DESIGN AND SYNTHESIS OF AMINERGIC GPCR's LIGANDS

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Motivation

The GPCR superfamily consists of at least 800 genes and is the main therapeutic target in medicinal chemistry.[1] Despite of the rapidly rising amount of available structural data from both crystalographic and NMR studies,[2,3] GPCR's ligand design remains notoriously difficult. Two main approaches towards ligand discovery are: structure based approach (relying on known structure of target protein or on homology models) and ligand based approach (exploiting known ligands chemical space). Hit to lead is a common strategy used to find chemical entities which can enter clinical trials. First an active molecule is searched for (hit). The hit is confirmed and optimized towards high affinity and druglikeness. Chosen lead compound is further tested to check its toxicity, membrane permeability, pharmacological profile, pharmacokinetics.[4]

5-HT_6 receptor is a recently recognized target for the treatment of neurodegeneratory disorders. One compound hit phase III clinical trials, while several are in phase I and phase II as augmentation therapeutics for Alzheimer's disease.[5]

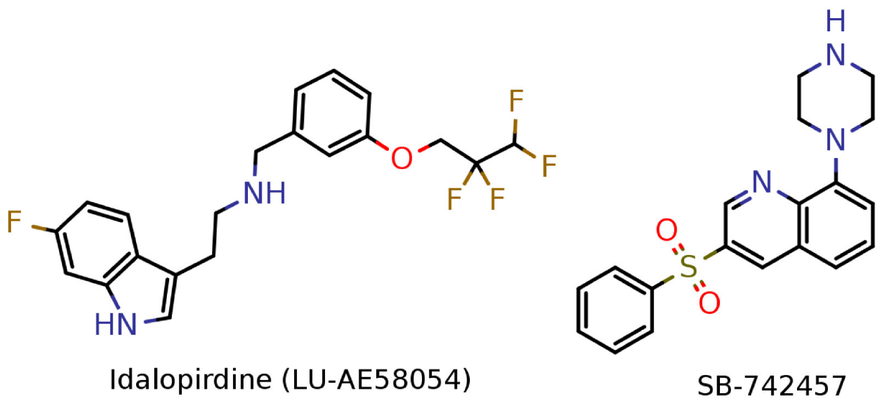

Fig. 1
Compounds which demonstrated efficiency in phase II clinical trials

Background and output

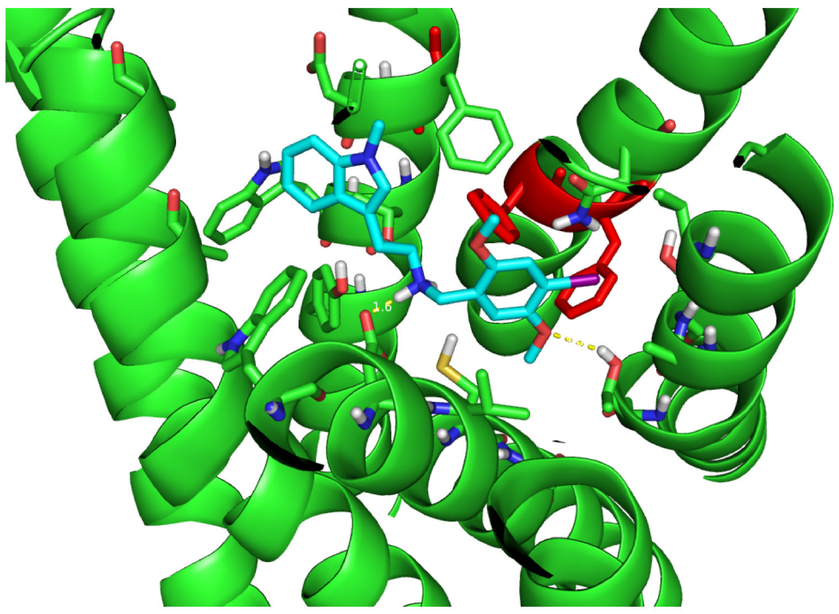

Fig. 2
Compound AH-125 (Serie 2) docked to 5-HT_6R homology model. Residues Phe6.51 and Phe6.52 are shown in red. Hydrogen bonds between ligand and Asp3.32 and Thr5.47 are shown with dashed yellow lines.

Two series of 5-HT_6 receptor ligands have been under developement and intense druglikeness evaluation.

Series 1 constitutes a new class of 5-HT_6 receptor ligands. Most of the 40 compounds in the series exhibit high binding affinity and very promising selectivity. Functional human 5-HT_6R assay confirmed that hit compounds AH-54 and AH-73 are 5-HT_6R antagonists. AMES test revealed no mutagenic properties of AH-54. AH-73 was proved not to block hERG channel in 10μM concentration. CNS screening panel revealed low affinity of AH-54 and AH-100 for muscarinic and adrenergic receptors. Several new compounds of this group are currently under developement.

Compounds of series 2 were readily synthesised in one-pot procedure. 64 compounds which can be divided into 6 chemotypes were evaluated. The compounds exhibit moderate affinities towards 5-HT_6R. Selective 5-HT_{1A}R ligands were discovered within the series. Combinatorial libraries based on the core structure of pilot compounds went through in-silico docking protocol using GPCR homology models and Glide methodology. Highly ranked derivatives are to be synthesised and tested in the search of potent and selective serotonin receptor ligands.

References

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2. http://www.rcsb.org/pdb/home/home.do
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4. Keserű G., M.; Makara G., M. "Hit discovery and hit-to-lead approaches". *Drug Discov. Today*, **2006**, *11*, 741–748,
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Summary and outlook

Compounds of series 1 are screened to find an orally bioavailable 5-HT_6R antagonist with good pharmacokinetic profile.

The chemical space close to series 2 is searched for dual 5-HT_{1A}/5-HT_6 receptor ligands. Such compounds might exhibit synergetic anti-depressant and procognitive properties.

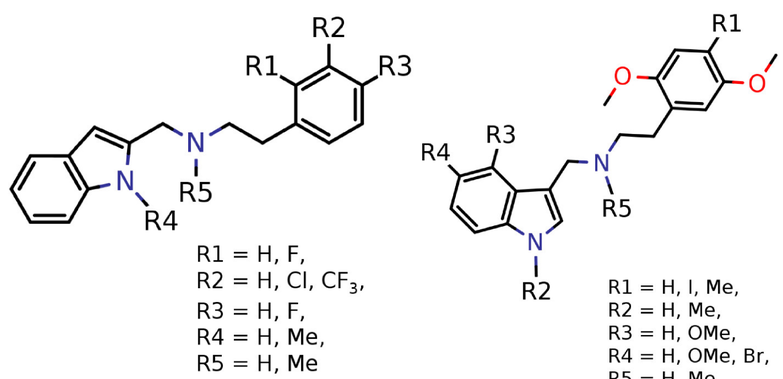

Fig. 3
Chemotypes from series 2 exhibiting 5-HT_6R and 5-HT_{1A}R activity

Acknowledgements

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