Design, synthesis and biological activity of new aminotriazine derivatives as selective 5-HT₇ receptor ligands

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BACKGROUND

Depression is a common mental disorder, with key symptoms including lowered mood, anxiety, decreased energy, feeling guilty or low self-esteem etc. [1] In the near future, depression will become one of the most common diseases leading to the destabilization of human life, and it is estimated to be the most frequently occurring disease by 2030. [1] Treatment of depression or other CNS disorders are related with affecting on dopamine receptor: D₂R and serotonin receptors: 5-HT_{1A}R, 5-HT₆R or 5-HT₇R. [2] Early studies of some antipsychotics and antidepressants revealed their high affinity for the 5-HT₇ receptor; and due to its distribution in particular areas of the brain it was proposed that this receptor might play a role in psychological disorders and other CNS pathologies. [3] Forced swim test and tail suspension test demonstrated that inhibition of the 5-HT₇R synergistically enhances effects of antidepressants used in clinical settings. [4] Having analysed prior art literature, we selected a group of poorly investigated compounds, namely aminotriazines. Aminotriazines have been described as compounds acting only on 5-HT₇R. [5] On the other hand, many ligands containing an indole or substituted indole moiety exhibit high affinity for serotonin receptors due to high structural similarity to serotonin. [6] Encouraged by the fact that aminotriazine derivatives are not particularly tested for their affinity to serotonin or dopamine receptors, we initiated preliminary research and design of new molecules with indole triazine scaffold. At the designing stage, molecular modelling including docking and molecular dynamic (MD) techniques have been utilized. Novologues were synthesized in eco-friendly, *solvent-free* microwave-assisted protocol. Then bioactivity, including radioligand binding and ADME-Tox (hepatotoxicity, metabolic stability), were evaluated.

MATERIAL AND METHODS

Molecular modeling

CNS MPO calculating

CNS MPO <3

POOR CANDIDATES

CNS MPO >3

PROMISING CANDIDATES

Chemistry solvent-free MW approach

In-vitro assays

Radioligand binding

D₂, 5-HT_{1A}, 5-HT_{2A},
5-HT₆, 5-HT₇

ADME-T

1. mouse liver microsomes incubation
2. MTS (HepG2 cell line)

RESULTS

Docking

Ligand 3

IMPOSED: 2 (brown), 3 (green), 4 (yellow)

IMPOSED: active 3 (green), and inactive 4 (blue)

Molecular Dynamic (5-HT₇)

Interaction fraction of 5c

Interaction fingerprint of 5c

In vitro K_i [nM]

Ligand No	R	D2	5-HT _{1A}	5-HT _{2A}	5-HT ₆	5-HT ₇
1	-CH ₃	-	-	-	-	>1000
2	-CH ₂ Ph	>1000	>1000	>1000	>1000	709
3	-(CH ₂) ₂ -Ph	>1000	>1000	>1000	665	8
4	-(CH ₂) ₂ -O-Ph	>1000	>1000	>1000	530	55
5	-(CH ₂) ₃ -O-Ph	>1000	>1000	>1000	>1000	243
6	-(CH ₂) ₄ -O-Ph	>1000	>1000	758	>1000	>1000
7	-(CH ₂) ₂ -Naphthyl	>1000	>1000	>1000	895	537
8	-(CH ₂) ₃ -O-Naphthyl	>1000	>1000	>1000	785	>1000
9	-(CH ₂) ₄ -O-Naphthyl	>1000	>1000	>1000	373	>1000
10	-	>1000	>1000	>1000	-	>1000
11	-	>1000	>1000	>1000	-	>1000

Distance between ligand and D3.32/E7.34 for 5c

Angle between ligand and D3.32/E7.34 for 5c

ADME-T

Ligand No	CNS-MPO	Metabolic stability	Hepatotoxicity
3	3.8	Unstable	Non-toxic
4	3.7	Unstable	Non-toxic

CONCLUSIONS

- We proved that compounds may be obtained in a rapid, eco-friendly method via *solvent-free* reactions supported by microwave irradiation
- Indole-derived aminotriazine novologues can exhibit high affinity and selectivity to 5-HT₇R
- Amino substituent attached to the triazine core, as well as an alkylaryl substituent attached to the triazine core (ligands 3 and 4), are of a significant importance
- According to molecular dynamic, the typical salt bridge (for most aminergic GPCRs) with D3.32 is highly unstable, while hydrogen bond with E7.34 is stable
- In our research, we found that promising compounds 3 and 4 do not exhibit hepatotoxicity, however at This stage they are metabolically unstable yet

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<http://ligandy-lider.pk.edu.pl/#Projekt>

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