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Synthesis, Spectral and QSAR Studies of Danazol-Carbamazepine Conjugate

FIGUEROA-VALVERDE LAURO[1,*], DÍAZ-CEDILLO FRANCISCO[2], LÓPEZ-RAMOS MARÍA[1] and GARCÍA-CERVERA ELODIA[1]

[1]Facultad de Ciencias Químico-Biológicas, Lab. de Investigación, Universidad Autónoma de Campeche, Av. Agustín Melgar s/n, Col Buenavista C.P. 24039 Campeche, México
[2]Escuela de Ciencias Biológicas del IPN. Plan de San Luís y Díaz Mirón s/n Col. Santo Tomas, D.F. C.P. 11340, México

*Corresponding author: Fax: +981 8119800 Ext. 73099; Tel: +981 8119800 Ext. 73006; E-mail: lauro_1999@yahoo.com

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In this work, two danazol-carbamazepine conjugate was synthesized and characterized by spectroscopy and spectral analyses. In order to characterize the structural chemical requirements of danazol-carbamazepine conjugate, several parameters such as log P, π, R_m and V_m, P_c and S_t were evaluated. The results showed an increase in the values of log P for danazol-carbamazepine conjugate in comparison with danazol. The danazol-carbamazepine conjugate showed an increase in the values of π, R_m and V_m, P_c and S_t with respect to danazol. In conclusion, all data suggest a relationship of the physicochemical descriptors evaluated with degree of lipophilicity from the danazol-carbamazepine conjugate.

Key Words: Danazol, Lipophilicity, Steric impediment, QSAR.

INTRODUCTION

The steroid nucleus is one of the largest rigid units readily available with multiple chiral centers and the biological importance of this structural entity is well documented[1-3]. In this sense, there is increasing interest in developing new strategies to introduce functional groups into specific positions of steroid nucleus to modify their biological properties. For example, the hydroformylation of several Δ^4-androstenes with the rhodium-*tris*(2-*tert*-butylphenyl)-phosphite catalyst to form the corresponding, 4-formyl-androstane[4]. Other studies show the methylation of 17β-acetoxy-19-norandrosta-4,9-dien-3-one using $Ni(acac)_2$ as catalyst to form 5β/5α-methyl derivatives[5]. In addition, other reports indicate that 17-iodo-5R-androst-16-ene was used as substrates during the coupling with allyl acetate or methyl acrylate in the presence of the $Pd(OAc)_2$ catalyst and triethylamine as a base to formation of 21-formyl-pregn-16-ene[6].

On the other hand, the androgen derivative (3-ethynyl-17,-acetyl-androsta-3,5-diene) was synthesized[7] by reaction of 3-ethynyl-17β-acetyl-androsta-3,5-diene with trimethylsilylacetylene in presence of $(Ph_3P)_2Pd(OAc)_2$. Additionally, the androgen derivative (17α-propargyl phenyl-ethynyl malonate-androstan) was developed[8] using 17α-propargyl ethynyl malonate-androstan derivative, iodobenzene and $(Ph_3P)_4Pd/CuI/Et_3N$. Other reports showed the reaction of 17-pregna-2,4-dien-20-yno[2,3-d]-isoxazol-17-ol (danazol) with pregnenolone succinate using 1,3-dicyclohexylcarbodiimide as catalyst to form the danazol-pregnenolone conjugate[9]. All these experimental report show several procedures that are available for synthesis of several androgen derivatives by use of reaction different; nevertheless, recently[10] has been used the three component system (thiourea/benzaldehyde/dihydrotestosterone) for development of a succinate-dihydrotestosterone-dihydropyrimidine conjugate. Therefore, in this work, our initial design included a facile synthesis of danazol-carbamazepine conjugate (**4**) using the three component system (danazol, carbamazepine and benzaldheyde) using cupric chloride as catalyst. It is important to mention that **4** contains in its chemical structure a spacer arm with both phenyl and amide functional groups bound to dibenzo-annulene fragment and the steroid nucleus of **4**. Additionally, the relationship with the physicochemical descriptors such as log P, π, R_m, V_m, P_c and S_t was evaluated.

EXPERIMENTAL

The 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. Infrared spectra were recorded on a Perkin-Elmer Lambda 40 spectrometer from KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Varian VXR-300/5 FT NMR spectrometer at 300 and 75.4 MHz in $CDCl_3$ using TMS as internal standard. EIMS spectra were obtained with a Finnigan Trace GCPolaris Q spectrometer. Elementary analysis data were

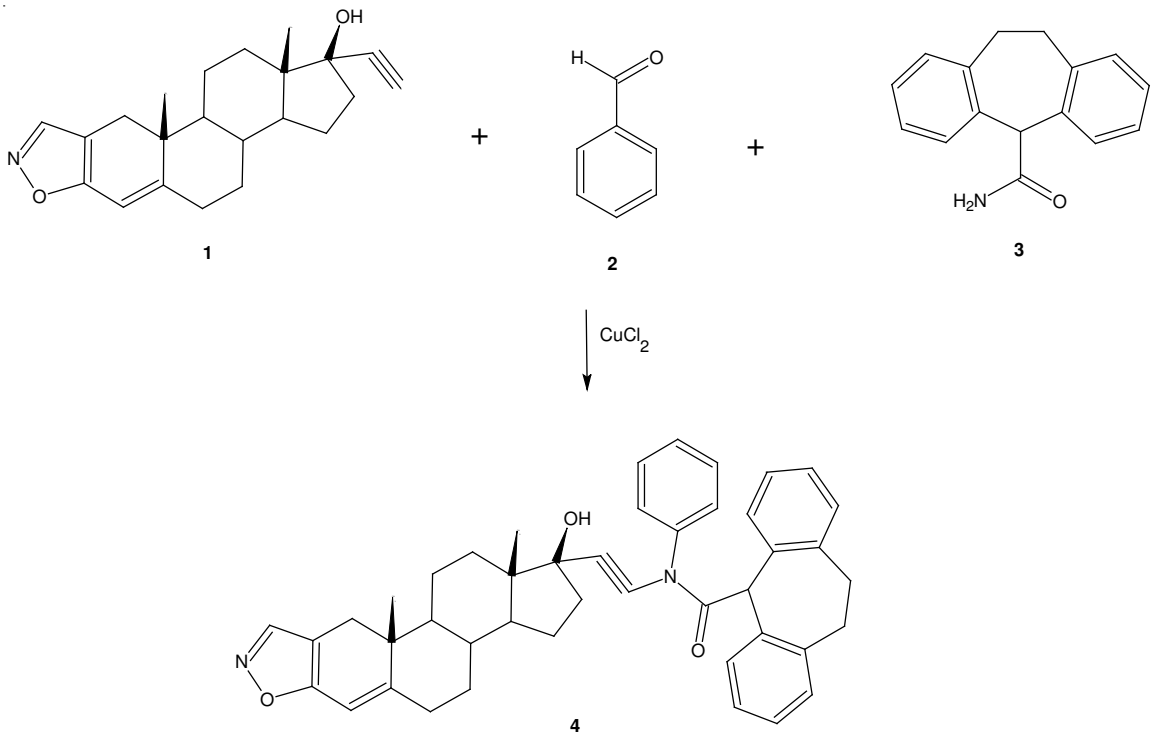
acquired from a Perkin-Elmer Ser. II CHNS/0 2400 elemental analyzer.

10,11-Dihydro-5*H*-dibenzo[a,d]cycloheptene-5-carboxyl acid (1-hydroxy-10a,12a-dimethyl-2,3,3a,3b, 4,5,10,10a,10b, 11,12,12a-dodecahydro-1*H*-7-oxa-8-aza-dicyclopenta- [a,h]phenanthren-1-ylethynyl)-phenyl-amide (4): A solution of danazol (1) [100 mg, 0.30 mmol], benzaldehyde (**2**) [50 μL, 0.49 mmol] and carbamazepine (**3**) [75 mg, 0.62 mmol) in ethanol 10 mL (2:1) was stirring by 48 h at room temperature. After the solvent was removed under vacuum and the crude product was purified by crystallization from methanol:hexane:water (3:2:1) yielding 75 mg of product; m.p. 134-136 ºC; IR (KBr, ν_{max}, cm^{-1}): 3300, 2242, 1670. ^1H NMR (300 MHz, $CDCl_3$) δ_H: 0.78 (s, 3H), 1.00 (s, 3H), 1.01-1.32 (m, 3H), 1.44-1.59 (m, 2H), 1.66-1.75 (m, 4H), 1.79-1.89 (m, 5H), 2.20-2.30 (m, 4H), 2.32 (m, 2H), 2.36-254 (m, 2H), 3.42 (m, 2H), 6.28 (s, 1H), 6.63 (s, 1H), 6.94 (m, 2H), 7.10-7.14 (m, 4H), 7.30 (m, 2H), 7.39 (m, 2H), 7.48-7.60 (m, 3H), 7.96 (s, 1H), 8.30 (s, 1H) ppm. ^{13}C NMR (75.4 MHZ, $CDCl_3$) δ_C: 12.61 (C-22), 19.60 (C-21), 20.97 (C-19), 22.94 (C-13), 31.35 (C-17) , 31.49 (C-38, 39), 31.71 (C-18), 33. 07 (C-20), 33.69 (C-5), 35.95 (C-6), 36.90 (C-12), 38.48(C-8), 45.50 (C-10), 52.88 (C-7), 52.94 (C-9), 56.77 (C-35), 67.26 (C-24), 88.78 (C-11), 91.03(C-25), 110.51 (C-15), 121.62 (C-4), 125.21 (C-43, 47), 127.03 (C-44, 48), 127.28 (C-45, 49), 128.31 (C-30, 34), 129.21 (C-32), 129.47 (C-31, 33), 130.55 (C-36, 41), 13.40 (C-36, C-41), 142.70 (C-29), 144.01 (C-16), 144.79 (C-37, 40), 149.59 (C-3), 156.97 (C-14), 162.07 (C-27) ppm. EI-MS, m/s 648.30 (M^+, 12), 298.00, 100.20. Anal. calcd. (%) for $C_{44}H_{44}N_2O_3$; C, 81.45, H, 6.84, N, 4.32, O, 7.40. Found (%): C, 81.40, H, 6.78.

QSAR study: In present study, physicochemical descriptors such as log P, π, R_m, V_m, P_c and S_t were evaluated using the methods reported by Mannhold, Waterbeemd and Petrauskas, Kolovanov[11,12].

RESULTS AND DISCUSSION

It is important to mention that many procedures that involved the three component system for formation of several compounds are available in the literature. The most widely practiced methods employed boric acid[13], silica sulfuric acid[14], poly-(4-vinylpyridine-co-divinylbenzene)-Cu(II) complex[15], H_2SO_4[16], silica triflate[17] and phosphorus pentoxide[18]. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks. Some reagents are of limited stability and preparation can be dangerous. Therefore, in this work we report a straightforward route for the synthesis of a new steroid derivative (**4**), this procedure was achieved by reacting danazol (**1**) with benzaldehyde (**2**) and carbamazepine (**3**) using cupric chloride as catalyst to form **4**. The nature of functional groups contained in the chemical structure of **4** involves both an amide and phenyl groups in the spacer arm between the dibenzo-annulene fragment and the steroid nucleus of **4** (**Scheme-I**). ^1H NMR spectra of **4** showed chemical shifts at 0.96 and 1.00 ppm corresponding to methyls presents in the steroid nucleus. Several signals at 1.01-2.54, 6.28 and 7.96 ppm for methylenes involved in steroid nucleus and at 2.32-3.42 and 6.63-7.39 ppm for dibenzo-annulene fragment were found. Additionally, other signals at 7.30-7.60 ppm for methylenes involved in phenyl-ring were display. Finally, other signal at 8.05 ppm for hydroxyl group was found. The ^{13}C NMR spectra display chemical shifts at 12.61 and 19.60 ppm for the carbons of methyls presents in the steroid nucleus of compound **4**. Another chemical shifts at 20.97-52.94 and 88.78-156.97 ppm for carbons of methylenes involved in the steroid nucleus were exhibited. Several signals at 31.35-52.77 and 125.21-144.79



Scheme-I: Synthesis of danazol-carbamazepine conjugate (**4**). Reaction of danazol with benzaldehyde and carbamazepine using cupric chloride as catalyst

ppm for carbons corresponding to methylenes involved in the dibenzo-annulene were found. Additionally, other chemical shifts at 67.26 and 91.03 ppm for alkyne group; at 128.31-142.70 ppm for phenyl ring were display. Finally, other signal at 162.07 ppm for amide group was found. The presence of **4** was further confirmed from mass spectrum which showed a molecular ion at m/z 648.30.

QSAR analyses: To analyze the molecular properties of **4**, two parameters such as the descriptors log P and π were calculated[19]. log P 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 log P values is conditioned by the π value for a particular substituent. Hammett showed that π values measure the free energy change caused by a particular substituent to relate to biological activity[21]. Therefore, in this work, the log P and π parameters were calculated by the method reported by some investigators[11,12]. It is important to mention that fragments **1** involved in the chemical structure of **4** was also evaluated with the purpose to know if the compound **1** induce changes in the lipophilicity degree of **4**. The results (Tables 1 and 2) showed an increase in log P and π values in the **4** compound with respect to **1**. This phenomenon is conditioned mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds. These results showed that aliphatic carbons (-CH_2-, -CH-) and aromatic carbon in compound **4** contribute to the high lipophilicity in comparison with **1**. All data indicate that an increase in the degree of lipophilicity depend of structural chemistry characteristic of **4**. Nevertheless, it is important to mention that there are studies which suggest that log P is relationship with some steric constants such as the molar volume (V_m) and molar refractivity (R_m)[22,23], these physicochemical parameters are a useful tool for the correlation of different properties that depend on characteristics of substituents attached to a constant reaction center. Therefore in study, both V_m and R_m descriptors were evaluated using the ACDLabs program[24]. The results showed an increase in both R_m and V_m values for **4** in comparison with **1** (Table-3). These data indicate that steric impediment, conformational preferences and internal rotation of **4** could influence the degree of lipophilicity of this compound. It is important to mention that there are reports which suggest that V_m is directly related to parachor (P_c) and surface tension (S_t) which are cumulative effects of the different intra- and intermolecular forces involved in the structural chemistry of some compounds[25,26]. Therefore, in this study these physiochemical descriptors were evaluated. The results indicate that both values of P_c, S_t for **4** were high in comparison with **1** (Table-3), these data indicate that this physicochemical parameters can also conditioned the degree of lipophilicity of **4**. In conclusion, all data suggest a relationship of the physicochemical descriptors evaluated with degree of lipophilicity from the danazol-carbamazepine conjugate.

TABLE-1
PHYSICOCHEMICAL PARAMETERS log Kow AND π OF DANAZOL (**1**)

Compound	log Kow fragment	Contributions
1	-CH_3 [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	3.4377
	-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	0.8820
	Aromatic oxygen	0.0423
	Aromatic nitrogen [5-member ring]	0.5262
	-tert Carbon [3 or more carbon attach]	0.8028
	Fused aliphatic ring unit correction	2.0526
	Oxazole ring (non-fused) correction	0.3279
	Equation constant	0.2290
	log Kow	4.2067
	π	0.1767

TABLE-2
PHYSICOCHEMICAL PARAMETERS log Kow AND π OF DANAZOL-CARBAMAZEPINE CONJUGATE (**4**)

Compound	log Kow Fragment	Contributions
4	-CH_3 [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	4.4199
	-CH [aliphatic carbon]	1.4456
	=CH- or =C< [olefinc carbon]	0.7672
	#C [acetylenic carbon]*n*]	0.2668
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic carbon	6.1740
	-N [aliphatic N, one aromat-C(=O)N [aliphatic attach]ic attach]	-0.9170
	Aromatic oxygen	-0.0423
	Aromatic nitrogen [5-member ring]	-0.5262
	-tert Carbon [3 or more carbon attach]	0.8028
	Di-N urea/acetamide aromatic correction	-0.7203
	Fused aliphatic ring unit correction	-2.0526
	Oxazole ring (non-fused) correction	-0.3279
	Equation constant	0.2290
	log Kow	8.6814
	π	4.4747

TABLE-3
*PHYSICOCHEMICAL PARAMETERS OF BOTH **1** AND **4** COMPOUNDS

Compound	R_m (cm^3)	V_m (cm^3)	P_c (cm^3)	S_t (dyne/cm)
1	95.82 ± 0.4	278.6 ± 5.0	759.0 ± 6.0	55.0 ± 5.0
4	190.61 ± .4	500.1 ± 5.0	1431.0 ± 6.0	667.7 ± 5.0

*R_m (Molar refractivity), V_m (molar volume), P_c (parachor) and S_t (surface tension).

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