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# Synthesis of Amino-Estradiol Derivative: Relationship with the Physicochemical Descriptors log P, π, $R_m$, $V_m$, $P_c$ and $S_t$

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In this investigation our initial design included the synthesis of an estradiol derivative (**4**) and its relationship with several physico-chemical parameters. $^1$H NMR spectrum of **4** showed signals at 0.80 corresponding to methyl present in the steroid nucleus. Additionally, other signals at 2.56-2.58 ppm for methylenes involved in arm bound to D ring; at 2.60-3.64 ppm for methylenes present in the arm bound to A ring of **4** were found. Finally, a signal at 4.22 ppm for both hydroxyl and amino groups was found. Other results showed an increase in the values of log P, π, $P_c$ and $S_t$ in **3** with respect to **4** and **2**. These data suggest that physicochemical parameters can affect the degree of lipophilicity of **3** and **4**.

**Key Words: Amino-estradiol, Derivative, Physico-chemical, 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 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 Bravia[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].

There are QSAR studies which suggest a correlation between log P and lipophilicity degree for some steroids[13] for example, the reports of Li and coworkers[14] 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, In this work our initial design included the synthesis of an estradiol derivative and its relationship with the physico-chemical descriptors log P, π, $R_m$, $V_m$, $P_c$ and $S_t$.

## 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). An infrared spectrum (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.

**4-[(2-Amino-ethyl amino)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthrene-3,17-diol (2):** A solution of estradiol (200 mg, 0.73 mmol), ethylendiamine (98 µL 1.46 mmol), in 10 mL of formaldehyde was gently refluxed for 48 h and then cooled to 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 70 % of product, m.p. 132 ºC; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3330, 3402; $^1$H NMR (300 MHz, $CDCl_3$)

$\delta_H$: 0.64 (s, 3H), 0.82 (m, 1H), 1.03 (m, 1H), 1.05-1.18 (m, 2H), 1.28-1.45 (m, 4H), 1.70 (m, 1H), 2.06 (m, 1H), 243-256 (m, 3H), 262 (s, 2H, *J* = 5.9 Hz), 2.78 (s, 2H, *J* = 5.9 Hz), 3.67 (m, 1H), 3.70 (s, 2H), 3.80 (broad), 6.58 (d, 1H, *J* = 8.65 Hz), 6.80 (d, 1H, *J* = 8.65 Hz) ppm. $^{13}$C NMR (74.5 MHz, $CDCl_3$) $\delta_C$: 11.30 (C-19), 23.57 (C-9), 26.23 (C-6), 27.69 (C-4), 27.71 (C-10), 30.83 (C-8), 37.40 (C-7), 39.00 (C-4), 41.52 (C-23), 43.63 (C-2), 44.48 (C-5), 44.50 (C-20), 50.53 (C-3), 53.28 (C-22), 81.78 (C-1), 112.55 (C-15), 122.26 (C-13), 128.26 (C-16), 131.70 (C-17), 137.20 (C-12), 148.26 (C-14) ppm. EI-MS, m/z = 344.55 ($M^+$, 12). Elemental analysis calcd. $C_{21}H_{32}N_2O_2$: C 73.22; H, 9.36; N, 8.13. Found: C, 73.18, H 9.32.

**Succinic acid mono-[4-[(2-amino-ethylamino)methyl]-3-(3-carboxy-propionyloxy)-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl]ester (3):** A solution of **2** (200 mg, 0.58 mmol), succinic anhydride (120 mg 1.2 mmol), 2 mL pyridine in 10 mL of toluene was gently refluxed for 48 h and then cooled to room temperature. After the solvent was removed under vacuum and the crude product was purified by crystallization from methanol:hexane:water (5:2:1); yielding 62 % of product, m.p. 166-168 ºC; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3396, 1725, 1615; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.80 (s, 3H), 1.15-1.17 (m, 2H) 1.29 (m, 1H), 1.43-1.51 (m, 3H), 1.73-1.91 (m, 4H), 2.15-240 (m, 3H), 2.51-2.53 (m, 2H), 2.56 (s , 2H), 2.58 (s, 2, H), 2.60 (s, 2H), 2.65 (s, 2H), 2.77 (s, 2H), 2.82 (s, 2H), 3.64 (s, 2H), 4.60 (m, 1H), 5.25 (s, 5H), 6.69 (m, 1H), 6.76 (m, 1H) ppm. $^{13}$C NMR (74.5 MHz, $CDCl_3$) $\delta_C$: 12.61 (C-18), 19.81 (C-9), 20.97 (C-5), 22.54 (C-8), 27.02 (C-11), 27.12 (C-10), 30.98 (C-35), 31.75 (C-30, C-31), 33.93 (C-34), 37.22 (C-6), 38.04 (C-3), 39.42 (C-25), 41.17 (C-1), 45.50 (C-4), 46.19 (C-22), 51.90 (C-2), 54.41 (C-24), 85.85 (C-7), 107.45 (C-15), 120.30 (C-16), 135.50 (C-17), 137.44 (C-13), 147.44 (C-12), 148.66 (C-14), 168.09 (C-20), 168.40 (C-28), 170.02 (C-32), 173.04 (C-36) ppm. EI-MS, m/z = 544.20 ($M^+$, 13). Elemental analysis calcd. $C_{29}H_{40}N_2O_8$: C 63.95; H, 7.40; N, 5.14. Found: C, 63.21; H, 7.18.

**Succinic acid mono-{4-[(2-amino-ethylamino)methyl]-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]phenanthren-17-yl}ester (4)**

**Method A:** A solution of **3** (200 mg, 0.37 mmol), $NaHCO_3$ (100 mg, 1.19 mmol) in 10 mL of methanol was stirring for 12 h at room temperature. The solution was reduced to a small volume, diluted with water and extracted with ether. The alkaline aqueous phase was acidified with concentrated hydrochloric acid. The resulting precipitate was extracted with ether, and the ether extract washed with water, dried over sodium sulfate and evaporated to dryness. The crude product was purified by crystallization from methanol:water (3:1); yielding 36 % of product, m.p. 160-162 ºC; IR (KBr, $\nu_{max}$, $cm^{-1}$): 3384, 1725, 1610; $^1$H NMR (300 MHz, $CDCl_3$) $\delta_H$: 0.80 (s, 3H), 1.15-1.17 (m, 2H) 1.29 (m, 1H), 1.43-1.51 (m, 3H), 1.73-1.91 (m, 4H), 2.15-240 (m, 3H), 2.51-2.53 (m, 2H), 2.56 (s , 2H), 2.58 (s, 2, H), 2.64 (s, 2H), 2.77 (s, 2H), 3.64 (s, 2H), 4.22 (s, 5H), 4.28 (s, 1H), 6.69 (m, 1H), 6.86 (m, 1H) ppm. $^{13}$C NMR (74.5 MHz, $CDCl_3$) $\delta_C$: 12.58 (C-18), 19.86 (C-9), 20.97 (C-5), 26.54 (C-8), 27.02 (C-11), 27.12 (C-10), 29.30 (C-28, C-29), 37.22 (C-6), 38.04 (C-3), 39.42 (C-25), 41.17 (C-1), 45.50 (C-4), 46.19 (C-22), 51.90 (C-2), 54.41 (C-24), 85.85 (C-7), 107.45 (C-15), 120.26 (C-13), 128.02 (C-16), 135.50 (C-17), 137.25 (C-12), 148.66 (C-14), 168.09 (C-20), 170.02 (C-30) ppm. EI-MS, m/z = 444.20 ($M^+$, 13). Elemental analysis calcd. $C_{25}H_{36}N_2O_5$: C 67.54; H, 8.16; N, 6.30. Found: C, 67.48; H, 18.10.

**Method B:** A solution of estradiol 17-β hemisuccinate (200 mg, 0.54 mmol), ethylenediamine (98 μL 1.46 mmol) in 10 mL of formaldehyde was gently refluxed for 48 h and then cooled to room temperature. After the solvent was removed under vacuum and the crude product was purified by crystallization from methanol:water (3:1); yielding 76 % of product, mp 160-162 ºC; similar $^1$H NMR and $^{13}$C NMR data were obtained compared with method A product.

**QSAR study:** In study, physico-chemical 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[17,18].

## RESULTS AND DISCUSSION

Several steroid derivatives has been developed using the Mannich reaction. The structural chemistry of these compounds[19,20] involves an activated methyl group in ring A and B or the aliphatic side chain attached to $C_{17}$. In this work, the reactivity of hydrogen atom involved in the ring A of compounds **1** and **5** was studied. In this sense, the first step was achieved by reacting **1** with ethylendiamine and formaldehyde to form **2** (Fig. 1). The results indicate that $^1$H NMR spectrum of **2** showed a signal at 0.64 ppm for methyl involved in steroid nucleus. In addition, other signals at 2.62, 2.78 and 3.70 ppm for methylenes involved in the arm bound to A ring were found. Finally, a chemical shift at 3.80 ppm corresponding to both hydroxyl and amine groups was found. The $^{13}$C NMR spectra displays chemical shifts at 11.30 for methyl present in the steroid nucleus. Other signals at 41.52, 44.50 and 53.28 ppm for the carbons of methylenes involved in the arm bound to A ring. Additionally, several signals at 23.57-39.00, 43.63-44.48, 50.53 and 81.82-148.98 ppm for the protons involved in steroid nucleus. Finally, the presence of **2** was further confirmed from mass spectrum which showed a molecular ion at m/z 344.55.

The second stage was achieved by reacting **2** with succinic anhydride in presence of pyridine/toluene to form **3** (Fig. 1), using the method reported by some investigators[21,22] for the esterification of steroid derivatives. It is important to mention that structure of **3** had as its main characteristic, an arm bound to the carbon **4** of A ring with a free amine group. In addition, the structure of **3** contains in the carbons **3** and 17-β, two arms with identical characteristic that involve a free carboxyl group. The results indicate that $^1$H NMR spectra of **3** showed a chemical shift at 0.80 ppm for methyl present in the steroid nucleus. Additionally, other signals at 2.60 and 2.82 ppm for methylenes involved in the arm bound to the carbon 3; at 2.56 and 2.58 ppm for methylenes presents in the arm bound to the carbon 17-β; at 2.65, 2.77 and 3.64 ppm for methylenes involved in the arm bound to the carbon **4** were found. Finally, a signal at 5.25 ppm for both hydroxyl and amino groups was found. $^{13}$C

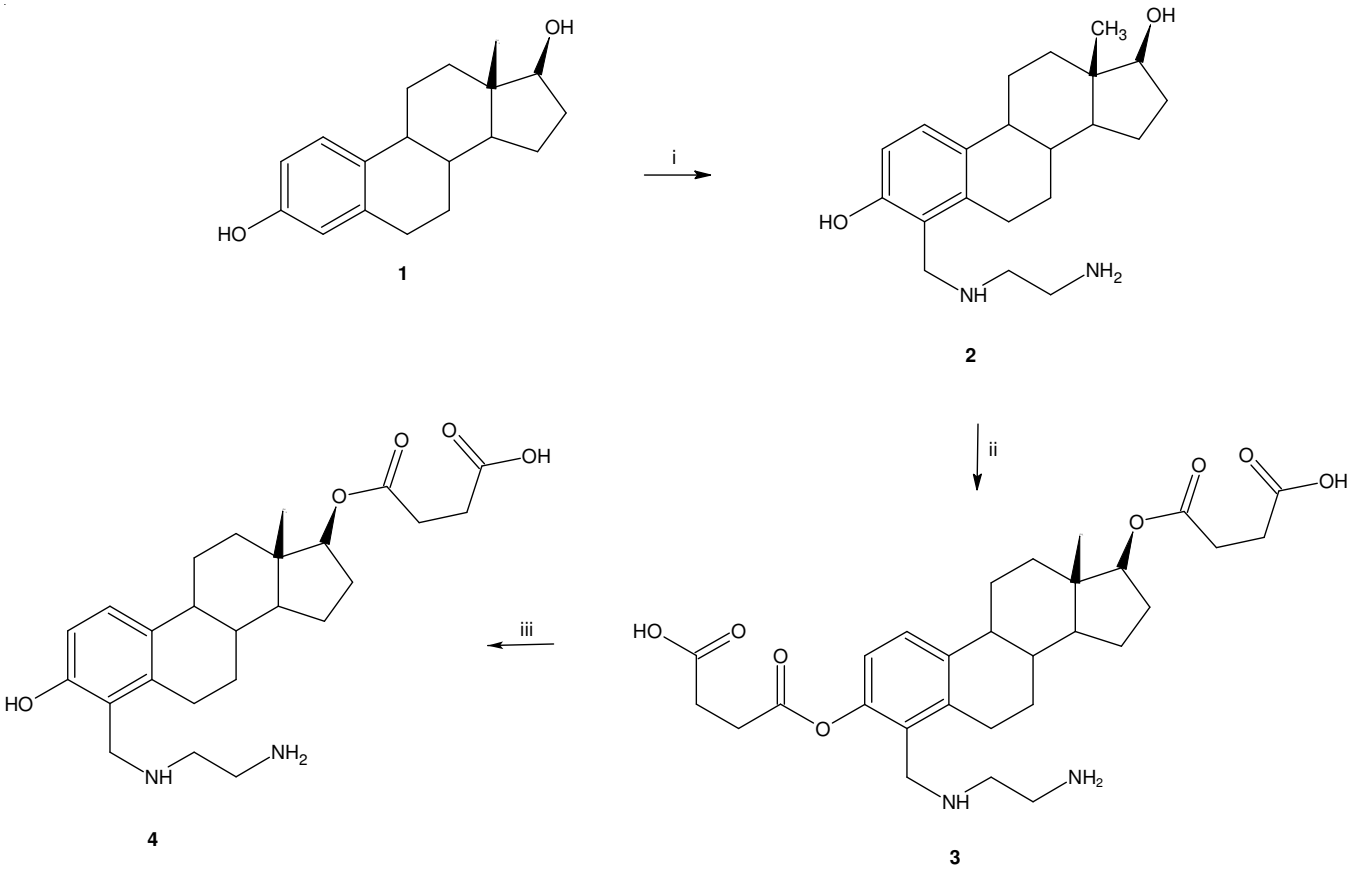


Fig. 1. Synthetic route to form **4**. Reagents and conditions: i = ethylendiamine/formaldheyde/reflux; ii = succinic anhydride/pyridine/reflux; iii = $NaHCO_3$-methanol/HCl

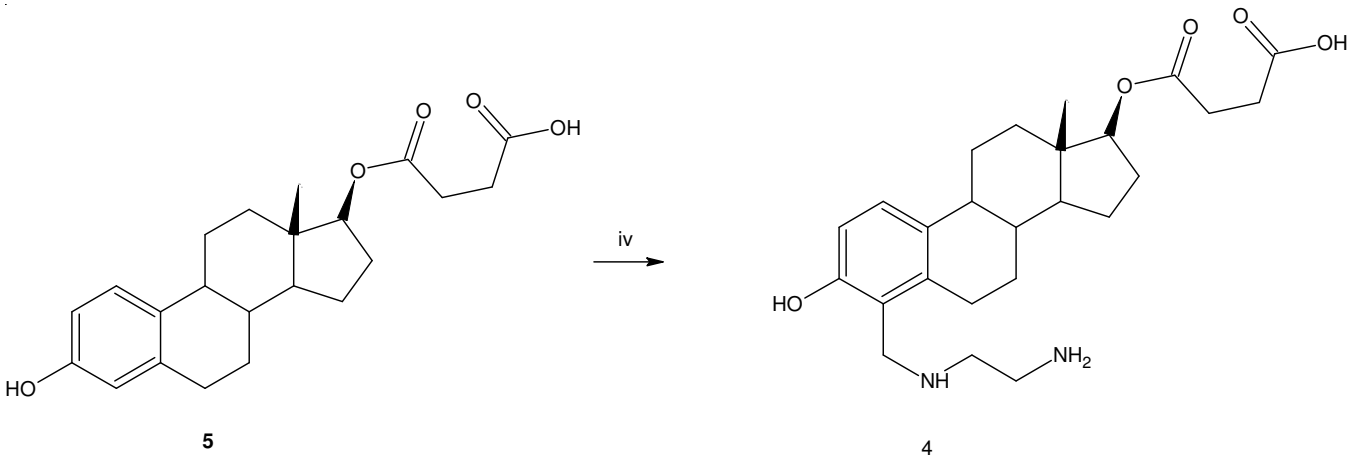


Fig. 2. Synthesis of **4**. Estradiol 17β-hemisuccinate (**5**) was used to form **4**. Reagents and conditions: iv = ethylendiamine/formaldehyde/reflux

NMR spectra displays chemical shifts at 12.61 ppm for methyl present in the steroid nucleus. Other signals at 31.75 ppm for methylenes involved in the arm bound to D ring; at 30.98 and 33.93 ppm for carbons presents in the arm bound to the carbon 3; at 39.42, 46.19 and 54.41 ppm for carbons involved in the arm bound to the carbon 4 were found. Additionally, several signals at 19.81-51.90 ppm and 85.85-148.66 ppm for carbons corresponding to methylenes steroid nucleus were found. The presence of **3** was further confirmed from mass spectrum which showed a molecular ion at m/z 544.20.

The third stage was achieved by a hydrolysis reaction. In this process the phenolic ester involved in the chemical structure of compound **3** it is hydrolyzed with bicarbonate in aqueous methanol to form **4**. Here it is important to mention that structure of **4** had as its main characteristic, an arm bound to the carbon **4** with a free amino group. In addition, in the D ring (17-β) have an arm with both ester and carboxyl groups. $^1$H NMR spectrum of **4** showed a signal at 0.80 ppm for methyl involved in steroid nucleus. In addition, other signals at 2.56 and 2.58 ppm for methylenes involved in the arm bound to D ring and at 2.64, 2.77 and 3.64 ppm for methylenes corresponding to arm bound to A ring of **4** were found. Finally, a signal at 4.22 ppm for both hydroxyl and amino groups was found. It is important to mention that signals of the groups involved in

the arm bound to the carbon **3** in the compound **3** were not found in compound **4**.

$^{13}$C NMR spectra display chemical shifts at 12.58 ppm for the carbon of methyl present in the steroid nucleus of **4**. Other chemical shifts at 29.30 ppm for carbons of methylenes involved in the arm bound to D ring and at 39.42, 46.19 and 54.41 ppm for carbons presents in the arm bound to A ring of **4** were found. Additionally, several signals at 19.81-51.90 ppm and 85.85-148.66 ppm for carbons corresponding to methylenes steroid nucleus were found. Finally, two signals at 168.09 ppm for ester group and at 170.02 ppm for carboxyl group were found. The presence of **4** was further confirmed from mass spectrum which showed a molecular ion at m/z 444.20. In order to verify the structure of **4**, another experimental alternative was realized, this process involve the reaction between the estradiol 17-β hemisuccinate (**5**) with ethylendiamine by means of the Mannich method[17,18]. It is important to mention here that the yield of **4** was higher in this stage. This phenomenon was possibly due to the hydrolysis reaction described above or the reaction time which can affect the yielding.

**Theoretical QSAR study:** To analyze the molecular properties of **2**, **3** and **4**, two parameters such as the descriptors log P and π were calculated[23], where 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[24]. 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[25]. Therefore, in this work, the log P and π parameters were calculated by the method reported by Mannhold and Waterbeemd[17]. It is important to mention that compounds **2**, **3** and **4** were evaluated with the purpose to know if there are differences in the lipophilicity degree between the compounds studied. The results (Table-1) showed a decrease in log P values in the **4** compound with respect to **2**, nevertheless was high with respect to **3**. Nevertheless, **4** showed an increase in π values in comparison with **2** and **3**. This phenomenon is conditioned mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds, as is showed in Tables 2-4. These results showed that both ester and carboxyl groups in compound **4** contribute to the low lipophilicity in comparison with **2**. Additionally, other results showed that the lipophilicity of **4** is high in comparison with **3**. This phenomenon is due to the presence of both di-ester and di-carboxyl groups in the steroid nucleus. All data indicate that a decrease 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 ($R_m$)[26,27]. These physicochemical parameters are useful tools for the correlation of different properties that depend on characteristics of substituents attached to a constant reaction center. Therefore in present 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 $V_m$ values for **3** in comparison with **4** and **2** (Table-5). In addition, the $R_m$ and $V_m$ values of **4** were high in coparison with **2**. These data indicate that steric impediment, conformational preferences and internal rotation of **3** and **4** 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[28,29]. The results indicate that both values of $P_c$ $S_t$ for **3** were high in comparison with **4** and **2** (Table-5), these data indicate that this physico-

TABLE-1
PHYSICO-CHEMICAL PARAMETERS (log P) OF COMPOUNDS **2**, **3** AND **4**

| Program | Compounds | | |
|---|---|---|---|
| | **2** | **3** | **4** |
| ALOGPs | 2.28 | -0.10 | -0.008 |
| AC log P | 2.14 | 2.01 | 2.200 |
| AB/log P | 2.21 | 2.29 | 2.480 |
| Mi log P | 2.19 | 1.30 | 2.160 |
| ALOGP | 2.52 | 2.58 | 2.720 |
| MLOGP | 2.67 | 2.70 | 2.650 |
| KOWWIN | 2.51 | -0.71 | 0.060 |
| XLOGP2 | 2.97 | 2.64 | 3.080 |
| XLOGP3 | 2.99 | -2.68 | 0.610 |
| Average log P | 2.50 (±0.33) | 1.11 (±1.88) | 1.77 (±1.22) |

TABLE-2
PHYSICO-CHEMICAL PARAMETERS (log Kow and π) OF COMPOUND **2**

| log Kow fragment | Contributions |
|---|---|
| -$CH_3$ [aliphatic carbon] | 0.5473 |
| -$CH_2$- [aliphatic carbon] | 4.4199 |
| -CH [aliphatic carbon] | 1.4456 |
| -OH [hydroxy, aliphatic attach] | -1.4086 |
| -$NH_2$ [aliphatic attach] | -1.4148 |
| -NH- [aliphatic attach] | -1.4962 |
| Aromatic carbon | 1.7640 |
| -OH [hydroxy, aromatic attach] | -0.4802 |
| -*tert*-Carbon [3 or more carbon attach] | 0.2676 |
| Fused aliphatic ring unit correction | -1.3684 |
| Equation constant | 0.2290 |
| log Kow | 2.5052 |
| π | -1.4348 |

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

| log Kow fragment | Contributions |
|---|---|
| -$CH_3$ [aliphatic carbon] | 0.5473 |
| -$CH_2$- [aliphatic carbon] | 6.3843 |
| -CH [aliphatic carbon] | 1.4456 |
| -$NH_2$ [aliphatic attach] | -1.4148 |
| -NH- [aliphatic attach] | -1.4962 |
| Aromatic carbon | 1.7640 |
| -COOH [acid, aliphatic attach] | -1.3790 |
| -C(=O)O [ester, aliphatic attach] | -1.9010 |
| -*tert*-Carbon [3 or more carbon attach] | 0.2676 |
| Multi-aliphatic carboxyl acids | -0.5865 |
| Fused aliphatic ring unit correction | -1.3684 |
| Amino acid (non-alpha carbon type) corr. | -3.2000 |
| Equation constant | 0.2290 |
| log Kow | -0.7081 |
| π | -3.2133 |

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

| log Kow fragment | Contributions |
|---|---|
| -$CH_3$ [aliphatic carbon] | 0.5473 |
| -$CH_2$- [aliphatic carbon] | 5.4021 |
| -CH [aliphatic carbon] | 1.4456 |
| -$NH_2$ [aliphatic attach] | -1.4148 |
| -NH- [aliphatic attach] | -1.4962 |
| Aromatic carbon | 1.7640 |
| -OH [hydroxyl, aromatic attach] | -0.4802 |
| -COOH [acid, aliphatic attach] | -0.6895 |
| -C(=O)O [ester, aliphatic attach] | -0.9505 |
| -*tert*-Carbon [3 or more carbon attach] | 0.2676 |
| Fused aliphatic ring unit correction | -1.3684 |
| Amino acid (non-alpha carbon type) corr. | -3.2000 |
| Equation Constant | 0.2290 |
| log Kow | 0.0560 |
| π | 0.9371 |

TABLE-5
PHYSICO-CHEMICAL PARAMETERS OF
**2**, **3** AND **4** COMPOUNDS

| Compd. | $R_m$ ($cm^3$) | $V_m$ ($cm^3$) | $P_c$ ($cm^3$) | $S_t$ (dyne/cm) |
|---|---|---|---|---|
| **2** | 100.81±0.3 | 294.4±3.0 | 788.7±4.0 | 51.4±3.0 |
| **3** | 141.32±0.4 | 414.7±5.0 | 1172.9±6.0 | 63.9±5.0 |
| **4** | 120.82±0.4 | 350.8±5.0 | 981.9±6.0 | 61.3±5.0 |

$R_m$ = Molar refractivity, $V_m$ = Molar volume, $P_c$ = Parachor, $S_t$ = Surface tension

chemical parameters can also conditioned the degree of lipophilicity of **3** and **4**. This presumption could be supported by other studies[30] 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 amino-esteroid derivatives was development and several physicochemical descriptors of QSAR study were evaluated. The results showed an increase in the values of log P, π, $P_c$ and $S_t$ in **3** with respect to **4** and **2**. These data suggest that physico-chemical parameters can affect the degree of lipophilicity of **3** and **4**.

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