Se-containing 5-HT$_6$R ligands in search for efficient therapy of Alzheimer's disease

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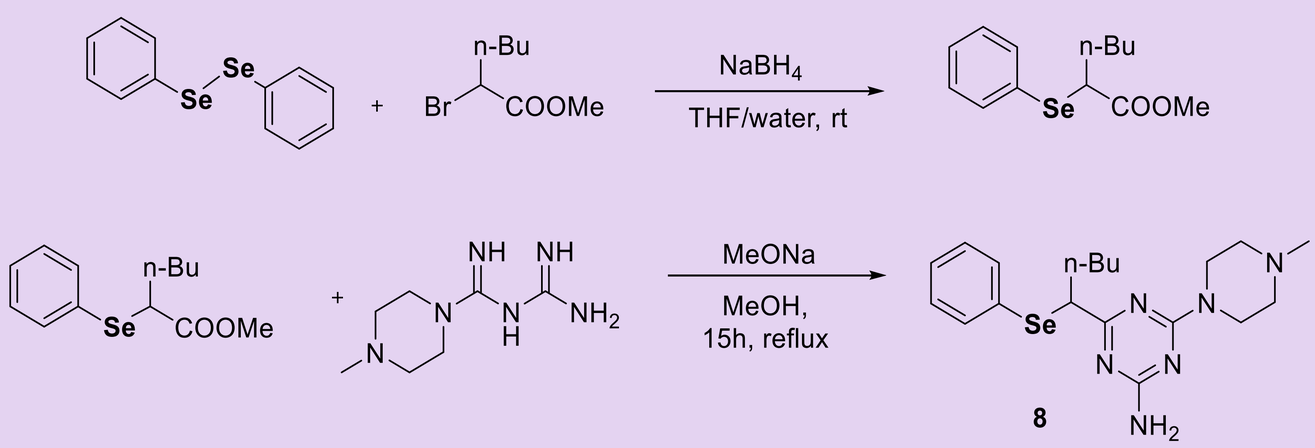
INTRODUCTION

Serotonin 5-HT$_6$ receptor has been an attractive protein target for over 20 years in the search for new therapeutic agents for the treatment of the central nervous system disorders, including depression, Alzheimer's disease (AD), schizophrenia or obesity [1]. Nonetheless, none from already designed 5-HT$_6$R agents have reached pharmaceutical market yet. This is enhanced by the fact that there is no effective treatment for AD, and therefore new drugs development becomes an urgent need. Searching for structurally novel, highly active 5-HT$_6$R ligands with desired pharmacokinetic profile is demanding in this field. Additionally, very recent studies have emphasized the neuroprotective properties of selenium-containing derivatives, which may turn out to be very useful for treatment of neurodegenerative disorders such as AD [2].

BACKGROUND

Previously we obtained the group of highly active 5-HT$_6$R ligands among triazine derivatives with a procognitive effect *in vivo,* which contained oxygen or sulphur as heteroatom in linker [3]. The aim of this study was to investigate how the presence of selenium will affect the *in vitro* activity. Hence, the subject of the presented research is a series of novel triazine-based selenium-containing derivatives varying in different length **(n,n')** and branching **(R^1)** of the linker (Fig. 1).

SYNTHESIS



Scheme 1. Synthetic route of the representative most active selenium derivative **8**.

IN VITRO SCREENING

All synthesized compounds were subjected to *in vitro* receptor screening with radioligands. Three compounds containing selenium as heteroatom were characterized by high affinity towards serotonin 5-HT$_6$ receptor (K_i < 100 nM) and high selectivity for competitive 5-HT$_{2A}$ and 5-HT$_7$ receptors.

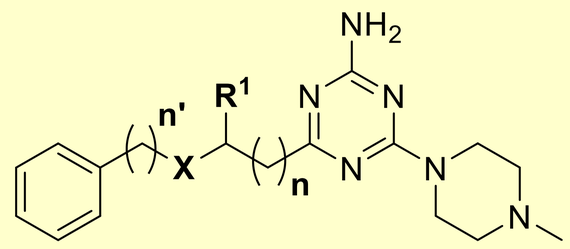


Figure 1. General structure for investigated compounds.

Table 1. Results of radioreceptor studies on the affinity to serotonin receptors.

Cpd.	R^1	n	n'	X	K_i [nM]		
					5-HT$_6$	5-HT$_{2A}$	5-HT$_7$
1	H	0	0	S	**26**	197	2871
2				Se	**242**	406	2329
3	Me			S	**176**	337	1737
4				Se	**111**	376	4247
5	Et			S	**127**	427	2470
6				Se	**122**	1011	4393
7	n-Bu			S	**59**	811	4500
8				Se	**33**	336	4177
9	di-Me			S	**144**	564	3495
10				Se	**165**	nd	nd
11	H	2		S	**25**	117	4240
12				Se	**193**	785	6522
13	H	3		S	**92**	959	3264
14				Se	**52**	623	3161
15	H	0	1	S	**27**	168	2777
16				Se	**278**	1018	4450
17	H	2		S	**137**	1247	4228
18				Se	**79**	729	7425
19	Et	0		S	**636**	957	9692
20				Se	**3065**	1022	8752

nd – no data
The tests used human serotonin 5-HT$_6$ and 5-HT$_{2A}$ and 5-HT$_7$ receptors. Radioligands: [3H] -5-CT for 5-HT$_7$, [3H] -ketanserin for 5-HT$_{2A}$ and [3H] -LSD for 5-HT$_6$ (Table 1).

DISCUSSION

- A series of novel selenium-containing compounds with submicromolar affinity for 5-HT$_6$ receptors and differential selectivity was obtained, including three compounds **(8, 14, 18)** with ***K$_i$* (5-HT$_6$) <100 nM.**
- Half of the selenium derivatives (**4, 6, 8, 14, 18,** red, Table 1) showed higher affinity for the 5-HT$_6$ receptor comparing to correspondig sulfur analog.
- The topology of the compounds shows the most favorable influence of the branching of the linker (**8**), as well as the extension of the carbon chain **(n, n')** without branching the linker **(R^1) (14, 18)** on the affinity and selectivity to 5-HT$_6$R in the group of selenium triazine derivatives under consideration.
- The key effect of the carbon chain length **(n, n')** on the affinity for the 5-HT$_6$ receptor was observed both in the case of: *(i)* the presence of a phenyl and benzyl ring and *(ii)* analogously when having the sulfur as heteroatom.
- The topology of 4-(4-methylpiperazin-1-yl)-6-(1-(phenylselanyl)pentyl)-1,3,5-triazin-2-amine favors a higher affinity for the 5-HT$_6$ receptor (Compound **8**, Table 1), and the topology of 4-(1-(benzylselanyl)propyl)-6-(4-methylpiperazin-1-yl)-1,3,5-triazin-2-amine (Compound **20**, Table 1) drastically reduces 5-HT$_6$R affinity.
- The novel Se-containing derivatives with the most promising activity **(8, 14, 18)** will be selected for further *in silico* and *in vitro* evaluation of ADMET and neuroprotective properties.

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