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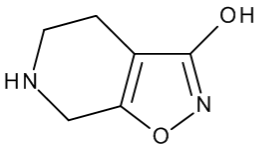
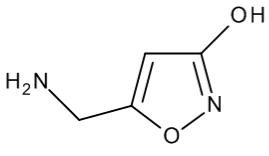
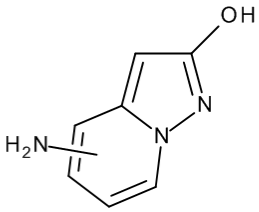
Isosteric replacement is a widely used approach within medicinal chemistry for improving properties of a lead compound such as bioavailability, selectivity, and potency. A number of bioisosteric relationships have been established for a number of functional groups including the carboxylic acid. Heterocyles such as tetrazole, 3-hydroxyisoxazole, 3-hydroxyisothiazole, 3-hydroxy-1,2,5-thiadiazole, 3-cyclobutene-1,2-dione and the 1,2,5-oxadiazole system have been successfully applied as carboxylic acid bioisosteres. Medicinal chemistry programmes have provided an extensive variety of bioisosteric replacements for the carboxylic acid in GABA, the major inhibitory neurotransmitter in the mammalian central nervous system. The 3-hydroxypyrazole ring system has previously been shown to be a bioisostere of the carboxylic acid of GABA within the $GABA_a$ receptor system. In this study, we introduce the bicyclic hydroxypyrazolo[1,5-*a*]pyridine scaffold (see scaffold **1**) as the main backbone of potential ligands for the orthosteric site in the $GABA_a$ receptor. Apart from mimicking the acidic properties of the carboxylic acid group in GABA and the 3-hydroxyisoxazole in the $GABA_a$ agonists, THIP and muscimol, the conformational locked hydroxypyrazolo[1,5-*a*]pyridine moiety offer additional positions for introducing substituents in fixed directions. Taking advantage of this option, we have investigated the effect of introducing the amino containing substituents in different positions of the scaffold (**1**) and of the corresponding piperidine scaffold (**2**), thus enabling investigation of the requirement for the mutual position of the functional groups and exposing access to cavities/channels associated to the orthosteric binding site, reaching out for subtype-selectivity.



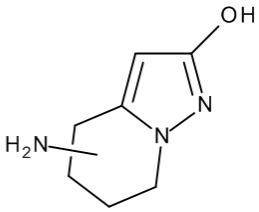
THIP



Muscimol



1



2

A series of hydroxypyrazolo[1,5-*a*]pyridine (**1**) and hydroxypyrazolo[1,5-*a*]piperidine (**2**) derivatives were synthesized and pharmacologically characterized in a [^{3}H]-muscimol displacement assay at native $GABA_a$ receptors and electrophysiological assays at relevant $GABA_a$ receptor subtypes. The synthesis and pharmacological properties are reported and discussed in terms of the structural knowledge available for the $GABA_a$ receptor.

References

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