Indole-imidazole conjugates as potential nootropics and antinociceptives for the treatment of neuropathic pain

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Introduction

Fluorine substitution, which had been merely perceived as a means of increasing the lipophilicity while not adding bulk, later gained a reputation of a complex personality, with effects such as increased metabolic stability due to strength of C-F bond, polar hydrophobicity, changes in acidity/basicity, changing conformation via hyperconjungation or dipole-dipole interaction, being constantly exploited. Ever since more and more subtle fluorine effects have been discussed such as the enhancement of halogen bonding via sigma hole enlargement.

A study of fluorinated 3-(1-alkyl-1H-imidazol-5-yl)-1H-indoles which were designed to optimize the halogen bond formation between ligand and the receptor backbone revealed **potent and highly drug-like 5-HT$_7$R agonists: 3-(1-alkyl-1*H*-imidazol-5-yl)-5-iodo-4-fluoro-1*H*-indoles.** Compounds exhibited high selectivity over related CNS targets, high metabolic stability and low toxicity in HEK-293 and HepG2 cell cultures. A rapid absorption to the blood, high blood-brain barrier permeation and a very high peak concentration in the brain were found for compounds AGH-192 and AGH-194 after *i.p.*, *p.o.* and *i.v.* (2.5 mg/kg) administration in mice. AGH-194 was shown to produce procogonitive effects at very low doses in NOR and ASST tests. Both 5-HT$_7$R agonists were shown to produce potent anti-nociceptive effect in mice model of neuropathic pain.

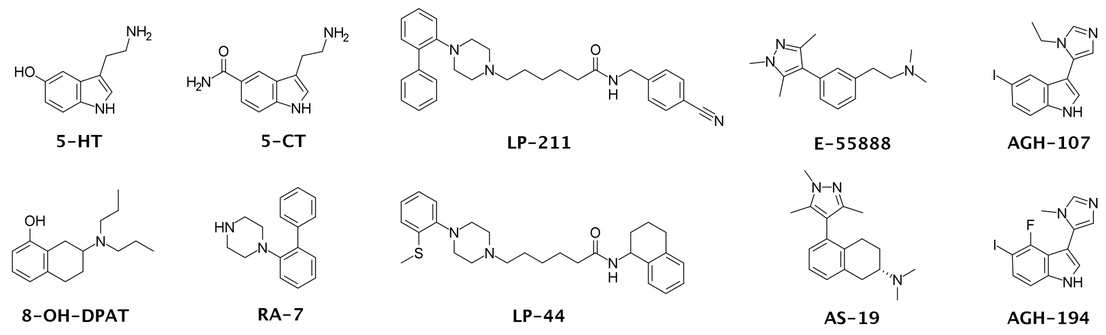


Fig. 1 5-HT$_7$R agonists that have been used in research. Only two groups of selective compounds had been available: the long chain arylpiperazines of the LP series and bisaryl derivatives derived from E-55888.

receptor	Ligand/K_i [nM]						
	serotonin[3]	5-CT[3]	LP-211[4]	RA-7[4]	AS-19[5]	**AGH-107**[2]	**AGH-194***
5-HT$_{1A}$	3.2	0.3	188	99	89.7	1053	425
5-HT$_{2A}$	11.6	5012	626	1190	N.D.	>10000	5427
5-HT$_{5A}$	251	20	178	76	98.5	>1000	>10000
5-HT$_6$	98.4	720	1571	596	N.D.	1673	684
5-HT$_7$	8.1	0.4	0.6	1.4	0.6	6	2
D$_2$	N.D.	N.D.	142	N.D.	N.D.	4847	>10000

* unpublished data

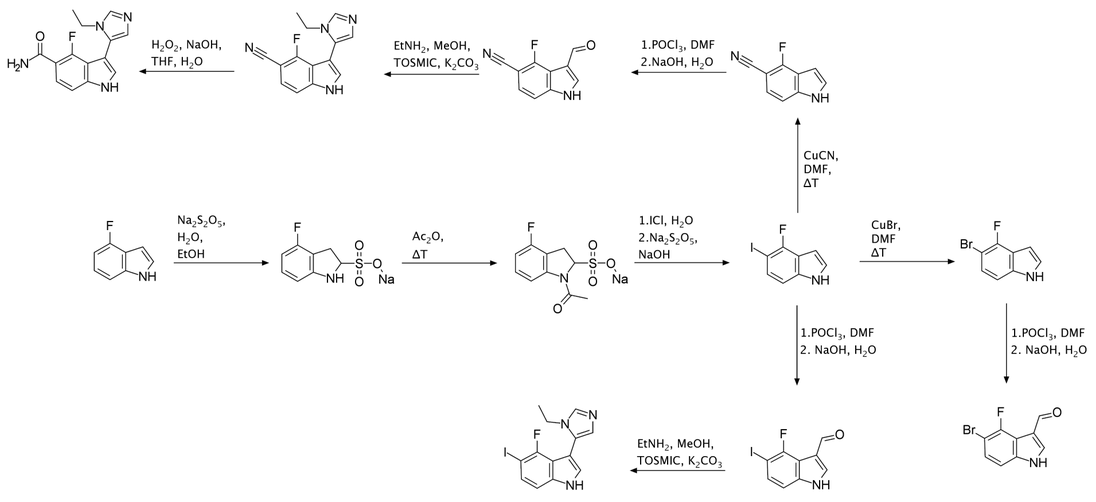
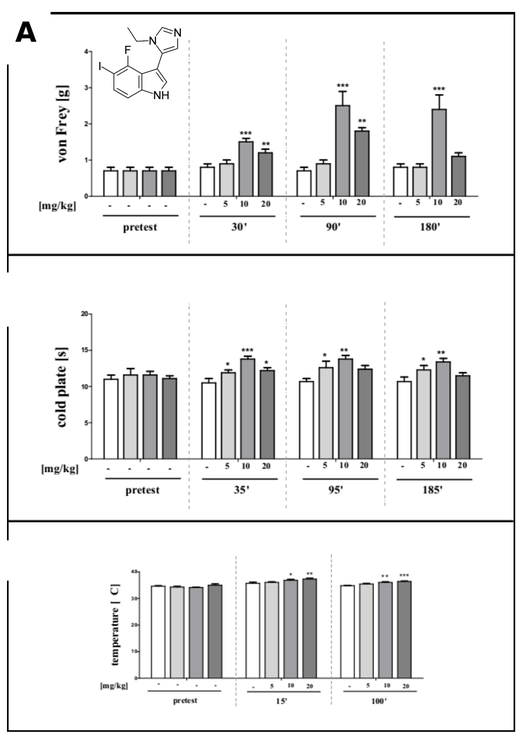
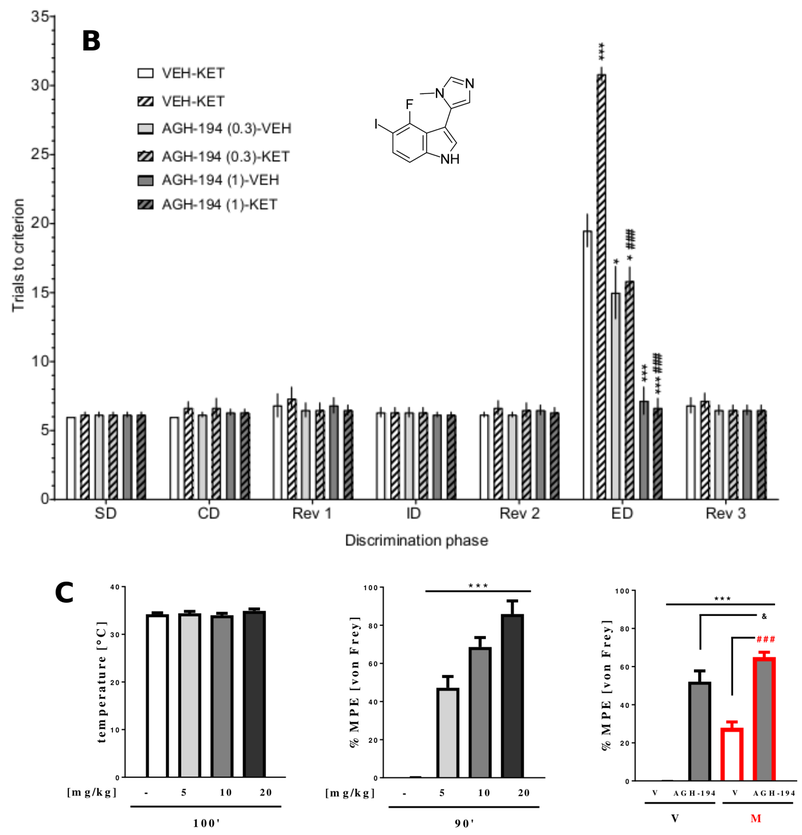


Fig. 2 4-Fluoro-5-iodoindole was assembled via sequential protection yielding an aniline derivative, -para electrophilic iodination and subsequent rearomatization. The iodine atom can be conveniently substituted with other functional groups. AGH-194 was synthesized via Vilsmeier-Haack formylation and van Leusen reaction.

Behavioural studies





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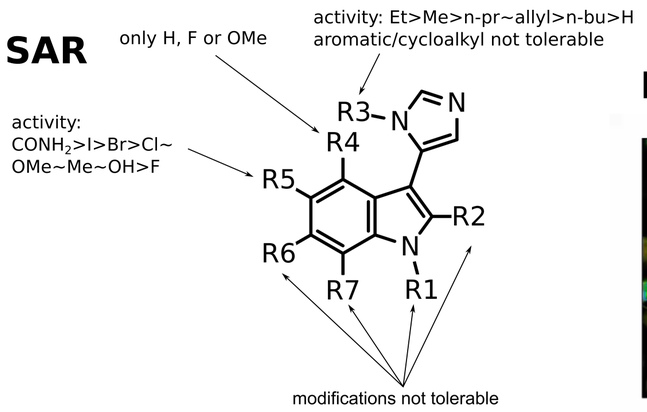

Fig. 3 Structure-Activity relationship of indole-imidazole 5-HT$_7$R agonists

Function

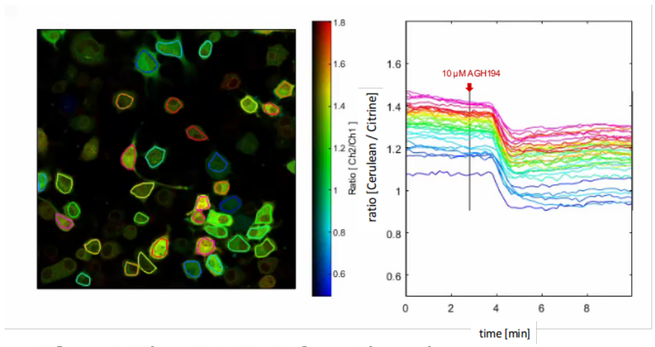

Fig. 4 The 5-HT$_7$R functional response was measured in living cells with TR-FRET using a cAMP specific biosensor.

Selectivity

Serotonin receptors and transporters	5-HT$_{1A}$	5-HT$_{1B}$	5-HT$_{1D}$	5-HT$_{1E}$	5-HT$_{2A}$	5-HT$_{2B}$	5-HT$_{2C}$
	5-HT$_3$	5-HT$_{5A}$	5-HT$_6$	5-HT$_7$	SERT		
Adrenergic receptors and transporters	α_{1A}	α_{1B}	α_{1D}	α_{2A}	α_{2B}	α_{2C}	β_1
	β_2	β_3	NET				
Dopamine receptors	D1	D2	D3	D4	D5	DAT	DOR
Histamine receptors	H1	H2	H3	H4			
Muscarinic receptors	M1	M2	M3	M4	M5		
Opioid receptors	δ	κ	μ	σ_1	σ_2		
miscellaneous	BZP RBS	GABA A	PBR				

Fig. 5 AGH-194 was shown to be exceptionally selective over a panel of 42 CNS targets. Study conducted within the Psychoactive Drug Screening Programme

Pros and cons of low-basicity 5-HT$_7$R receptor agonists

+ very high activity at low doses in behavioral assays
+ distinctively high selectivity,
+ unprecedented blood-brain barrier permeation,
+ very good metabolic stability,
+ rigid structure, low molecular weight = can accept more functional groups,
+ simple synthesis,
+ very high water solubility,
+ higher *in vivo* activity compared to classical agonists,
+ very high efficacy in electrophysiological assays,
- lower *in vitro* potency in cAMP assay compared to arylpiperazines and tryptamines,
- small chemical space i.e. only minor structural modifications are acceptable.

Fig. 7 A - AGH-192 alleviated the symptoms of neuropathic pain, **B** - Compound AGH-194 was shown to induce potent procognitive effects at very low doses (0.3 and 1 mg/kg) in the ASST test, **C** - AGH-194 posessed strong antinociceptive properties in the mouse model of neuropathic pain: administered alone at 5, 10 and 20 mg/kg *i.p.* and in combination with morphine

Pharmacokinetics

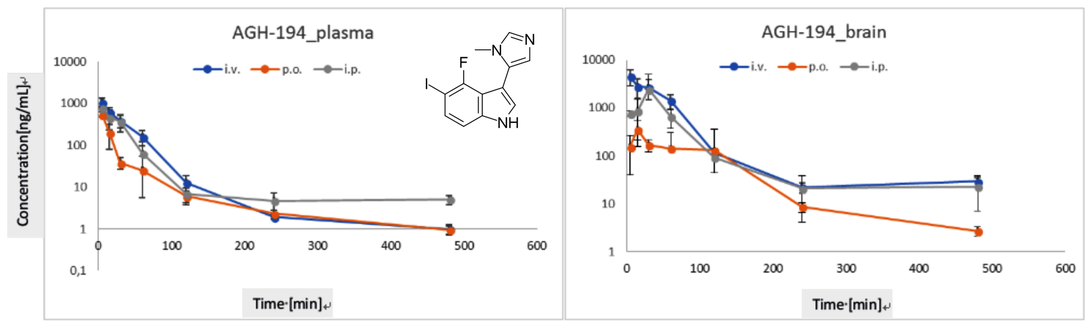

Fig. 6 The lead compound AGH-194 exhibits excellent pharmacokinetic profile, *i.e.* rapid absorption to the brain and good bioavailability after i.p. and p.o. administration at 2.5 mg/kg

Binding mode

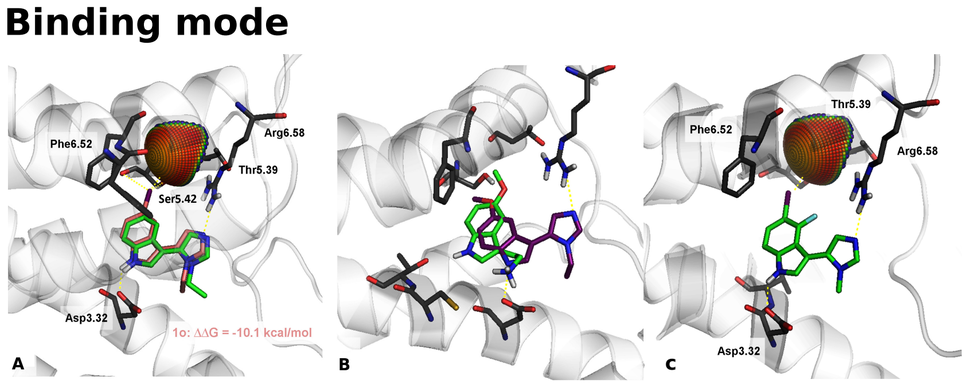

Fig. 8 Docking of the title compounds to the 5-HT$_7$R homology model. **A** - the first generation of agonists, **B** - comparison of binding mode with classical ligands, **C** - the second generation of agonists.

ACKNOWLEDGEMENTS

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