A NEW ARYLPIPERAZINE DERIVATIVE PK47 - DUAL SEROTONIN 5-HT1A/5-HT2A RECEPTOR LIGAND WITH ANXIOLYTIC ACTIVITY

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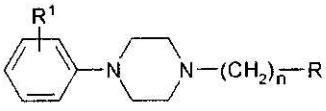
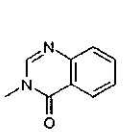
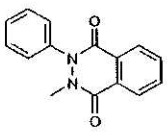
Of the many brain neuronal systems, the serotonin (5-HT) one is currently the common biological target for development of new psychotropic drugs. Recently, a considerable attention has centered on compounds acting at both 5-HT1A and 5-HT2A receptors as potential anxiolytic and antidepressant agents. Thus, based on our previous systematic study on structure-activity relationship in arylpiperazine group of serotonin ligands we designed and synthesized 12 new derivatives, containing quinazolidin-4(3H)-one (a), 2-phenyl-2,3-dihydrophthalazine-1,4-dione (b) and 1-phenyl-1,2-dihydropyridazine-3,6-dione (c) as a terminal fragment.



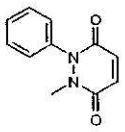
R =



a



b



c

R^1 \ n	3	4
o-OCH_3	1	2
m-Cl	3	4

All compounds were evaluated for affinity at 5-HT1A and 5-HT2A receptors and the most potent were further tested *in vivo* to assign their agonistic/antagonistic properties.

Affinity for 5-HT1A receptors varied from 11 nM (2c) to 415 nM (3b) whereas for 5-HT2A ones extend from 16 nM to 2100 for 3a and 1c, respectively. Ortho-methoxyphenylpiperazine derivatives (1 and 2) were always more active at 5-HT1A than the respective meta-chloro analogues 3 and 4. Moreover, compounds with 4-membered alkyl chain spacer (2 and 4) were more potent 5-HT1A ligands than those containing 3 methylene groups. Thus, these *in vitro* results were in line with commonly observed trends of affinities within arylpiperazine group of ligands. With regard to the 5-HT2A receptors only two significantly active compounds were found, both containing R^1 = m-Cl and R = a fragments.

All 7 compounds (2a, 4a, 1b, 2b, 1c, 2c and 4c) tested *in vivo* reveal antagonistic activity at postsynaptic 5-HT1A receptors whereas two derivatives (3a and 4a) behaved like 5-HT2A antagonists. On the basis of functional results compound 4a (PK47) was selected for further *in vivo* preclinial study as a potential anxiolytic and/or antidepressant agent. It was found that 4a exerts an anxiolytic-like activity in the conflict drinking test in rats, since it dose-dependently increased the number of punished licks. Moreover, this effect of PK47 was more potent in terms of active dose than that produced by diazepam (used as a reference drug).

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