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2-Alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles as novel 5-HT$_6$ receptor agonists

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Abstract—A series of 2-alkyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indoles were synthesized and evaluated for their 5-HT$_6$ activity. The most potent agonist in this series was 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole with an IC$_{50}$ = 7.4 nM in ^{3}H-LSD binding and an EC$_{50}$ = 1.0 nM in a functional assay measuring production of cyclic AMP.

1. Introduction

The human 5-hydroxytryptamine$_6$ (5-HT$_6$) receptor is one of the most recently identified members of the serotonergic receptor superfamily; today at least 14 different serotonin receptor subtypes are identified in the mammalian CNS.[1] The 5-HT$_6$ receptor is a G-protein-coupled receptor and positively linked to adenylylcyclase activity. Within the transmembrane region, the human 5-HT$_6$ receptor shows ~30–40% homology to other human 5-HT receptors.[2]

The mRNA of 5-HT$_6$ receptors is predominantly localized in brain regions such as nucleus accumbens, striatum, olfactory tubercle, substantia nigra and hippocampus. The localization together with high affinity at the 5-HT$_6$ receptors for several antipsychotics led to the suggestion that these receptors might play a role in certain types of psychoses and that they can be used as a target in the development of new treatments for schizophrenia.[3] In addition, it has also been speculated that the 5-HT$_6$ receptors are involved in cognition and learning.[4,5]

For the investigation of the functional role of receptors in vivo, selective agonists are widely used as pharmacological tools. However, in the 5-HT$_6$ receptor field, only a few publications have appeared on 5-HT$_6$ receptor agonists (Fig. 1).[6–8] In addition, many of them have also been found to be partial agonists in functional assays measuring the production of cyclic AMP [i.e., LSD (**2**), 2-Br-LSD].[9]

In 2000, Glennon et al. reported on the investigation of the binding of tryptamine derivatives at human 5-HT$_6$ receptors (compounds **3**–**5**, Fig. 1).[6] An interesting finding from this work was that the human 5-HT$_6$ receptors tolerate alkyl groups in the 2-position of the indole ring and that the size of the alkyl group has a strong influence on the pharmacological properties at the 5-HT$_6$ receptors. For example, 2-ethyl-5-methoxy-*N*,*N*-dimethyltryptamine (EMTD, **4**) was found to be a potent and selective 5-HT$_6$ receptor agonist (K_i = 16 nM), while the corresponding phenyl analogue **5** was found to display 5-HT$_6$ receptor antagonist properties.[6]

Substitution on the indole nitrogen with aryl-sulfonyl groups has been reported to yield potent and selective 5-HT$_6$ antagonists (**7** and **9**) or, in a few cases, partial agonists (**8**) at the 5-HT$_6$ receptor.[10–12] However, moving the aryl-sulfonyl group from the indole nitrogen to the indole 5-position generally yields potent and selective 5-HT$_6$ receptor agonists (**10**, **12**, and **13**). Depending on the chemical structure of the amino-alkyl side chain,

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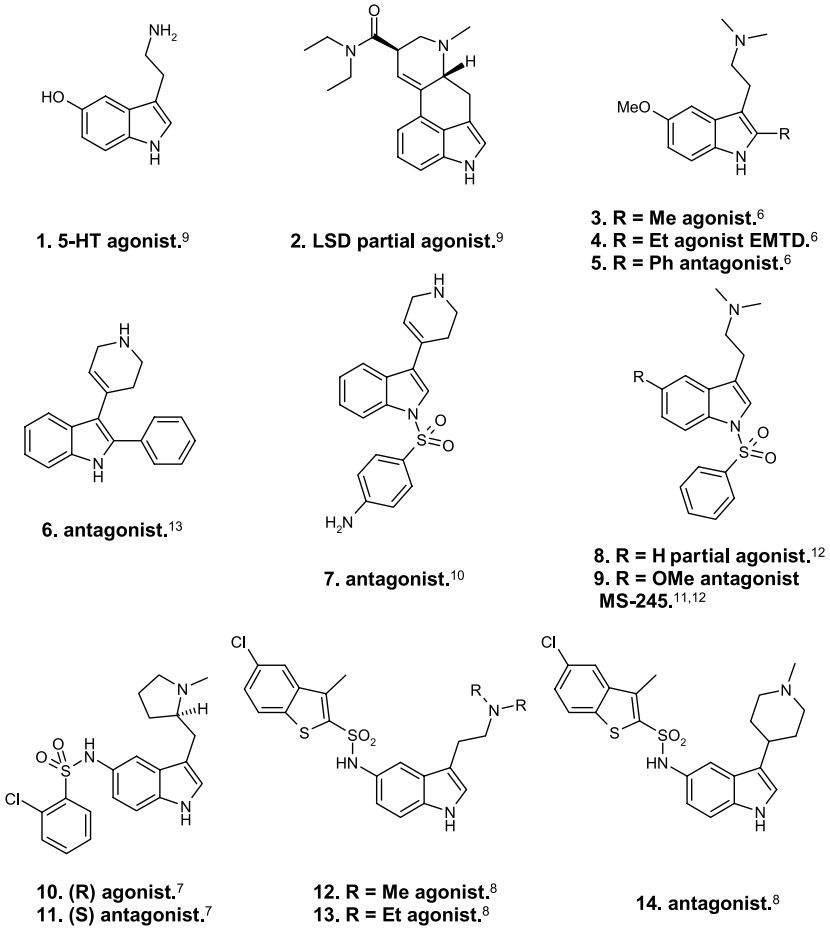


Figure 1. Structures of 5-HT_6 receptor ligands.

antagonists can also be achieved (**11** and **14**).[7,8] For instance, in the 5-arylsulfonamido-3-(pyrrolidin-2-ylmethyl)-1*H*-indole class, the stereochemistry was found to influence the functional activity. The (*R*)-enantiomers (**10**) were found to be potent agonists, while the (*S*)-enantiomers (**11**) displayed antagonist activity.[7]

As part of a medicinal chemistry programme directed towards the design and synthesis of new potent and selective 5-HT_6 receptor agonists for the evaluation of the function of 5-HT_6 receptors in vivo, we performed a high throughput screening on the Merck KGaA chemical library in order to identify new chemical leads. Compound **6** was discovered to be a potent and selective 5-HT_6 receptor ligand (IC_{50} = 2 nM), and when **6** was tested in the cAMP assay, it was found to be a 5-HT_6 receptor antagonist.[13] For the tryptamine series, it is known that the size of the 2-alkyl/aryl group influence the agonist/antagonist property at the 5-HT_6 receptors.[6] Therefore, we speculated that a similar approach could switch compound **6** into agonist properties by replacing the 2-phenyl group with smaller alkyl groups.

Herein, we report on the structure–activity relationship (SAR) for analogues to compound **6** with the aim to find novel 5-HT_6 receptor agonists.

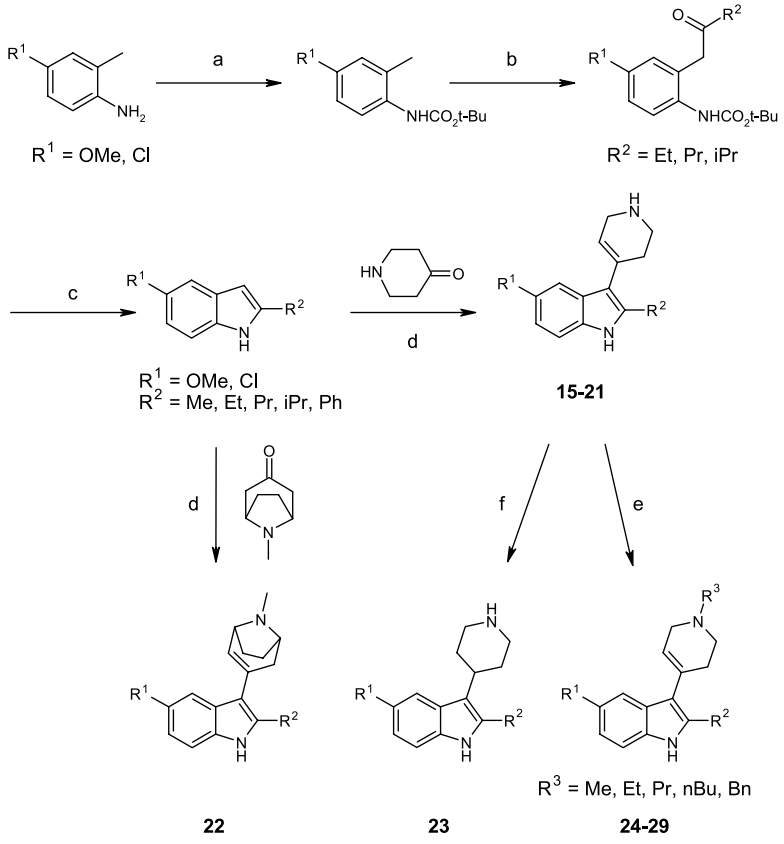
2. Chemistry

The 3-substituted tetrahydropyridine-indoles (**15**–**21** and **24**–**29**), piperidine-indole (**23**) and the 8-azabicyclo[3.2.1]oct-2-en-3-yl-indole (**22**) derivatives were made from the corresponding 2,5-disubstituted indoles according to Scheme 1.[14] Some of these indoles are commercially available and others were made by an improved Madelung synthesis.[15,16]

3. Results and discussion

The affinity of the compounds for human 5-HT_6 receptors, stably expressed in HEK cells, was evaluated.[2] The intrinsic activity (IA) of the compounds at the 5-HT_6 receptor was determined by measuring their effect on cAMP production in BHK cells and compared to the effect elicited by 5-HT.[17] In addition, the potency for the agonists was measured and presented as the EC_{50} level. The results are presented in Tables 1–4. EMTD (**4**) is included for comparative purposes.

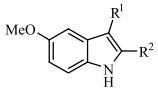
In the first screening campaign, we examined the effect of small alkyl groups in the 2-position on the 5-methoxy-indole scaffold. According to Table 1, the unsubstituted 5-methoxy-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-



Scheme 1. Reagents and conditions: (a) $(t\text{-}BuO_2C)_2O$, THF, heat; (b) 2 equiv *s*-BuLi, $R_2CON(OMe)Me$, THF, −40 °C to room temperature; (c) CF_3CO_2H, CH_2Cl_2; (d) H_3PO_4, AcOH, 80 °C; (e) $NaB(OAc)_3H$, CH_2O, AcOH, THF or R3-X, K_2CO_3, CH_3CN; (f) Pd/C, NH_4HCO_2, EtOH.

indole (RU 24969, known as 5-$HT_{1A/1B}$ agonist, **17**) was found to display moderate affinity to the 5-HT_6 receptors (IC_{50} = 79 nM).[18] In the intrinsic activity assay, this

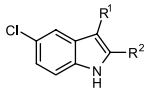
Table 1. 5-HT_6 binding affinity and functional cAMP data for different derivatives of 5-methoxy substituted indoles

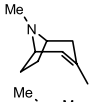


Compound	R^1	R^2	IC_{50} [a] (nM)	EC_{50} [b] (nM)	IA[b] (%)
4[6]		—Et	85 (±15)[c]	710	113
23		—Et	300	ND	ND
15		—Et	90	7.9	100
16[18]		—Me	80	5.8	100
17[18]		—H	79	200	55

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT_6 receptors stably expressed in HEK cells.[2] Single determination.
[b] Stimulation of cAMP production in BHK cells.[17] Single determination. ND, not determined.
[c] Mean of two determination (±SEM).

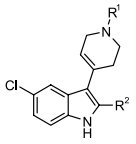
Table 2. 5-HT_6 binding affinity and functional cAMP data for different derivate of 5-chloro substituted indoles



Compound	R^1	R^2	IC_{50} [a] (nM)	EC_{50} [b] (nM)	IA[b] (%)
22		—Me	40	10,000	75
30[20]		—Me	40	16	53
18[19]		—Me	7.4 (±1.6)[c]	1.0 (±0.40)[d]	92[d]
19		—Et	30	ND	ND
20		—Pr	40	ND	ND
21		—*i*Pr	100	ND	ND

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT_6 receptors stably expressed in HEK cells.[2] Single determination.
[b] Stimulation of cAMP production in BHK cells.[17] Single determination. ND, not determined.
[c] Mean of four determination (±SEM).
[d] Mean of three determination (±SEM).

Table 3. Substitution at the basic nitrogen in the 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole moiety



Compound	R^1	R^2	IC_{50} [a] (nM)	EC_{50} [b] (nM)	IA[b] (%)
18[19]	—H	—Me	7.4 (±1.6)[c]	1.0 (±0.40)[d]	92[d]
24[14]	—Me	—Me	10	2.9	152
25	—Et	—Me	30	ND	ND
26	—Pr	—Me	60	ND	ND
27	—*n*Bu	—Me	50	ND	ND
28	—Bn	—Me	600	ND	ND
29	—Et	—Et	70	ND	ND

[a] Displacement of [^{3}H]-LSD binding to cloned h5-HT_6 receptors stably expressed in HEK cells.[2]Single determination.
[b] Stimulation of cAMP production in BHK cells.[17] Single determination. ND, not determined.
[c] Mean of four determination (±SEM).
[d] Mean of three determination (±SEM).

compound turned out to be a partial agonist with low potency (EC_{50} = 200 nM). However, the introduction of a methyl (**16**) or ethyl (**15**) group in the 2-position did not alter affinity but rendered compounds with full agonist properties with high potency (EC_{50} = 5.8 and 7.9 nM, respectively).[18] Interestingly, these compounds were found to be more potent agonists than EMTD (**4**, EC_{50} = 710 nM).[6] The reduction of the piperidene double bond yielded a compound (**23**) with three- to four fold lower affinity for the 5-HT_6 receptors, indicating the importance of a π–π stabilized conformation of the piperidene ring for an optimal interaction with the 5-HT_6 receptors.

A second screening campaign was performed with the 5-chloro-indole scaffold and different 2-alkyl groups. In contrast to the 5-methoxy-indole analogues, the 5-chloro-indole moiety seems to be more sensitive to the size of the 2-alkyl group (Table 2). The affinity trend, when increasing the size and bulkiness of the 2-alkyl group, shows that the optimal size is a methyl group (**18**).[19] Interestingly, this compound proved to be a full and potent agonist at the 5-HT_6 receptors in the cAMP assay with an EC_{50} = 1.0 nM.

Replacing the piperidene ring in **18** with a tropinen ring (**22**) or a dimethyl-aminoethyl side chain (**30**) reduced the affinity, potency and intrinsic activity at 5-HT_6 receptors.[20]

The influence of different *N*-alkyl groups on the 5-HT_6 receptor affinity in the 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole series was also investigated. The data in Table 3 indicate that further improvement in 5-HT_6 receptor affinity is not possible to achieve for this agonist series by increasing the size of the *N*-alkyl group. A bulky group, such as a benzyl, was found to be detrimental to the 5-HT_6 receptor affinity. The data are also in good agreement with data from published 5-HT_6 receptor antagonists, both in the tetrahydropyridine and the tryptamine series.[10,21] The affinity for these 5-HT_6 antagonists was found to be sensitive to increasing the size of the alkyl group on the basic nitrogen.

The 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**18**) was examined further for selectivity against several serotonergic and dopaminergic receptors and compared with EMTD (**4**) (Table 4). The selectivity of compound **18** for 5-HT_6 was greater than 20-fold over 5-HT_{1A}, 5-HT_{1B}, 5-HT_{1D}, 5-HT_{2A}, 5-HT_{2C}, 5-HT_4, 5-HT_7, D_2, D_3, D_4 receptors and the 5-HT transporter protein but showed significant affinity for the 5-HT_3 receptors. By reintroducing the 5-methoxy group (**16**), selectivity against 5-HT_3 can be achieved as shown in the tryptamine series.[6]

In summary, a new class of potent and selective 5-HT_6 receptor agonists has been discovered and they may become useful tools in the investigation of the functional role of 5-HT_6 receptors. By replacing the more flexible amino ethyl side chain in the tryptamine series with a rigidified piperidene ring, potent 5-HT_6 receptor agonists were achieved. The most promising candidate was found to be 5-chloro-2-methyl-3-(1,2,3,6-tetrahydropyridin-4-yl)-1*H*-indole (**18**) having an IC_{50} of 7.4 nM for the 5-HT_6 receptors and in the functional assay, measuring production of cyclic AMP, **18** was found to display full agonist properties with an EC_{50} value of 1.0 nM.

Table 4. Binding affinity for other 5-HT receptors

Compound	IC_{50} [a] (nM)								
	r5-HT_{1A}	r5-HT_{1B}	5-HT_{1D}	h5-HT_{2A}	h5-HT_{2C}	5-HT_3	5-HT_4	h5-HT_6	h5-HT_7
4[6]	>1000	>1000	1400	620	5500	>1000	44	85 ± 15[b]	1500
18[19,e]	660 (±65)[b]	180 (±15)[b]	110 (±3.3)[c]	240 (±5.7)[c]	450 (±23)[c]	34 (±11)[b]	620 (±240)[b]	7.4 (±1.6)[d]	3000 (±700)[b]
16[18]	430	310	>1000	>1000	>1000	>1000	9800	80	9800

[a] Binding methods according to Bartoszyk et al.[22] 5-HT_{1D} (calf), 5-HT_3 (NG 108 cells), 5-HT_4 (guinea pig).[22] Single determination.
[b] Mean of two determination (±SEM).
[c] Mean of three determination(±SEM).
[d] Mean of four determination (±SEM).
[e] hD_2, hD_3 and hD_4 IC_{50} > 1000 nM, 5-HT transporter protein IC_{50} 4500 nM.

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