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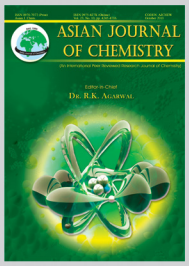

Synthesis of Montelukast-Androsterone Derivative and its Relationship with Physico-chemical Descriptors log P, π, R_m, V_m, P_c and S_t

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In this work our initial design included the synthesis of montelukast-androsterone (**5**) and its relationship with several physico-chemical parameters as log P, π, R_m, V_m, P_C and S_T. The first step was achieved by the reacting between hemisuccinate of androsterone (**1**) with ethyleneadiamine to form an androsterone derivative (**3**) using N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide or boric acid as catalysts. In the second stage, was achieved by reacting **3** with montelukast (**4**) to form **5** in presence of N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide. Other results showed an increase in the values of log P, π, R_m, V_m, P_C and S_T in **5** with respect to **1**, **3** and **4**. These data suggest that physico-chemical parameters can affect the degree of lipophilicity of **5**.

Key Words: Montelukast, Androsterone, Physicochemical, Parameters.

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].

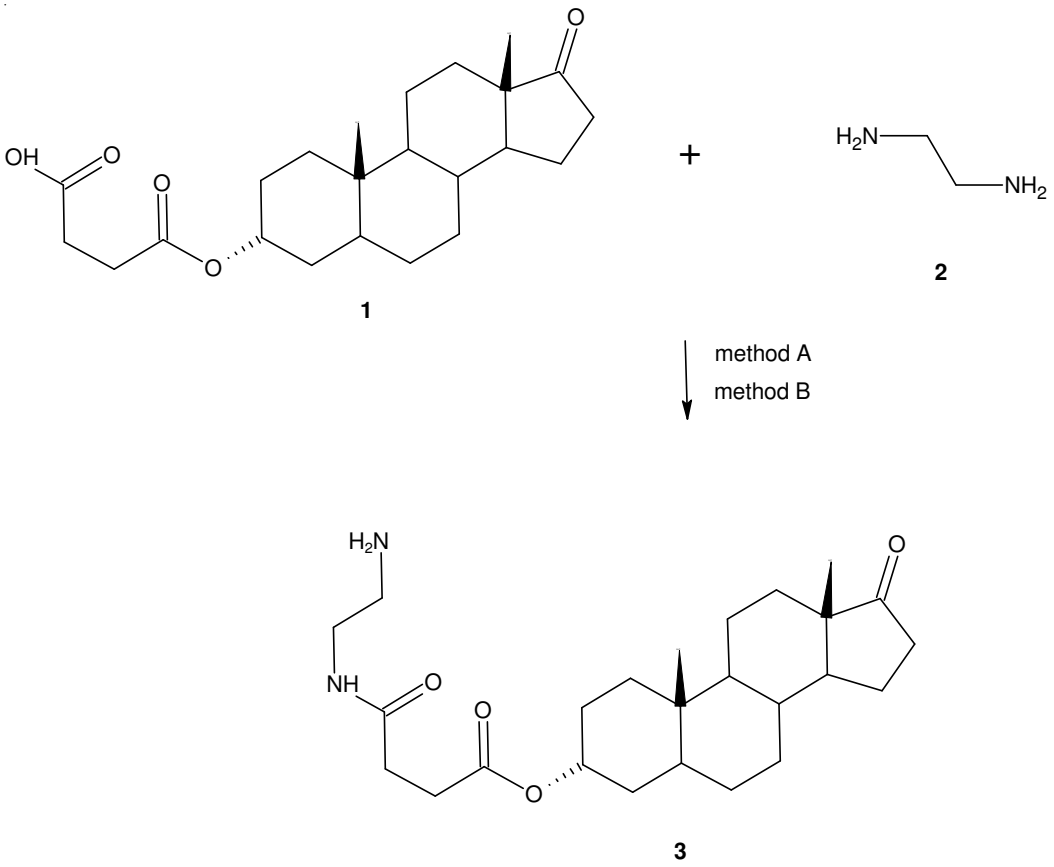
On the other hand, there are QSAR studies which suggest a correlation between log P and lipophilicity degree for some steroids[13] for example, the reports of Li *et al.*[14] which showed that log P have a correlation with the passive diffusion from some steroids. Additionally, recently was determinate the relationship of some steroid derivative with of log P, π, R_m and V_m[15,16]. All these works show several protocols for QSAR study of steroids that involved the geometry optimization and conformational analysis. Therefore, in this work our initial design included the synthesis of montelukast-androsterone derivative and its relationship with the descriptors log P, π, R_m, V_m, P_c and S_t involved in QSAR study.

EXPERIMENTAL

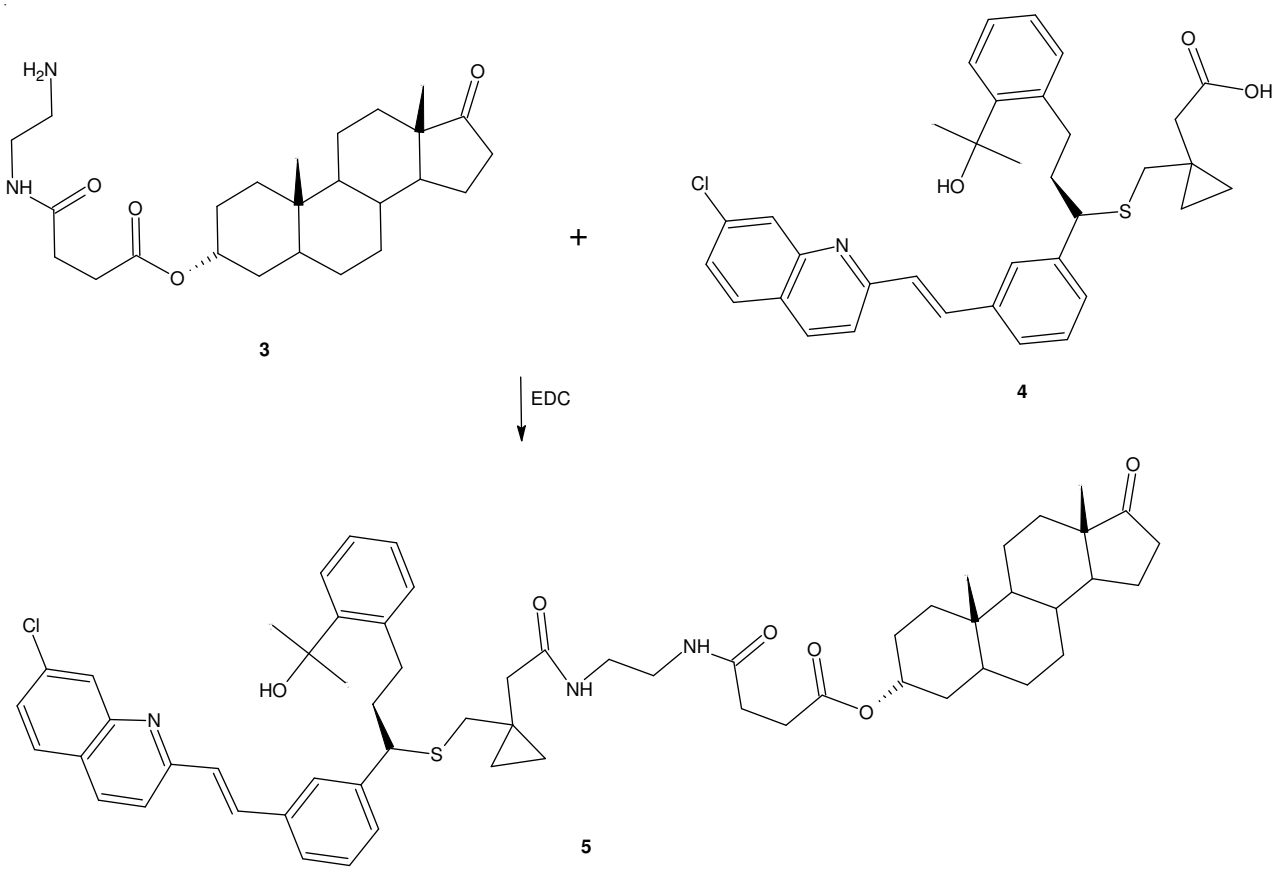
General methods: Hemisuccinate of androsterone (**2**) was prepared according to a previously reported method[17,18]. The other compounds evaluated in this study were purchased from Sigma-Aldrich Co. Ltd. The melting points for the different compounds were determined on an Electrothermal (900 model). Infrared spectra (IR) was recorded using KBr pellets on a Perkin-Elmer Lambda 40 spectrometer. ^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.

N-(2-Amino-ethyl)succinamic acid 10,13-dimethyl-17-oxo-2,3,6,7,8,9,10,11,12,13,14,15,16,17-tetradecahydrocyclopenta[a]phenanthren-3-yl ester (3) (Scheme-I)

Method A: A solution of hemisuccinate of androsterone (**1**) [200 mg, 0.51 mmol], ethylendiamine (**2**) [67 µL, 1.0 mmol] and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide



Scheme-I: Synthesis of androsterone-derivative (**3**). Reaction of hemisuccinate of androsterone (**1**) with ethylenediamine (**2**) using N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide (method A) or boric acid (method B) as catalysts to form compound **3**



Scheme-II: Synthesis of montelukast-androsterone derivative (**5**). Reaction between **3** and montelukast (**4**) to form compound **5** using N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide as catalyst

[130 µL, 0.73 mmol] in methanol 5 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:water (3:2:1) yielding 150 mg of product; m.p. 126 ºC; IR (KBr, ν_{max}, cm^{-1}) 3386, 1738, 1642. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.80 (s, 3H), 0.86 (s, 3H), 0.93-1.05 (m, 2H), 1.26-1.33 (m, 6H), 1.44-1.48 (m, 3H), 1.55-1.65 (m, 3H), 1.66-1.77 (m, 3H), 1.85-2.02 (m, 3H), 2.44-2.50 (m, 2H), 2.52 (t, 2H, *J* = 6 Hz), 2.57, 2.98 (t, 2H, *J* = 6 Hz), 3.22 (t, 2H, *J* = 6 Hz), 4.67 (m 1H), 4.90 (broad, 2H) ppm. ^{13}C NMR (75.4 MHZ, $CDCl_3$) δ_C: 13.63 (C-20), 18.80 (C-18), 20.43 (C-10), 21.73 (C-5), 27.05 (C-17), 28.02 (C-14), 28.40 (C-16), 29.20 (C-24), 30.83 (C-25), 31.95 (C-9), 35.02 (C-1), 35.11 (C-3), 35.23 (C-15), 35.53 (C-6), 37.20 (C-12),41.60 (C-29), 42.02 (C-11), 42.68 (C-30), 47.47 (C-8), 50.90 (C-2), 53.16 (C-4), 71.06 (C-13), 169.81 (C-26), 170.47 (C-22), 219.96 (C-7) ppm. EI-MS, m/z, 432.10 (M^+, 12). Anal. calcd. (%) for $C_{25}H_{40}N_2O_4$: C, 69.40; H, 9.32; N, 6.48; O, 14.79. Found (%): C, 69.36, H, 9.30.

Method B: A solution of **1** [200 mg, 0.51 mmol], ethylendiamine [67 µL, 1.0 mmol] and boric acid [62 mg, 1.0 mmol] in acetonitrile-water (10 mL, 4:1) was stirring by 72 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 90 mg of **3**. It is important to mention that ^{1}H and ^{13}C NMR data obtained were similar in comparison with the method A.

N-{2-[2-(1-{1-{3-[2-(7-Chloro-quinolin-2-yl)vinyl]-phenyl}-3-[2-(1-hydroxy-1-methyl-ethyl)-phenyl]-propylsulfanylmethyl}cyclopropyl)acetylamino]ethyl}-succinamic acid 10,13-dimethyl-17-oxo-hexadecahydro-cyclopenta[a]phenanthren-3-yl ester (5) (Scheme-II): A solution of montelukast (**4**) [200 mg, 0.34 mmol], compound **3** [148 mg, 0.34 mmol] and N-(3-dimethylaminopropyl)-N'-ethylcarbodiimide [130 µL, 0.73 mmol] in acetonitrile: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; m.p. 260-264 ºC; IR (KBr, ν_{max}, cm^{-1}) 3328, 1738, 1642. ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.86 (s, 3H), 0.88 (s, 3H), 0.92 (m, 1H), 1.04 (m, 1H), 1.10 (m, 4H), 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), 1.90 (m, 1H), 1.94 (m, 1H), 1.96 (m, 1H), 208 (m, 1H), 2.37 (m, 2H), 2.40 (m, 2H), 2.42 (m, 2H), 2.45 (m, 1H), 2.49 (m, 1H), 2.54 (s, 2H), 2.86 (m, 2H), 3.30 (s, 2H), 3.44 (s, 2H), 3.79 (m, 1H), 4.71 (m, 1H), 6.05 (broad, 3H), 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, 1H), 7.96-8.37 (m, 2H) ppm. ^{13}C NMR (75.4 MHZ, $CDCl_3$) δ_C: 11.20 (C-24, C-25), 13.63 (C-71), 16.80 (C-69), 19.20 (C-23), 20.43 (C-64), 21.73 (C-59), 27.00 (C-67), 28.08 (C-65), 28.83 (C-68), 29.40 (C-48), 31.97 (C-63), 32.02 (C-47), 32.69 (C-45, C-46), 32.82 (C-27), 34.88 (C-55), 35.10 (C-57), 35.23 (C-66), 35.70 (C-60), 37.20 (C-53), 37.72 (C-26), 37.86 (C-40), 42.76 (C-34), 42.80 (C-54), 42.92 (C-41), 44.90 (C-22), 47.47 (C-62), 50.90 (C-56), 53.16 (C-58), 56.19 (C-20), 71.06 (C-37), 74.06 (C-52), 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), 169.80 (C-43), 173.81 (C-35), 174.02 (C-49), 219.96 (C-61) ppm. EI-MS, m/z, 999.40 (M^+, 12). Anal. calcd. (%) for $C_{60}H_{74}N_3O_6SCl$: C, 72.01; H, 7.45; Cl, 3.54; N, 4.20; O, 9.59; S, 3.20. Found (%): C, 72.04, H, 7.40.

QSAR study: In 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[19,20].

RESULTS AND DISCUSSION

In this study, a straight forward route is reported for the synthesis of montelukast-androsterone derivative, the first stage was achieved by reacting hemisuccinate of androsterone with ethylenediamine resulting in amide bond formation in the compound **3**. It is important to mention that many procedures for the formation of amide groups are known in the literature, the most widely practiced method[21] employs carboxylic acid chlorides as the electrophiles which react with the amine in the presence of an acid scavenger. Despite its wide scope, this protocol suffers from several drawbacks. The most notable are the limited stability of many acid chlorides and the need for hazardous reagents[22] for their preparation (thionyl chloride). In this work, two different methods for amide formation were employed, in the first one the technique reported by Pingwah[23] for boric acid catalyzed amidation of carboxylic acids and amines (method B) was used, in the second one we used a derivate of carbodiimide (method A) as catalyzer[24] for amide bond formation in the new arm formed in the steroid nucleus. It is important to mention that in this reaction the use of carbodiimide as catalyst showed in higher yields compared to the amide bond formed with method A. The results indicate that ^{1}H NMR spectrum of **3** showed two signals at 0.80 and 0.86 ppm for methyls involved in steroid nucleus. Additionally, several signals at 0.93-2.50 ppm for methylenes presents in steroid nucleus; at 2.52-3.22 ppm for methyenes corresponding to arm bound to A ring of steroid nucleus were found. Other chemical shift at 4.90 for protons involved in the amine groups was found. ^{13}C NMR spectra display chemical shifts at 13.63 and 18.80 ppm for methyls of steroid nucleus. Several signals at 20.43-28.40, 31.95-37.20, 42.02 and 47.47-71.06 ppm for methylenes corresponding to steroid nucleus were found. In addition, other signals at 29.20, 30.83, 41.60 and 42.68 ppm for methylenes involved in the arm bound to A ring of androsterone were showed. Other signals at 169.81, 170.47 and 219.96 ppm were obtained from amide group, ester group and ketone group, respectively. Finally, the presence of **3** was further confirmed from mass spectrum which showed a molecular ion at m/z 432.10.

The second stage was achieved by reacting **3** with montelukast (**4**) to form the compound **5** in presence of a carbodiimide derivative. It is important to mention that **5** contain an ester and amide groups in the spacer arm between the steroid nucleus and montelukast fragment. The results indicate that ^{1}H NMR spectra of **5** showed a chemical shift at

0.86 and 0.88 ppm for methyl group present in the steroid nucleus. Additionally, several signals at 0.92-1.04, 1.22-1.40, 1.54-1.90, 1.96, 240, 2.49 and 4.71 ppm for methylenes involved in steroid nucleus. Other signals at 1.10 ppm for methylenes presents in cyclopropane ring and at 1.52 ppm for propanol group were found. In addition, other signals at 6.89-7.04, 7.08-7.13, 7.22-7.69 and 7.96-8.37 ppm for phenyl groups were showed. Finally, a signal at 6.05 ppm for both hydroxyl and amide groups were found. The ^{13}C NMR spectra displays chemical shifts at 11.20 and 19.20 ppm for methylenes involved in the cyclopropane ring and at 13.63 and 16.80 ppm for methyls of steroid nucleus. Several signals at 20.43-28.83, 31.97, 34.88-37.20, 42.11, 47.47-53.16 and 74.06 ppm for methylenes corresponding to steroid nucleus were found. A signal at 32.69 ppm for methyl groups involved in the propanol group was showed. In addition, other signals at 29.40, 32.02, 37.86, 42.76 and 42.92 ppm for methylenes involved in the spacer arm between the montelukast and androsterone. In addition other signals at 122.25-135.13 and 135.96-152.51 ppm for methylenes contained in the phenyl groups were found. Finally, several signals at 169.80-173.81 ppm for amide groups; at 174.02 ppm for ester group and at 219.96 ppm for ketone group were showed. The presence of **5** was further confirmed from mass spectrum which showed a molecular ion at m/z 999.40.

QSAR study: To analyze the molecular properties of copound **5**, two parameters such as the descriptors log P and π were calculated[25]. 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[26]. The difference between the substituted and unsubstituted log P 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 relate to biological activity[27]. Therefore, in this work, the log P and π parameters were calculated by the method reported by Mannhold and Waterbeemd[19]. It is important to mention here that the compounds **1**, **3** and **4** were also evaluated with the purpose to know if there are differences in its lipophilicity degree with respect to **5**. The results (Tables 1-5) showed a increase in log P and π values in the compound **5** with respect to compounds **1**, **3** and **4**. 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 **5** contribute to increase the lipophilicity in comparison with compounds **1**, **3** and **4**. 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 in relationship with some steric constants such as the molar volume (V_m) and molar refractivity (R_m)[28,29]. 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[19,20]. The results showed an increase in both R_m and V_m values for compound **5** in comparison with compounds **1**, **3** and **4** (Table-5). These data indicate that steric impediment, conformational preferences and internal rotation of compound **5** could influence the degree of lipophilicity of this compound.

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[30,31]. The results indicate that both values of P_c, S_t for compound **5** were high in comparison with compounds **1**, **3** and **4** (Table-5). These data

TABLE-1
PHYSICO-CHEMICAL PARAMETERS log Kow AND π OF HEMISUCCINATE OF ANDROSTERONE (**1**)

Compound	log Kow fragment	Contributions
1	-CH_3 [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	5.4021
	-CH [aliphatic carbon]	1.8070
	-C(=O)- [carbonyl, aliphatic attach]	-1.5586
	-COOH [acid, aliphatic attach]	-0.6895
	-C(=O)O [ester, aliphatic attach]	-0.9505
	-*tert* carbon [3 or more carbon attach]	0.5352
	Fused aliphatic ring unit correction	-2.0526
	Equation constant	0.2290
	log Kow	3.8167
	π	0.7467

TABLE-2
PHYSICO-CHEMICAL PARAMETERS log Kow AND π OF HEMISUCCINATE OF ANDROSTERONE-ETHYLENDIAMINE CONJUGATE (**3**)

Compound	log Kow fragment	Contributions
3	-CH_3 [aliphatic carbon]	1.0946
	-CH_2- [aliphatic carbon]	6.3843
	-CH [aliphatic carbon]	1.8070
	-NH_2 [aliphatic attach]	1.4148
	-NH- [aliphatic attach]	1.4962
	-C(=O)- [carbonyl, aliphatic attach]	1.5586
	-C(=O)O [ester, aliphatic attach]	0.9505
	-C(=O)N [aliphatic attach]	0.5236
	-tert Carbon [3 or more carbon attach]	0.5352
	Fused aliphatic ring unit correction	2.0526
	Equation constant	0.2290
	log Kow	2.0538
	π	1.7629

TABLE-3
PHYSICO-CHEMICAL PARAMETERS log Kow AND π OF MONTELUKAST (**4**)

Compound	log Kow fragment	Contributions
4	-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-5
PHYSICOCHEMICAL PARAMETERS OF COMPOUNDS **1**, **3**, **4** AND **5**. R_m = MOLAR REFRACTIVITY; V_m = MOLAR VOLUME; P_C = PARACHOR; S_T = SURFACE TENSION

Compound	R_m (cm^3)	V_m (cm^3)	P_C (cm^3)	S_t (dyne/cm)
1	103.90 ± 0.4	328.9 ± 5.0	868.7 ± 6.0	48.6 ± 5.0
3	118.91 ± 0.4	374.9 ± 5.0	989.8 ± 6.0	48.5 ± 5.0
4	173.71 ± 0.3	460.7 ± 3.0	1281.2 ± 4.0	59.7 ± 3.0
5	285.60 ± 0.4	795.0 ± 5.0	2228.1 ± 6.0	61.6 ± 5.0

TABLE-4
PHYSICOCHEMICAL PARAMETERS log Kow AND π OF THE COMPOUND (**5**)

Compound	log Kow fragment	Contributions
5	$-CH_3$ [aliphatic carbon]	2.1892
	$-CH_2-$ [aliphatic carbon]	9.3309
	-CH [aliphatic carbon]	2.1684
	=CH- or =C< [olefinc carbon]	0.7672
	-OH [hydroxy, aliphatic attach]	1.4086
	-NH- [aliphatic attach]	2.9924
	Aromatic carbon	6.1740
	Aromatic nitrogen	0.7324
	-Cl [chlorine, aromatic attach]	0.6445
	-C(=O)- [carbonyl, aliphatic attach]	1.5586
	-C(=O)O [ester, aliphatic attach]	0.9505
	-C(=O)N [aliphatic attach]	1.0472
	-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	1.4268
	π	1.9093

indicate that this physicochemical parameters can also conditioned the degree of lipophilicity of compound **5**. This view could be supported by other studies as well[32] 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.

Conclusion

In this study a facile synthesis of montelukast-androsterone derivative was development and several physicochemical descriptors of QSAR study were evaluated. The results showed an increase in the values of log P, π, R_m, V_m, P_c and S_t in compound **5** with respect to compounds **1**, **3** and **4**. These data suggest that physicochemical parameters can affect the degree of lipophilicity of compound **5**.

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