2-AMINOIMIDAZOLE-BASED ANTAGONISTS OF A SEROTONIN RECEPTOR, A NEW CONCEPT IN AMINERGIC GPCR LIGAND DESIGN

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Introduction

5-HT_6 is a G_S coupled serotonin receptor involved in the regulation of cholinergic transmission.[1,2] It has been a long lasting hope for Alzheimer's disease patients since in animal models the receptor's antagonists were shown to significantly relieve the symptoms, possibly by restoring the physiological acetylcholine levels in the brain.[3]
Till date, the aminergic GPCR ligand chemical space was expanded mainly by the employment of novel bioisosteric building blocks, resulting in a large diversity of core scaffolds, aromatic systems, linkers, hydrogen bond donors and acceptors. This is in sharp contrast to the very narrow pool of aminergic groups used as a replacement for the aminoalkyl chains of endogenous neurotransmitters and classical ligands. **There were hardly any attempts to employ aromatic basic groups in the design of aminergic GPCR ligands .**
2-Aminoimidazole (2-AI) remains an unexplored highly basic scaffold that has been found to be a common molecular framework of numerous marine alkaloids and synthetic antibacterial agents.[4] The serotonergic activity of marine alkaloids containing 2-AI motif was revealed in 1984, well before the discovery and cloning of several subtypes of serotonin receptors (Fig. 1).[5]

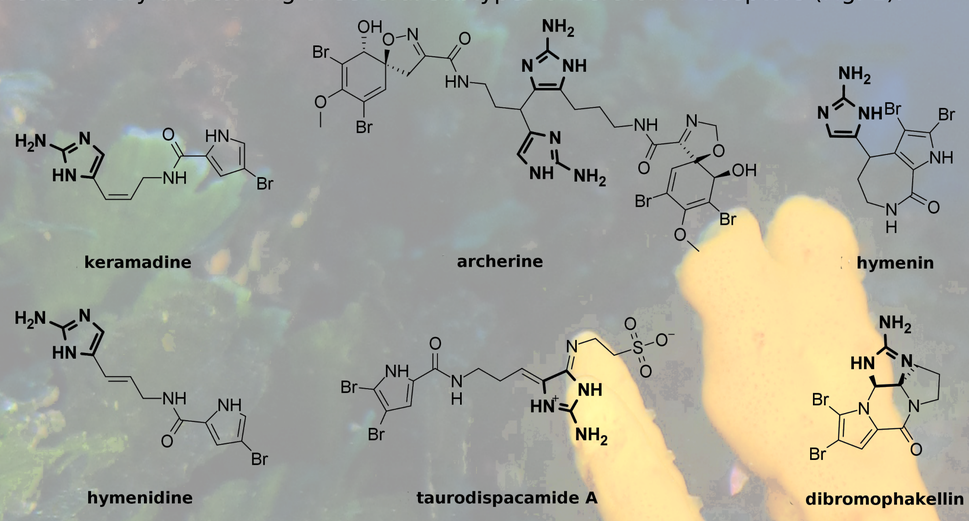
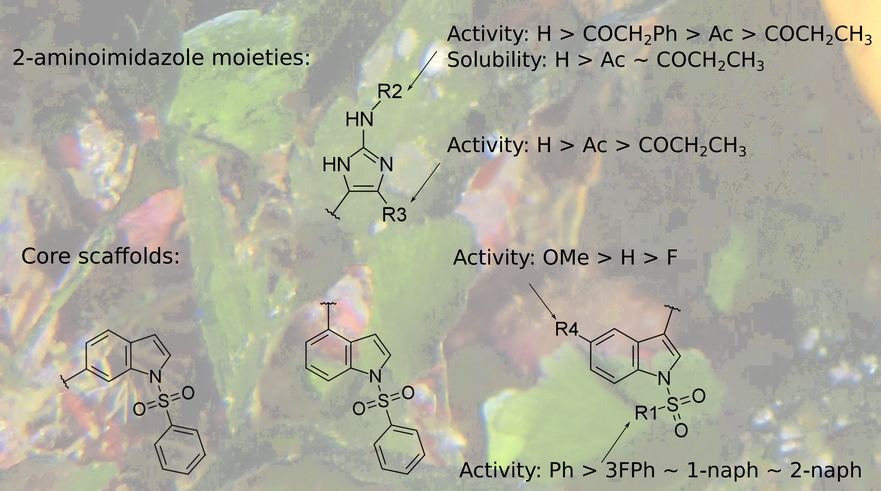


Figure. 1. Keramadine and hymenidine at 15 μM reversed the contractile effect of 1 μM of serotonin on isolated rabbit aorta, while the contraction caused by KCl or noradrenaline was not affected. Archerine and taurodispacamide A at a high concentration blocked the effects of histamine in a screening assay conducted on guinea pig ileum. Hymenin acted as a competitive antagonist of α-adrenoreceptors in vascular smooth muscles in a screening assay. Dibromophakellin showed agonistic activity against α2B adrenoreceptor with EC50 of 4.2 μM.

Structure Activity Relationship

A diverse library has been constructed and the relationships between structure and activity, metabolic stability, and solubility were studied. Compounds from the ***N*-(1*H*-imidazol-2-yl)acylmide chemotype exhibited high affinity for 5-HT_6R** and ultimate selectivity over 5-HT_{1A}, 5-HT_{2A}, 5-HT_7 and D_2 receptors, which can be attributed to their very low basicity.



Lead compound: AHN-208

Figure 2. Structure-activity relationship of the 1-arylsulphonyl-1H-indol-X-yl core (X = 3, 4, 6) and 2-aminoimidazole conjugates. The basic scaffold was attached to the 3rd, 4th or 6th position of indole (imidazole attachment point is marked as a cut bond). On the right: the structure of lead compound: AHN-208.

Crystal structure and binding mode analysis

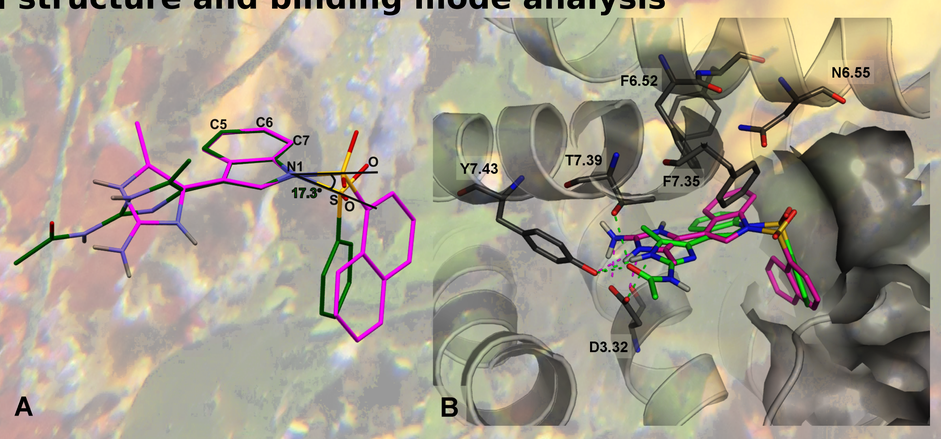


Figure 3. A – superposition of the molecular conformations observed in the crystal structure, showing a nearly co-planar orientation of the sulfur atom with respect to the indole ring for compound AHN-208 (magenta) and the angular deviation of the sulfur atom from the mean plane of indole observed in the conformation of molecule AHN-98 (green); B – the superposition of compounds AHN-208 and AHN-98 docked to the 5-HT_6R homology model built on the β2 adrenergic template.

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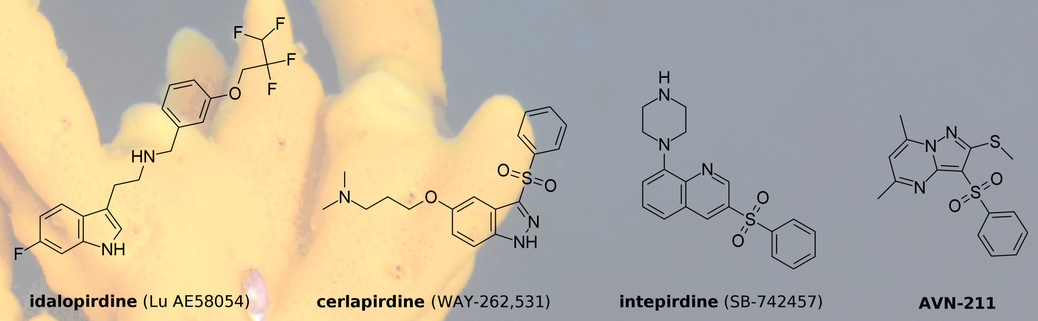
2-Aminoimidazole: a platform for non-classical ligands?

- Aromatic basic groups (imidazoles, thiazoles) incorporated in serotonin receptor antagonists for the first time; a diverse series of highly active 5-HT_6R antagonists is reported,
- 2-Aminoimidazole motif emerged as a platform for structurally unique aminergic GPCR ligand synthesis,
- Very high potential for chemical modifications due to multiple functionalization sites,
- Lead compound (**AHN-208**) exhibits high affinity for 5-HT_6 receptor, possesses procognitive potential, is non-toxic, not mutagenic, free of hERG and 5-HT_{2B} mediated cardiac side effects risk,
- **AHN-208** was shown to reverse the cholinergic mediated cognitive decline caused by the administration of scopolamine,
- Publication in review,
- **Patent application**: Hogendorf, A. S.; Hogendorf, A.; Bojarski, A. J.; Satała, G.; Kurczab, R.; Staroń, J.; Bugno, R.; Lenda, T.; Popik, P.; Kos, T.; Matłoka, M.; Dubiel, K.; Moszczyński-Pętkowski, R.; Pieczykolan, J.; Wieczorek, M.; Zajdel, P. Pochodne N-arylosulfonyloindolowe do leczenia chorób CNS. P.422539.

5-HT_6R antagonists in clinical trials



	Idalopirdine	Cerlapirdine	Intepirdine	AVN-211
5-HT_6R K_i	0.8 nM	1.3 nM	0.2 nM	1.2 nM
Current developer	Lundbeck	Pfizer (suspended)	Axovant	Avineuro
Indication	AD/ Schizophrenia	AD/ Schizophrenia	AD/dementia with Levy bodies	Schizophrenia
Phase I	Well tolerated	Well tolerated	Well tolerated	Well tolerated
Phase II	Effective for schizophrenia but not for AD patients	Program suspended	Some efficacy reported in AD patients, dose dependent	Effective vs placebo
Phase III	No improvement vs placebo in AD patients (lower dosage used than in phase II)	-	No improvement versus placebo in AD patients in test scores; the subjective condition of the patient significantly improved vs placebo	Recruiting ongoing

Figure 4. Outcome of 5-HT_6R antagonist clinical trials. Despite the high expectations regarding the efficacy as a treatment for cognitive impairment, there have been no successful phase III trials to date in AD patients.

Novel Object Recognition

It has been concluded, that the lack of effectiveness of the current Alzheimer's disease treatments may be overcome with the use of combined therapy. One of the latest approaches involves the administration of 5-HT_6R antagonist together with an acetylcholinesterase inhibitor.[6] The effectiveness of AHN-208 as a part of an 5-HT_6R antagonist-AChEI cocktail was thus tested. **Co-administration of inactive doses of the compound AHN-208 (0.3 mg/kg) with donepezil (0.3 mg/kg), facilitated cognitive performance.**

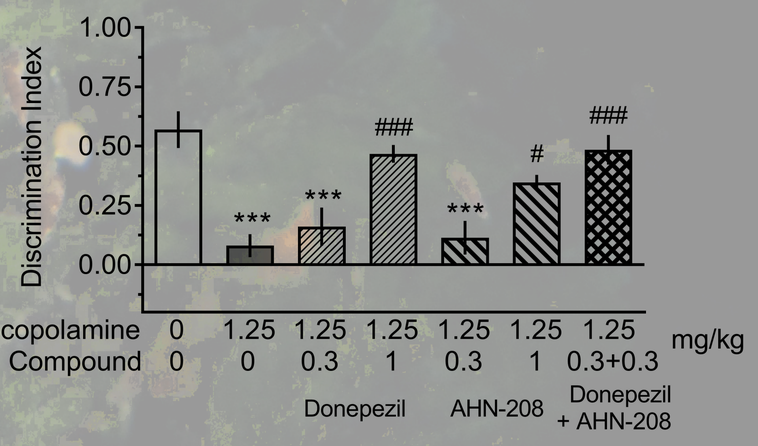


*Figure 5. Effects of AHN-208, donepezil and their joint administration on scopolamine-induced cognitive impairment in rats. Animals were treated with the experimental compounds and scopolamine, 120 and 30 min, before the learning trial, respectively, and were tested 1 hour later in the recognition trial. The data are presented as the mean ± standard error of the mean of DI. N=9-10 animals per group. Symbols: ***p < 0.001, significant reduction in DI compared with the vehicle-treated group; # p < 0.05, ### p < 0.001, significant increase in DI as compared with the scopolamine-treated group. Note that one rat from the scopolamine + AHN-208 (1 mg/kg) group was excluded to fulfill the D'Agostino & Pearson and Shapiro-Wilk normality tests criteria (Prism 7 software).*

Acknowledgements

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