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ORIGINAL PAPER

Synthesis and theoretical QSAR study of a naphthalene–androsterone derivative

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Abstract A new naphthalene–androsterone derivative was synthesized by the reaction of naphthalenyl succinate with an androsterone–succinate–ethylenediamine conjugate in the presence of 1-ethyl-3-(3-dimethylaminopropyl)carbodiimide. In order to delineate the structural chemical requirements of naphthalene–androsterone some physicochemical descriptors were evaluated. The results showed an increase in the values of these for the naphthalene–androsterone derivative in comparison with naphthalenyl succinate and androsterone–succinate–ethylenediamine. These data suggest a relationship between the evaluated physicochemical parameters and the degree of lipophilicity of the naphthalene–androsterone derivative.

Keywords Naphthalene · Androsterone · Physicochemical descriptors

Introduction

Quantitative structure–activity relationship (QSAR) studies are very important in medicinal chemistry [1–3]. There are reports of QSAR studies on several steroid types [4–6]. For example, the structure–activity analysis of a series of steroids binding to globulin was made using the electrotopological state index for each atom in the molecule [7]. Bravi [8] and Tong [9] reported comparative 3D QSAR studies of a series of steroids using the comparative molecular field (CoMFA) method. Additionally, Waller [10] reported a comparative QSAR study using CoMFA and hologram quantitative structure–activity relationship (HQSAR) methods for the steroid–receptor interaction. Other studies have developed a minimal topologic difference (MTD) model to evaluate such interactions [11, 12].

On the other hand, there are QSAR studies which suggest a correlation between log*P* and degree of lipophilicity for some steroids [13], e.g., the reports by Li and coworkers [14] which showed that log*P* is correlated with the passive diffusion of some steroids. Additionally, the QSAR of a ciprofloxacin–steroid derivative in terms of log*P*, π, R_m, and V_m was recently determinated [15]. All these works demonstrate several protocols for the QSAR study of steroids that involve geometry optimization and conformational analysis. In this work our aims were the synthesis of a naphthalene–androsterone derivative and the determination of its QSAR in terms of the descriptors lipophilicity parameters (log*P* and π), molar volume (V_m), molar refractivity (R_m), parachor (P_c), refractive index (n), surface tension (St), density, and polarizability.

Results and discussion

Chemical evaluation

In this study we report a straightforward route for the synthesis of naphthalene–androsterone derivative **6**. The first step involves the esterification of the hydroxyl group of β-naphthol (**1**) to form **2** (Scheme 1). Although there are

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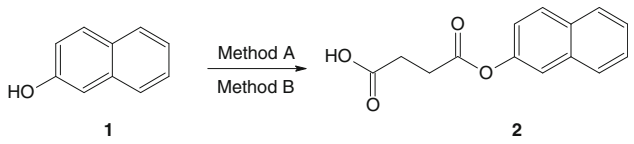


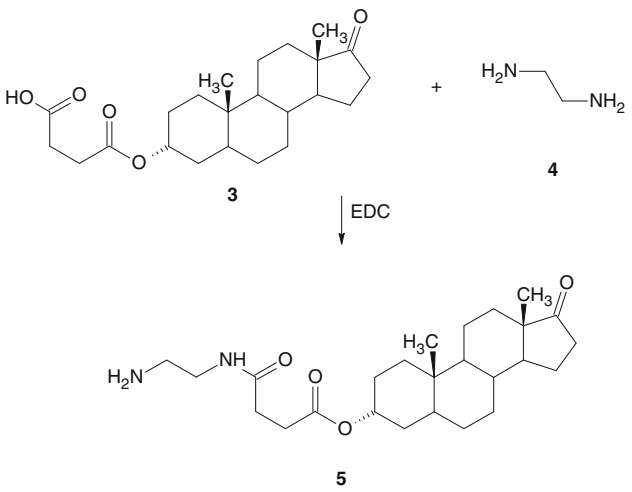
Scheme 1

diverse reagents available to produce ester derivatives [16, 17], most of the conventional methods are of only limited use for some compounds. Therefore, in this study two methods (A and B) were used. Method A involves a modification of the method reported by Erlanger and coworkers [18] for esterification of other compounds. Thus, compound **2** was synthesized by the reaction of **1** with succinic anhydride in the presence of pyridine using toluene to avoid ester hydrolysis.

In method B ester **2** was formed by reacting compound **1** and succinic acid under different conditions (acetonitrile/water) using 1,3-dicyclohexylcarbodiimide (DCC) as coupling reagent. Nevertheless, it is important to note that when DCC is used alone as condensing agent in ester synthesis, the yield of esters is often unsatisfactory due to formation of an *N*-acylurea by-product. Some reports showed that addition of a catalytic amount of a strong acid to the esterification reaction in the presence of DCC considerably increases the yield of esters and decreases the formation of the *N*-acylurea [19]. Therefore, *p*-toluenesulfonic acid was used to increase the yield of **2** in the esterification of **1** with succinic acid in the presence of DCC.

The ^{1}H NMR spectrum of **2** shows signals at 2.60 and 2.80 ppm corresponding to the methylene carbons of the aliphatic side chain, signals at 7.10–7.90 ppm for hydrogen atoms of the naphthalene nucleus, and a signal at 8.60 ppm corresponding to the acidic hydrogen of C(=O)–OH. The ^{13}C NMR spectrum of **2** displays signals at 29.00 and 29.66 ppm for the methylene carbons of the aliphatic side chain, signals at 118.02–148.44 ppm due to the naphthalene carbon atoms, a signal at 169.70 ppm for the ester group, and one at 174.02 ppm corresponding to the carboxyl group. Finally, the presence of **2** was further confirmed from the mass spectrum which showed a molecular ion at $m/z = 244.02$.

The second step was achieved by reacting **3** with ethylenediamine hydrochloride (**4**) to form amide **5** (Scheme 2). Although many procedures for the formation of amides are known in the literature, the most widely used employs carboxylic acid chlorides as the electrophiles which react with the amino group in the presence of an acid scavenger [20]. Despite its wide scope, this protocol suffers from several drawbacks: most notable are the limited stability of many acid chlorides and the need for hazardous reagents for their preparation (e.g., thionyl chloride) [21]. Therefore, in

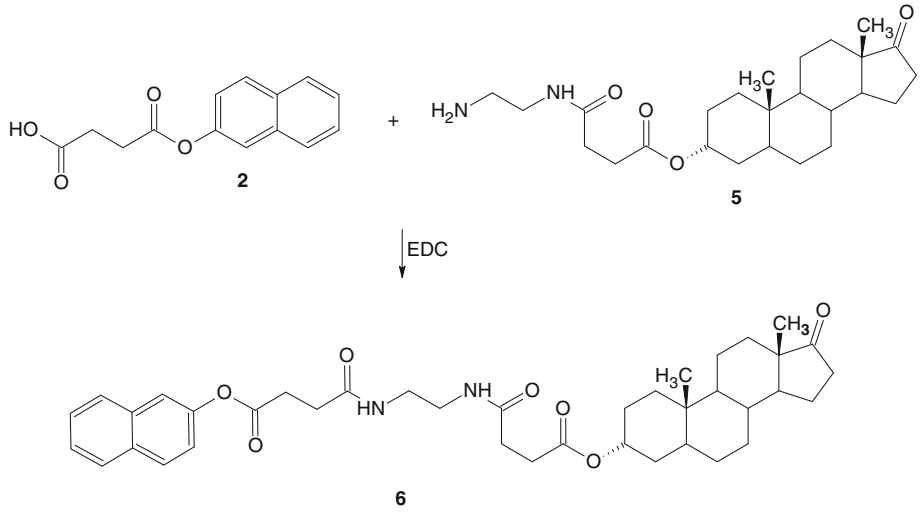


Scheme 2

this study 1-ethyl-3(3-dimethylamino-propyl)carbodiimide (EDC) [22] was used to form compound **5**. The ^{1}H NMR spectrum of **5** showed signals at 0.80 and 0.86 ppm for methyl groups in the steroid nucleus, signals at 0.94–2.39 ppm for hydrogen atoms in the steroid nucleus, signals at 2.42–3.20 ppm for the methylene carbons in the aliphatic side chain bound to the androsterone fragment, and a signal at 4.90 ppm corresponding to both amide and amine protons. The ^{13}C NMR spectrum of **5** displays signals at 13.74 and 17.08 ppm for the methyl groups in the steroid nucleus, signals at 20.08–29.45, 30.57, 34.92–42.11, and 47.67–73.97 ppm for the methylene carbons in the steroid nucleus, signals at 29.50, 31.44, 42.60, and 46.00 ppm for methylene carbons in the aliphatic side chain, as well as signals at 73.97 ppm for the amide group, 171.68 ppm for the ester group, and 221.00 for the ketone group. The presence of **5** was further confirmed from its mass spectrum which showed a molecular ion at $m/z = 432.02$.

The third step was achieved by reacting **2** with **5** in the presence of EDC to form **6** (Scheme 3). The ^{1}H NMR spectrum of **6** showed signals at 0.84 and 0.86 ppm corresponding to methyl groups in the steroid nucleus, signals at 2.42–3.42 ppm for methylene carbons in the spacer arm between the steroid nucleus and the naphthalene fragment, and a signal at 8.60 ppm for the amide group. The ^{13}C NMR spectrum displays signals at 13.74 and 18.36 ppm for the methyl groups in the steroid nucleus of **6**, signals at 29.50–35.89 ppm for methylene carbons in the spacer arm between the steroid nucleus and naphthalene fragment, signals at 117.72–148.00 ppm for naphthalene carbons, as well as signals at 169.40 and 171.94 ppm for ester groups, at 171.77 and 173.30 ppm for amide groups, and at 220.02 ppm for the ketone group. The presence of **6** was further confirmed from its mass spectrum which showed a molecular ion at $m/z = 658.05$.

Scheme 3



Evaluation of physicochemical parameters

For several years, physicochemical parameters such as log*P* and π have been used to measure the electronic and lipophilicity properties of many compounds [23]. Log*P* describes the logarithmic octanol–water partition coefficient at room temperature; therefore, it represents the lipophilic effects of a molecule that includes the sum of the lipophilic contributions of the parent molecule and its substituent [24]. The difference between the substituted and unsubstituted log*P* values gives the π value for a particular substituent. Hammett showed that π values, which measure the free energy change caused by a particular substituent, are related to biological activity [25]. In this study it was interesting to evaluate these physicochemical descriptors (log*P* and π) involved in the chemical structure of compound **6** using the method reported by Mannhold and Waterbeemd [26]. Note that fragments **2** and **5** involved in the chemical structure of **6** were also evaluated to determine whether they induce changes in the degree of lipophilicity of **6**. The results (Table 1) showed an increase in log*P* and π values in compound **6** with respect to **2** and **5**. This phenomenon is caused mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds, as shown in

Table 1 Log*P* of compounds **2**, **5**, and **6**

Program	Compounds		
	2	**5**	**6**
ALOGPs	1.88	2.34	5.08
AC logP	2.17	2.47	5.68
AB/LogP	2.64	2.59	5.05
miLogP	2.25	2.67	5.06
ALOGP	2.33	2.42	5
MLOGP	2.68	2.92	4.22
KOWWIN	2.51	2.05	4.42
XLOGP2	2.44	3.42	6.22
XLOGP3	2.16	2.51	5.33
Average log*P*	2.40 (±0.27)	2.53 (±0.42)	5.12 (±0.60)

Table 2 LogK_{OW} and π of compound **2**

LogK_{OW} (fragment description)	Contributions
–CH_2– (aliphatic carbon)	0.9822
Aromatic carbon	2.94
–COOH (aliphatic acid)	−0.6895
–C(=O)O (aliphatic ester)	−0.9505
Equation constant	0.229
LogK_{OW}	2.5112
π	0.18

Table 3 LogK_{OW} and π of androsterone–succinate–ethylenediamine conjugate **5**

LogK_{OW} (fragment description)	Contributions
–CH_3 (aliphatic carbon)	1.0946
–CH_2– (aliphatic carbon)	6.3843
–CH– (aliphatic carbon)	1.807
–NH_2 (aliphatic primary amine)	−1.4148
–NH– (aliphatic secondary amine)	−1.4962
–C(=O)– (aliphatic carbonyl)	−1.5586
–C(=O)O (aliphatic ester)	−0.9505
–C(=O)N (aliphatic amide)	−0.5236
–Tertiary carbon (3 or more carbons attached)	0.5352
Fused aliphatic ring unit correction	−2.0526
Equation constant	0.229
LogK_{OW}	2.0538
π	−0.64

Table 4 LogK_{OW} and π of naphthalene–androsterone derivative **6**

LogK_{OW} (fragment description)	Contributions
–CH_3 (aliphatic carbon)	1.0946
–CH_2– (aliphatic carbon)	7.3665
–CH– (aliphatic carbon)	1.807
–NH– (aliphatic attach)	−2.9924
Aromatic carbon	2.94
–C(=O)– (aliphatic carbonyl)	−1.5586
–C(=O)O (aliphatic ester)	−1.901
–C(=O)N (aliphatic amide)	−1.0472
–Tertiary carbon (3 or more carbons attached)	0.5352
Fused aliphatic ring unit correction	−2.0526
Equation constant	0.229
LogK_{OW}	4.4205
π	1.3667

Tables 2, 3, and 4. These results showed that aliphatic carbons (–CH_2–) in compound **6** contribute to the high lipophilicity in comparison with **5** and aliphatic carbons (–CH_3 and –CH_2–) with respect to **2**. Additionally, other results showed that the lipophilicity of **5** is high in comparison with **2**; this phenomenon is due to the presence of the methyl groups in the steroid nucleus and the aliphatic carbons. All data indicate that an increase in the degree of lipophilicity is characteristic of the structural chemistry of **6**. Nevertheless, there are studies which suggest that log*P* is related to some steric constants such as the molar volume (V_m) and molar refractivity (R_m) [27, 28]. 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 this study, both V_m and R_m descriptors were evaluated using the ACDLabs program [29]. The results showed an increase in both R_m and V_m values for **6** in comparison with **2** and **5** (Table 5). These data indicate that steric impediment, conformational preferences, and internal rotation of **6** could influence the degree of lipophilicity of this compound. Note that there are reports which suggest that V_m is directly related to parachor (P_c) and surface tension (*St*), which are cumulative effects of the different intra- and intermolecular forces involved in the structural chemistry of some compounds [30, 31]. The results indicate that both values of P_c and *y* for **6** were high in comparison with **2** and **5** (Table 5); these data indicate that these physicochemical parameters can also modify the degree of lipophilicity of **6**. In addition, other physicochemical parameters such as *n* (refractive index), density, and polarizability were determined to evaluate if these descriptors could be related to the degree of lipophilicity of compound **6**. The results (Table 5) showed that values of *n* for **6** were low in comparison with **2**. Nevertheless, the polarizability for **6** was high in comparison with **2** and **5**. In conclusion, all theoretical data suggest a relationship between the physicochemical descriptors evaluated and the degree of lipophilicity of the naphthalene–androsterone derivative.

Experimental

Androsterone succinate was prepared according to a method reported by several investigators [18, 32]. The other compounds used in this study were purchased from Sigma-Aldrich Co., Ltd. Melting points were determined on an Electrothermal 900 model. Infrared spectra were 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 $CDCl_3$ 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.

Butanedioic acid mono-2-naphthalenyl ester (**2**)
Method A: A solution of 100 mg **1** (0.69 mmol), 142 mg succinic anhydride (1.42 mmol), and 3 cm^3 of pyridine in 10 cm^3 of toluene was gently refluxed for 12 h, and then cooled to room temperature. 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/hexane/water (3:2:1) to give 46 mg. M.p.: 190 °C; IR: $\bar{\nu}$ = 1,738, 1,700 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ = 2.60 (t, 2H, *J* = 6.0 Hz), 2.80 (t, 2H, *J* = 6.0 Hz), 7.10–7.22 (m, 2H), 7.40–7.66 (m, 3H), 7.78–7.90 (m, 2H), 8.60 (s, 1H) ppm; ^{13}C NMR (74.5 MHz, $CDCl_3$): δ = 29.00 (C-15), 29.66 (C-14), 118.02 (C-6), 120.04 (C-2), 125.8 (C-8), 126.80 (C-9), 127.02 (C-10), 127.60 (C-7), 128.90 (C-3),

Table 5 Physicochemical parameters of compounds **2**, **5**, and **6**

Compound	R_m/cm^3	V_m/cm^3	P_c	*n*	*St*/10^{-3} N m^{-1}	Density/g cm^{-3}	Polarizability/10^{-24} cm^3
2	66.26 ± 0.3	188.8 ± 3.0	513.9 ± 4.0	1.619 ± 0.02	54.9 ± 3.0	1.29 ± 0.006	26.27 ± 0.5
5	118.91 ± 0.4	374.9 ± 5.0	989.8 ± 6.0	1.547 ± 0.03	48.5 ± 5.0	1.15 ± 0.1	47.13 ± 0.5
6	181.70 ± 0.4	533.3 ± 5.0	1,458.0 ± 6.0	1.596 ± 0.03	55.8 ± 3.0	1.23 ± 0.1	72.03 ± 0.5

R_m, molar refractivity; V_m, molar volume; P_c, parachor; *n*, refractive index; *St*, surface tension

131.02 (C-4), 133.90 (C-5), 148.44 (C-1), 169.70 (C-15), 174.02 (C-16) ppm; MS (70 eV): $m/z = 244.02$ ($[M + 10]^+$), 188.39.

Method B: A solution of 100 mg **1** (0.69 mmol), 160 mg succinic acid (1.35 mmol), 285 mg DCC (1.38 mmol), and 260 mg *p*-toluenesulfonic acid monohydrate (1.36 mmol) in 10 cm^3 acetonitrile/water (2:1) was stirred for 48 h at room temperature. The solvent was removed under vacuum and the crude product was purified by crystallization from methanol/hexane/water (3:2:1) to give 55 mg. Similar ^1H NMR and ^{13}C NMR data were obtained compared to method A.

4-[(2-Aminoethyl)amino]-4-oxobutanoic acid 17-oxoandrostan-3-yl ester (**5**, $C_{25}H_{40}N_2O_4$)

Compound **3** (200 mg, 0.51 mmol) was added to a solution of 100 mg ethylenediamine hydrochloride (0.75 mmol) and 150 mg EDC (0.78 mmol) in 10 cm^3 acetonitile/water (2:1) and stirred for 48 h at room temperature. After the solvent was removed under vacuum, the crude product was purified by crystallization from methanol/hexane/water (3:2:1) yielding 150 mg of product **5**. M.p.: 150–152 °C; IR: $\bar{\nu}$ = 3,330, 1,712 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.80$ (s, 3H), 0.86 (s, 3H), 0.94–1.08 (m, 2H), 1.19–1.38 (m, 7H), 1.40–1.71 (m, 7H), 1.75–1.83 (m, 2H), 1.89–2.39 (m, 3H), 2.42 (m, 2H), 2.48 (m, 1H), 2.53 (m, 2H), 2.92 (m, 2H), 3.20 (m, 2H), 4.55 (m, 1H), 4.90 (bs, 3H) ppm; ^{13}C NMR (74.5 MHz, $CDCl_3$): $\delta = 13.74$ (C-20), 17.08 (C-18), 20.08 (C-10), 21.61 (C-5), 27.63 (C-17), 28.04 (C-14), 29.45 (C-16), 29.50 (C-24), 30.57 (C-9), 31.44 (C-25), 34.92 (C-1), 35.11 (C-3), 35.36 (C-15), 35.74 (C-6), 38.23 (C-12), 42.11 (C-11), 42.60 (C-30), 46.00 (C-29), 47.67 (C-8), 48.81 (C-2), 51.49 (C-4), 73.97 (C-13), 171.68 (C-26), 171.85 (C-22), 221.00 (C-7) ppm; MS (70 eV): $m/z = 432.02$ ($[M + 10]^+$), 372.00, 272.39.

4,4′-(1,2-Ethanediyldiimino)bis(4-oxobutanoic acid) 1-(2-naphthalenyl) 1′-(17-oxoandrostan-3-yl) ester (**6**, $C_{39}H_{50}N_2O_7$)

A solution of 100 mg **2** (0.41 mmol), 177 mg **5** (0.41 mmol), and 120 mg EDC (0.62 mmol) in 10 cm^3 acetonitile/water (2:1) was stirred for 48 h at room temperature. The solvent was removed under vacuum and the crude product was purified by crystallization from methanol/hexane/water (3:2:1) to give 55 mg of **6**. M.p.: 170 °C; IR: $\bar{\nu}$ = 1,740, 1,634 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$): $\delta = 0.84$ (s, 3H), 0.86 (s, 3H), 0.96–1.01 (m, 2H), 1.21–1.41 (m, 8H), 1.51–1.61 (m, 3H), 1.64–1.71 (m, 3H), 1.78–1.83 (m, 2H), 1.90–1.95 (m, 2H), 2.39–2.41 (m, 2H), 2.42 (s, 2H), 2.44 (m, 1H), 2.46 (s, 2H), 2.55 (s, 2H), 2.72 (s, 2H), 3.34 (s, 2H), 3.42 (s, 2H), 4.60 (m, 1H), 7.12–7.20 (m, 2H), 7.30–7.97 (m, 5H), 8.60 (s, 2H) ppm;^{13}C NMR (74.5 MHz, $CDCl_3$): $\delta = 13.74$ (C-20), 18.36 (C-10), 20.08 (C-18), 21.60 (C-5), 27.79 (C-17), 28.02 (C-16), 29.42 (C-35), 29.50 (C-24), 30.40 (C-34), 30.52 (C-14), 31.50 (C-9), 31.90 (C-25), 34.30 (C-1), 35.11 (C-3), 35.23 (C-15), 35.70 (C-6), 35.89 (C-30), 38.42 (C-12), 42.11 (C-11), 42.40 (C-29), 47.60 (C-8), 48.81 (C-2), 51.49 (C-4), 75.03 (C-13), 117.72 (C-43), 120.87 (C-39), 126.10 (C-45), 126.78 (C-46), 127.60 (C-47), 127.76 (C-44), 129.32 (C-40), 131.42 (C-41), 133.06 (C-42), 148.00 (C-38), 169.40 (C-36), 171.77 (C-26), 171.94 (C-22), 173.30 (C-32), 220.02 (C-7) ppm; MS (70 eV): $m/z = 658.05$ ($[M + 17]^+$), 171.04, 289.12.

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