SEARCHING FOR THE 5-HT$_7$ RECEPTOR LIGANDS IN THE SERIES OF NEW 1,2,3,4-TETRAHYDROISOQUINOLINES WITH IMIDE FRAGMENT

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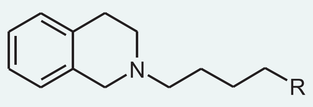
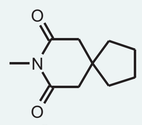
Introduction

1,2,3,4-tetrahydroisoqunolines (THIQ) are of great importance to many different biological targets [1] and are frequently used as tool compounds to investigate the ligand-serotonergic receptor interactions [2, 3]. The screening of our library of THIQ derivatives for 5-HT$_7$ receptor affinity led to the identification of **1** (MM 199) and **2** (AK 30) THIQ analogs of buspirone and NAN-190, respectively, having good 5-HT$_7$ receptor affinity.

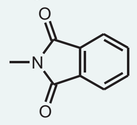
To continue our studies on development of potent and selective 5-HT$_7$ receptor ligands we designed and synthesized a series of MM 199 analogs with modified THIQ fragment and aliphatic spacer. We studied the effect of the introduction of methyl and benzyl substituent into the 2 position of amine moiety and spacer elongation on 5-HT$_7$ receptor affinity. Moreover, we also synthesized imide analogs of **2** and we compared their 5-HT$_7$ and 5-HT$_{1A}$ receptor affinities with these described earlier for *o*-methoxyphenylpiperazine counterparts. (Tables 1 and 2).



MM 199 (**1**): R =



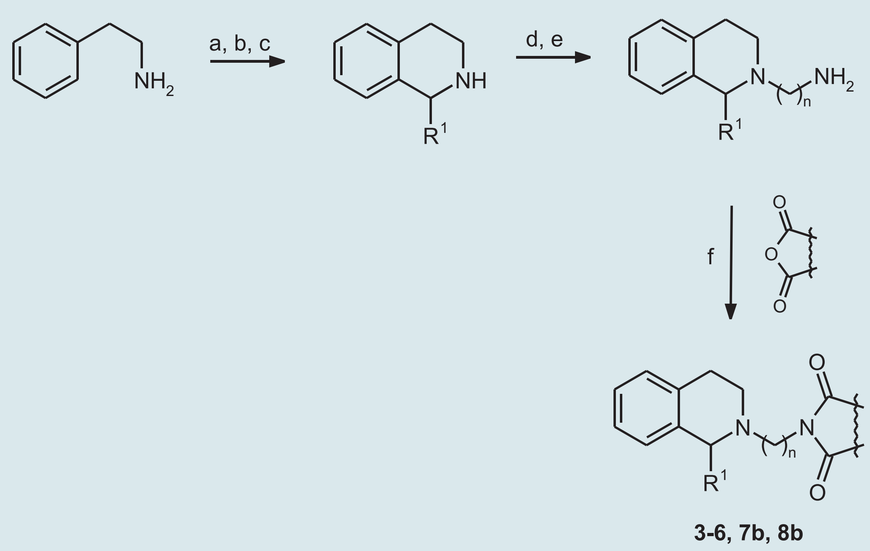
AK 30 (**2**): R =



Chemistry

The method employed to prepared target compounds **3-6**, **7b** and **8b** are summarized in the Scheme.

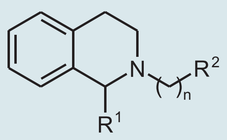
Scheme. Synthesis of new compounds

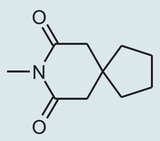
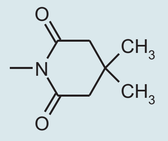


3-6, 7b, 8b

a) $(CH_3CO)_2O$, C_6H_6, reflux; b) PPA, 130-180 ^oC; c) $NaBH_4$, MeOH, reflux; d) N-(4-bromobutyl)- or N-(5-bromopentyl)phthalimide, BuOH, e) reflux; N_2H_4, EtOH, H^+; f) appropriate anhydride, xylene, reflux

Table 1. Chemical structure and 5-HT$_7$ receptor affinity of MM 199 analogs.



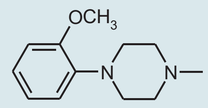
Compound	R^1	R^2	n	K_i (nM) 5-HT$_7$
1 (MM 199)	H		4	36
2	H		5	174
3	CH_3		4	628
4	$CH_2C_6H_5$		4	258
5	H		4	256

Binding experiments

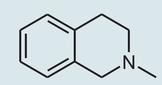
Radioligand binding assays on membranes from HEK293 cells stably expressing human 5-HT$_{7b}$ receptor were performed according to the methods previously described by us [4]. The binding affinity of the investigated compounds for 5-HT$_7$ receptor was evaluated on the basis of their ability to displace [^{3}H]-5-CT (93.0 Ci/mmol. Amersham). For selected compounds their 5-HT$_{1A}$ receptor affinity were determined using native rat hippocampal membranes and [^{3}H]-8-OH-DPAT (170 Ci/mmol, NEN Chemical) as radioligand. In both experiments serotonin was used for nonspecific binding.

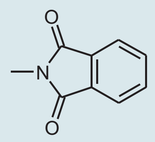
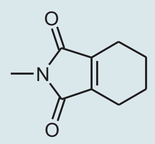
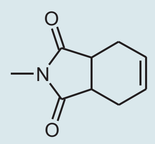
Table 2. Structure, 5-HT$_7$ and 5-HT$_{1A}$ receptors affinities of AK 30 analogs and their *o*-methoxyphenylpiperazine counterparts

A: **a**



b



Compound	R	K_i (nM) 5-HT$_7$	K_i (nM) 5-HT$_{1A}$
2a (NAN 190)		87	0.6 [5]
2b (AK 30)		62	140 [6]
7a		65	7
7b		67	214
8a		82	3.5
8b		120	520

Results and Discussion

For all new compounds their affinity for 5-HT$_7$ receptor was determined (Table 1 and 2).

In general, MM199 analogs demonstrated low or very low affinity for 5-HT$_7$ receptors (Table 1):

- elongation of the aliphatic spacer in MM 199 structure led to compound **3** which was 5 times less active than **1**,
- introduction of methyl and benzyl substituents into the 1 position of THIQ system also caused decrease of 5-HT$_7$ receptor affinity of modified compounds **4** and **5**,
- replacement of the buspirone imide fragment by the gepirone imide moiety was also unprofitable structure modification, compound **6** showed lower affinity than **1**.

THIQ analog of NAN-190 (**2a**) compound **2b** showed, like **2a**, good 5-HT$_7$ receptor affinity (62 and 87 nM, respectively) (Table 2). The applied modifications of the terminal moiety did not significantly influence the level of the 5-HT$_7$ binding of the new ligands compared to their o-methoxyphenylpiperazine counterparts (**7b** *vs* **7a**, **8b** *vs* **8a**).

On the other hand, replacement of the 1-(*o*-methoxyphenyl)piperazine moiety in the structure of NAN-190 and its analogs **7a** and **8a** by THIQ caused significant decrease in 5-HT$_{1A}$ receptor affinity of the resultant compounds.

Among presented new 1,2,3,4- tetrahydroisoquinoline derivatives compound **7b** is the potent 5-HT$_7$ receptor ligand with good selectivity over 5-HT$_{1A}$ receptors.

Acknowledgment

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References

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