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Novel family of fused tricyclic [1,4]diazepines: Design, synthesis, crystal structures and molecular docking studies

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ABSTRACT

An efficient one-pot strategy for the synthesis of a new family of imidazo[1,4]diazepines has been developed and its mechanism has been proposed, which follows a seven-membered ring closure reaction. The condensation of 2- and 4-imidazolecarboxaldehyde with pyrazole amines provides six compounds **1**–**6**, which are based on two types of fused tricyclic scaffolds. All presented compounds were fully spectroscopically characterized and their structure was unambiguously determined by single crystal X-ray crystallography. Molecular docking studies reveal a high similarity between binding modes of diazepines **1**, **6** and eticlopride in the dopamine D_3 receptor, as well as between enantiomers **2**S, **6**S and nortriptyline in dopamine transporter DAT.

1. Introduction

Diazepines are a well-known class of heterocycles because they possess a wide spectrum of biological activity including anxiolytic, hypnotic, sedative, anticonvulsant, skeletal, amnestic and muscle relaxant properties.[1]

The diazepine scaffold has gained importance since 1957, when the first benzodiazepine (chlordiazepoxide) was synthesized and studied in terms of psychotropic activity.[2] The discovery of the sedative effect of chlordiazepoxide resulted in its introduction to medical practice in the 1960s, in parallel giving new insight on benzodiazepine systems.[3] In the following years, extensive research commenced, with the main focus given to the synthesis of other representatives of this group, including: 1,4-benzodiazepine (lorazepam), 1,5-benzodiazepine (triflubazam, clobazam), triazolobenzodiazepines (estazolam, loprazolam) thienodiazepine (clotiazepam, brotizolam) and imidazolobenzodiazepine (midazolam).[4] To date, over 40 benzodiazepines find applications as drugs that greatly impact the central nervous system (CNS), especially in the brain. The mechanism of action of benzodiazepines is based on the formation of a supramolecular complex with the $GABA_A$ chloride ion channel *via* an allosteric binding site of benzodiazepine receptors (BzR).[5] Conformational enantiomerism of the benzodiazepine scaffold has beneficial implications on their ability to bind to the benzodiazepine binding site.[6] Such a complex modulates the action of GABA (γ-aminobutyric acid)[7] on chloride ion flux,[8] thus resulting in inhibition of the neuro-transmission process. 1,4-Benzodiazepines such as diazepam and lorazepam belong to the family of positive modulators of $GABA_A$ receptors, thus they show muscle relaxant, anxiolytic, and anticonvulsant activity.[9]

In recent decades, a number of modifications that focus on the diazepine core have been performed, which has broadened their applicative spectrum in terms of antifungal, antibacterial, antiviral, antitumor and psychotropic properties.[10] A key role in the synthesis of the diazepine scaffold is a cyclocondensation process, which should proceed with high regioselectivity.[11] The fusion of a heterocyclic system to the seven-member diazepine ring is a promising method for the synthesis of a wide spectrum of diazepine derivatives so as to tune their biological functions as well as reach higher degree of medical selectivity. In recent years, microwave-assisted reactions of cyclocondensation have gained importance

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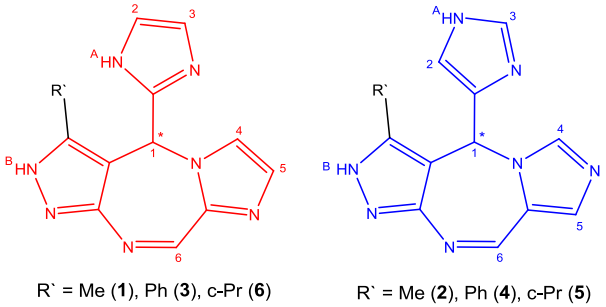
due to milder reaction conditions, increasing reaction yields and formation of cleaner products.[12] An intramolecular Mitsunobu cyclization can be employed for the synthesis of bi- and tri-cyclic benzofused thiadiazepine-dioxides.[13] Significantly, the diazepine ring can be obtained by recyclization of lactones in the presence of hydrazine[14] or cyclization of aminopyrazoles.[15] Although diazepines are mostly obtained by the use of multistep reactions, in recent years there has been an increase in the number of reported one-pot syntheses, including intramolecular amidation of amino acid esters[16] or condensation of diamines with various 1,3-diketones in the presence of heteropolyacid (HPA) as catalysts.[17] The formation of the diazepine core may be accomplished by rearrangement reactions such as the Stevens reaction,[18] or rearrangement from the eight-membered lactone to the seven-membered lactam (diazepine ring) under acidic conditions.[19] Such synthetic strategies allowed the introduction of a wide variety of desired groups into the diazepine scaffold, which further extended their applications.

Pyrrolo-benzodiazepines (PBDs) have the ability to recognize and bind specific sequences of DNA, thus they can play a role as regulators of gene expression and find application in the treatment of genetic disorders as well as cancer. In addition, PBDs are highly selective anti-infective agents.[20] Imidazodiazepines exhibit high in vitro activity and selectivity against lung, breast, ovarian and prostate cancer cell lines.[21] Heterocycles that contain an imidazodiazepine ring act as inhibitors of guanase, thus can be effectively used in viral and bacterial therapies.[22] The imidazole moiety is nowadays widely used in the drug design strategy due to its pharmacological activity.[23] In addition, the imidazodiazepine scaffold shows high activity against rotavirus and dual anti-HCV/anti-HIV properties.[24] Another interesting aspect of imidazodiazepines is their antiproliferative activity resulting in antitumor,[25] antibacterial and antifungal activity.[26] Another representative that belongs to this group of compounds is midazolam (introduced in the treatment under the commercial name Dormicum) which has gained importance and popularity as a psychotropic drug due to its potent anxiolytic and sedative properties.[27]

In this paper, we describe a simple and efficient one-pot strategy for the synthesis of a new family of imidazodiazepines. The condensation of 2- or 4-imidazole carboxaldehyde with a pyrazole moiety provides two types of fused tricyclic scaffolds (Scheme 1). The use of 2-imidazolecarboxaldehyde with pyrazole moieties leads to methyl (**1**), phenyl (**3**) and cyclopropyl (**6**) derivatives of 2-imidazo[1,4]diazepines, while the use of 4-imidazolecarboxaldehyde provides methyl (**2**), phenyl (**4**) and cyclopropyl (**5**) derivatives of 4-imidazo[1,4]diazepines. All compounds presented herein were fully determined by spectroscopic methods as well as unambiguously confirmed by single crystal X-ray crystallography. A possible mechanism for these reactions was also proposed. Obtained structures were docked to membrane



Scheme 1. Schematic representation of diazepines 1–6 based on 2-imidazodiazapine scaffold (left) and 4-imidazodiazepine core (right).

($GABA_A$, dopamine D_3, serotonin $5HT_{1B}$), neurotransmitter transporter (DAT) as well as enzyme (monoamine oxidase B) receptors so as to gain insight if those newly synthesized compounds could be of use as therapeutics in medicine.

2. Results and discussion

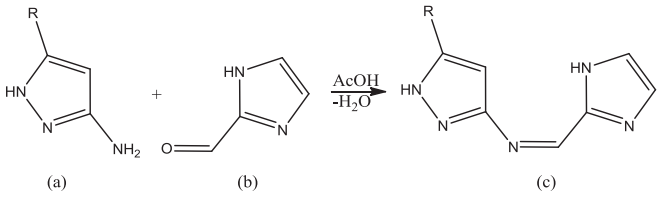
2.1. Proposed mechanism for the synthesis of [1,4]-diazepines

One-pot synthesis of [1,4]-diazepines occurs *via* two main stages, the first of which is based on the acid-catalysed condensation of a primary amine (a) and an aldehyde (b) (Scheme 2) in accordance with the known mechanism of imine formation.[28]

The Schiff Base (c) was isolated from the reaction mixture of **1** and its presence was confirmed by ^{1}H NMR spectroscopic analysis (cf. Fig. S17). The presence of a secondary amine group in the resulting imine (c) allows for its further reaction with a second molecule of aldehyde (b), which is the starting point of the second stage. This reaction is initialized in the same way as the process of enamine formation and includes an identical molecular pathway as described by Patil and Sunoj until the formation of carbinolamine.[29]

The proposed mechanism for this reaction (Scheme 3) is started by the protonation of the carbonyl group of the aldehyde, which makes it more electrophilic and susceptible to attack by a neutral nucleophilic amine. The carbonyl carbon atom is attacked by the lone pair of electrons on the amine nitrogen atom (step I), which results in the formation of a protonated tetrahedral intermediate. The deprotonation of the imidazole ring (N–H) allows for movement of the electron pair (step II) to the imidazole ring and further towards the protonated tetrahedral nitrogen, which leads to a neutral carbinolamine (step III). Next steps involve the protonation of hydroxyl group (step IV), which contributes to the subsequent removal of a water molecule (step V). The latter stage gives rise to the flat carbocation, which is stabilized by the resonance of imidazole ring. Finally, π-electrons of the pyrazole ring attack the carbocation (step VI), resulting in the ring closure. This stage is initiated by the deprotonation of the H–N bond from the pyrazole ring, which allows for the attack on the carbocation as a result of the electron density shift from the N-heterocyclic ring. The detachment of a proton from the pyrazole moiety (step VII) leads to the movement of electrons to neighboring nitrogen, which then attach the proton (step VIII), thus restoring the aromaticity of the pyrazole ring.

A proposed mechanism for this reaction is based on nucleophilic substitution S_N1. A key step of this mechanism is the attack of π-electrons of the pyrazole ring onto the flat carbocation at the imidazole ring. Please note that such a mechanism allowed us to explain the racemic character of the synthesized diazepines, since the trivalent carbocation is prochiral and the nucleophile can approach its *re*- or *si*-faces with the same probability. Moreover, we carried out the same reaction by using 3-aminoisoxazole, but the diazepine core was not formed (in this reaction, the amide and imine of isoxazole were obtained, included in the SI – Figs. S18–S19). Thus, deprotonation of the pyrazole ring activates



Scheme 2. The synthesis of imines as the first step in formation of diazepines.