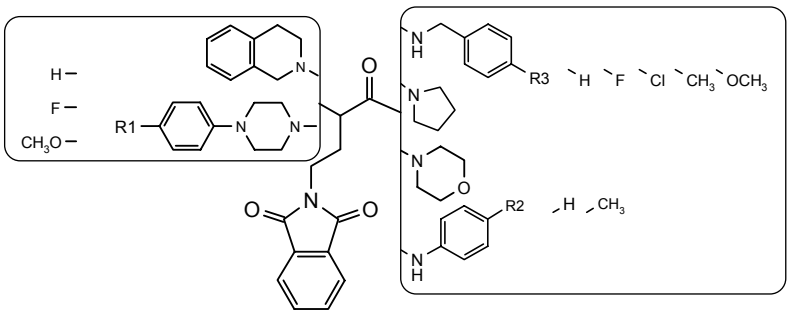
DESIGN AND SYNTHESIS OF NEW DERIVATIVES OF α-SUBSTITUTED AMIDES OF γ-PHTHALIMIDOBUTYRIC ACID WITH POTENTIAL GABA-ERGIC ACTIVITY

Anna Musiał, Krzysztof Więckowski, Magdalena Wójcik, Jacek Kamiński, Barbara Malawska

Department of Physicochemical Drug Analysis; Laboratory of Pharmacobiology, Faculty of Pharmacy, Medical College, Jagiellonian University, Kraków, Poland

4-Aminobutyric acid (GABA) is the major inhibitory neurotransmitter in the central nervous system, and exerts its action through three classes of GABA receptors. $GABA_A$ receptor agonists can be useful in certain neurological and psychiatric disorders as antiepileptic, myorelaxant, antinociceptive, anxiolytic and hypnotic agents. It was proved that among different chemical classes of compounds with GABA-ergic activity, appropriate gabaamides act as a full agonists of $GABA_A$ receptors [1]. Progabide, which structurally belongs to 4-aminobutyramides group is well known antiepileptic drug which functiones as a GABA prodrug.

Searching for a novel ligands of the GABA binding site of GABA-A receptors, we have prepared a series of α-substituted amides of γ-phthalimidobutyric acid. These phthalimide series may be considered as analogues of GABA prodrugs, in which the amino function is converted into an imido group and the acid group is changed into an amido group.



The newly synthesized compounds were tested *in vitro* in [^{3}H]muscimol binding assay (as indicates of GABA-A receptor affinity). Among investigated compounds the most active was *N*-(4-methylbenzylamide) of 2-(4-phenylpiperazine)-4-phthalimidobutyric acid with IC_{50} = 8.1 ± 2.8 μM value. Preliminary anticonvulsant *in vivo* tests of these compounds i.e. a maximal electroshock (MES) test, a subcutaneous metrazole (scMet) induced seizures, and a rotorod toxicity (Tox) assay on mice were employed.

[1]. R. Carlier, E. S.-H. Chow, R. L. Barlow, J. R. Bloomquist, Bioorg. Med. Chem. Lett., 2002, **12** 1985.

Acknowlegements: We thank Dr J. P. Stables for anticonvulsant testing and to the Anticonvulsant Screening Project (ASP), National Institute of Neurological Disorders and Stroke, NIH, Bethesda, Maryland USA.