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Synthesis of (3*S*,3a*S*,6a*S*)-2-Acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide *via* an Oxidative Cleavage Using M-CPBA. ADME Approach

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Abstract

Novel (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide has been synthesized by oxidative cleavage in the presence of m-CPBA in good yield. The analysis of the 1D and 2D NMR spectra unambiguously confirms the stereochemistry of the synthesized product. Bioinformatic study were carried out for the synthesized compound using Swiss ADME program to get insight of its appropriate ADME properties and to avoid the failure of candidate drugs at the clinical stage. Results show that (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide was within the range set by Lipinski's rule of five, displayed higher gastrointestinal absorption and inhibition of all CYP isoforms.

Keywords: epoxy, isoxazolidine, oxidative cleavage, enantiopure, ADME properties

Introduction

Isoxazolidines have been used as precursors to access natural and non-natural bioactive molecules [1-5]. Also, some derivatives of isoxazolidines have shown remarkable biological activities such as antimicrobial [6,7], antioxidant [6,8], antifungal [9], anticancer [10], and anti-inflammatory [11]. Recently, we have shown that isoxazolidines can be considered as powerful antihyperglycemics [12,13].

In this communication, we propose the synthesis of an unprecedented chiral isoxazolidine derivative, namely (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4**). The synthesized analogue was further for its physicochemical, pharmacokinetic, and druglikeness properties.

Materials and methods

General methods

Chemicals were bought from Merck and Sigma-Aldrich and used without further purification. TLC was performed using aluminium plates pre-coated with silica gel 60 or 60 F254 (Merck) and visualized by UV light (254 nm). The NMR spectra were recorded on a Bruker DRX 400 spectrometer at 25 °C, unless otherwise stated. ^{1}H- and ^{13}C-NMR signals were referenced to TMS and the solvent shift ($CDCl_3$). Coupling constants are given in Hz and without signs. HRMS (LSIMS) data were recorded in the positive mode (unless stated otherwise) using a Thermo Finnigan Mat 95 XL spectrometer.

Synthesis of (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (4)

To a solution of the cycloadduct **3 [12]** in dichloromethane cooled to 0 °C, was added dropwise a solution of m-CPBA in CH_2Cl_2 and the mixture was stirred for 2 min at 0 °C. The reaction was quenched with a sat. aqueous solution of $Na_2S_2O_3$ and a sat. aqueous solution of Na_2CO_3. The resulting mixture was then poured into H_2O and extracted with dichloromethane. The organic

phase was dried over $MgSO_4$, filtered and then concentrated. The residue was purified by flash chromatography on silica gel (7/3 PE/EtOAc) to give the product **4**.

(3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (4)

^{1}H NMR ($CDCl_3$, 400 MHz) 2.21 (s, 3H, CH_3); 2.81 (d, 3H, *J* = 4.8 Hz, CH_3); 3.59 (dd, 1H, *J* = 4.0 Hz, 11.2 Hz, H-7); 3.76 (dd, 1H, *J* = 7.2 Hz, 9.6 Hz, H-6); 3.85 (t, 1H, *J* = 7.2 Hz, H-4); 3.95 (brd, 1H, *J* = 9.6 Hz, H-6′); 4.13 (brd, 1H, *J* = 11.2 Hz, H-7′); 4.87 (dd, 1H, *J* = 3.6 Hz, 7.2 Hz, H-5); 5.02 (s, 1H, H-3) ; 6.51 (brs, 1H, NH).

^{13}C NMR ($CDCl_3$, 100 MHz) 20.6, 26.3, 49.0, 65.1, 73.8, 74.2, 85.5, 168.8, 174.2.

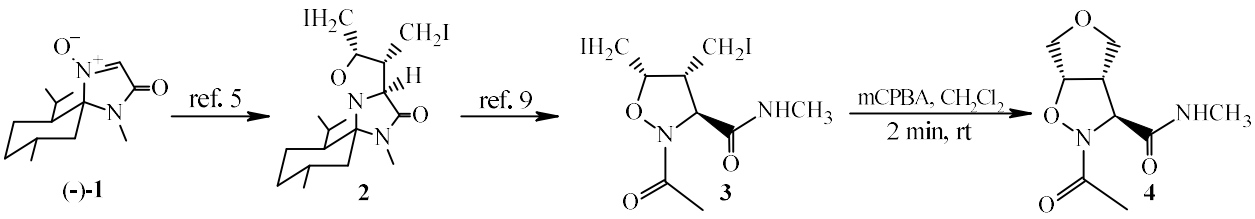
HRMS, calcd $C_9H_{14}N_2NaO_4$ $[M+Na]^+$: 237.2076 found 237.2086.

ADME prediction

Prediction of physicochemical, pharmacokinetic and drug-likeness properties of the synthesized compounds were analyzed through SwissADME web-based tool (http://www.swissadme.ch/).

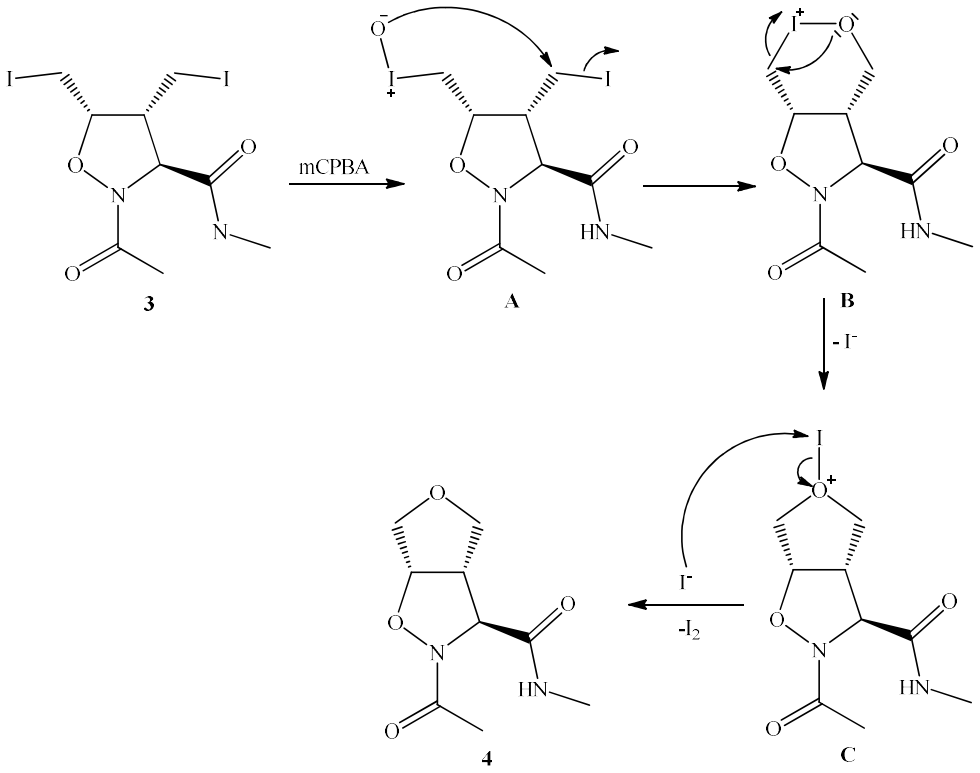
Results and discussion

We have used (3*S*,4*R*,5*S*)-2-acetyl-4,5-bis(iodomethyl)-*N*-methyl-1,2-oxazolidine-3-carboxamide (**3**) as an intermediate to access the desired product **4**. Indeed, intermediate **3** was obtained by applying the same procedures already published by Ghannay *et al*. (scheme 1) [12]. The nitrone derived from (-)-menthone reacts with 1,4-diiodo-2-butene to give the cycloadduct **2** enantiomerically pure and in good yield. The acid cleavage of the chiral auxiliary applied to intermediate **2** promotes the formation of isoxazolidine **3**. By reacting the diiodine derivative 3 with mCPBA under normal conditions and in the presence of dichloromethane, (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4)** could be isolated with an excellent yield of 93% (scheme 1).



Scheme 1. Synthesis of (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4**).

The proposed mechanism for this reaction proceeds in three steps: (i) an I-oxide intermediate **A** is formed firstly, followed by a nucleophilic substitution of the second iodine by oxygen to form a six-ring links **B**, (ii) the oxygen attacks the alpha carbon of iodine followed by cleavage of the C-I+ bond to yield 1-iodooxolanium **C**, (iii) iodide I- reacts with iodine followed by cleavage of the I-O+ bond to access epoxide **4** (scheme 2). This mechanism was inspired by a mechanistic study on the oxidative cleavage of isoxazolidine conducted by Ali *et al.* [14,15].



Scheme 2. Proposed mechanism for the formation of (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4**).

The stereochemistry of synthesized product **4** was based on the interpretation of the NOESY spectrum. Indeed, the spectrum showed strong correlations between the H4-H5 protons and no correlations between the H3 and H4 protons. This means that H4 and H5 are pointing in the same direction and are in an *anti*-position with respect to H3 (figure 1).

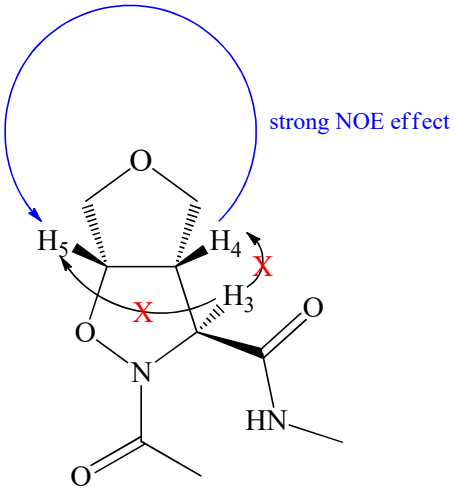


Figure 1. NOE effects for compound **4**

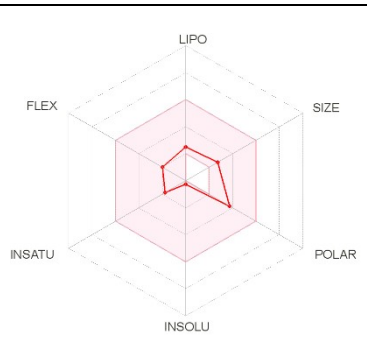
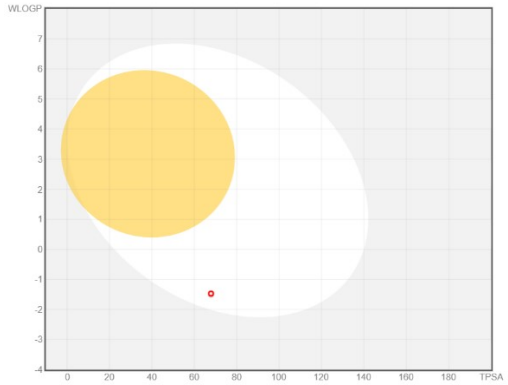
Pharmacokinetics studies

To screen quantitatively the chance for a molecule to become an oral drug, in silico prediction of molecular physicochemical parameters, druglikeness and pharmacokinetics are more important and crucial at the earlier phase of drug discovery and development [16-22]. It provides reliable data with low cost in a quick and easy manner. As shown (Table 1) the synthesized compound was found to be adhered to Lipinski's rule of five displaying good lipophilicity and a total polar surface area (TPSA) of 67.87 Å^2 which characterize a significant permeability in the cellular plasma membrane. An acceptable molar refractivity value and good bioavailability score of 0.55 have been also predicted.

The compound was non-P-glycoprotein (P-gp) substrates indicating its high absorption from the gastrointestinal (GI) tract and did not exhibit the property of blood brain barrier (BBB) penetration. Its skin permeation (LogK_P) was found to be-8.41 cm/s. the screened of compound **4** for CYP450 isoenzymes which are mainly involved in drug metabolism revealed non-inhibition of all CYP450 enzymes revealing that the designed compound do not suppress the metabolic function of the enzymes.

To get insight into the human gastrointestinal absorption (HIA) and blood-brain-barrier (BBB) permeability, BOILED-egg evaluation has been assessed *via* LogP and TPSA curves suggesting that it exert high gastrointestinal absorption (HIA) and appeared with red color indicating that was PGP^-.

Table 1. ADMET properties of Novel (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4**)

Physicochemical properties/Lipophilicity		**Druglikeness/Pharmacokinetics**	
Num. heavy atoms	15	**GI absorption**	High
Num. arom. heavy	0	**BBB permeant**	No
Fraction Csp3	0.78	**P-gp substrate**	No
Num. rotatable bonds	3	**CYP1A2 inhibitor**	No
Num. H-bond	4	**CYP2C19 inhibitor**	No
Num. H-bond donors	1	**CYP2C9 inhibitor**	No
Molar Refractivity	53.33	**CYP2D6 inhibitor**	No
TPSA	67.87 Å²	**CYP3A4 inhibitor**	No
Consensus Log $P_{o/w}$	-0.51	**Log Kp (skin permeation)**	-8.41 cm/s
Lipinski's Rule	Yes	**Bioavailability Score**	0.55
Bioavailability radar		**BOILED-Egg diagram**	
			

Conclusion

In this study, a new (3*S*,3a*S*,6a*S*)-2-acetyl-*N*-methylhexahydrofuro[3,4-*d*][1,2]oxazole-3-carboxamide (**4**) has been synthesized by oxidative cleavage reaction with mCPBA in good yield. The predictive ADME study revealed acceptable pharmacokinetics and druglikeness of the synthesized compound.

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