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A Facile Synthesis of an Androsterone derivative. QSAR Study

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Abstract: In this work our initial design included the synthesis of an androsterone derivative and its relationship with several physicochemical parameters. The first step was achieved by the reacting between montelukast (**1**) with androsterone (**2**) to form **3** using 1,3-dicyclohexylcarbodiimide as catalyst. In the second stage, the results showed an increase in the values of of *logP*, π, R_m, V_m, and P_c in **3** with respect to **1** and **2**, nevertheless, S_t was high in **3** in comparison with **2** and similar to **1.** These data suggest that physicochemical parameters can affect the degree of lipophilicity of 3 and 5.
Keywords. Androsterone, physicochemical, descriptors, montelukast.

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 from a series of steroids binding to globulin was made using the electrotopological state index for each atom in the molecule.[7] Other studies reported by Bravi[8] and Tong[9] showed a comparative 3D QSAR study in a series of steroids using the comparative molecular Field (CoMFA) method. Additionally, there is a report of a comparative QSAR study using CoMFA, HQSAR (hologram quantitative structure-activity relationship) methods for the steroid-receptor interaction.[10] Other studies have developed a MTD model (minimal the topologic difference) to evaluate the steroid-receptor interactions.[11,12]

On the other hand, there are QSAR studies which suggest a correlation between *logP* and lipophilicity degree for some steroids[13] for example, the reports of Li and coworkers[14] which showed that *LogP* have a correlation with the passive diffusion from some steroids. Additionally, recently was determinate the relationship of some *steroid* derivative with of *logP* π, R_m and V_m[15,16], all these works show several protocols for QSAR study of steroids that involved; geometry

optimization and conformational analysis. Therefore, in this work our initial design included the synthesis of an androsterone derivatives and its relationship with the physicochemical descriptors *logP* π, R_m, V_m, P_c and S_t.

Materials and methods

General methods

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 (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 $CDCl_3$ 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.

N-(1-{1-{3-[2-(7-chloro-quinolin-2-yl)vinil]-phenyl}-3-[2-(1-hydroxy-1-methyl-ethyl)-phenyl]-propylsulfanylmethyl}-cyclopropyl)-acetyc acid 10,13-dimethyl-17-oxo-2,3, 6,7,8,9,10, 11,12, 13,14,15, 16,17-tetradecahydro-1*H*-cyclopenta[α]phenanthren-3-yl ester. (3)

A solution of montelukast (**1**) [200 mg, 0.34 mmol], androsterone (**2**) [100 mg, 0.34 mmol] and 1,3-dicyclohexylcarbodiimide [140 mg, 0.68 mmol] in acetonitile:water 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 175 mg of product; mp 236-240 ^{o}C; IR V_{max} 3320, 1738, 767 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H : 0.86 (s, 3H), 0.88 (s, 3H), 0.92 (m, 1H), 0.94 (m, 4H), 1.04 (m, 1H), 1.22-1.36 (m, 6H), 1.38-1.40 (m. 2H), 1.52 (s, 6H), 1.54-1.63 (m, 5H), 1.72-1.80 (m, 3H), 1.82 (s, 1H), 1.90 (m, 1H), 1.94 (m, 1H), 1.96 (m, 1H), 208 (m, 1H), 2.37 (m, 1H), 2.40 (m, 1H), 2.45 (m, 1H), 2.49 (m, 1H), 2.51 (s, 2H), 2.86 (m, 2H), 3.79 (m, 1H), 4.81 (m, 1H), 6.89-7.04 (m, 2H), 7.08-7.13 (m, 4H), 7.22 (m, 1H), 7.24-7.38 (m, 2H), 7.40-7.49 (m, 2H), 7.69 (m, 1H), 7.73 (m, 2H), 7.96-8.37 (m, 2H) ppm. ^{13}C NMR (75.4 MHZ, $CDCl_3$) δ_C: 5.60 (**C**-24, **C**-25), 13.63 (**C**-61), 16.08 (**C**-23), 16.80 (**C**-59), 20.43 (**C**-52), 21.73 (**C**-47), 27.00 (**C**-55), 28.08 (**C**-53), 28.83 (**C**-56), 31.97 (**C**-51), 32.69 (**C**-57, **C**-58), 32.82 (**C**-27), 34.88 (**C**-43), 35.10 (**C**-45), 35.23 (**C**-54), 35.70 (**C**-48), 37.20 (**C**-41), 37.72 (**C**-26), 42.10 (**C**-42), 43.76 (**C**-34), 44.90 (**C**-22), 47.47 (**C**-50), 50.90 (**C**-44), 53.16 (**C**-46), 56.19 (**C**-20), 71.06 (**C**-37), 74.06 (**C**-40), 122.25 (**C**-30), 122.78 (**C**-3), 124.60 (**C**-9), 124.80 (**C**-18), 124.97(**C**-5), 125.08 (**C**-31), 125.30 (**C**-14), 125.33 (**C**-32), 126.42 (**C**-11), 127.24 (**C**-7), 127.92 (**C**-16), 128.10 (**C**-33), 129.88 (**C**-15), 131.16 (**C**-28), 132.39 (**C**-10), 135.13 (**C**-4), 135.17 (**C**-12), 135.96 (**C**-29), 137.60 (**C**-8), 139.76 (**C**-13), 140.78 (**C**-17), 148.54 (**C**-6), 152.51 (**C**-2), 173.81 (**C**-35), 219.96 (**C**-49) ppm. EI-MS, *m/z,* 857.19 (M^+, 06), 263.06 (100), 153.18 (79). Anal. Calcd for $C_{54}H_{64}ClNO_4S$: C, 75.54; H, 7.51; Cl, 4.13; N, 1.63; O, 7.45; S, 3.73. Found: C, 75.50, H, 7.48.

QSAR study.

In study, physicochemical descriptors such as *LogP*, π, R_m, V_m, P_c and S_t were evaluated using the methods reported by Mannhold, H. Waterbeemd and Petrauskas, A. Kolovanov. [17,18].

Results and Discussion

In this study, a straightforward route is reported for the synthesis of an androsterone derivative (Figure 1, see), the first step was achieved by the synthesis of **3** which contains in the A ring of the steroid nucleus a spacer arm with ester functional group coupled to the montelukast fragment. It is important to mention that there are diverse reagents to produce esters derivatives[19,20], nevertheless; most of the conventional methods have found only a limited use for this purpose; therefore, in this work a modification of the method reported by Erlanger and coworkers[21] for esterification of steroids was used. This stage involve the reacting between montelukast (**1**) with androsterone (**2**) to form **3** using as catalyst 1,3-dicyclohexylcarbodiimide. The results indicate that ^{1}H NMR spectrum of **3** showed two signals at 0.86 and 0.88 ppm for methyls involved in steroid nucleus. In addition, several signals at 0.94 ppm for methylenes presents in cyclopropane ring; at 0.92, 1.04-1.40, 1.54-1.80, 1.90-1.96, 2.40-2.49 and 4.81 ppm for methylenes involved in steroid nucleus; at 1.52 ppm for methyls corresponding to propanol group were found. Other signal at 1.82 ppm for the proton of hydroxyl group was showed. Finally, several chemical shifts at 6.89-7.04, 7.08-7.69 and 7.96-8.37 ppm for protons involved in the phenyl groups were found. The ^{13}C NMR spectra displays chemical shifts at 5.60 and 16.08 for methylenes present in the cyclopropane ring. Two signals at 13.63 and 18.80 ppm for the carbons of methyls involved in the steroid nucleus were found. Additionally, several signals at 20.43-31.97, 34.88-37.20, 42.10, 47.47-53.16 and 74.06 ppm were showed. Other chemical shifts at 32.69 ppm for methyls of propanol group; at 122.25-152.51 ppm for phenyl groups; at 173.81 ppm for ester group and at 219.96 ppm for ketone group were found. Finally, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at *m/z* 857.19.

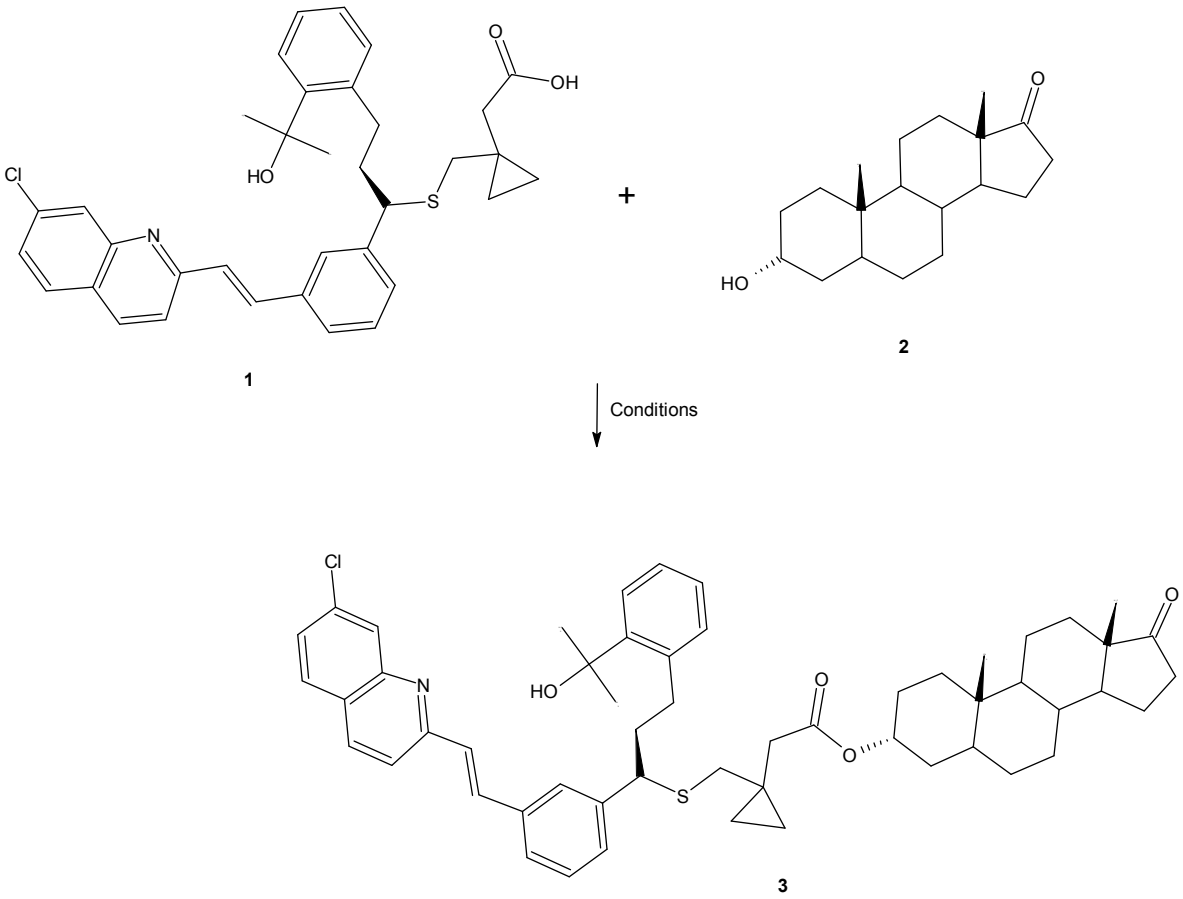

Figure1. Synthesis of an androsterone derivative (3). Reaction between montelukast (1) and androsterone (2). Conditions: 1,3-dicyclohexylcarbodiimide/acetonitile:water.

Table 1. Physicochemical parameters LogKow and π of montelukast (1).

Compound	LogKow Fragment	Contributions
1	-CH_3 [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	2.9466
	-CH- [aliphatic carbon]	0.3614
	=CH- or =C< [olefinc carbon]	0.7672
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	6.1740
	Aromatic Nitrogen	0.7324
	-Cl [chlorine, aromatic attach]	0.6445
	-COOH [acid, aliphatic attach]	-0.6895
	-S- [aliphatic attach]	-0.4045
	-tert Carbon [3 or more carbon attach]	0.5352
	Equation Constant	0.2290
	Log Kow	9.5175
	π	0.6445

Table 2. Physicochemical parameters LogKow and π of androsterone (2).

Compound	LogKow Fragment	Contributions
2	-CH_3- [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	4.4199
	-CH- [aliphatic carbon]	1.8070
	OH [hydroxy, aliphatic attach]	-1.4086
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-tert Carbon [3 or more carbon attach]	0.5352
	Fused aliphatic ring unit correction	-2.0526
	Equation Constant	0.2290
	Log Kow	3.0659
	π	0.5159

Table 3. Physicochemical parameters LogKow and π of 3.

Compound	LogKow Fragment	Contributions
3	-CH_3- [aliphatic carbon]	2.1892
	-CH_2- [aliphatic carbon]	7.3665
	-CH [aliphatic carbon]	2.1684
	=CH- or =C< [olefinc carbon]	0.7672
	-OH [hydroxy, aliphatic attach]	-1.4086
	Aromatic Carbon	6.1740
	Aromatic Nitrogen	-0.7324
	-Cl [chlorine, aromatic attach]	0.6445
	-C(=O)-[carbonyl,aliphatic attach]	-1.5586
	-C(=O)O[□ster,aliphatic attach]	-0.9505
	-S- [aliphatic attach]	-0.4045
	-tert Carbon [3 or more carbon attach]	1.0704
	Fused aliphatic ring unit correction	-2.0526
	Equation Constant	0.2290
	Log Kow	13.5020
	π	10.4361

Table 4. Physicochemical parameters of compounds 3 and 5. R_m molar refractivity; V_m molar volume

Compound	R_m (cm^3)	V_m (cm^3)	P_C (cm^3)	S_T (dyne/cm)
1	173.71 ± 0.3	460.7 ± 3.0	1281.2 ± 4.0	59.7 ± 3.0
2	83.49 ± 0.3	267.6 ± 3.0	677.7 ± 6.0	411.1 ± 3.0
3	250.28 ± 0.4	691.5 ± 5.0	1920.8 ± 6.0	59.5 ± 5.0

Theorical QSAR study

To analyze the molecular properties of **1, 2** and **3**, two parameters such as the descriptors *logP* and π were calculated.[22] *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.[23] The difference between the substituted and unsubstituted *logP* values is conditioned by the π value for a particular substituent. Hammett showed that π measured the free energy change caused by a particular substituent and its relate to biological activity.[24] Therefore, in this work, the *logP* and π parameters were calculated by the method reported by Mannhold and Waterbeemd.[17] It is important to mention that compounds **1, 2** and **3** were evaluated with the purpose to know if there are differences in its lipophilicity degree. The results (Table 1, 2 and 3, see) showed a increase in *logP* and π values in the **3** compound with respect to **1** and **2**. 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_3, CH_2 and CH) in compound **3** contribute to increase the lipophilicity in comparison with **1** and **2**. These data indicate that a change in the degree of lipophilicity depend of structural chemistry characteristic of compounds studied. 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) [25,26], 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.[17,18] The results showed an increase in both R_m and V_m and values for **3** in comparison with **1** and **2** (Table 4, see). These data indicate that steric impediment, conformational preferences and internal rotation of **1**, **2** and **3** could influence the degree of lipophilicity of these compounds.

On the other hand, 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.[27,28] The results indicate that values of P_c for **3** were high in comparison with **1** and **2** (Table 3, see), nevertheless, S_t was high for **3** with respect to **2** and similar to **1. T**hese data indicate that this physicochemical parameters can also conditioned the degree of lipophilicity of **3** and **5**. This premise could be supported by other studies[29] which indicate that R_m, V_m, P_c and S_t can condition by the degree of lipophilicity of some steroid derivatives and consequently affect its biological activity.

Conclusions

In this study a facile synthesis of an androsterone derivative was development and several physicochemical descriptors of QSAR study were evaluated. The results showed an increase in the values of *logP*, π, R_m, V_m, and P_c in **3** with respect to **1** and **2**, nevertheless, S_t was high in **3** in comparison with **2** and similar to **1.** These data suggest that physicochemical parameters can affect the degree of lipophilicity of **3**.

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