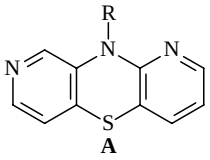
P-45

New Dipirydothiazine Derivatives – Potential Inhibitors of Dopaminergic and Serotoninergic Receptors.

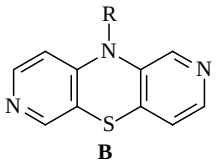
Beata Morak-Młodawska [1], Andrzej J. Bojarski [2], Grzegorz Satała [2], Krystian Pluta [1], Małgorzata Jeleń [1]

[1] Department of Organic Chemistry, Faculty of Pharmacy, Silesia Medical University, Jagiellońska 4, Sosnowiec, Poland
[2] Department of Medicinal Chemistry, Institute of Pharmacology, Polish Academy of Science, Smętna 12, Kraków, Poland
e-mail: bmlodawska@sum.edu.pl

Phenothiazines belong to the oldest, synthetic antipsychotic drugs, which do not have their precursor in the world of natural compounds. They are used as neuroleptics, interact with various receptors in CNS, especially strongly block the dopaminergic receptors. Phenothiazines also inhibit other receptors on neurons in CNS including serotonin, histamine, □-adrenergic or GABA-ergic receptors, however the affinity for dopaminergic receptors is the strongest [1].
In our search we modified the phenothiazine structure with the pyridine rings to form new diazaphenotiazines being 10*H*-1,8-diazaphenothiazine **A** [2] and 10*H*-2,7-diazaphenothiazines **B** [3]. We transformed these compounds to the 10-substituted derivatives possessing dialkylaminoalkyl substituents **1A,B** - **7A,B.**

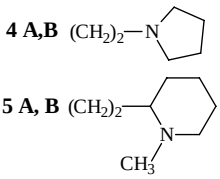


A

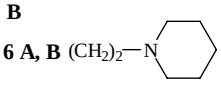


B

1 A, B $CH_2CH_2CH_2N(CH_3)_2$,
2 A, B $CH_2CH_2N(C_2H_5)_2$,
3 A, B $CH_2CH(CH_3)CH_2N(CH_3)_2$,

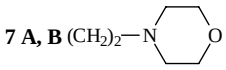


4 A,B $(CH_2)_2$—N



6 A, B $(CH_2)_2$—N

5 A, B $(CH_2)_2$—N(CH_3)



7 A, B $(CH_2)_2$—N—O

The synthesized compounds **1A,B** - **7A,B** were *in vitro* screened towards monoaminoergic receptors (D_2, 5-HT_{1A}, 5-HT_6, 5-HT_7). The compounds showed lower activity than the neuroleptic phenothiazines: promazine and thioridazine.
It seems that affinity for the monoaminoergic receptors is depended on the conformation of the diazaphenothiazines structures.

[1] Sudeshna G., Parimal K.: *Eur. J. Pharmacol.* **648** (2010), 6-14,
[2] Morak-Młodawska B., Pluta K., Jeleń M.: *in preparation for publication.*
[3] Morak-Młodawska B., Pluta K.: *Heterocycles* **78** (2009), 1289 -1298.

Acknowledgement: The Synthesis were financially supported by The Medical University of Silesia (grant KNW-1-073/P/1/0), Radioligand binding experiments were financially supported by the Norwegian Financial Mechanism as part of the Polish–Norwegian Research Fund, Grant No. PNRF–103–AI-1/07