The medicinal chemistry of arylpiperazines with potential antidepressant efficacy
Mensonides, Marguerite

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The research described in this thesis focuses on the use of aryl piperazines in antidepressant research.

**Chapter 1** gives a general introduction into the field of antidepressant research and serves as a background for chapters 2-6. In this chapter, the history of the pathogenesis of depression and the discovery of the 1st generation of antidepressants is reviewed. The currently used definition of depression is a syndrome consisting of affective, cognitive, motor and somatic signs and symptoms, which should be prominent, persistent and represent a change from previous function. The first antidepressant, imipramine (TCA), was marketed in 1952, followed by iproniazid (MAOI) in 1957 and the second TCA amitryptiline in 1961. It was in the early 1960s that a standard for the assessment of depression and of antidepressant effects, the Hamilton rating scale, was put forward. This scale, together with the first TCAs and MAOIs served as a blueprint in early antidepressant research.

In 1965, Schildkraut put forward the catechol hypothesis of depression. Although he described the hypothesis to be ‘an oversimplification’ and ‘of heuristic value’ and despite several limitations and inconsistencies, it persisted for over two decades. Following the introduction of the first SSRIs in the early 1980s, the scientific discussion on the mechanisms of action of antidepressants and background of depression has been focussed more on the 5-HT hypothesis of depression. The first SSRI, zimeldine, was withdrawn after it had been associated with cases of Guillain-Barré syndrome. Several others, like fluoxetine (Prozac®) which had first been synthesized in 1972 and was marketed in 1987, proved quite capable of conquering the market for antidepressants.

The need for this 2nd generation of antidepressants with more specific receptor targets, came mainly from the fact that the 1st generation suffered from serious adverse events and small therapeutic windows. The TCAs and MAOIs were associated with anticholinergic and cardiovascular side effects, sometimes life-threatening. The SSRIs, though not devoid of side effects, proved more tolerable and much safer in respect to overdosing. Other 2nd generation antidepressants include the atypical antidepressants, like the tetracyclics mianserin (a NA reuptake inhibitor) and mirtazapine (an α2 adrenoceptor antagonist), trazodone and nefazodone (5-HT2A antagonists) and bupropion (DA reuptake inhibitor).

The classification, distribution and characterization of the 5-HT receptors is described in section 1.4. Based on the molecular biological properties and pharmacological profiles, seven distinct classes of 5-HT receptors are distinguished (5-HT1-7), several being further divided in different subtypes (*e.g.* 5-HT2A-2C). Bar the 5-HT3 receptor,
which is a ligand-gated ion channel, the 5-HT receptors belong to the G-protein
coupled receptor (GPCR) superfamily.

Several animal models used in antidepressant research are described. These models
are either acute (forced-swim test, learned helplessness and tail suspension) or chronic
(chronic mild stress and olfactory bulbectomy). Despite the fact that all these animal
models detect false positives and negatives, and although, in practice, they are used
primarily to follow-up on leads, in theory they would require no preconceptions as to
the mechanisms of action of new antidepressant compounds and thus could generate
novel neurochemical hypotheses for depression.

The last part of the chapter concerns the different strategies currently followed in the
development of future, 3rd generation antidepressants. The principal advantage of the
2nd generation over the 1st was their improved side-effect profile. However, two major
therapeutic objectives are still to be met: an improved overall and instant onset of
clinical efficacy. One of the strategies involves the combination of SSRIs (or other
classes of antidepressants) with a 5-HT autoreceptor antagonist. The justification of
this combination comes from the hypothesis that desensitization of these
autoreceptors is obligatory for the therapeutic efficacy of antidepressants. This
hypothesis forms the justification of the scientific efforts described in chapters 2-4.

Other strategies focus on the endogenous tetrapeptide 5-HT moduline, which shows
high affinity and selectivity for the 5-HT1B (auto)receptors, calcium channel
antagonists, NMDA antagonists, and the σ receptors and the role of its endogenous
neuropeptide Y.

In Chapter 2, the synthesis and preliminary in vitro (5-HT1A affinity and pA2 values
at guinea pig ileum tissue) and in vivo (ultrasonic vocalization, hypothermia and 5-
HTP accumulation) pharmacology of several o-substituted aryl piperazine, N-
substituted aminopiperidine and p-substituted (sulfon)benzamide analogues of
WAY100635 is described. It is shown that the O-desmethyl analogue is the functional
most potent 5-HT1A antagonist at postsynaptic 5-HT1A receptors. In a biochemical
assay, it is demonstrated that the 5-HTP accumulation following the administration of
WAY100635 in the nucleus accumbens and striatum (tendency), and in the tubercule
(significant) is decreased. From these results in can be concluded that WAY100635
does not act as a full, silent antagonist in these brain areas. The aminopiperidine
analogues display no in vitro affinity nor functional in vitro or in vivo antagonistic
efficacy. The p-acetyl (p-MPPOAc) and p-hydroxy (p-MPPOH) benzamide
analogues show high affinity for the 5-HT1A receptor, mixed in vitro efficacy and no
antagonistic potency in the rat hypothermia assay (10 μmol/kg sc. vs. 1 mg/kg 8-OH-
DPAT sc.). This is inconsistent with previous obtained results with two other
benzamide analogues, p-MPPI and p-MPPF (full antagonists with ED50 of 3 and 5
mg/kg vs. 0.5 mg/kg 8-OH-DPAT sc.).

Chapter 3 describes a more detailed pharmacological evaluation of the para
substituted benzamides. It is shown that the p-hydroxy analogue, p-MPPOH, has the
highest affinity for the h5-HT1A receptor and the highest antagonistic efficacy in the
cAMP assay. In vivo, both WAY100635 and \( p \)-MPPOH act as full antagonists vs. 0.2 mg/kg 8-OH-DPAT sc. at pre- (microdialysis) and postsynaptically (hypothermia) located 5-HT\(_{1A}\) receptor sites. In the microdialysis assay, WAY100635 is 20 times more potent and in the hypothermia assay 400 times more potent than \( p \)-MPPOH. The postsynaptic 5-HT\(_{1A}\) receptors appear to be 80 times more sensitive to WAY100635 as compared to the 5-HT\(_{1A}\) autoreceptors. This is probably due to the large receptor reserve for the somatodendritic 5-HT\(_{1A}\) receptors. However, notwithstanding the presence of a somatodendritic receptor reserve, the 5-HT\(_{1A}\) autoreceptors are two times more sensitive to \( p \)-MPPOH than the postsynaptic receptor subtype. Such a selective antagonist would instantly mimic 5-HT\(_{1A}\) autoreceptor desensitization, without interfering with the required activation of postsynaptic 5-HT\(_{1A}\) receptors via the enhanced 5-HT release.

**Chapter 4** deals with the synthesis and *in vitro* (r5-HT\(_{1B}/c5-HT_{1B}\) affinity and 5-HT uptake in synaptosomes) and *in vivo* (microdialysis in rat ventral hippocampus) pharmacology of structural analogues of the 5-HT\(_{1B/1D}\) antagonist GR127935 (o-MeO-phenylpiperazine) and the 5-HT\(_{1B}\) inverse agonist SB224289 (spiropiperidino indoline). It is shown that the incorporation of the arylpiperazine part of GR127935 in a tetracyclic azepine ringsystem or the substitution of the arylpiperazine for a chromane structure provides structural analogues devoid of 5-HT\(_{1B}\) receptor affinity. Introduction of a second o-methoxy substituent in the arylpiperazine increases the selectivity for the r5-HT\(_{1B}\) receptor. Furthermore, it is shown that the spiropiperidine SB222553 is equipotent to SB224289. Substitution of the spiropiperidinoindoline of SB224289 for a 6-piperazinoindoline moiety also provides structural analogues with nanomolar affinity for the r5-HT\(_{1B}\) receptor. Substitution of the 5-membered oxadiazole ring for N-alkylamidines decreases receptor affinity by a factor 10. In vivo, GR127935, SB222553 and the 6-piperazinoindoline analogue of SB224289 all augmented the citalopram-induced increase in 5-HT release in the rat ventral hippocampus. Thus, despite previous claims, it is shown that the oxygen substituent in both GR127935 and SB224289 is not essential for antagonist functionality at terminal 5-HT\(_{1B}\) receptors *in vivo*. The N-methyl-piperazinoamidine analogues of GR127935 and SB222553, notwithstanding their high r5-HT\(_{1B}\) receptor affinity, failed to enhance the citalopram-induced increase in 5-HT release.

In *Chapter 5*, the synthesis and preliminary *in vitro* (binding profile) and *in vivo* (microdialysis) pharmacology of several 6- and 6,9-substituted analogues of mianserin are described. The currently marketed tetracyclics mianserin (NA reuptake inhibitor) and its successor mirtazapine (\( \alpha_2 \)-antagonist) both act as antidepressants. Mianserin elevates the NA release, while mirtazapine elevates both NA and 5-HT release in the brain. Both antidepressants suffer from side effects that are related to their high affinity for the histamine H\(_1\) receptor (sedation, weight gain). The new tetracyclics presented in *Chapter 5* all showed diminished affinity for the H\(_1\) receptor (5 - 100 times). 6-TfO- and 6-TsO-mianserin showed a remarkable selectivity for the
5-HT$_{2A}$ receptor subtype. 6-MeO-mianserin showed the highest affinity for the 5-HT$_{2A/2C}$ receptor. An electrochemical oxidation study of mianserin, showed the formation of oxidation products with molecular weights corresponding to those of known mianserin metabolites. MS-MS studies showed, that no hydroxylation products were formed and that in the conditions used, oxidation took place only at the 6-membered ring containing the basic nitrogen. Similar oxidation patterns were shown for 6-MeO-mianserin and several other tetracyclic analogues. 6-TfO-mianserin required a higher oxidation potential then the other compounds. This is yet another indication that aryltriflates are metabolically more stable and that they can serve as an alternative for aromatic methoxy substituents.

In vivo, 6-methoxymianserin elevates both NA and 5-HT release. The in vitro binding profile of 6-methoxymianserin suggests that the inhibitory tone on NA release might be blocked via 5-HT$_{2A/2C}$ receptors. The elevated NA levels, in turn, then stimulate the firing of 5-HT neurons via the $\alpha_1$ receptor, which results in an increase in hippocampal 5-HT release. The in vivo effects of 6-methoxymianserin and the diminished affinity for the H$_1$ receptor suggests that 6-methoxymianserin might provide a new tetracyclic antidepressant with fewer of the H$_1$-related side-effects.

Chapter 6 describes the resolution and in vitro (binding profile) and in vivo (microdialysis in rat ventral hippocampus) pharmacological evaluation of the enantiomers of 6-methoxymianserin. An attempt to obtain the enantiomers via asymmetric synthesis failed, due to racemization during the conversion of a secondary alcohol into a chlorine atom (simultaneous S$_{N}$2 and S$_{N}$i substitution). The optically pure enantiomers were obtained by means of chiral HPLC over a cellulose-based OD column. The absolute configuration was determined chemically, via O-demethylation, triflation and subsequent reduction of (-)-6-methoxymianserin to (R)-(−)-mianserin. The (S)-enantiomer displays higher affinity for the 5-HT$_{2A/2C}$ receptors than the (R)-enantiomer. The (S)-enantiomer also shows high selectivity for the 5-HT$_{2A/2C}$ receptors (>100 times). The (R)-enantiomer, on the other hand, also shows reasonable affinity for the $\alpha_1$- and $\alpha_2$-adrenoceptors (no selectivity), the 5-HT$_{1D}$ receptor and the dopamine D$_2$ and D$_{4,2}$ receptors. The (R)-enantiomer has a favorable ‘Meltzer’ ratio (5-HT$_{2A}$/D$_2$) over the atypical neuroleptic clozapine. Therefore, if the (R)-(−)-6-methoxymianserin proves to be a D$_2$ antagonist, it might also have potential as an atypical antipsychotic.