NEW 4-[ω-(DIARYLMETHYLAMINO)ALKYL]- AND 4-[ω-(DIARYLMETHOXY)ALKYL]-1-ARYLPIPERAZINES AS SELECTIVE 5-HT_{1A}/5-HT_{2A} RECEPTOR LIGANDS WITH DIFFERENTIATED IN VIVO ACTIVITY

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Two series of novel 4-ethyl- or 4-propyl-1-arylpiperazines (5–12) with the 4,4’-disubstituted diphenylmethylamino (series a) or the diphenylmethoxy (series b) terminal fragment were synthesized and evaluated for their binding affinity at 5-HT_{1A} and 5-HT_{2A} receptors. The influence of the introduction of 4-methyl, 4-chloro or 4-fluoro substituents at both phenyl rings of that terminal moiety on in vitro and in vivo 5-HT_{1A} receptor activity of those modified compounds was discussed. Compounds 5a, 6a, 9a–12a, 5b, 6b, 9b, 11b and 12b displayed high to fairly high affinity for 5-HT_{1A} receptors (Kᵢ = 2.4–72 nM). Compounds of both series showed low or very low 5-HT_{2A} receptor affinity (Kᵢ = 155–5400 nM). Amines 5a, 6a, 11a, and their ether analogs 5b, 6b and 11b, also possessed high or moderate α₁-adrenoceptor affinity (Kᵢ = 6–104 nM). The functional activity of compounds 5a, 6a, 9a–12a, 5b, 8b, 9b, 11b and 12b was tested in vivo in the commonly used animal models. The majority of those ligands behaved like 5-HT_{1A} receptor antagonists, their influence on the pre- and/or postsynaptic sites being diverse, though. They exhibited characteristics of partial agonists of postsynaptic 5-HT_{1A} receptors (11a), of weak antagonists of pre- and postsynaptic sites (12a, 9b), of antagonists of presynaptic (5a) or of antagonists of postsynaptic 5-HT_{1A} receptors (9a, 10a, 5b, 8b, 11b and 12b) while, 6a was devoid of functional activity at those receptors. The above findings indicate that introduction of 4-methyl, 4-chloro or 4-fluoro substituents to the diphenylmethyl part of the 1-(2-methoxyphenyl)piperazines tested in vivo may modify their 5-HT_{1A} receptor functional activity.

**Key words:** selective 5-HT_{1A}/5-HT_{2A} ligands, arylpiperazine derivatives, structure-activity relationship