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Development of Novel Serotonin 5-HT_6 and Dopamine D_2 Receptor Ligands and MAO A Inhibitors

Synthesis, Structure-Activity Relationships and Pharmacological Characterization

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Abstract

It is known since the 1950s that enhancement of the levels of the monoamines dopamine (DA), serotonin (5-hydroxytryptamine, 5-HT) and norepinephrine (NE) in the brain will relieve the symptoms of major depression, and current therapies are still based on this mechanism. However, all available antidepressants today are still suffering from slow onset of therapeutic action, as well as adverse effects and lack of efficacy. Therefore, development of compounds with new mechanisms of action for treatment of depression is needed.

One of the most important stages of the drug discovery process is the generation of lead compounds. Structure-activity relationships (SARs) are well integrated in modern drug discovery and have been used in the process of developing new leads. The tetrahydropyridine/piperidine indoles are known to affect multiple targets of the dopaminergic and serotonergic systems in the brain. This class of indoles can easily be modified and they possess the necessary properties for a lead, such as low molecular weight and high water solubility. This thesis is focused on further exploring the SAR around tetrahydropyridine/piperidine indoles by introduction of substituents and/or bioisosteric replacements of the indole core with the aim of developing novel compounds acting at the dopaminergic and serotonergic systems in the brain. By using *in vivo* and *in vitro* screening approaches, 5-HT type 6 receptor (5-HT_6) agonists, DA type 2 receptor (DA D_2) antagonists, 5-HT reuptake transporters (SERT) inhibitors, dual DA D_2 antagonists/SERT inhibitors and finally reversible monoamine oxidase A (MAO A) inhibitors were identified after modifications of the chemical lead. In addition, the SAR of 6-substituted 3-(pyrrolidin-1-ylmethyl)chromen-2-ones (coumarin derivatives) were also investigated and were identified as selective and reversible MAO A inhibitors.

Three compounds, i.e. the 5-HT_6 agonist **81**, the dual DA D_2 antagonist/SERT inhibitor **158** and the MAO A inhibitor **134** have been identified to be of potential interest as novel antidepressants.

Keywords: dopamine D_2 receptor, serotonin reuptake transporter, monoamine oxidase, 5-HT_6 receptor, DOPAC, 5-HIAA, 3-tetrahydropyridine indole, 3-piperidine indole, 3-(pyrrolidin-1-ylmethyl)chromen-2-one