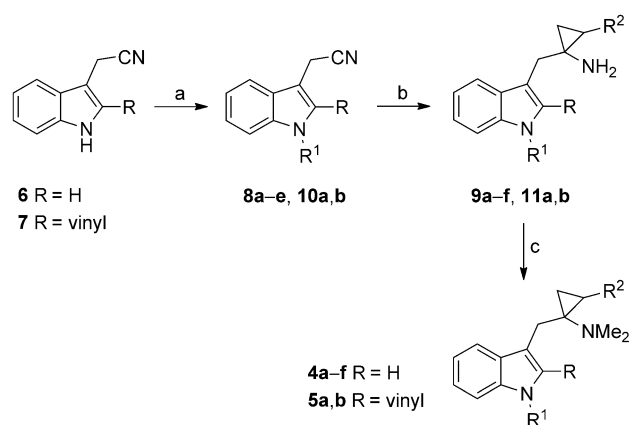
The synthesis of diversely substituted tryptamine analogues 4a–f was achieved starting from commercially available indol-3-ylacetonitriles 6.[16] The synthetic route followed is shown in Scheme 1, and the yields and substituents of both intermedi-

Scheme 1. Preparation of tryptamine analogues **4a–f** and **5a,b**. *Reagents and conditions*: a) NaOH, CH_2Cl_2/H_2O (2:1), 0 °C, 15 min; then MeI, BnBr or $ArSO_2Cl$, RT, 12 h; b) $R^2(CH_2)_2MgBr$, MeTi(OiPr)$_3$, THF, RT, 1.5 h; then $BF_3 \cdot OEt_2$, RT, 30 min; c) $NaBH_3CN$, AcOH, MeOH, 0 °C, 5 min; then HCHO, 0 °C, 1.5 h.

ates and final compounds are given in Table 1. Firstly, substitution on the indole nitrogen was performed by treatment of the nitriles with sodium hydroxide in a biphasic system at

Table 1. Structures and isolated yields of intermediary and final compounds shown in Scheme 1.

R	R^1	R^2	Step a		Step b		Step c	
					Product (Yield [%])			
H	Bn	H	**8a**	(72)	**9a**	(46)	**4a**	(92)
H	$PhSO_2$	H	**8b**	(39)	**9b**	(66)	**4b**	(82)
H	p-MeC$_6$H$_4$SO$_2$	H	**8c**	(37)	**9c**	(59)	**4c**	(97)
H	p-ClC$_6$H$_4$SO$_2$	H	**8d**	(60)	**9d**	(53)	**4d**	(88)
H	2-NaphthylSO$_2$	H	**8e**	(45)	**9e**	(65)	**4e**	(94)
H	$PhSO_2$	Et	–	–	**9f**[a]	(58)	**4f**[b]	(94)
Vinyl	Me	H	**10a**	(69)	**11a**	(40)	**5a**	(76)
Vinyl	Bn	H	**10b**	(75)	**11b**	(47)	**5b**	(60)

[a] 60:40 Mixture of diastereoisomers. [b] Reaction performed with (*cis*)-**9f**.

room temperature in the presence of methyl iodide, benzyl bromide or arylsulfonyl chlorides. The corresponding N-functionalized indolylacetonitriles (**8a–e**) were isolated in 37–72% yields after purification by column chromatography or crystallization. We next turned to the titanium-mediated cyclopropanation step.[17] While this reaction has been previously studied with a variety of nitriles, including carbohydrates,[18] to the best of our knowledge, the use of nitriles bearing indole or sulfonamide moieties is unprecedented. After initial optimization steps,[16] we found that the use of 1.5 equivalents of the alkyltitanium reagent, MeTi(OiPr)$_3$[19] and 1.5 equivalents of ethylmagnesium bromide in tetrahydrofuran (THF), followed by the addition of boron trifluoride diethyl etherate led to the total consumption of the starting nitriles and gave the corresponding primary cyclopropylamines **9a–e** in 40–66% yields. Use of *n*-butylmagnesium bromide instead of ethylmagnesium bromide afforded the cyclopropylamine **9f**, bearing an additional sub-

stitution at the cyclopropyl ring. The final step involved the efficient convertion of primary cyclopropylamines **9a–f** to the corresponding N,N-dimethyl analogues using the formaldehyde/sodium cyanoborohydride/acetic acid/methanol system to furnish functionalized tryptamines **4a–f** in good yields (82–97%).[20] This sequence was also applied for the synthesis of 2-vinyl analogues (**5**) from 2-vinyl-indol-3-ylacetonitrile (**7**), prepared according to a well-known method.[21] Cyclopropanation was found to be compatible with the additional vinyl moiety, and the corresponding cyclopropylamines **11a** and **11b** were obtained in 40% and 47% yield, respectively. Reductive amination with formaldehyde afforded the targeted compounds **5a** and **5b**.

All synthesized compounds were evaluated against 5-HT$_{1A}$, 5-HT$_4$ and 5-HT$_6$ receptors (Table 2). Results were expressed as a percentage of radioligand binding inhibition in the presence of compounds at 10^{-6} M (1 μM) concentration and at 10^{-8} M (10 nM) for the most potent ones.

Initial structure–activity relationship development showed that all of the N,N-dimethyl arylsulfonyltryptamines bearing a cyclopropyl ring on the α-position of the ethylamine side chain (**4b–e**) exhibited similar activities and selectivities, with interesting percent inhibition values at 1 μM against the 5-HT$_6$ receptor. The affinities (K_i) of these cyclopropyl analogues for the 5-HT$_6$ receptor were determined to between 0.12 μM and 0.14 μM (**4b–d**), except for compound **4e**, with a more bulky naphthyl substituent that exhibited a K_i value of 0.53 μM (Table 2). Contrary to our initial expectation, the weak affinity observed could be explained by a more limited conformational flexibility and an increasing hydrophobic character of the modified ethylamine side chain.[22] In addition, it could also be the consequence of a slightly lower pK_a value of cyclopropylamines.[23, 24] Increasing the hydrophobicity by ethyl substitution on the three-membered ring (compound **4f**) drastically decreased the affinity of **4f** for serotonin receptors.

Next, our attention turned to the N-substituent of the indole ring (R^1). An arylsulfonyl moiety in this position was considered to be optimal as benzyl derivative **4a** ($K_i = 1.38$ μM) was approximately tenfold less potent than the corresponding sulfonylated analogue (**4b**; $K_i = 0.12$ μM), suggesting that a H-bond acceptor in this position is essential for affinity. Interestingly, this functionality can be omitted without significant loss of potency when a vinyl group is present at the 2-position of the indole system (**5b**; $K_i = 0.19$ μM). Replacing the benzyl substituent with a less hydrophobic methyl group dramatically decreases the pharmacological effect of the vinyl containing derivatives (**5a** vs **5b**); compound **5a** was found to be practically inactive at concentrations in the micromolar range.

The more active cyclopropyl-tryptamine was 4-chlorobenzenesulfonyl derivative **4d**, exhibiting 87% inhibition of 5-HT$_6$ at 1 μM, with both a K_i and IC$_{50}$ value of approximately 0.15 μM. Derivative **4d** displayed good selectivity for 5-HT$_6$ over the other serotonin receptors evaluated (5-HT$_{1A}$ and 5-HT$_4$). However, **4d** is around tenfold less active than the previously described benzenesulfonyl-2-vinyltryptamine (**1**, Ar = Ph).[10]

In conclusion, N,N-dimethyltryptamine analogues bearing a cyclopropyl ring on the α-position of the tryptamine side

Table 2. Biological evaluation of cyclopropyl-tryptamine analogues against 5-HT receptors.[a]

Compd	R^1	R^2	R	5-HT$_{1A}$ @1 µM	5-HT$_{1A}$ @10 nM	5-HT$_4$ @1 µM	5-HT$_4$ @10 nM	5-HT$_6$ @1 µM	5-HT$_6$ @10 nM	K_i[c] [µM] 5-HT$_6$	IC$_{50}$[c] [µM] 5-HT$_6$
4a	Bn	H	H	–	–	–	–	22	0	1.38	0.67
4b	SO$_2$Ph	H	H	0	–	5	–	78	3	0.12	0.16
4c	pMeC$_6$H$_4$SO$_2$	H	H	0	–	11	0	81	2	0.14	0.43
4d	pClC$_6$H$_4$SO$_2$	H	H	0	–	6	–	87	22	0.13	0.16
4e	2-NaphthylSO$_2$	H	H	0	–	5	–	88	1	0.53	1.10
4f	SO$_2$Ph	Et	H	–	–	–	–	40	0	1.87	0.59
5a	Me	H	Vinyl	–	–	–	–	18	0	9.86	5.27
5b	Bn	H	Vinyl	21	1	13	7	74	0	0.19	0.37
1[10]				–	–	22	1	97	45	0.016	0.0058
MS-245[10]				–	–	14	0	90	24	0.0041	NR

[a] Experimental protocols are given in the Supporting Information. [b] Compounds were evaluated at the concentration stated for their ability to inhibit radioligand binding: [^{3}H]8-hydroxy-2-(di-n-propylamino)tetralin (8-OH-DPAT) at 2 nM (5-HT$_{1A}$); [^{3}H]GR 113808 at 0.6 nM (5-HT$_4$); [^{3}H]lysergic acid diethylamide (LSD) at 2 nM (5-HT$_6$). Data are the result of a single experiment. –: not determined. [c] Inhibition constant (K_i) and the concentration required to inhibit 50 % radioligand binding (IC$_{50}$) calculated according to the Cheng–Prusoff equation. Data represent the mean ± SD of three experiments.

chain were prepared in just a few steps from substituted 3-indolylacetonitriles through a titanium-mediated cyclopropanation and evaluated as potential 5-HT$_6$ receptor ligands. Among the prepared compounds, the N,N-dimethyl-1-arylsulfonyltryptamine derivatives exhibited promising selectivity for 5-HT$_6$ over 5-HT$_{1a}$ and 5-HT$_4$ receptors and interesting activity against 5-HT$_6$ (K_i = ~0.15 µM; IC$_{50}$ = ~0.20 µM). Other structural modifications are currently under investigation to enhance the activity of this new class of compounds.

Acknowledgements

Keywords: conformational restriction · inhibitors · structure–activity relationships · serotonin receptors · tryptamines

[1] D. E. Nichols, C. D. Nichols, Chem. Rev. 2008, 108, 1614–1641.

[2] F. J. Monsma, Jr., Y. Shen, R. P. Ward, M. W. Hamblin, D. R. Sibley, Mol. Pharmacol. 1993, 43, 320–327.

[3] C. D. Unsworth, P. B. Molinoff, J. Pharmacol. Exp. Ther. 1994, 269, 246–255.

[4] R. Kohen, M. A. Metcalf, N. Khan, T. Druck, K. Huebner, J. E. Lachowicz, H. Y. Meltzer, D. Sibley, B. L. Roth, M. W. Hamblin, J. Neurochem. 1996, 66, 47–56.

[5] For Review articles, see a) K. G. Liu, A. J. Robichaud, Drug Dev. Res. 2009, 70, 145–168; b) W. J. Geldenhuys, C. J. Van der Schyf, Curr. Top. Med. Chem. 2008, 8, 1035–1048; c) R. A. Glennon, J. Med. Chem. 2003, 46, 2795–2812; d) J. Holenz, P. J. Pauwels, J. L. Diaz, R. Merce, X. Codony, H. Buschmann, Drug Discovery Today 2006, 11, 283–299; e) S. L. Davies, J. S. Silvestre, X. Guitart, Drugs Future 2005, 30, 479–495.

[6] A. Sleight, F. G. Boess, M. Bös, B. Levet-Trafit, C. Riemer, A. Bourson, Br. J. Pharmacol. 1998, 124, 556–562.

[7] Y. Tsai, M. Dukat, A. Slassi, N. MacLean, L. Demchyshyn, J. E. Savage, B. Roth, S. Hufesein, M. Lee, R. A. Glennon, Bioorg. Med. Chem. Lett. 2000, 10, 2295–2299.

[8] a) S. M. Bromidge, A. M. Brown, S. E. Clarke, K. Dodgson, T. Gager, H. L. Grassam, P. M. Jeffrey, G. Joiner, F. D. King, D. N. Middlemiss, S. F. Moss, H. Newman, G. Riley, C. Routledge, P. Wyman, J. Med. Chem. 1999, 42, 202–205; b) W. D. Hirst, J. A. Minton, S. M. Bromidge, S. F. Moss, A. J. Latter, G. Riley, C. Routledge, D. N. Midlemiss, G. W. Price, Br. J. Pharmacol. 2000, 130, 1597–1605; c) S. M. Bromidge, S. E. Clarke, T. Gager, K. Griffith, P. Jeffrey, A. J. Jennings, G. F. Joiner, F. D. King, P. J. Lovell, S. F. Moss, H. Newman, G. Riley, D. Rogers, C. Routledge, H. Serafinowska, D. R. Smith, Bioorg. Med. Chem. Lett. 2001, 11, 55–58.

[9] C. Riemer, E. Borroni, B. Levet-Trafit, J. R. Martin, S. Poli, R. H. Porter, M. Bos, J. Med. Chem. 2003, 46, 1273–1276.

[10] M. Raoul, D. Patigny, F. Fabis, F. Dauphin, S. Rault, J.-Y. Laronze, J. Sapi, J. Enzyme Inhib. Med. Chem. 2006, 21, 251–260.

[11] For a Review article on the use of cyclopropyl rings in drug design, see: J. Salaün, Top. Curr. Chem. 2000, 207, 1–67, and references cited therein.

[12] a) R. Wise, J. M. Andrews, L. J. Edwards, Antimicrob. Agents Chemother. 1983, 23, 559–564; b) Y. Todo, J. Nitta, M. Miyajima, Y. Fukuoka, Y. Yamashiro, N. Nishida, I. Saikawa, H. Narita, Chem. Pharm. Bull. 1994, 42, 2063–2070; c) K. E. Brighty, M. J. Castaldi, Synlett 1996, 1097–1099; d) M. Högberg, C. Sahlberg, P. Engelhardt, R. Noréen, J. Kangasmetsä, N. G. Johansson, B. Öberg, L. Vrang, H. Zhang, B.-L. Sahlberg, T. Unge, S. Lövgren, K. Fridborg, K. Bäckbro, J. Med. Chem. 1999, 42, 4150–4160; e) S. M. Daluge, M. T. Martin, B. R. Sickles, D. A. Livingston, Nucleosides Nucleotides Nucleic Acids 2000, 19, 297–327; f) M. S. Tichenor, K. S. MacMillan, J. S. Stover, S. E. Wolkenberg, M. G. Pavani, L. Zanella, A. N. Zaid,

G. Spalluto, T. J. Rayl, I. Hwang, P. G. Baraldi, D. L. Boger, *J. Am. Chem. Soc.* **2007**, *129*, 14092–14099.

[13] S. Vangveravong, A. Kanthasamy, V. L. Lucaites, D. L. Nelson, D. E. Nichols, *J. Med. Chem.* **1998**, *41*, 4995–5001.

[14] A. Tsotinis, M. Vlachou, D. P. Papahatjis, T. Calogeropoulou, S. P. Nikas, P. J. Garratt, V. Piccio, S. Vonhoff, K. Davidson, M.-T. Teh, D. Sugden, *J. Med. Chem.* **2006**, *49*, 3509–3519.

[15] D. J. Heal, S. L. Smith, A. Fisas, X. Codony, H. Buschmann, *Pharmacol. Ther.* **2008**, *117*, 207–231.

[16] C. Szalata, J. Sapi, J. Szymoniak, P. Bertus, S. Gérard, *Synlett* **2008**, 1479–1482.

[17] For a Review article dealing with the titanium-mediated cyclopropanation of nitriles, see: P. Bertus, J. Szymoniak, *Synlett* **2007**, 1346–1356.

[18] For examples, see: a) P. Bertus, M. S. M. Pearson, R. Plantier-Royon, J. Szymoniak, J. B. Behr, *Synthesis* **2007**, 3589–3594; b) M. S. M. Pearson, N. Floquet, C. Bello, P. Vogel, R. Plantier-Royon, J. Szymoniak, P. Bertus, J. B. Behr, *Bioorg. Med. Chem.* **2009**, *17*, 8020–8026; c) D. Declerck, A. Nguyen Van Nhien, S. Josse, J. Szymoniak, P. Bertus, C. Bello, P. Vogel, D. Postel, *Tetrahedron* **2012**, *68*, 1802–1809.

[19] For the first use of this reagent in titanium-mediated cyclopropanation reactions, see: V. Chaplinski, H. Winsel, M. Kordes, A. de Meijere, *Synlett* **1997**, 111–114.

[20] L. J. Street, R. Baker, J. L. Castro, M. S. Chambers, A. R. Guiblin, S. C. Hobbs, V. G. Matassa, A. J. Reeve, M. S. Beer, D. N. Middlemiss, A. J. Noble, J. A. Stanton, K. Scholey, R. J. Hargreaves, *J. Med. Chem.* **1993**, *36*, 1529–1538.

[21] J. Sapi, Y. Grébille, J.-Y. Laronze, J. Lévy, *Synthesis* **1992**, 383–386.

[22] The 5-methoxy group was shown to have little impact on affinity in the *N*-sulfonyltryptamine family, as exemplified by the slightly lower activity of des-methoxy MS-245 relative to the parent compound MS-245 ($K_i =$ 4.1 nM vs 2.3 nM). For details, see: a) M. G. Russell, R. J. Baker, L. Barden, M. S. Beer, L. Bristow, H. B. Broughton, M. Knowles, G. McAllister, S. Patel, J. L. Castro, *J. Med. Chem.* **2001**, *44*, 3881–3895; b) M. R. Pullagurla, M. Dukat, V. Setola, B. Roth, R. A. Glennon, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3355–3359.

[23] a) J. D. Roberts, V. C. Chambers, *J. Am. Chem. Soc.* **1951**, *73*, 5030–5034; b) M. L. Gillaspy, B. A. Lefker, W. A. Hada, D. J. Hoover, *Tetrahedron Lett.* **1995**, *36*, 7399–7402.

[24] Theoretical calculations performed with ACD/pK_a version 8.02 (Advanced Chemistry Development, Inc., Toronto, Canada) indicated a pK_a value of 8.46 for **4b**, compared with the pK_a values of 9.30 and 9.22 obtained for demethoxylated analogues of MS-245 and **1**, respectively. L. Dupont-Leclercq, C. Szalata, unpublished results.