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A facile Synthesis of two quaternary amino-steroids derivatives and its correlation with descriptors LogP and π

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Abstract: In this work, two quaternary amino-steroids derivatives were synthesized and its correlation with descriptors *LogP* and π was evaluated. The results showed an increase in *logP* and π values of **5** with respect to **3**. All this data suggest that compounds studied have different lipophilicity degree which depends of the substituents involved in its structural chemistry.

Key words: Synthesis of two quaternary amino-steroids derivatives, correlation with descriptors LogP and π.

Introduction

During the last past decades, several amino steroid-derivatives were synthesized with a wide spectrum of biological actions, as antibacterial[1,2], antimalarial[3] as well as antiviral[4] drugs. For example, there are reports[4] which show the synthesis of 17β-[N-methyl-N-(aminoethyl)amino-5a-androsterone by reduction of oxime-androsterone derivative using LiAlH[5]. Additionally, other reports[6] showed the synthesis of a series of 7-amino- and polyaminosterol analogues of squalamine and trodusquemine as catalyst[6]. Another studies made by Walker and coworkers[7] reported the synthesis of several amino-steroids derivatives by the reaction between cholic acid methyl ester with polyamines (spermine, pentamine, or hexamine) using N-hydroxysuccinamide. Other studies made by Acs and coworkers[8] showed the synthesis of 11-carboxamido-androstan-4,9(11)-diene using via palladium as catalyst. In addition, another reports indicate the synthesis of 7a-[4′-(aminophenyl) thio]pregna-4-ene-3,20-dione by the reaction between pregna-4,6-diene-3,20-dione with 4-aminothiophenol in presence of sodium hydroxide. All these experimental data show several protocols for synthesis of amino steroid-derivatives, nevertheless, the use of some reagents requires of special conditions. Recently, some studies indicate the synthesis of a quaternary nitrogen-steroid using 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide as catalyst[9]. Therefore in this work our initial design included a facile synthesis of two quaternary nitrogen-steroid derivatives in presence of carbodiimide derivative. It is important to mention that these androgen derivatives contains in the cyclopentene-ring of steroid nucleus a spacer arm with both ester and amide functional groups bound to ring-pyrimidin of vitamin B1 fragment involved in the two steroid derivatives.

Experimental

Hemisuccinates of dihydrotestosterone **(1)** and danazol (**4**) were prepared accord to methods reported previously[10-12]. 3-((4-Amino-2-methyl-5-pyrimidinyl)methyl)-5-(2-hydroxyethyl)-4-methylthiazolium chloride (Vitamin B1) and the other compounds evaluated in this study were purchased from Sigma-Aldrich Co., Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Ultraviolet spectroscopy (UV) was carried out in dry methanol on a Perkin-Elmer model 552 spectrophotometer and infrared spectra (IR) was recorded using KBr pellets on a Perkin Elmer Lambda 40 spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in CDCl3 using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q. spectrometer. Elementary analysis data were acquired from a Perkin Elmer Ser. II CHNS/0 2400 elemental analyzer.

3-{4-[3-(10,13-dimethyl-3-oxo-hexadecahydro-cyclopenta[a]phenanthren-17-yl-oxycarbonyl)-propionylamino]2-methyl-pyrimidin-5-ylmethyl)-5-2(2-hydroxy-ethyl)-4-methyl-thyazol-3-ium;chloride (3)

A solution of **1** (200 mg, 0.51 mmol), Vitamin B1 hydrochloride (253 mg, 0.75 mmol), 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide 150 mg (0.78 mmol) in 15 mL of acetonitrile:water (2:1) was stirred at room temperature for 72 hours. The reaction mixture was evaporated to a smaller volume, diluted with water, and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 60 % of product, mp 82-84 °C; UV (MeOH) λ_{max} (log ε) 214 (0.74) nm; IR V_{max} 3330, 3200, 1730 cm^{-1}; ^{1}H NMR (300 MHz, DMSO$_{d6}$) δ_H: 0.80 (s, 3H), 0.90 (m, 1H), 0.96 (s, 3H), 0.99 (m, 1H), 1.01-1.22 (m, 6H), 1.36-1.53 (m, 4H), 1.60-1.80 (m, 4H), 1.89 (m, 1H),2.01-2.27 (m, 5H), 2.51 (m, 2H), 2.52 (s, 3H), 2.55 (m, 2H), 2.58 (s, 3H), 3.18 (d, J = 6Hz, 2H), 3.90, (d, J = 6Hz, 2H), 4.65 (m, 1H), 5.68 (s, 2H), 7.62 (broad, 2H), 7.91(s, 1H), 9.71 (s, 1H) ppm. ^{13}C NMR (75.4 MHz, DMSO$_{d6}$) δ_C: 11.85 (C-11), 12.00 (C-43), 17.00 (C-44) 20.75 (C-38), 23.51, (C-36) 25.32 (C-17), 26.69 (C-14), 27.05 (C-33), 27.60 (C-35), 28.85 (C-34), 29.57 (C-22), 31.44 (C-21), 35.20 (C-29), 35.30 (C-31), 36.90 (C-37),37.50 (C-40), 37.80 (C-39), 42.72 (C-23), 43.45 (C-42), 45.40 (C-32), 47.20, (C-30) 50.65 (C-28), 53.72 (C-6), 63.66 (C-15), 82.40 (C-26), 119.27 (C-7), 130.29 (C-4), 140.60 (C-5) , 151.32 (C-8), 160.68 (C-12) , 161.23 (C-2), 167.91(C-10) , 172.24 (C-23), 174.81 (C-19) , 212.45 (C-41) ppm. MS (70 eV): m/z = 673.04 ([M + 9]$^+$), 290.25, 231.17, 149.16. Anal. Calcd. for $C_{35}H_{49}Cl\ N_4O_5S$:C, 62.34; H, 7.47; Cl, 5.26; N, 8.31, O, 11.86; S, 4.76. Found. C, 62.33; H, 7.28.

3-{4-[3-(2-ethynyl-10a-12a-dimethyl-2,3,3a-3b-4,5,10,10a,10b,11,12,12a-dodeca- hydro-1*H*-7-thia-8-aza-dicyclopenta[a,h]phenantthren-1-yl-oxycarbonyl)-proprio-nylamino]-2-methyl-pirimidin-5-ylmethyl}-5-(2-hydroxy-ethyl)-4-methyl-thiazol-3-lum;chloride (5)

A solution danazol 17-hemisuccinate 200 mg (0.45 mmol), vitamin B1 hydrochloride 250 mg (0.74 mmol), 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide 150 mg (0.78 mmol) in 15 mL of acetonitrile:water (2:1) was stirred at room temperature for 72 hours. The reaction mixture was evaporated to a smaller volume, diluted with water, and extracted with chloroform. The organic phase was evaporated to dryness under reduced pressure, the residue was purified by crystallization from methanol:water (3:1) yielding 52 % of product, mp 96 °C; UV (MeOH) λ_{max} (log ε) 237 (0.31) nm; IR V_{max} 3330, 2850, 1730 cm-1; ^{1}H NMR (300 MHz, DMSO$_{d6}$) δ_H: 0.98 (s, 3H), 1.00 (s, 3H), 1.00 (m, 1H), 1.04 (m, 1H), 1.35-1.68 (m, 3H), 1.73-1.84 (m, 5H),1.87- 2.21 (m, 5H), 2.33-2.40 (m, 2H), 2.50 (m, 2H) 2.52 (s, 3H), 2.55 (m), 2.58 (s, 3H), 2.68 (m, 2H), 3.04 (m, 1H), 3.18 (t, J = 6 Hz, 2H), 3.90 (t, J = 6 Hz, 2H), 5.69 (s, 2H), 6.53 (s, 1H), 7.26 (broad, 2H), 7.94 (s, 1H), 8.32 (s, 1H), 9.70 (s, 1H) ppm. ^{13}C NMR (75.4 MHz, DMSO$_{d6}$) δ_C: 11.87 (C-49), 15.63 (C-22), 19.66 (C-21), 20.83 (C-19), 23.30 (C-13), 25.30 (C-39), 26.69 (C-46), 29.57 (C-28), 31.40 (C-17), 31.44 (C-18), 31.71 (C-20), 32.17 (C-12), 33.90 (C-29), 35.60 (C-6), 37.20 (C-5), 37.48 (C-8), 45.13 (C-10), 51.48 (C-7), 53.06 (C-9), 53.72 (C-40), 63.66 (C-47), 67.55 (C-27), 87.62 (C-26), 87.88 (C-11), 113.05 (C-15), 119.27 (C-38), 130.29 (C-45) , 140.60 (C-16), 141.06 (C-44), 142.37 (C-4), 144.32 (C-14), 151.31 (C-3), 156.62 (C-3), 160.68 (C-33), 161.23 (C-42), 167.91 (C-35), 168.30 (C-24) , 174.81(C-30) ppm. MS (70 eV): m/z = 736.10 ([M + 8]$^+$), 2.83.15, 149.60. Anal. Calcd. for $C_{38}H_{46}Cl\ N_5O_4S_2$: C, 61.89; H, 6.42; Cl, 4.81; N, 9.50; O, 8.68; S, 8.70. Found. C, 61.94; H, 6.26.

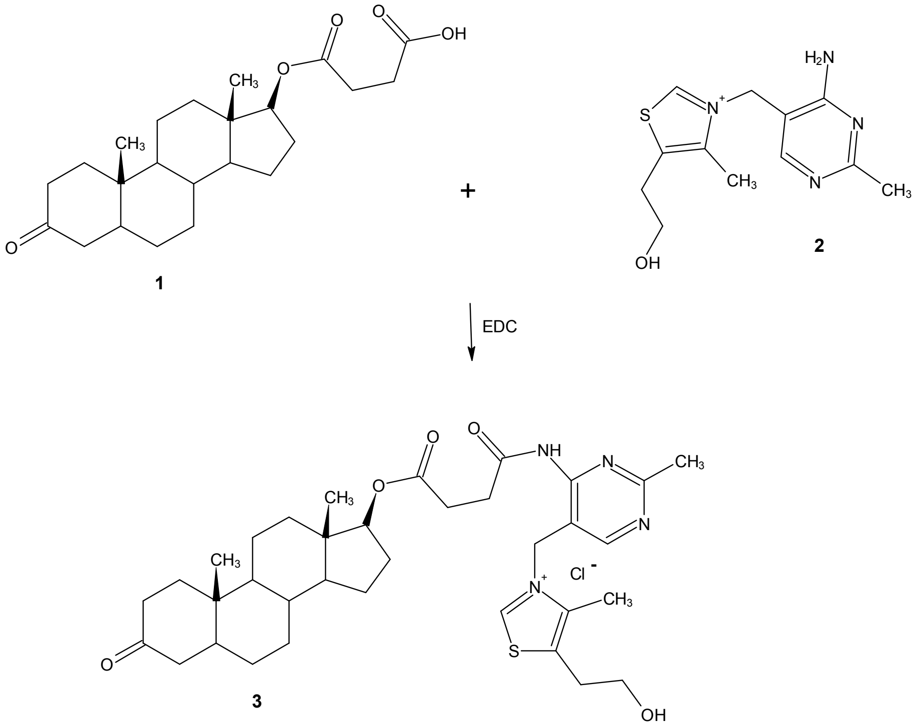

Figure 1. Synthesis of dihydrotestosterone-vitamin B1 conjugate (3). The dihydrotestosterone (1) was bound to vitamin B1 (2) using 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide (EDC) as catalyst.

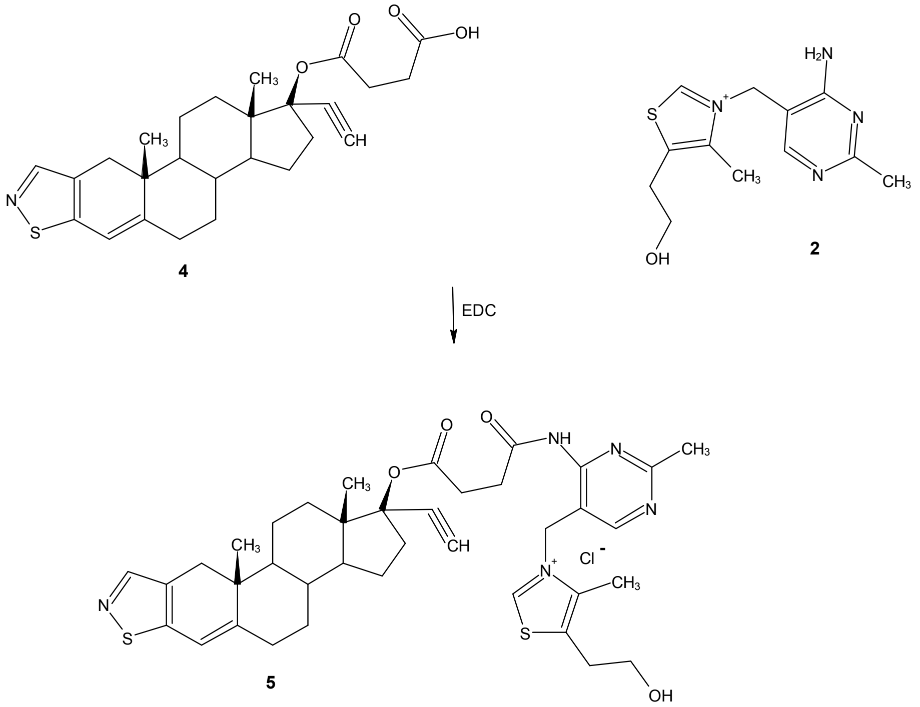

Figure 2. Synthesis of danazol-vitamin B1 conjugate (5). The danazol (4) was bound to vitamin B1 (2) using 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide (EDC) as catalyst to form 5.

Table 1. Physicochemical parameters *LogP* of compounds 3 and 5.

Program	Compounds	
	3	5
ALOGPs	1.30	1.80
AC logP	4.39	3.61
AB/LogP	4.69	6.15
miLogP	0.09	1.55
ALOGP	3.40	5.67
MLOGP	4.07	4.38
KOWWIN	2.20	4.12
XLOGP2	*	3.56
XLOGP3	4.87	5.54
Average *logP*	3.12(± 1.75)	4.04 (± 1.62)

*not available

Results and Discussion

In this work we report a straightforward route for the synthesis of two quaternary amino-steroid derivatives (see figure 1). This procedure involves the formation of amide group between the steroid-nucleus and vitamin B1 fragment (**2**). It is important to mention that many procedures for the formation of amide groups are known in the literature[13-15]. The most widely practiced method employs carboxylic acid chlorides as the electrophiles which react with the amino group in the presence of an acid scavenger[16]. Despite its wide scope, the former protocol suffers from several drawbacks; most notable are the limited stability of many acid chlorides and the need for hazardous reagents for their preparation (thionyl chloride)[17]. Therefore, in this work was used, a derivative of carbodiimide[18] for amide bond formation in the two quaternary amino-steroids derivatives.

In the first step, the vitamin B1 was coupled to dihydrotestosterone-succinate (**1**) to form **3** in presence of 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide. The results indicate that ^{1}H NMR spectrum of **3** showed signals at 0.80 and 0.96 ppm corresponding to methyls presents in the steroid nucleus. Other signals at 2.51 and 2.54 ppm for methylenes involved in the spacer arm between the danazol nucleus and vitamin B1 fragment were found. Additionally, several signals at 3.18 and 3.90 ppm for methylenes of the hydroxietilen moiety bonded to thiazol ring and for the *hydrogens* of the methylene between the pyrimidine and *thiazol* ring appears at 5.68 ppm. Finally, at down field a chemical shift (7.62 ppm) corresponding to proton in hydroxyl group was found.

The ^{13}C NMR spectra displays chemical shifts at 11.85 and 12.00 ppm for the carbons of methyl groups presents in the steroid nucleus. The chemical shifts of the methylenes involved in the spacer arm between the danazol nucleus and vitamin B1 fragment is found out at 29.57-31.44 ppm. In addition, several signals at 20.75-82.40 ppm corresponding to carbons involved in the steroid nucleus; at 26.69 and 63.60 for methylene group bonded to thiazol ring were found. Finally, there are two signals at 174.81 ppm for amide group and at 212.40 corresponding to ketone group. Additionally, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at m/z 673.04. The second step was achieved by the reaction of **4** with vitamin B1 in presence of 1-ethyl-3(3-dimethylamino-propyl)-carbodiimide to form **5** (scheme 2, see). The ^{1}H NMR spectra of the **5** showed upfield chemical shifts at 0.98 and 1.00 ppm for methyls present in the steroid nucleus. Two signals at 2.52 and 2.68 ppm were found for methylenes involved in arm spacer between the steroid nucleus and pyrimidine ring of vitamin B1 fragment. Additionally, several signals at 3.18 and 3.90 ppm for methylenes of the hydroxietilen moiety bonded to thiazol ring and for the *hydrogens* of the methylene between the pyrimidine and *thiazol* ring appears at 5.68 ppm. Finally, other signal at 7.26 ppm corresponding to hydroxyl group was found.

Table 2. Physicochemical parameters LogKow and π of dihydrotestosterone-vitamin B1 conjugate (3).

Compound	LogKow Fragment	Contributions
3	-CH3 [aliphatic carbon]	2.1892
	-CH2- [aliphatic carbon]	6.8754
	-CH [aliphatic carbon]	1.8070
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	2.0580
	Aromatic Nitrogen	-1.4648
	-N [aliphatic N, one aromatic attach]	-0.9170
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	Aromatic Sulfur	0.4082
	-C(=O)O [ester, aliphatic attach]	-0.9505
	-C(=O)N [aliphatic attach]	-0.5236
	-tert Carbon [3 or more carbon attach]	0.5352
	Aromatic nitrogen [+5 valence; H attach]	-4.5000
	Fused aliphatic ring unit correction	-2.0526
	Ring reaction -> ortho to -NHC(=O) type	-0.5634
	Ring Rx (2+ aromatic n) -> -NHC(=O)-	0.7900
	Reaction: nitrogen[+5] / polar group	1.2500
	Equation constant	0.2290
	Log Kow	3.12
	π	-0.3100

Table 3. Physicochemical parameters LogKow and π of the danazol-vitamin B1 conjugate (5).

Compound	LogKow Fragment	Contributions
5	-CH3 [aliphatic carbon]	2.1892
	-CH2- [aliphatic carbon]	5.8932
	-CH [aliphatic carbon]	1.0842
	=CH- or =C< [olefinc carbon]	0.7672
	#C [acetylenic carbon]	0.2668
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	2.9400
	Aromatic Nitrogen	-1.4648
	-N [aliphatic N, one aromatic attach]	-0.9170
	Aromatic Sulfur	0.8164
	-C(=O)O [ester, aliphatic attach]	-0.9505
	-C(=O)N [aliphatic attach]	-0.5236
	Aromatic Nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.8028
	Aromatic nitrogen [+5 valence; H attach]	-4.5000
	Fused aliphatic ring unit correction	-2.0526
	Ring reaction -> ortho to -NHC(=O) type	-0.5634
	Reaction: nitrogen[+5] / polar group	0.7900
	Ring Rx (2+ aromatic n) -> -NHC(=O)-	1.2500
	Equation Constant	0.2290
	Log Kow	4.0400
	π	-0.3800

On the other hand, ^{13}C NMR spectra displays chemical shifts at 15.63 and 19.66 ppm for the carbons of methyls groups presents in the steroid nucleus of **5**. Another chemical shifts at 29.57 and 33.90 ppm for carbons of methylenes involved in arm spacer between the steroid nucleus and pyrimidine ring were exhibited. In addition, several signals at 20.83-87-88 ppm corresponding to carbons involved in the steroid nucleus and two signals at 26.69 and 63.60 for methylene group bonded to thiazol ring were found. Finally, other signals at 67.55 ppm for alkyne group; at 168.30 ppm for ester group and at 174.81 ppm for amide group were found. Additionally, the presence of **5** was further confirmed from mass spectrum which showed a molecular ion at m/z 736.10.

On the order hand, in order to characterize the structural chemical requirements of the compounds **3** and **5,** the descriptors[19] *logP* and π were calculated. *LogP* describes the logarithmic octanol-water partition coefficient; therefore, it represents the lipophilic effects of a molecule that includes the sum of the lipophilic contributions of the parent molecule and its substituents[20]. The difference between the substituted and unsubstituted logP values is conditioned by the π value for a particular substituent[21]. In this work, the *logP* and π parameters were calculated by the methods reported by several investigators[22-28] and the LogKow Fragment method was used for the contributions of substituents[29]. The results (Table 1 and 2) showed an increase in *logP* and π values of **5** with respect to **3**. Additionally, other results showed that olefinic carbon (=CH-) and aromatic sulfur in compound **5** contribute to the high lipophilicity in comparison with **3**. All this data suggest that compounds studied have different lipophilicity degree which depends of the substituents involved in its structural chemistry.

Conclusions

In this work, we report an easy methodology to synthesize two quaternary amino-steroids derivatives and its correlation with descriptors LogP, π.

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