Egyptian Journal of Chemistry
http://ejchem.journals.ekb.eg/

Synthesis of a novel enantiopure imidazo-isoxazole derivatives and in silico prediction of ADME/pharmacokinetics properties

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Abstract

Some novel enantiopure 3-carboxylic isoxazolidine derivatives were synthesized by stereocontrol 1,3-dipolar cycloaddition (1,3-DC) between nitrone derived (-)-menthone with alkenes derived from phenol and benzyl alcohol. Furthermore, the synthesized molecules were optimized for their drug-likeness and pharmacokinetics parameters by using in silico methods.

***Keywords*:** isoxazolidines, enantiopure, chiral nitrone, drug-likeness, pharmacokinetics.

1. Introduction

Interest in amino-acids continues to grow over the years due to their crucial and diverse role in the organism [1-3]. In addition, many studies have confirmed the effectiveness of amino-acids to treat certain diseases [4-8]. Forthermore, they are widely used in the synthesis of biologically active peptide analogues [9-10]. The stereoselective synthesis of amino-acids, which constitute one of the most widespread classes of natural compounds in nature, has been widely studied in the literature [11-12]. However, chemists are still interested in developing new synthetic routes to access unnatural amino-acids. In our former work, we reported a particular and interesting methodology based on 1,3-dipolar cycloaddition which leads to natural and unnatural α-amino acids such as 4-hydroxyisoleucine [13-14], 4S-hydroxyornithine [15] and α-amino-(4-hydroxy-pyrrolidin3-yl)acetic acid derivatives [16] and other analogues [17-18].

3-Carboxylic isoxazolidine derivatives are considered as first-order precursors to access α-amino-acids [19]. In this context, we propose in this work the synthesis of new 3-carboxylic isoxazolidine derivatives via the 1,3-DC of nitrone with olefines derived from phenol and benzyl alcohol. In addition, to account for further *in vitro* biological activity data of the designed compounds,

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Receive Date: 08 March 2022, Revise Date: 29 March 2022, Accept Date: 07 April 2022.
DOI: 10.21608/EJCHEM.2022.126231.5597 .

in silico prediction of adsorption–distribution–metabolism–excretion (ADME)/pharmacokinetics properties were assessed.

2. Experimental

General methods

Reagents and solvents were used as purchased from Aldrich. Thin-layer chromatography (TLC) was performed on Silica Gel 60 F254 (Merck). The plates were visualized under UV light, or by gentle heating. ^{1}H and ^{13}C NMR spectra were recorded using a Bruker DRX300 spectrometer. Chemical shifts are quoted in parts per million, referenced to the residual solvent peak. The following abbreviations are used: (s, singlet), (d, doublet), (dd, doublet of doublets), (ddd, doublet of doublet of doublets), (t, triplet), (q, quadruplet), (quin, quintuplet), (m, multiplet), (br, broad). Coupling constants are reported in Hertz (Hz). HRMS (LSIMS) data were recorded in the positive mode (unless stated otherwise) using a Thermo Finnigan Mat 95 XL spectrometer. MS (ESI) data were recorded in the positive mode using a Thermo Finnigan LCQ spectrometer.

General procedure for synthesis of 3a-h:

To a solution of **1** (1 eq.) in toluene was added a various allyl phenyl ether **2a-h** (1 eq.). The mixture was refluxed for 72h with stirring. The obtained cycloadduct was purified by flash chromatography to separate the desired compound **3a-h**.

3a: (((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)benzene

Prepared from **1** (1 eq.) and (allyloxy)benzene **2a** (1 eq.) to afford **3a** (278 mg, 89 %) as white solid. NMR ^{1}H (Chloroform-D, 300 MHz) 0.84 (d, 3H, *J* 6.6 Hz), 0.86 (d, 3H, *J* 6 Hz), 0.90 (d, 3H, *J* 6.3 Hz), 0.85-0.90 (m, 1H), 1.23-1.27 (m, 2H), 1.35-1.37 (m, 1H), 1.44 (dd, 1H, *J* 13.8, 6.9Hz), 1.65-1.71 (m, 1H), 1.75-1.81 (m, 1H), 1.95-2.04 (m,1H), 2.04-2.07 (m,1H), 2.37 (dt, 1H, *J* 17.7, 8.7Hz), 2.75 (s, 3H, NCH_3), 2.75-2.79 (m, 1H), 3.99 (d, 1H, 9.6 Hz), 4.04 (t, 1H, *J* 8.4Hz), 4.07-4.11 (m, 1H), 4.20 (m, 1H), 6.89 (dd, 2H, *J* 2.1, 9.0 Hz), 6.93-6.97 (m, 1H), 7.20-7.26 (m, 1H), 7.26-7.30 (m, 1H). NMR ^{13}C (Chloroform-D, 75 MHz): 18.4; 22.3; 24.1; 24.3; 26.0; 29.4; 34.6; 35.5; 40.6; 48.1; 65.6; 68.0; 75.1; 89.5; 114.6; 121.0; 129.4; 158.5; 172.8. HRMS, calcd $C_{22}H_{32}N_2NaO_3$ $[M+Na]^+$: 395.2297, found 395.2305.

3b: 4-(((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)methoxybenzene

Prepared from **1** (1 eq.) and 4-(allyloxy)benzonitrile **2b** (1 eq.) to afford **3b** (278 mg, 89 %) as colorless oil. NMR ^{1}H (Chloroform-D, 300 MHz) 0.79-0.89 (m, 9H), 0.85-0.87 (m, 1H), 1.20-1.25 (m, 2H), 1.34 (dd, 1H, *J* 3Hz, 11.1 Hz), 1.41 (dd, 1H, *J* 6.6, 13.5 Hz), 1.60-1.66 (m,1H), 1.76 (d, 1H, *J* 14.4 Hz), 1.84-1.90 (m, 1H), 1.99 (d, 1H, *J* 12.9 Hz), 2.29-2.34 (m, 1H), 1.72 (s, 3H, NCH_3), 2.73-2.79 (m, 1H), 3.97 (d, 1H, *J* 9 Hz), 4.04 (dd, 1H, *J* 4.5, 10.5 Hz), 4.09-4.13 (m, 1H), 4.18-4.22 (m, 1H), 6.93 (dd, 2H, *J* = 8.7 Hz), 7.54 (dd, 2H, *J* = 8.4 Hz). NMR ^{13}C (Chloroform-D, 75 MHz): 18.4; 22.2; 22.3; 24.1; 24.3; 26.0; 29.3; 34.5; 35.1; 40.6; 48.0; 65.4; 68.4; 74.8; 89.4; 104.4; 115.4; 119.0; 133.9; 161.8; 172.5 (C=O). HRMS, calcd $C_{23}H_{31}N_3NaO_3$ $[M+Na]^+$: 420.2252, found 420.2258.

3c: 4-(((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)phenol

Prepared from **1** (1 eq.) and 4-(allyloxy)phenol **2c** (1 eq.) to afford **3c** (248 mg, 76%) as red oil. NMR ^{1}H (DMSO, 300 MHz) 0.78 (d, 3H, *J* 6.6 Hz), 0.83 (d, 3H, *J* 6.6 Hz), 0.84 (d, 3H, *J* 6 Hz), 0.97 (m, 1H), 1.26 (dd, 1H, *J* 6.3 Hz, 12.9 Hz), 1.34-1.39 (m, 2H), 1.52-1.58 (m, 2H), 1.69 (d, 1H, *J* 12.3 Hz), 1.83-2.01 (m, 2H), 2.24-2.28 (m, 1H), 2.43-2.48 (m, 1H), 2.64 (s, 3H, NCH_3), 3.17 (d, 1H, *J* 4.2 Hz), 3.88 (dd, 1H, *J* 3.6 Hz, 8.7 Hz), 3.96 (dd, 1H, *J* 3.9 Hz, 10.8 Hz), 4.04-4.08 (m, 1H), 6.65 (dd, 2H, *J* 2.4, 6.9 Hz), 6.74 (dd, 2H, *J* 2.4, 6.9 Hz), 8.91 (s, 1H). NMR ^{13}C (DMSO, 75 MHz): 18.5; 22.2; 22.3; 23.9; 24.2; 25.7; 29.2; 34.1; 34.7; 47.1; 65.0; 68.5; 75.0; 88.5; 115.8; 115.8; 151.4; 151.6; 172.1. HRMS, calcd $C_{22}H_{32}N_2NaO_4$ $[M+Na]^+$: 411.2262, found 411.2254.

3d: 4-(((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)-2-methoxyphenol

Prepared from **1** (1 eq.) and 4-(allyloxy)-2-methoxyphenol **2d** (1 eq.) to afford **3d** (253 mg,

72%) as red oil. NMR ^{1}H (DMSO, 300 MHz) 0.78 (d, 3H, *J* 6.6 Hz), 0.83 (d, 3H, *J* 6.6 Hz), 0.85 (d, 3H, *J* 5.4 Hz), 0.92-0.94 (m, 1H), 1.25-1.34 (m, 2H), 1.41 (t, 1H, *J* 6.9 Hz), 1.53-1.58 (m, 2H), 1.69 (d, 1H, *J* 12.3 Hz),1.83-2.01 (m, 2H), 2.24-2.30 (m, 1H), 2.46 (td, 1H, *J* 1.8 Hz, 6.9 Hz), 2.64 (s, 3H, NCH_3), 3.73 (s, 3H, OCH_3), 3.88 (d, 1H, *J* 8.7 Hz), 3.95-3.99 (m, 2H), 4.05-4.09 (m, 1H), 6.33 (dd, 1H, *J* 2.7, 8.7 Hz), 6.52 (d, 1H, *J* 2.7 Hz), 6.64 (d, 1H, *J* 8.4 Hz), 8.43 (s, 1H). NMR ^{13}C (DMSO, 75 MHz): 18.5; 22.2; 22.3; 24.0; 24.2; 25.7; 29.2; 34.1; 34.7; 47.1; 55.7; 65.0; 68.3; 75.0; 88.5; 101.2; 105.5; 115.4; 140.8; 148.3; 151.8; 172.1. HRMS, calcd $C_{23}H_{34}N_2NaO_5$ $[M+Na]^+$: 441.2356 found 441.2360.

3e: 2-(((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)benzoic acid

Prepared from **1** (1 eq.) and 2-(allyloxy)benzoic acid **2e** (1 eq.) to afford **3e** (283 mg, 81%) as yellow oil. NMR ^{1}H (DMSO, 300 MHz) 0.73 (d, 3H, *J* 6.6 Hz), 0.74 (d, 3H, *J* 6.3 Hz), 0.81 (d, 3H, *J* 6.6 Hz), 0.79-0.85 (m, 1H), 1.23-1.30 (m, 2H), 1.38-1.44 (m, 1H), 1.50-1.56 (m, 2H), 1.66 (d, 1H, *J* 12.6 Hz), 1.84-2.04 (m, 2H), 2.30-2.34 (m, 1H), 2.50-2.56 (m, 1H), 2.63 (s, 3H, NCH_3), 3.89 (d, 1H, *J* 8.4 Hz), 4.20-4.23 (m, 1H), 4.35 (dd, 1H, *J* 7.5, 11.4 Hz), 4.44 (dd, 1H, *J* 3.3, 11.4 Hz), 6.89-4.93 (m, 1H), 6.97 (td, 1H, *J* 0.6, 8.1 Hz), 7.50-7.54 (m, 1H), 7.79 (dd, 1H, *J* 1.8, 8.1 Hz), 10.47 (s, 1H). NMR ^{13}C (DMSO, 75 MHz): 18.5; 22.0; 22.1; 23.9; 24.2; 25.7; 29.1; 34.1; 34.2; 47.1; 64.8; 73.8; 88.2; 112.9; 117.6; 119.4; 130.1; 136.0; 160.0; 160.5; 168.5; 172.0. HRMS, calcd $C_{23}H_{32}N_2NaO_5$ $[M+Na]^+$: 439.2206, found 439.2203.

3f: 4-(((1S,2S,2'S,3a'S,5R)-2-isopropyl-5,5'-dimethyl-4'-oxotetrahydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-2'-yl)methoxy)methylbenzene

Prepared from **1** (1 eq.) and 1-(allyloxy)-4-methylbenzene **2f** (1 eq.) to afford **3f** (283 mg, 81%) as yellow oil. NMR ^{1}H (Chloroform-D, 300 MHz) 0.84 (d, 3H, *J* 5.1 Hz, CH_3), 0.86 (d, 3H, *J* 5.4 Hz, CH_3), 0.91 (d, 3H, *J* 4.8 Hz, CH_3), 0.88-0.94 (m, 1H), 1.26 (t, 1H, *J* 4.5 Hz), 1.37 (dd, 1H, *J* 9.9, 2.4 Hz),1.44 (dd, 1H, *J* 4.8, 9.9 Hz), 1.60 (dd, 1H, *J* 2.4, 9.9 Hz), 1.71 (td, 1H, *J* 2.4, 9.6 Hz), 1.78-1.82 (m, 1H), 2.00-2.04 (m, 1H), 2.07 (d, 1H, *J* = 10.2 Hz), 2.27 (s, 3H), 2.34-2.38 (m, 1H), 2.70-2.80 (m, 4H), 3.98 (d, 1H, J 7.2 Hz); 4.00-4.04 (m, 1H), 4.05 (dd, 1H, *J* 4.5, 7.8 Hz), 4.18-4.20 (m, 1H), 6.79 (d, 2H, *J* 6.3 Hz), 7.06 (d, 2H, *J* 6.3 Hz). NMR ^{13}C (Chloroform-D, 75 MHz): 18.3; 20,3; 22.1; 24.0; 24.2; 25.9; 29.2; 34.5; 35.2; 40.4; 47.9; 65.5; 68.1; 75.1; 89.4; 114.4; 129.7; 130.1; 156.3; 172.7. HRMS, calcd $C_{23}H_{34}N_2NaO_3$ $[M+Na]^+$: 409.2454, found 409.2465.

3g: (1S,2S,2'S,3a'S,5R)-2-Isopropyl-2'-(benzyloxymethyl)-5,5'-dimethyldihydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-4'(5'H)-one

Prepared from **1** (1 eq.) and ((allyloxy)methyl)benzene **2g** (1 eq.) to afford **3g** (282 mg, 87%) as yellow oil. NMR ^{1}H (Chloroform-D, 300 MHz) 0.83 (d, 3H, *J* 6.9 Hz, CH_3), 0.85 (d, 3H, *J* 7.2 Hz, CH_3), 0.93 (d, 3H, *J* 6.3 Hz, CH_3), 0.92-0.95 (m, 1H), 1.22-1.26 (m, 1H), 1.29-1.33 (m, 1H), 1.38-1.42 (m, 1H), 1.61 (dt, 2H, *J* 9.9, *J* 3.3 Hz), 1.71 (td, 1H, *J* 12.6, 3.6Hz), 1.80-1.86 (m, 1H), 2.05-2.09 (m, 1H), 2.20.2.24 (m, 1H), 2.64 (ddd, 1H, *J* 12.3, 0.6 Hz), 2.74 (s, 3H, NCH_3), 3.55 (dd, 1H, *J* 6.6, 10.8Hz), 3.64 (dd, 1H, *J* 3.6, 10.8 Hz), 3.94 (d, 1H, *J* 8.7Hz), 4.02-4.04 (m, 1H), 4.54-4.58 (m, 2H), 7.31-7.34 (m, 5H). NMR ^{13}C (Chloroform-D, 75 MHz): 18.4; 22.3; 22.4; 24.2; 24.3; 26.0; 29.5; 34.7; 35.5; 40.7; 48.1; 65.6; 70.4; 73.2; 77.2; 89.6; 127.5; 127.6; 128.3; 138.1; 172.8. HRMS, calcd $C_{23}H_{34}N_2NaO_3$ $[M+Na]^+$: 409.2454, found 409.2462.

3h: (1S,2S,2'S,3a'S,5R)-2-Isopropyl-2'-(3-bromobenzyloxymethyl)-5,5'-dimethyldihydro-2'H-spiro[cyclohexane-1,6'-imidazo[1,5-b]isoxazol]-4'(5'H)-one

Prepared from **1** (1 eq.) and 1-((allyloxy)methyl)-3-bromobenzene **2h** (1 eq.) to afford **3h** (356 mg, 91%) as yellow oil. NMR ^{1}H (Chloroform-D, 300 MHz) 0.82 (d, 3H, *J* 6.9 Hz, CH_3), 0.85 (d, 3H, *J* 7.2 Hz, CH_3), 0.92 (d, 3H, *J* 6.6 Hz, CH_3), 0.91-0.93 (m, 1H), 1.23-1.27 (m, 1H), 1.32 (dd, 1H, *J* 3 Hz, 10.2 Hz), 1.38-1.42 (m, 1H), 1.50-1.56 (m, 1H), 1.62-1.66 (m, 1H), 1.74 (dd, 1H, *J* 3.3Hz, 12.6 Hz), 1.80-1.84 (m, 1H), 2.03-2.08 (m, 1H), 2.19-2.23 (m, 1H), 2.64 (ddd, 1H, *J* 1.2, 5.1, 12.3Hz,), 2.74 (s, 3H, NCH_3), 3.53 (dd, 1H, *J* 6.9, 11.1 Hz), 3.64 (dd, 1H, *J* 3.6, 11.1Hz), 3.94 (d, 1H, *J* 8.7Hz), 4.00-4.06 (m, 1H), 4.52 (q, 2H, *J* 12.3 Hz), 7.10-7.30 (m, 2H), 7.39 (dt, 1H, *J* 1.8, 7.5 Hz), 7.38-7.42 (m, 1H). NMR ^{13}C (Chloroform-D, 75 MHz): 18.4; 22.3; 22.4; 24.1; 24.3; 26.0; 29.5; 34.6; 35.4; 40.6; 48.1; 65.6; 70.6; 72.3; 76.4; 89.6; 122.5; 125.8; 129.9; 130.3; 130.6;

140.5; 172.8. HRMS, calcd $C_{23}H_{33}BrN_2NaO_3$ $[M+Na]^+$: 487.1583, found 487.1567.

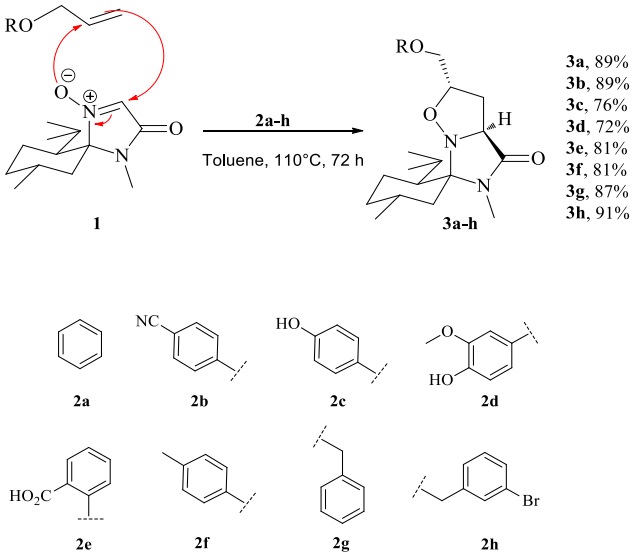
ADMET prediction

Prediction of ADME parameters of the synthesized analogues were performed using the SwissADME (http://www.swissadme.ch/) server.

3. Results and discussion

Alkenes are obtained via an alkylation of phenol and benzyl alcohol derivatives by applying the same procedures already described in the literature [20-21]. The latter were engaged in 1,3-DC reaction with chiral nitrone **1** in toluene at reflux for 72 h. The 1,3-DC occurred in an exo approach of monosubstituted alkenes on the less crowded side of the nitrone derived from (-)-menthone **1** to access isoxazolidines **3a-h** with simultaneous creation of two stereogenic centers and stereo- and regiospecifically (scheme 1). This was approved based on our previous work [18,22-23] and NMR data.

Indeed, in our previous work we have shown that the protons H_3 and H_{4proR} in *syn* orientation have a high coupling constant ($^3J_{3\text{-}4proR}$ (syn) ≥ 7.0 Hz) [24]. While, the $^3J_{3\text{-}4proS}$ coupling constant is lower ($^3J_{3\text{-}4proS}$ (anti) ≤ 3.7 Hz) [25]. For H_4 and H_5 protons with an *syn* position, the coupling constant is greater than 7 Hz [26]. The coupling constant is lower for protons arranged *anti*. The interpretation of the 1H NMR spectra of the cycloadducts **3a-h** showed that $^3J_{3\text{-}4proR}$(*syn*) is between 7.2 and 9.6 Hz, the coupling constant $J_{3\text{-}4proS}$ (*anti*) is low (0.6 ≤ $^3J_{3\text{-}4proS}$ (*anti*) ≤ 1.8 Hz) and the coupling constant $^3J_{4proR\text{-}5}$ (*syn*) is greater than 7 Hz. This comparative analysis of the coupling constants led to the stereochemistry of cycloadduct **3** proposed in figure 1. Moreover, the interpretation of the Noesy spectra confirmed the presence of: (i) strong correlations between the protons H_5-H_{proS}, H_5-H_8 and H_3-H_{proR}, (ii) weak correlations between H_3-H_{proS} protons, (iii) medium correlations between H_3-H_{methyl} and H_3-H_{13} protons. These observations further confirm the structure shown in figure 1.



Scheme 1. Synthesis 3-carboxylic isoxazolidine derivatives

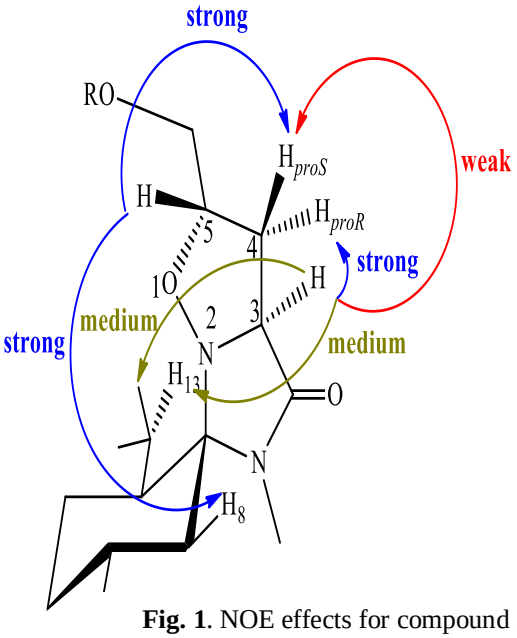


Fig. 1. NOE effects for compound **3**

Pharmacokinetics studies

In order to guide the selection of molecules in the early phases of drug discovery and development for a successful drug, ADME profile including physicochemical properties, lipophilicity and druglikeness of the synthesized compounds have been predicted [27-34]. As shown, all ligands were found to meet to the Lipinski's rule of five, having a total polar surface areas (TSPA) in the range of 42.01-79.31 Å and a good lipophilicity, expressed by the consensus Log Po/w which is in the range of 2.49-4.10. They exhibited a high GI absorption and were computed to possess good bioavailability score

(55%), with only 3e was not permeable to BBB. All compounds are non-P-glycoprotein (P-gp) substrates suggesting that absorption from the gastrointestinal tract and across the BBB may be not compromised. Consequently, this lead to an increasing bioavailability as well as decraese in the possibility of their resistance by tumor cell lines through efflux. Their skin permeation ($LogK_P$) parameters ranged from -7.31 to -5.09, thus facilitating the accessibility of the bioactive molecules through the skin. Their cytochrome P450 isoenzymes (CYP1A2/ CYP2C19/ CYP2C9/ CYP2D6/ CYP3A4), playing a fundamental role in the biotransformation of drugs through O-type oxidation reactions have been also predicted (table 1).

Table 1. ADME properties of compounds **3a-h**.

Entry	3a	3b	3c	3d	3e	3f	3g	3h
Physicochemical Properties/Lipophilicity/Druglikeness								
Molecular weight	372.50	397.51	388.50	418.53	416.51	470.60	386.53	465.42
Num. heavy atoms	27	29	28	30	30	34	28	29
Num. arom. heavy atoms	6	6	6	6	6	6	6	6
Fraction Csp3	0.68	0.65	0.68	0.70	0.65	0.63	0.70	0.70
Num. rotatable bonds	4	4	4	5	5	9	5	5
Num. H-bond acceptors	4	5	5	6	6	6	4	4
Num. H-bond donors	0	0	1	1	1	0	0	0
Molar Refractivity	113.64	118.36	115.66	122.16	120.60	138.65	118.01	125.71
TPSA	42.01	65.80	62.24	71.47	79.31	68.31	42.01	42.01
Consensus Log $P_{o/w}$	3.41	3.26	3.04	3.19	2.49	4.04	3.44	4.10
Lipinski's Rule	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Bioavailability Score	0.55	0.55	0.55	0.55	0.55	0.55	0.55	0.55
Pharmacokinetics								
GI absorption	High	High	High	High	High	High	High	High
BBB permeant	Yes	Yes	Yes	Yes	No	Yes	Yes	Yes
P-gp substrate	No	No	No	No	No	No	No	No
CYP1A2 inhibitor	No	No	No	No	No	No	No	No
CYP2C19 inhibitor	No	No	Yes	Yes	No	No	No	Yes
CYP2C9 inhibitor	No	No	No	No	No	No	No	No
CYP2D6 inhibitor	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
CYP3A4 inhibitor	No	No	No	No	No	Yes	No	No
Log Kp (cm/s)	-5.09	-5.44	-5.44	-5.64	-7.31	-5.38	-5.41	-5.40

The bioavailability of the synthesized compounds was also estimated based on their pink area of radar chart (Figure 2). All compounds were completely included in the pink area and justifying their good predicted oral bioavailability.

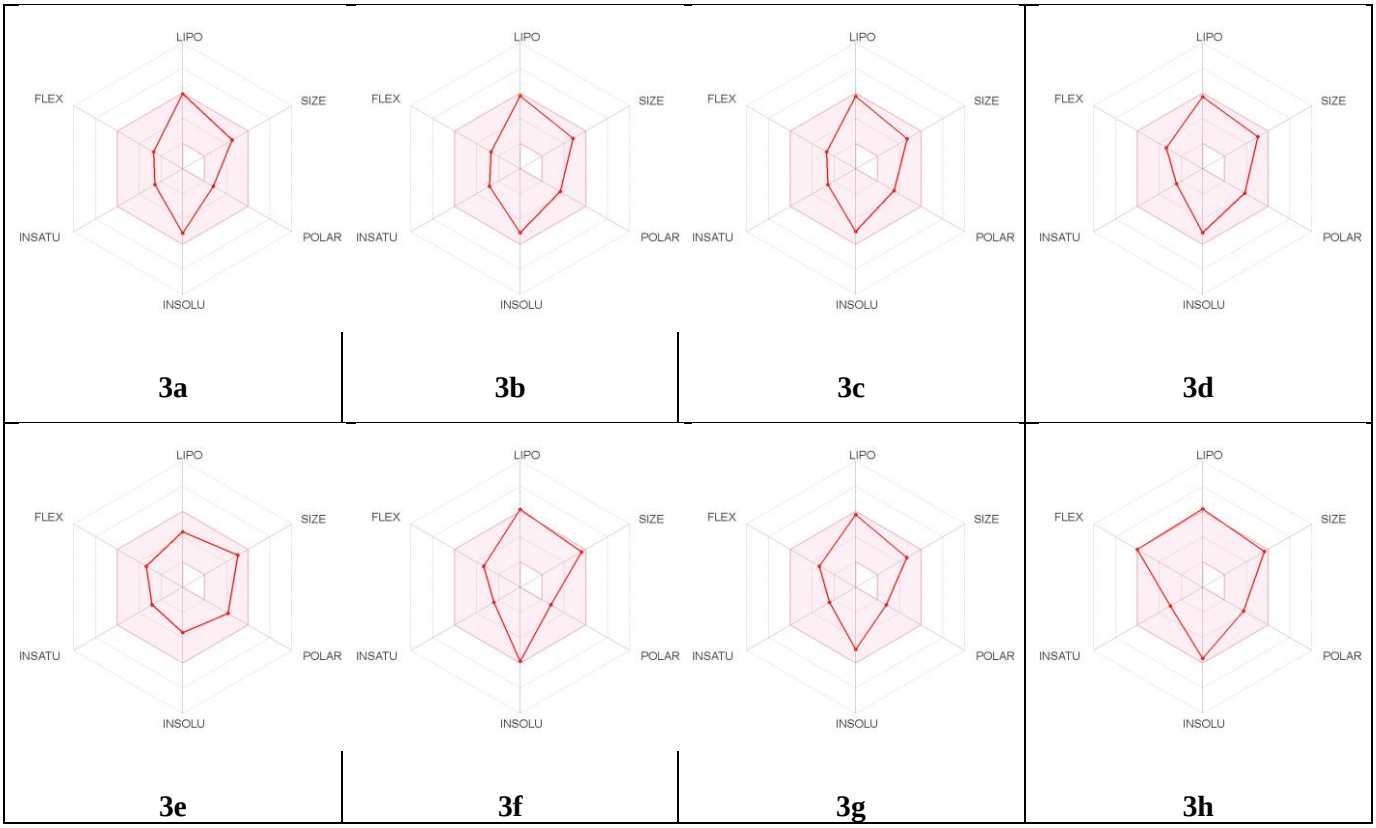


Fig. 2. Bioavailability radar of compounds 3a-h based on physicochemical indices ideal for oral bioavailability. LIPO, Lipophilicity: -0.7 < XLOGP3 < þ 5; SIZE, Molecular size: 150 g/mol < mol. wt. < 500 g/mol; POLAR, Polarity: 20 $Å^2$ < TPSA <130 $Å^2$; INSOLU, Insolubility: 0 < Log S (ESOL) < 6; INSATU, Insaturation: 0.25 < Fraction Csp3 < 1; FLEX, Flexibility: 0 < Number of rotatable bonds < 9. The colored zone is the suitable physicochemical space for oral bioavailability. (B) Boiled-egg (B) model of compounds **3a-h**.

Based on their LogP and TPSA parameters, the GI absorption and BBB permeation as given by the BOILED-Egg method (Brain or intestinal estimated permeation), have been estimated. Data outlined clearly that all compound were in the yellow zone (with high probability to permeate through BBB to access CNS) with red color making them not a substrate for P-glycoprotein (PGP-) which reduced the possibility of their resistance by tumor cell lines through efflux (figure 3**).**

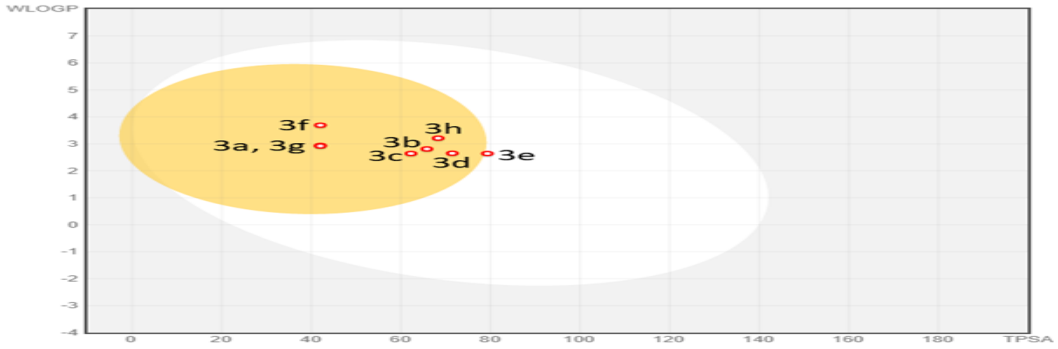


Fig. 3. Boiled-egg (B) model of compounds **3a-h**.

4. Conclusion

In this study, a new some enantiopure 3-carboxylic isoxazolidine derivatives has been synthesized *via* 1,3-DC with various monosubstituted alkenes. Assessment of in silico ADME properties/pharmacokinetics revealed that the synthesized molecules possess good permeability and bioavailability with high chance to be well absorbed by the gastrointestinal tract.

5. Conflicts of interest

There are no conflicts to declare.

6. Formatting of funding sources

Not funding sources

7. References

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