FLEXIBLE AND CONFORMATIONALLY CONSTRAINED 1-ARYLPIPERAZINE ANALOGS OF GEPIRONE

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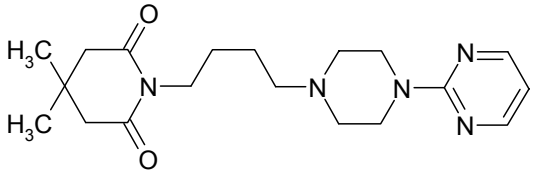
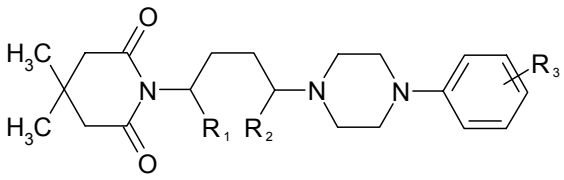
Recently, clinical trials have demonstrated that gepirone is effective and well-tolerated agent in the treatment of major depressive disorder.[1,2] In continuation of our chemical and pharmacological studies in arylpiperazine group of 5-HT_{1A} receptor ligands we designed and synthesized series of gepirone analogs containing tetramethylene (**1a**–**3a**) and conformationally restricted 1e,4e-cyclohexylene (**1b**–**3b**) spacer which connected arylpiperazine pharmacophore and imide fragment.



gepirone



1a–**3a** and **1b**–**3b**

series **a**: $R_1 = R_2 = H$
series **b**: $R_1, R_2 = -(CH_2)_2-$
$R_3 = o\text{-}OCH_3$, m-Cl, m-CF_3

1-Arylpiperazines **1**–**3** were formed by the reaction of appropriate amines with 3,3-dimethylglutaric anhydride in boiling xylene, and their structure was confirmed by ^{1}H NMR spectra. The key step in the preparation of compounds of series **b** was a multistage synthesis of new constrained 4-(1-arylpiperazine)cyclohexylamines. These *m*-chloro and *m*-trifluoromethyl substituted amines were obtained according to the procedure described earlier by us for the synthesis of 4-[1-(*o*-methoxyphenyl)piperazine]cyclohexylamine.[3] For pharmacological experiments free bases of the tested compounds were converted into hydrochloride salts and their molecular formulae and molecular weights were established on the basis of elemental analyses.

The newly synthesized compounds were evaluated for affinity at 5-HT_{1A} and D_2 receptors. The flexible derivatives **1a**–**3a** showed very high 5-HT_{1A} receptor affinity (K_i = 4–8 nM) and their constrained counterparts (**1b**–**3b**) only slightly lower (K_i = 9–22 nM) whereas for gepirone K_i = 32 nM was found.[4] All new gepirone analogs have been examined *in vivo* in animal models to determine their functional effects on pre- and postsynaptic 5-HT_{1A} receptors.

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[2] D. S. Robinson et al., *Clin. Ther*. **2003**, *25*, 1618–1633.
[3] M. H. Paluchowska et al., *J. Med. Chem*. **1999**, *42*, 4952–4960.
[4] J. L. Mokrosz et al., *J. Med. Chem*. **1992**, *35*, 2369–2374.