THREE-POINT PHARMACOPHORE INVESTIGATION LEADS TO NOVEL SEROTONERGIC CHEMOTYPES

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Motivation

Alzheimer's Disease (AD) is a devastating neurodegeneratory condition. Recently, the mortality rate for AD has been constantly growing, while the average lifespan after diagnosis has not improved and is estimated at seven years.

Discovered in the early 90's, 5-HT_6 receptor is now an important therapeutic target. Selective 5-HT_6R antagonists have been proposed for treatment of cognitive impairment. Two 5-HT_6R antagonists (Lu AE58054, SB-742457) have completed phase II clinical trials as an augmentation therapy for AD patients till date; several other substances are in phase I.[1]

5-HT_6R blockade induces acetylcholine release which might restore function in deteriorated cholinergic system of AD patients. The receptor is expressed almost exclusively in brain which implicates low probability of peripheral side effects. Moderately selective PET radioligand for the use in humans has been researched (11C-gsk215083). In our efforts to discover new 5-HT_6R ligands of high selectivity and proper ADMET parameters including high BBB permeability we have developed series of compounds incorporating a priviledged structure – indole.

Background and methodology

Over 86% 5-HT_6R ligands contain sulphonyl group. Our idea was to find new non-sulphonyl ligands within chemical space close to a known 5-HT_{2A}R and 5-HT_6R ligand 25I-NBOMe (CIMBI-5). Non-classical bioisosteric substitution led to compound AH-122 (Fig. 1).

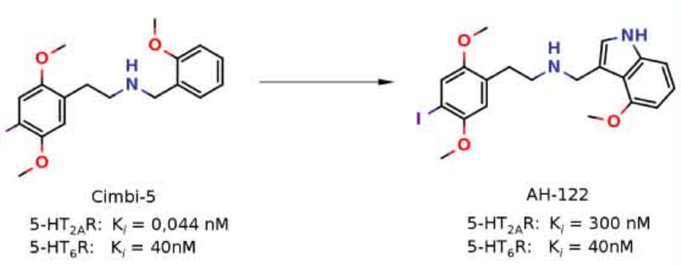
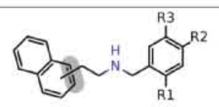
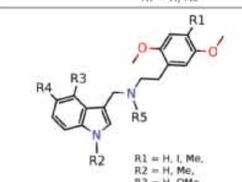
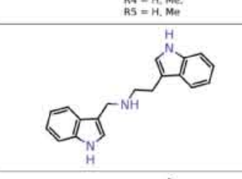
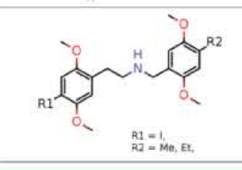


Fig. 1. Non-classical bioisosteric substitution

A concise synthetic protocol has been established: reduction of arylacetonitriles to arylethylamines and subsequent reductive amination with aromatic carboxaldehydes. Diversity of aromatic systems were incorporated into general scaffold. Binding affinities for 5-HT_{1A}, 5-HT_{2A}, 5-HT_6, 5-HT_7 and D_2 receptors were measured in radioligand displacement assays ([^{3}H]-8-OH-DPAT for 5-HT_{1A}R, [^{3}H]-ketanserin for 5-HT_{2A}, [^{3}H]-LSD for 5-HT_6R, [^{3}H]-5-CT for 5-HT_7R and [^{3}H]-raclopride for D_2R). Six distinctive chemotypes have been developed.

Outcome

Tab. 1. Serotonergic chemotypes found in the study.

No.	CHEMOTYPE	Number of entries	K_i range [nM] 5-HT_6	5-HT_{2A}	5-HT_{1A}
1	 1. R1 = R2 = R3 = H, 2. R1 = R2 = OMe, R3 = I, 3. R1 = R2 = H, R3 = CF_3	6	**95 – 952**	225≤	>1000
2	 R1 = H,F, R2 = H,F,CF_3, Cl, R3 = H, F, Cl, Me, R4 = H, Me, R5 = H, OMe, R6 = H, OMe, Br, R7 = H, Me	27	**73≤**	610≤	>1000
3	 R1 = H, I, Me, R2 = H, Me, R3 = H, OMe, R4 = H, OMe, Br, R5 = H, Me	14	**39 – 543**	**10≤**	>1000
4	 R1 = H, F, R2 = H, Cl, CF_3, R3 = H, F, R4 = H, Me, R5 = H, Me	12	281≤	339≤	**19 – 733**
5		1	**20**	172	1531
6	 R1 = I, R2 = Me, Et,	2	**40 – 120**	779 – 963	N. D.

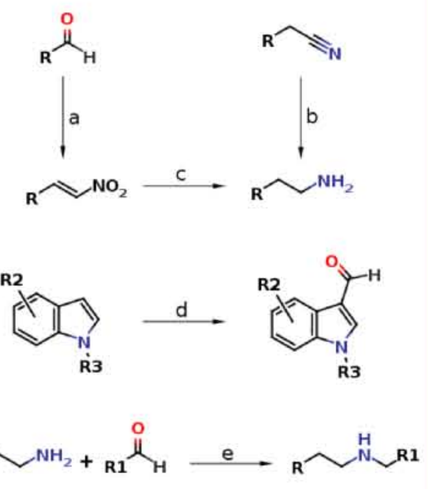


Fig. 2. Synthetic protocol
Conditions:
a) CH_3COONH_4, CH_3NO_2, 100°C
b) $LiAlH_4$, $AlCl_3$, Et_2O, reflux
c) $LiAlH_4$, THF, reflux
d) 1.DMF, $POCl_3$, 0°C, 2.NaOH, heating
e) 1. MeOH, 4Å MS, 2. $NaBH_4$
R = aryl;
R1 = Ph, 1-Naph, 2-Naph, 2-indole, 3-indole;
R2 = H, OMe, Br;
R3 = H, Me

Pharmacophore models

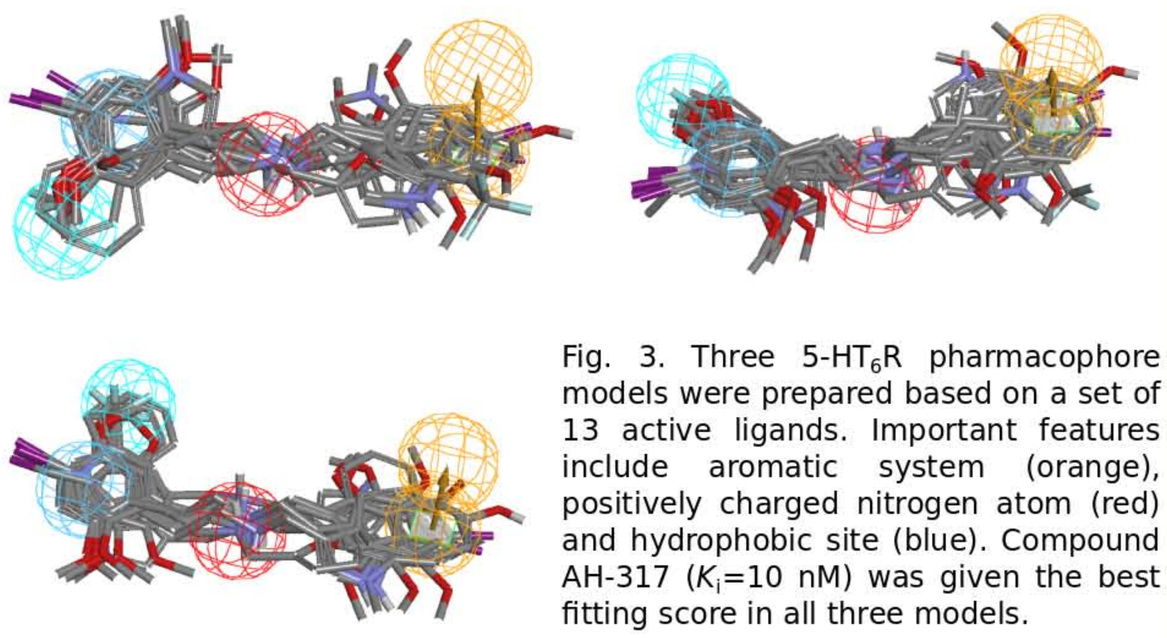


Fig. 3. Three 5-HT_6R pharmacophore models were prepared based on a set of 13 active ligands. Important features include aromatic system (orange), positively charged nitrogen atom (red) and hydrophobic site (blue). Compound AH-317 (K_i=10 nM) was given the best fitting score in all three models.

Summary and outlook

Six groups totalling 62 compounds have been synthesized till date (table 1). Very good selectivity over 5-HT_7 and D_2 receptors was found for all described derivatives. Ligands within groups **1**, **2**, **3** and **6**. exhibit moderate binding affinities towards 5-HT_6 receptor with fair selectivities over related targets. Only one pilot compound from chemotype **5** was synthesized; it shows a strong preferention towards 5-HT_{2A} subtype. Chemotype **4** sets a completely new class of 5-HT_{1A} receptor ligands. Further experiments including functional assays for class **4** hit compound AH-246 (5-HT_{1A}R K_i=19 nM, 5-HT_6R K_i=475 nM) are scheduled. It is probable that we are going to find a mixed 5-HT_6/5-HT_{1A} ligands within N-(2-indolemethyl)phenylethylamines - such substances could preserve 5-HT_{1A} mediated therapeutic potential while exhibiting procognitive properties.

Our study fixed a hole between formerly described serotonergic ligands: N-benzylphenylethylamines[2] and N-benzyltryptamines.[3,4] 5-HT_{2A}R activity remains the main topic of interest for these groups of ligands. Undoubtedly the 5-HT_6R component is present in both series and can be further exploited. Ligands lacking arylsulphonyl moiety show more promising ADMET properties as CNS drugs, partially owing to lower molecular weight.

We plan to investigate the possible binding modes of described compounds by means of docking to homology models. A virtual combinatorial library will be docked to 5-HT_{2A}, 5-HT_{2C} and 5-HT_6 receptor models using Glide software and the results will be compared with SAR and ligand based studies.

References

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