P50

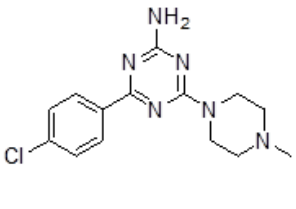
Methylpiperazine derivatives with 1,3,5-traizine scaffold - a novel group of ligands for serotonin receptors 5-HT$_6$

Dorota Łażewska,[a] Rafał Kurczab,[b] Małgorzata Więcek,[a] Katarzyna Kamińska,[a] Grzegorz Satała,[b] Andrzej J. Bojarski,[b] Katarzyna Kieć-Kononowicz,[a] Jadwiga Handzlik[a]

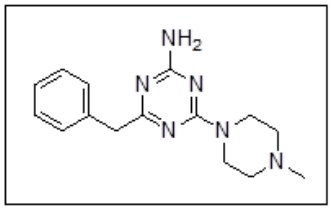
[a]Department of Technology and Biotechnology od Drugs, Jagiellonian University Medical College, Medyczna 9, 30-688 Cracow, Poland
[b]Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Science, Smętna 12, 31-343 Cracow, Poland

e-mail: j.handzlik@uj.edu.pl

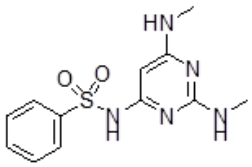
The 5-HT$_6$ receptor is the most recently identified member of the 5-HT receptor superfamily. Intensive preclinical studies have shown that 5-HT$_6$R antagonists could be a promising drug with cognitive improvement in psychiatric (*e.g.* schizophrenia, depression) or neurodegenerative diseases (*e.g.* Alzheimer's disease), and for obesity treatment [1]. Not only antagonists but also agonists have potency for the treatment of obesity or cognitive disfunctions [2]. In this context, the search for new ligands of the 5-HT$_6$R is a current topic in medicinal chemistry. Recently, 2-amino-4-(4-methylpiperazin-1-yl)-1,3,5-triazine derivatives have been described as histamine H$_4$ receptor ligands [3], i.e. **TR7** and **TR20** (Fig. 1). As first known selective 5-HT$_6$ ligands, e.g. **RO046790** (Fig. 1), contain some structural similarities to 2,4,6-trisubstituted 1,3,5-triazines, we decided to investigate this interesting chemical group on its potency toward 5-HT$_6$ receptors.



TR7
hH$_4$R K$_I$ = 203 nM



TR20 (lead)
hH$_4$R K$_I$ = 7499 nM



RO046790
h5-HT$_6$ K$_i$ = 55 nM

Fig. 1

Docking studies and radioligand binding assays for compounds **TR7** and **TR20** indicated significant 5-HT$_6$ affinity for compound **TR20,** whereas the **TR7** was almost inactive. Thus, the compound **TR20** was selected as a lead structure for further modifications to give a series of 14 benzyl-triazine derivatives of methylpiperazine. Synthesis, molecular modelling and radioligand binding assays have been performed. Nine new compounds displayed higher affinity for 5-HT$_6$ than **TR20**. The docking-based SAR studies indicated a crucial role of substituent at *m*-position of benzyl ring for the considered 5-HT$_6$ affinity.

[1] D. Marazziti, et al. *Curr. Med. Chem*. 20 (2013) 371-377.
[2] D. Karila, et al. *J. Med. Chem.* 58 (2015) 7901-7912.
[3] D. Łażewska et al. *Eur. J. Med. Chem.* 83 (2014) 534-546.

Acknowledgements:
Supported by National Science Center (NCN), grant No UMO-2015/17/B/NZ7/02973.