Structure-Activity Relationship of 3-Aryloxypyridyl-4*H*-1,2,4-triazoles as Novel Flexible Benzodiazepine Analogues

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Abstract

Background/aim: Benzodiazepines (BZDs) are among one of the most important drugs affecting central nervous system, clinically used as anxiolytic, sedative/hypnotic, muscle relaxant, and anticonvulsant agents. BZDs operate through binding to a specific domain of $GABA_A$ receptor, a chloride ion channel, and modulate the action of GABA (γ-amino butyric acid). In previous works, diverse non-rigid structures, preserving an aromatic or heteroaromatic A-ring (participating in π-π stacking interactions with aromatic amino acids of the receptor), a coplanar proton-accepting group at position 2 at a suitable distance from ring A, (interacts with histidine residue of the receptor) and an out-of-plane phenyl ring, were reported to have considerable anticonvulsant activity. In most benzodiazepines, the presence of electron withdrawing substituents at ortho position of out-of-plane phenyl ring improves the activity, while in meta and para position eliminate the activity. Docking studies have shown the possible different mode of interaction for the non-rigid analogs with the binding site. Therefore, it is interesting to investigate if meta or paras-substituted analogs preserve affinity on benzodiazepine receptors.

Materials and methods: The new non-rigid 3-aryloxypyridyl-4*H*-1,2,4-triazoles were synthesized and their binding affinity to $GABA_A$/BZD Receptor complex was evaluated by their ability to displace [^{3}H]-flumazenil (Ro15-1788) from its specific binding in rat cortical membrane tissue.

Results: The concentration of the tested compounds (non-radioactive ligands) that inhibits the binding of [^{3}H]-flumazenil by 50% is considered as IC_{50} values. Interestingly, the meta and para of non-rigid analogs, in contrary to classic benzodiazepines were shown significant affinity to BZD receptors.

Conclusion: Recent introduced flexible BZDs show very high affinity to $GABA_A$/BZD Receptor complex, but possible different mode of interaction requires structure-activity relationship studies.

Keywords: 1,2,4-triazole, flexible benzodiazepines, $GABA_A$/BZD receptor binding assay