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DESIGN AND SYNTHESIS OF A NEW EPOXIDE-STEROID CARBOXAMIDE DERIVATIVE.

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ABSTRACT
In the literature there are protocols for the preparation of several epoxide analogs which use some reagents which are dangerous and require special conditions. In this way, the aim of this study was to prepare an epoxide-steroid carboxamide derivative using some chemical reactions such as [2 + 2] addition, hydroxyl group protection/deprotection, acylation and cyclation. The chemical structure of compounds was determined by spectroscopic and spectrometric methods. In conclusion, in this work were prepared epoxide-steroid carboxamide derivative using several chemical techniques, which are simple procedures and easy to handle.

INTRODUCTION
Over the past several years, several epoxide-analogs have been developed using protocols different: For example, the preparation of 1-tetrahydrothiophenium Bromide by the reaction of a tetrahydrothiophene derivative from ethyl bromoacetate[i]. In addition, a study showed the synthesis of 3-oxyranil-chlorophyll analog via reaction of Methyl pyropheophorbide with a chlorophyll[ii]. Other report, showed the preparation of a epoxide derivative from vinyl sulfonium salt,α-]aminoaldehyde, and 1,8-Diazabicyclo(5.4.0)undec-7-ene[iii]. Also, an epoxycyclohexane derivative was prepared via reaction of 1,1-Bis(2-cyclohexenyloxymethyl)-3-cyclohexene and meta-chloroperbenzoic acid[iv]. Besides, a study showed the reaction of a quinine derivative with quaternary ammonium salts to give the corresponding epoxide[v]. Besides, a report showed the synthesis of a vinyl carbamate-epoxide via reaction of vinyl carbamate with dimethyldioxirane[vi]. Also, an oxirane-carboxamide derivative was prepared from a propanamide anolg and sodium hydroxide[vii]. In addition, a study showed the synthesis of an epoxide derivative via reaction of chlorohydrin with sodium hydroxide[viii]. Other data

indicated that zeylanone-epoxide was prepared via dimerization of 2-methyl-1,4-naphtoquinone[ix]. Additionaly, a diol-estradiol epoxide was synthesized by reaction of diol-estradiol with meta-Chloroperoxybenzoic acid[x]. Besides, an epoxide-progesterone derivative was prepared by condensation of an 11α-hydroxyprogesterone derivative with 2-hydroxy-1-naphthaldehyde[xi]. Recently, was prepared an epoxide-steroid from 2-nitroestone and 2-hydroxy-1-naphthaldehyde[xii]. All these experimental results show several methods to synthesize some epoxide analogs; analyzing these data in this study a new steroid-derivative was prepared using several chemical strategies which was no require special conditions.

EXPERIMENTAL

2.1 General methods

The reagents used in this research were acquired from Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were evaluated with a Thermo Scientific iSOFT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded using a Varian VXR300/5 FT NMR spectrometer at 300 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.2 Chemical synthesis

8-Aminomethyl-11a-methyl-2,3,3a,3b,4,5,7a,9a,9c,10,11,11a-dodecahydro-1H-cyclobuta[g]cyclopenta[a]phenanthrene-1,7-diol (2)

A solution of estradiol (200 mg, 0.72 mmol), propargylamine (50 µl, 0.78 mmol), Copper(II) chloride (80 mg,0.60mmol) in methanol (5 ml) was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was extracted using the chloroform:agua (3:1) system; yielding 48% of product; m.p. 82-84 ºC; IR (V_{max}, cm^{-1}) 3400 and 3222: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.80 (s, 3H), 1.32-2.00 (m, 13H), 2.12-2.44 (m, 3H), 3.12 (m, 2H), 3.56-3.66 (m, 2H), 4.70 (broad, 4H), 5.44 (m, 1H), 6.46 (d, 1H, J = 0.80 Hz) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.32, 22.22, 23.02, 27.30, 28,10, 30.66, 30.70, 37.14, 37.90, 41.80, 43.62, 43.74, 49.82, 50.84, 81.73, 92.30, 124.30, 136.12, 137.22, 142.74, 153.50 ppm. EI-MS m/z: 327.21. Anal. Calcd. for $C_{21}H_{29}NO_2$: C, 77.02; H, 8.93; N, 4.28; O, 9.77. Found: C, 77.00; H, 8.90.

[(16S,17S)-7,16-bis[[tert-butyl(dimethyl)silyl]oxy]-17-methyl-5-pentacyclo[10.7.0.02, 9.03,6.013,17]nonadeca-2(9),4,7-trienyl]methanamine (3)

A solution of **2** (200 mg, 0.61 mmol), *tert*-butyldimethylsilyl chloride (200 µL, 1.07 mmol) chloroform (5 ml) was stirring for 48 h at room temperature. Then the solvent was evaporated at room temperature. Following the product was precipitated with water; yielding 63% of product; m.p. 60-62 ºC; IR (V_{max}, cm^{-1}) 3400 and 1226: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.08 (s, 6H), 0.12 (s, 6H), 0.84 (s, 9H), 0.88 (s, 3H), 0.90 (s, 9H), 1.02 (broad, 2H), 1.32-2.00 (m, 13H), 2.04-3.06 (m, 3H), 3.10 (m, 2H), 3.56-5.28 (m, 3H), 6.32 (d, 1H, J = 0.80 Hz) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: -4.50, -4.22, 11.32, 18.02, 18.50, 22.22, 24.44, 25.43, 25.52, 27.86, 30.42, 31.02, 34.72, 36.00, 38.44, 42.12, 43.10, 46.66, 49.44, 51.42, 81.66, 97.88, 111.44, 130.83. 134.65, 147.00, 155.50 ppm. EI-MS m/z: 555.39. Anal. Calcd. for $C_{33}H_{57}NO_2Si_2$: C, 71.29; H, 10.33; N, 2.52; O, 5.76; Si, 10.10. Found: C, 71.26; H, 10.30.

N-[[(16S,17S)-7,16-bis[[tert-butyl(dimethyl)silyl]oxy]-17-methyl-5-pentacyclo[10.7. 0.02, 9.03,6.013,17]nonadeca-2(9),4,7-trienyl]methyl]-2-chloro-acetamide (4)

A solution of compound **3** (200 mg, 0.36 mmol), chloroacetyl chloride (64 µL; 0.80 mmol), triethylamine (112 µL; 0.8 mmol), chloroform (5 ml) was stirring for 48 h at room temperature. Then, the solvent was evaporated at room temperature and following the product was purified using the chloroform:agua (3:1) system; yielding 40% of product; m.p. 120-122 ºC; IR (V_{max},

cm^{-1}) 1630 and 1228: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.08 (s, 6H), 0.14 (s, 6H), 0.86 (s, 9H), 0.88 (s, 3H), 0.90 (s, 9H), 1.32-2.00 (m, 13H), 2.04-3.44 (m, 3H), 3.54 (m, 2H), 3.56 (m, 1H), 4.10 (m, 2H), 4.86-5.26 (m, 2H), 6.70 (m, 1H), 8.30 (broad, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: -4.50, -4.22, 11.32, 18.04, 18.50, 22.22, 24.44, 25.42, 25.52, 27.86, 30.44, 31.02, 34.72, 36.12, 38.44, 42.12, 42.42, 42.80, 43.16, 46.66, 49.44, 81.68, 97.88, 115.62, 127.12, 137.66, 144.40, 152.02, 165.60 ppm. EI-MS m/z: 631.36. Anal. Calcd. for $C_{35}H_{58}ClNO_3Si_2$: C, 66.47; H, 9.24; Cl, 5.61; N, 2.21; O, 7.59; S, 8.88. Found: C, 66.44; H, 9.22.

N-[[(16S,17S)-7,16-bis[[tert-butyl(dimethyl)silyl]oxy]-17-methyl-5-pentacyclo[10.7.0.02,9.03,6.013,17]nonadeca-2(9),4,7-trienyl]methyl]-3-phenyl-oxirane-2-carboxamide (5)

A solution of compound **4** (200 mg, 0.32 mmol), benzaldehyde (200 µl), sodium hydroxide (30 mg, 0.75 mmol) in methanol (5 ml) was stirring for 48 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was puriefied using the chloroform:hexane:methanol (3:1:1) system; yielding 53% of product; m.p. 136-138 ^oC; IR (V_{max}, cm^{-1}) 1638 and 1228: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.08 (s, 6H), 0.14 (s, 6H), 0.84 (s, 9), 0.88 (s, 3H), 0.92 (s, 9H), 1.32-2.00 (m, 13H), 2.04-3.44 (m, 3H), 3.52 (m, 2H), 3.54 (m, 1H), 3.66-3.80 (m, 2H), 4.84-5.26 (m, 2H), 5.44 (broad, 1H), 6.70 (d, 1H, J = 0.80 Hz),), 6.92-7.26 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: -4.50, -4.22, 11.32, 18.04, 18.50, 22.22, 24.44, 25.42, 25.52, 27.86, 30.44, 31.02, 34.72, 36.12, 38.44, 42.12, 43.10, 43.42, 46.66, 49.44, 55.54, 58.90, 81.68, 97.88, 115.62, 125.80, 127.12, 128.22, 128.52, 135.96, 137.66, 144.40, 152.02, 174.94 ppm. EI-MS m/z: 701.42. Anal. Calcd. for $C_{42}H_{63}NO_4Si_2$: C, 71.85; H, 9.04; N, 1.99; O, 9.11; Si, 8.00. Found: C, 71.82; H, 9.00.

N-[[(16S,17S)-7,16-dihydroxy-17-methyl-5-pentacyclo[10.7.0.02,9.03,6.013,17]nonadeca-2(9),4,7-trienyl]methyl]-3-phenyl-oxirane-2-carboxamide (6)

A solution of compound 5 (200 mg, 0.28 mmol), hydrofluoric acid (48%, 5 ml), was stirring for 72 h at room temperature. Then, the solvent was evaporated under reduced pressure and following the product was purified using the chloroform:agua (3:1) system; yielding 44% of product; m.p. 178-180 ^oC; IR (V_{max}, cm^{-1}) 3222 and 1226: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.80 (s, 3H), 1.32-2.00 (m, 13H), 2.04-3.36 (m, 3H), 3.52 (m, 2H), 3.64 (m, 1H), 3.66-3.80 (m, 2H), 4.76-5.30 (m, 2H), 6.76 (d, 1H, J = 0.80 Hz), 6.92-7.26 (m, 5H), 7.84 (broad, 3H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 11.32, 22.22, 23.02, 27.86, 30.44, 30.72, 31.34, 35.44, 37.12, 42.14, 43.42, 43.63, 46.66, 49.82, 55.54, 58.90, 81.74, 103.50, 117.30, 125.76, 126.80, 128.22, 128.52, 134.88, 135.94, 144.40, 156.74, 174.95 ppm. EI-MS m/z: 701.42. Anal. Calcd. for $C_{42}H_{63}NO_4Si_2$: C, 71.85; H, 9.04; N, 1.99; O, 9.11; Si, 8.00. Found: C, 71.82; H, 9.00. EI-MS m/z: 473.25. Anal. Calcd. for $C_{30}H_{35}NO_4$: C, 76.08; H, 7.45; N, 2.96; O, 13.51. Found: C, 76.04; H, 7.42.

Physicochemical and Pharmacokinetics properties

To evaluate the both physicochemical Pharmacokinetics parameters involved in the chemical structure of compound **6** SwissADME software was used[xiii-xv].

RESULTS AND DISCUSSION

In this study, an epoxide-steroid carboxamide derivative was prepared using some chemical strategies as follows:

Preparation of a cyclobutene-steroid derivative

There are several protocols for synthesis of cyclobutene analogs through [2 + 2] cycloaddition of alkene with alkynes groups or cycloaddition of alkyne groups to alkyne derivatives using some reagents such as ruthenium[xvi], $Ni(PPh_3)_2Cl_2$[xvii], Cobalt[xviii] and others[xix-xxi]. In this investigation, a cyclobutene-steroid derivative (**2**) was synthesized from of estradiol and propargylamine (Figure 1) in the presence of Cooper(II).

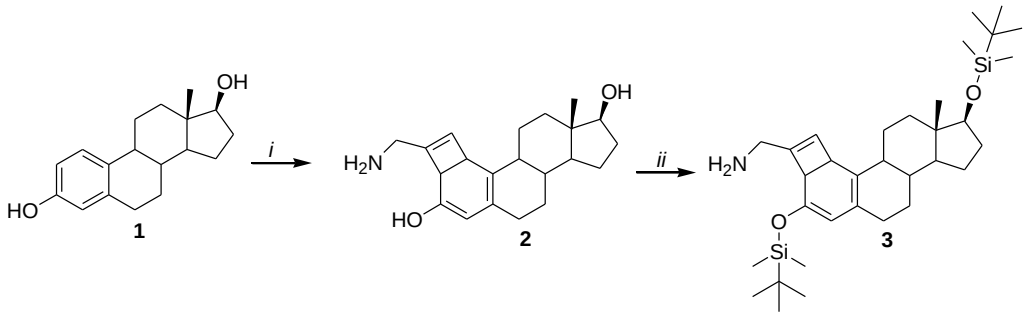

Figure 1. Synthesis of a cyclobutene-steroid derivative (**3**). *Reagents and conditions*: *i* = propargylamine, Cooper(II) chloride, MeOH, room temperature; *ii* = *tert*-butyldimethylsilyl chloride, chloroform, room temperature.

The ^{1}H NMR showed several signals at 0.80 ppm for methyl group bound to steroid nucleus; at 1.32-2.44, 3.56-3.66 and 5.44 ppm for steroid moiety; at 3.12 ppm for methylene group bound to both cyclobutene ring and amino group; at 4.70 ppm for both hydroxyl and amino groups; at 6.46 ppm for cyclobutene ring. ^{13}C NMR spectra showed chemical shifts at 11.32 ppm for methyl group bound to steroid nucleus; at 22.22-49.82, 81.73-124.30, 137.22 and 153.50 ppm for steroid moiety; at 50.84 ppm for methylene group bound to both cyclobutene ring and amino group; at 136.12 and 142.74 ppm for cyclobutene ring. Besides, the mass spectrum from **2** showed a molecular ion (m/z) 327.21.

Protection of hydroxyl groups.

Several organosilyl groups have been employed for protection of hydroxyl groups such as *tert*-butyldimethylsilyl and *tert*-butyldiphenylsilyl[xxii]. Analyzing these data in this investigation, the compound **2** reacted with *tert*-butyldimethylsilyl chloride to form the compound **3**. The ^{1}H NMR showed several signals at 0.008-0.84 and 0.90 ppm for *ter*-butyldimethylsilane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.02 ppm for amino group; at 1.32-3.06 and 3.56-5.28 ppm for steroid moiety; at 3.10 ppm for methylene bound to both cyclobutene ring and amino group; at 6.32 ppm for cyclobutene ring. ^{13}C NMR spectra showed chemical shifts at 14.20 ppm for methyl group bound to steroid nucleus; at 22.22-24.32, 27.72-49.90, 85.12-131.26, 137.60 and 152.00 ppm for steroid moiety; at 24.44-26.00 and 51.65-52.80 ppm for *ter*-butyldimethylsilane fragment; at 50.80 ppm for methylene group bound to both cyclobutene ring and amino group; at 136.12 and 142.82 ppm for cyclobutene ring. In addition, the mass spectrum from **3** showed a molecular ion (m/z) 555.39.

Preparation of a chloroamide derivative

It is noteworthy that several methods have been to preparation of chloroamide analogs using some reagents such as trichloroisocyanuric Acid[xxiii], N-chlorobenzotriazole[xxiv] and chloroacetyl chloride[xxv]. In this study, a chloramine derivative (compound **4**) was synthesized via reaction of compound **3** with chloroacetyl chloride using triethylamine as catalyst. The ^{1}H NMR spectrum of compound **4** shows signals at 0.08-0.86, 0.90 ppm for *ter*-butyldimethylsilane fragment; at 0.88 ppm for methyl bound to steroids nucleus; at 1.32-3.44, 3.56 and 4.86-5.26 ppm for steroid moiety; at 3.54 for methylene group bound to both cyclobutene ring and amide groups; at 4.10 ppm for methylene group bound to both chloride and amide group; at 6.70 ppm for cyclobutene ring; at 8.30 ppm for amide group. The ^{13}C NMR spectrum of 4 display signals at -4.50, -4.22, 18.04-18.50 and 25.42-25.52 ppm for *ter*-butyldimethylsilane fragment; at 11.32 ppm for steroid moiety; at 22.22-24.44, 27.86-42.12, 43.16-127.12 and 152.02 ppm for steroid moiety; at 42.80 ppm for methylene group bound to both cyclobutene ring and amide group; at 42.42 ppm for methylene group bound to both

chloride and amide group; at 137.66-144.40 ppm for cyclobutene ring; at 165.60 ppm for amide group. Additionally, the mass spectrum from **4** showed a molecular ion (m/z) 631.36.

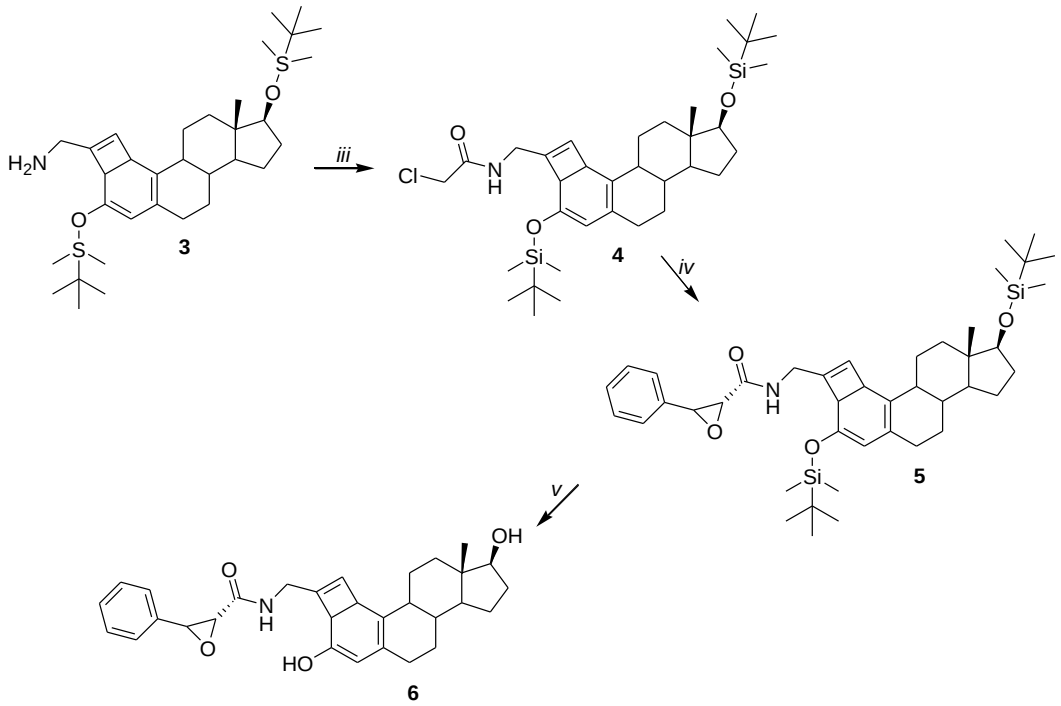

Figure 2. Synthesis of an epoxide-steroid carboxamide derivative (**6**). *Reagents and conditions*: *iii* = chloroacetyl chloride, chloroform, room temperature; *iv* = benzaldehyde, sodium hydroxide, room temperature; *v* = hydrofluoric acid, room temperature.

Preparation of an epoxide derivative

Several studies have been reported for synthesis of oxirane derivatives which involve some reagents such as chlorophyll[xxvi], ethyl bromoacetate[xxvii], m-chloroperoxybenzoic acid[xxviii], potassium hydroxide[xxix], dimethyldioxiran[xxx] and others. In this study the compound **5** was prepared by the reaction of 4 benzaldehyde in basic medium. The ^{1}H NMR spectrum of **5** shows signals at 0.08-0.84 and 0.92 ppm for *ter*-butyldimethylsilane fragment; at 0.88 ppm for methyl group bound to steroid nucleus; at 1.32-3.44, 3.54 and 4.84-5.26 ppm for steroid moiety; at 3.52 ppm for methylene group bound to both cyclobutene ring and amide group; at 3.66-3.80 ppm for oxirane ring; at 5.44 ppm for amide group; at 6.70 ppm for cyclobutene ring; at 6.92-7.26 for phenyl group. The ^{13}C NMR spectrum of 4 display signals at -4.50, -4.22, 18.04-18.50 and 25.42-25.52 ppm for *ter*-butyldimethylsilane fragment; at 11.32 ppm for steroid moiety; at 22.22-24.44, 27.86-43.10, 46.66-49.44. 81.68-115.62, 127.12 and 152.02 ppm for steroid moiety; at 43.42 ppm for methylene group bound to both cyclobutene ring and amide group; at 55.54-58.90 ppm for oxirane ring; at 125.80 and 128.22-135.96 ppm for phenyl group; at 137.66-144.40 ppm for cyclobutene ring; at 174.94 ppm for amide group. Besides, the mass spectrum from **5** showed a molecular ion (m/z) 701.42.

Deprotection of hydroxyl groups

The following stage was achieved by the removal of silyl-protecting group of the compound 5. It is worth mentioning that several reagents have been used for the removal of silyl protecting groups from hydroxyl such as ammonium fluoride[xxxi, xxxii], tris(dimethylamino)sulfonium-difluorotrimethylsilicate[xxxiii], hydrofluoric acid[xxxiv] and others. Therefore, in this study, hydrofluoric acid was used to remove silyl-protecting group from hydroxyl of compound **5** (Figure 2) to form the compound **6**. The ^{1}H NMR spectrum of **6** shows signals at 0.80 ppm for

methyl group bound to steroid nucleus; at 1.32-3.36, 3.64 and 4.76-5.30 ppm for steroid moiety; at 3.52 ppm for methylene group bound to both cyclobutene ring and amide group; at 3.66-3.80 ppm for oxirane ring; at 6.76 ppm for cyclobutene ring; at 6.92-7.26 ppm for phenyl group; at 7.84 ppm for both amide and hydroxyl groups. The ^{13}C NMR spectrum of 6 display signals at 11.32 ppm for methyl group bound to steroid nucleus: at 22.22-42.14, 43.63-49.82. 81.74-117.30, 126.80 and 156.74 ppm for steroid moiety; at 43.42 ppm for methylene group bound to both cyclobutene ring and amide group; at 55.54-58.90 ppm for oxirane ring; at 125.76, 128.22-128.52 and 135.94 ppm for phenyl group; at 134.88-144.40 ppm for cyclobutene ring; at 174.95 ppm for amide group. Finally, the mass spectrum from **6** showed a molecular ion (m/z) 473.25.

Physicochemical and Pharmacokinetics Properties

The results on gastrointestinal absorption rate (Table 1) showed that compound **6** could interact with P-gp P glycoprotein which is an important protein of the cell membrane that efflux many foreign substances out of cells[xxxv]. This phenomenon could produce increase in the defense mechanism against harmful substances which may depend on lipophilicity degree and the chemical structure of compound **6** (Table 2-4).

Table 1. Pharmacokinetics properties of compound **6**.

GI absorption	High
BBB permeant	No
P-gp substrate	Yes
CYP1A2 inhibitor	No
CYP2C19 inhibitor	No
CYP2C9 inhibitor	No
CYP2D6 inhibitor	No
CYP3A4 inhibitor	No
Log K_p (skin permeation)	-7.06 cm/s

P-gp = P-glycoprotein

Table 2. Physicochemical properties

Molecular weight	473.60 g/mol
Num. heavy atoms	35
Num. arom. heavy atoms	6
Fraction Csp^3	0.57
Num. rotatable bonds	5
Num. H-bond acceptors	4
Num. H-bond donors	3
Molar Refractivity	134.42
TPSA	82.09 Å^2

Table 3. Lipophilicity degree of compound **6**.

Log $P_{o/w}$ (iLOGP)	3.38
Log $P_{o/w}$ (XLOGP3)	3.00
Log $P_{o/w}$ (WLOGP)	4.44
Log $P_{o/w}$ (MLOGP)	3.30
Log $P_{o/w}$ (SILICOS-IT)	3.77
Consensus Log $P_{o/w}$	3.58

Table 4. Water solubility of compound **6**.

Log *S* (ESOL)	-4.46
Solubility	1.63e-02 mg/ml ; 3.44e-05 mol/l
Class	Moderately soluble
Log *S* (Ali)	-4.39
Solubility	1.94e-02 mg/ml ; 4.09e-05 mol/l
Class	Moderately soluble
Log *S* (SILICOS-IT)	-5.06
Solubility	4.09e-03 mg/ml ; 8.63e-06 mol/l
Class	Moderately soluble

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