Binding mode analysis of a series of novel 5-HT$_{1A}$ ligands

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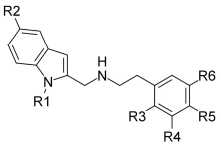
Introduction

The 5-HT$_{1A}$ receptor is one of the most abundant 5-HT receptors in the Central Nervous System. It is coupled to G_i/G_0 and mediates inhibitory neurotransmission. 5-HT$_{1A}$R is expressed both pre- and post-synaptically. It takes part in the regulation of physiological functions such as blood pressure,[1] body temperature,[2] mood,[3] agression[4] and patophysiological processess: depression and anxiety.[5]
Many classical CNS drugs such as an buspirone and tandospirone act as 5-HT$_{1A}$R agonist. Aripiprazole, an atypical antipsychotic, is a partial agonist of 5-HT$_{1A}$ receptor.
Flibanserin, a full 5-HT$_{1A}$R agonist, was orginally developed as an antidepressant. A new indication for the drug is the pre-menopausal hypoactive sexual desire disorder (HSDD).[6] The compound may improve the balance between the neurotransmitter systems in the regulation of sexual response.[7]

Results

A 18 member series of a novel 5-HT$_{1A}$ ligands was developed. The common feature of all the compounds is the indole-2-methyl scaffold attached to the basic nitrogen of the phenylethylamines.
The compounds are highly selective for 5-HT$_{1A}$ receptor.
Interestingly, the *-meta* substituted phenylethylamines exhibited highest affinities for the 5-HT$_{1A}$R. Derivatives of 2,5-dimethoxyphenylethylamine displayed more promiscuous pharmacological profiles while exhibiting much lower 5-HT$_{1A}$R activity.
The compound **1** is a weak partial 5-HT$_{1A}$R agonist (30% agonist response in 10^{-6} M).

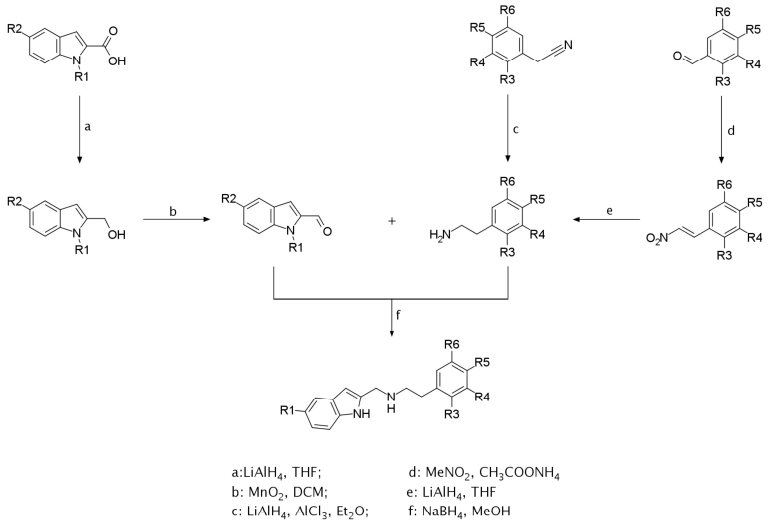
Table 1. *Structure-activity relationship of [(1H-indol-2-yl)methyl](2-phenylethyl)amine derivatives.*



ID	R1	R2	R3	R4	R5	R6	K_i [nM] 5-HT$_1$	5-HT$_{2A}$	5-HT$_6$
1	H	H	H	Cl	H	H	19	2006	475
2	H	H	H	Br	H	H	34	2269	750
3	H	H	H	OMe	H	H	47	2664	2700
4	H	H	H	Me	H	H	52	1995	1360
5	Me	H	H	Cl	H	H	63	3720	1097
6	H	H	H	CF_3	H	H	81	2728	1276
7	H	H	H	F	H	H	160	3981	1252
8	H	H	H	H	Cl	H	173	3422	1605
9	H	H	H	H	H	H	216	3180	1757
10	H	H	H	H	H	H	222	N.D.	780
11	H	H	H	H	F	H	225	N.D.	500
12	H	H	H	Cl	F	H	227	3379	604
13	H	H	OMe	H	H	OMe	398	1617	534
14	H	H	H	H	Me	H	416	2799	2879
15	H	H	Cl	H	H	H	474	1133	1299
16	H	H	OMe	H	Me	OMe	483	339	1566
17	H	OMe	H	Cl	H	H	547	3962	1079
18	H	H	OMe	H	I	OMe	733	394	281

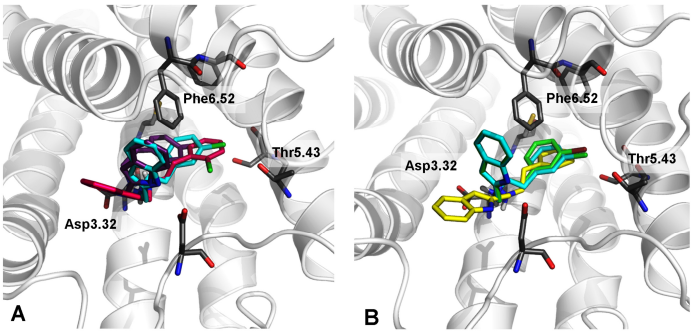
Synthesis

The synthetic pathway is featured in Scheme 1. The aldehydes were obtained from corresponding acids by sequential reduction and oxidation. The arylethylamines were synthesised by reduction of arylacetonitriles. The final reductive amination gave [(1*H*-indol-2-yl)methyl](2-phenylethyl)amines.



Scheme 1. *Synthesis of [(1H-indol-2-yl)methyl](2-phenylethyl)amines.*

Binding mode analysis



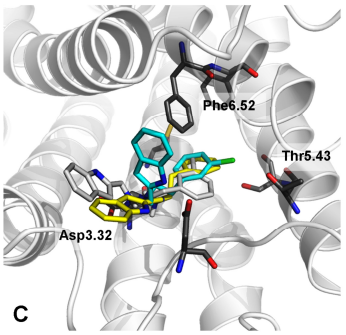


Figure 1. *Representative complexes (top scores based on ΔG) of selected ligands with the 5-HT$_{1A}$ receptor model (based on D_3R crystal template). Amino acids that were selected as crucial for the binding of the presented compounds are shown as sticks.* ***A****: halogen bond formation between the chlorine atom of* ***1*** *(blue) and Thr5.43 in comparison with compounds that do not pass the geometrical criteria to form strong halogen bonds (****15*** *- magenta,* ***8*** *- violet);* ***B****: comparison of binding modes of -Cl and -Br substituted and unsubstituted compounds (****2*** *- green,* ***10*** *- yellow);* ***C****: The binding mode of 3-Me derivative* ***4*** *(silver).*

Acknowledgements

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Databases in this study were created using ChemAxon JChem software.

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