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Synthesis and Pharmacological Evaluation of Quinolone- and Isoquinoline-Sulfonamides of Long-Chain Arylpiperazines as 5-HT$_7$ Antagonists.

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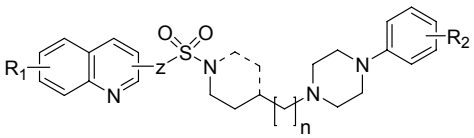
The most recently discovered member of the serotonin receptor family, the 5-HT$_7$ receptor, has received great interest over the past decade [1]. The prominent position of 5-HT$_7$ receptor in the thalamus, limbic and cortical regions of the brain, as well as high affinity for several antipsychotic and antidepressant agents suggest its involvement in depression and control of circadian rhythm. This was further supported by the results of several preclinical studies, in which 5-HT$_7$ receptor antagonism unveiled as a promising mechanism for the treatment of anxiolytic and antidepressant-like properties.
Although the structures of compounds active at 5-HT$_7$R are diversified, a relatively large group of ligands contain several common fragments, for example, an amine moiety (mostly 4-N-arylpiperazine, tetrahydroisoquinoline or 4-substituted tetrahydropyridine), which is connected by a different length alkyl chain (2–5 carbon atoms) to a terminal aromatic fragment.



z = 3, 4, 6, 8
R_1 = H, Cl
R_2 = 3-Cl, 4-Cl
n = 1, 2

Continuing search for new 5-HT$_7$ receptor antagonists in a group of sulfonamide derivatives, we designed a series of quinolone- and isoquinoline-sulfonamides of 3- and 4-chloro-phenylpiperazines containing different length flexible and rigid alkylen spacer [2]. The quinolinesulfonyl chlorides used were synthesized according to the previously reported method [3].
Herein we report synthesis, biological evaluation for 5-HT$_{1A}$, 5-HT$_{2A}$, 5-HT$_6$, and 5-HT$_7$ receptors and determination of therapeutic potential of the newly synthesized sulfonamides in animal model of depression and anxiety.

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[2] Zajdel P., Marciniec K., Maślankiewicz A., Grychowska K., Satała G., Partyka A., Jastrzębska-Więsek M., Wróbel D., Wesołowska A., Duszyńska B., Bojarski A.J., Pawłowski M.*: Joint Meeting on Medicinal Chemistry*, Catania, 2011.
[3] Marciniec K., Maślankiewicz A., Pawłowski M., Zajdel P.: *Heterocycles* 71 (2007), 1975.

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