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Theoretical Analyses of Glibenclamide-Estradiol Derivative and Its Relationship with Some Physico-chemical Descriptors

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A new glibenclamide-estradiol conjugate was synthesized by the reaction of glibenclamide-succinate and estradiol-ethylenediamine derivative using *N,N'*-diciclohexylcarbodiimide/*p*-toluensulfonic acid as catalysts. In order to evaluate the degree of lipophilicity and its relationship with some physicochemical descriptors involved in its chemical structure, the ACD log P and KOWWIN methods were used. The results showed an increase in the values of these physicochemical parameters for the glibenclamide-estradiol conjugate in comparison with glibenclamide and glibenclamide-succinate. These data suggest a relationship between the evaluated physicochemical parameters and the degree of lipophilicity of the glibenclamide-estradiol conjugate.

Key Words: Glibenclamide, Estradiol, Lipophilicity.

INTRODUCTION

Chromatography used as chemical tool for identification of several compounds[1-3]. The fundamental objective in chromatography involves a relationship between the structure of compound studied and its retention in a particular chromatographic system. It is important to mention that there are some investigations which are widely established and often used in prediction of a retention for new solutes, finding the most informative structure descriptors for retention explaining and checking their compliance with the molecular theory of the separation[4,5]. In this sense, some studies that use the thin layer chromatography resulted in many equations able to predict the retention for some functional groups. There are reports which involve the retention in reversed-phase systems, where retention is strictly correlated with the degree of lipophilicity from each compound[6-8]. The most reliable procedure to get lipophilicity values has been outlined by some investigators for the determination of degree of lipophilicity from several organic compounds and its relation with theoretical partition coefficients (log Ps) using different procedures[9,10]. For example some studies showed a relationship direct between log P and degree of lipophilicity of 96000 compounds using several methods[11]. In addition, in others reports the degree of lipophilicity of some synthetic dyes[12] and several isomers of organic compounds[13] and values obtained were compared with theoretical partition coefficients using different computation methods.

In this sense, also the XLOGP2 method has been used for estimating octanol-water partition coefficients of some hypoglycemic agents such as glibenclamide[14]. In addition, other reports indicate the use of CoMFA model for determination of the log P of several glibenclamide derivatives[15]. Recently, was evaluated the log P of a glibenclamide-pregnenolone conjugate using some programs such as the ACDlogP and KOWWIN methods[16]. In this study, a new glibenclamide derivative was synthetized and its relationship with the physicochemical descriptors such as log P, π, R_m, V_m, P_c and S_t were evaluated using ACD log P and KOWWIN programs.

EXPERIMENTAL

N-[2-(4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]-phenyl)-ethyl]-5-hydroxy-2-methoxybenzamide(1) and 4-[(2-amino-ethylamino)-13-methyl-7,8,9,11,12,13,14,15,16,17-dodeca-hydro-6*H*-cyclopenta[a]phenanthrene-3,17-diol (**4**) were prepared according to reported method of Figueroa *et al.*[16,17] and 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 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 DMSO-d_6 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.

Succinic acid mono-(4-metoxy-(3-*N*-(4-[*N*-(cyclohexylcarbamoyl)sulfamoyl]phenylethyl]carbamoyl)phenyl) ester(3): A solution of *N*-[2-(4-[*N*-(cyclohexylcarbamoyl)-sulfamoyl]-phenyl)-ethyl]-5-hydroxy-2-methoxybenzamide (120 mg, 0.21 mmol), succinic acid (25 mg, 0.21 mmol), *N,N'*-dicyclohexylcarbodiimide (87 mg, 0.42 mmol) and anhydrous *p*-toluensulfonic acid (72 mg, 0.42 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a small volume. After the mixture was 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 : water (3:1) yielding 75 % of product, m.p. 276-278 ºC; IR (ν_{max}, cm^{-1}): 2740, 1734, 1712 and 1670; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 1.34-1.52 (m, 5H), 1.60 (m, 1H), 1.87 (m, 2H), 2.04 (m, 2H), 2.60 (t, 2H, *J* = 6 Hz), 2.84 (t, 2H, *J* = 6.8 Hz), 2.89 (t, 2H, *J* = 6 Hz), 3.48 (t, 2H, *J* = 6.8 Hz), 3.76 (m, 1H), 3.95 (s, 3H), 7.14 (m, 3H), 7.48 (m, 2H), 7.80 (m, 2H), 8.22 ((broad, 4H) ppm. ^{13}C NMR (75.4 MHz, DMSO- d_6) δ_C: 24.60 (C-3, C-5), 25.47 (C-4), 29.31 (C-37), 29.73 (C-36), 33.56 (C-2, C-6), 36.06 (C-20), 40.32 (C-21), 47.28 (C-1), 55.30 (C-32), 112.87 (C-27), 120.34 (C-25), 121.55 (C-30), 128.98 (C-19, C-15), 129.54 (C-16, C-18), 130.91 (C-28), 136.17 (C-14), 141.41 (C-17), 146.58 (C-26), 147.32 (C-29), 154.75 (C-8), 168.57 (C-28), 171.24 (C-30), 174.16 (C-38). MS (70 ev): *m/z* = 575.30 (M$^+$), 477.6, 251.21, 169.20, 124.2. Anal calcd. (%) for $C_{27}H_{33}N_3O_9S$: C, 56.34; H, 5.78; N, 7.30; O, 25.02; S, 5.57. Found. C, 56.30; H, 5.80; N, 7.33.

Succinic acid 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-metoxy-(3-*N*-(4[*N*(cyclohexylcarbamoyl)sulfamoyl]phenylethyl]-carbamoyl)-phenyl ester (5): A solution of **3** (100 mg, 0.17 mmol), **4** (60 mg, 0.17 mmol) and *N,N'*-diciclohexylcarbodiimide (80 mg, 0.38 mmol) and anhydrous *p*-toluensulfonic acid (50 mg, 0.29 mmol) in 10 mL of methanol was stirring for 72 h to room temperature. The reaction mixture was evaporated to a smaller volume. After the mixture was 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:water (4:1) yielding 38 % of product, m.p. 264-266 ºC; IR (ν_{max}, cm^{-1}): 3380, 3330, 3310, 1730; ^{1}H NMR (300 MHz, DMSO-d_6) δ_H: 0.76 (s, 3 H), 0.92-1.23 (m, 2H), 1.24-1.43 (m, 2H), 1.46 (m, 2H), 1.50 (m, 1H), 1.51-1.62 (m, 4H), 1.70-1.74 (m, 3H), 1.76 (m, 2H), 1.94 (m, 1H), 2.07 (m, 2H), 2.16 M, 1H), 2.30-2.47 (m, 2H), 2.52 (M, 2H), 2.60 (t, 2H, *J* = 6 Hz), 2.65 (t, 2H, *J* = 6 Hz), 2.76 (t, 2H, *J* = 6 Hz), 2.81 (t, 2H, *J* = 6 Hz), 2.86 (t, 2H, *J* = 6 Hz), 3.48 (t, 2H, *J* =7 Hz), 3.67 (m, 1H), 3.75 (m, 2H), 3.95 (s, 3H), 5.79 (broad, 7H), 6.52-681 (m, 2H), 7.15-7.17 (m, 3H), 7.47-7.84 (m, 3H) ppm. NMR ^{13}C (74.5 MHz, DMSO-d_6) δ_C: 11.3 (C-58), 23.53 (C-49), 24.59 (C-3, C-5), 25.47 (C-4), 26.07 (C-46), 27.56 (C-48), 27.66 (C-51) 27.71 (C-50), 28.05 (C-37), 30.05 (C-36), 33.56 (C-2, C-6), 36.06 (C-20), 37.34 (C-47), 38.45 (C-44), 40.03 (C-21), 41.57 (C-62), 43.60 (C-42), 44.62 (C-45), 45.30 (C-59), 47.28 (C-1), 50.52 (C-43), 53.32 (C-61), 55.33 (C-32), 81.82 (C-41), 112.50 (C-55), 112.87 (C-27), 120.03 (C-25), 120.65 (C-30), 123.75 (C-53), 128.18 (C-56), 128.98 (C-19, C-15), 129.54 (C-18, C-16), 130.11 (C-28), 134,73 (C-57), 136,17 (C-14), 137.16 (C-52), 141.41 (C-17), 146.58 (C-26), 147.41(C-29), 154.75 (C-54), 163.68 (C-8), 168.57 (C-23), 172.25 (C-34), 172.62 (C-38) ppm. MS (70 ev) : *m/z* = 901.38 [M$^+$], 474.5, 403.49, 193.20, 178.15, 154.19. Anal calcd. (%) for $C_{48}H_{63}N_5O_{10}S$: C, 63.91; H, 7.04; N, 7.76; O, 17.74; S, 3.55. Found, C, 63.75; H, 7.02; N, 7.70.

RESULTS AND DISCUSSION

It is important to mention that there are some procedures for formation of glibenclamide derivatives are available in the literature. Nevertheless, despite their wide scope, these procedures suffer from several drawbacks *e.g.*, some reagents are of limited stability and preparation can be dangerous[18-20]. Therefore, in this study we report a straightforward route for synthesis of new glibenclamide derivative (**5**). The first step involves the esterification of the hydroxyl group (C-3 A ring) of compound **1** to form the **3** (Fig. 1). Although there are diverse reagents available to produce ester derivatives[21,22], most of the conventional methods are of only limited use for some compounds. Therefore, in this study the method reported by Erlanger *et al.*[23] for esterification of other compounds was used. Thus, compound **3** was synthesized by reacting compound **1** with succinic acid 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[24]. Therefore, *p*-toluenesulfonic acid was used to increase the yield of **3** in the esterification of **1** with succinic acid in the presence of DCC.

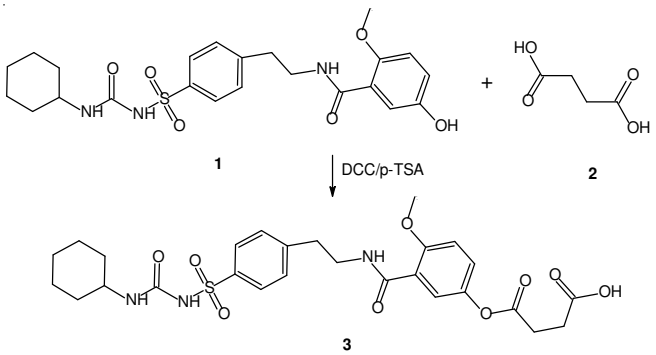

Fig. 1. Synthesis of succinic acid mono-(4-metoxy-(3-*N*-(4-[*N*-(cyclohexyl-carbamoyl)sulfa-moyl]phenylethyl]carbamoyl)phenyl) ester (**3**). Reaction between glibenclamide derivative (**1**) and succinic acid (**2**) using *N,N*'-diciclohexylcarbodiimide/*p*-toluensulfonic acid (DCC/*p*-TSA) as catalysts

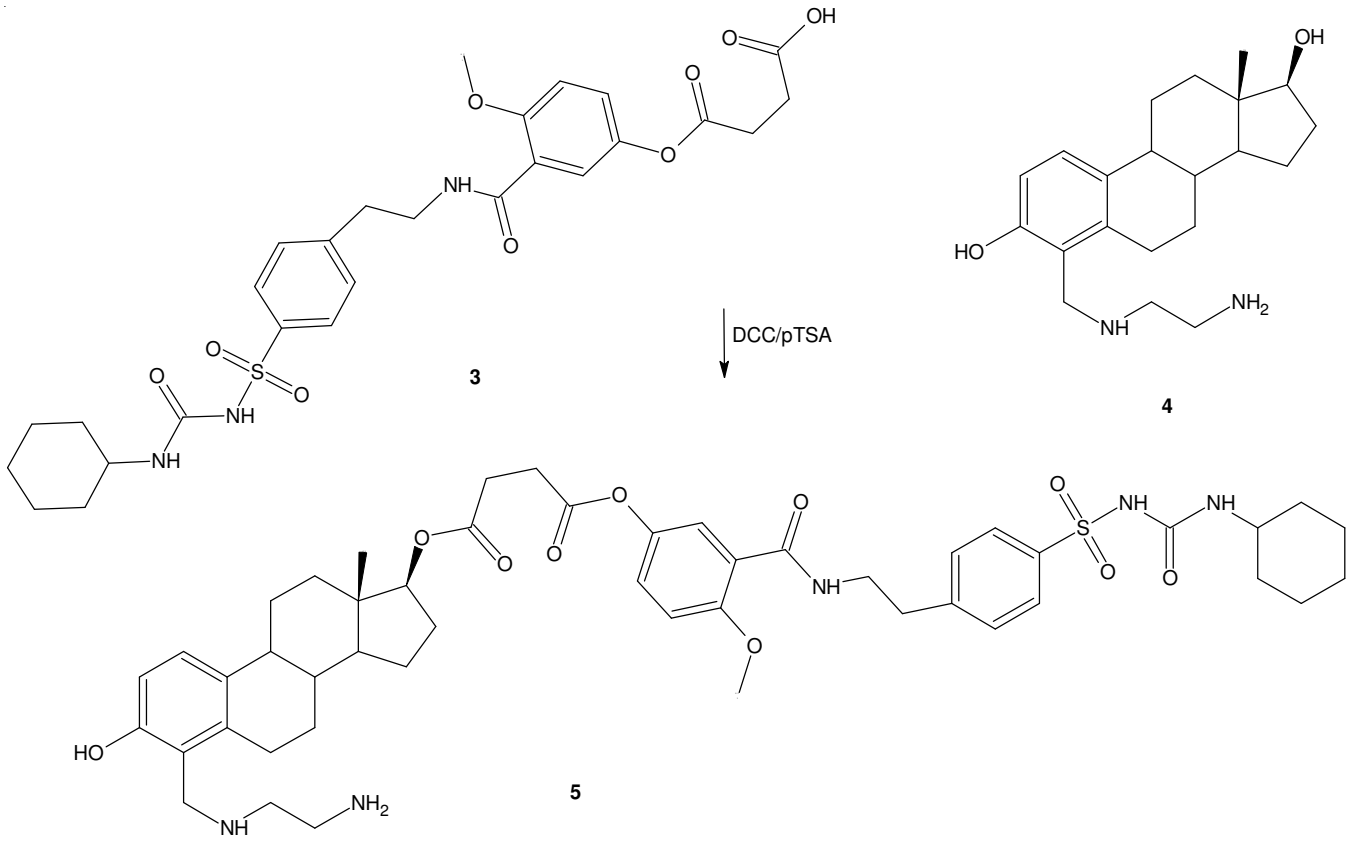

Fig. 2. Synthesis of succinic acid 4-[(2-amino-ethylamino)methyl]-3-hydroxy-13-methyl-7,8,9,11,12,13,14,15,16,17-decahydro-6*H*-cyclopenta[a]-phenanthren-17-yl ester 4-metoxy-(3-*N*-(4[*N*(cyclohexylcarbamoyl)sulfamoyl]phenylethyl]carbamoyl)phenylester (**5**). Reaction between glibenclamide derivative (**3**) and estradiol-ethylenediamine (**4**) using *N,N'*-diciclohexylcarbodiimide/p-toluensulfonic acid (DCC/*p*-TSA) as catalysts

On the other hand, the results of ^{1}H NMR spectrum of **3** shows signals at 1.34-2.06 ppm for protons involved in the cyclohexyl ring; at 2.60 and 2.89 ppm for methylenes of new arm, which are bound to phenyl group. Other signals at 2.84 and 3.48 ppm for the spacer arm between both amide and phenyl groups; at 3.76 ppm for the proton bound to both cyclohexyl ring and amide groups; at 3.95 ppm for methoxy group at; 7.14-7.80 ppm for phenyl groups were found. Finally, the spectrum contains a signal at 8.22 ppm for both hydroxyl and amide groups. The ^{13}C NMR spectrum contains peaks at chemical shifts of 24.60-25.47, 33.56 and 48.29 ppm for the carbons of the cyclohexyl ring; at 29.31 and 29.73 ppm for arm bound to phenyl group; at 36.06-40.32 ppm for spacer arm between both phenyl and amide groups. Other signals at 55.30 ppm for methoxy group; at 112.87-147.32 ppm for phenyl groups; at 154.75 and 168.57 ppm for amide groups; at 171.24 ppm for ester group and at 174.16 for carboxyl group were found. In addition, the presence of **3** was further confirmed from mass spectrum, which showed a molecular ion at *m/z* 575.30.

The second step involves the synthesis of **5** by reaction of **4** with **3** resulting in ester bond formation (Fig. 2). It is important to mention that yield of **5** was low relatively; perhaps this phenomenon could be because also another molecule of **3** reacted with the second hydroxyl group of **4** (data non-shown) to form other glibenclamide derivative. The ^{1}H NMR spectrum of **5** shows signals at 0.76 ppm for methyl of steroid fragment; at 0.92-1.43, 1.50, 1.70-1.74, 1.94 and 2.15-2.52 ppm for protons involved in the steroid nucleus; at 1.46, 1.51-1.62, 1.76, 2.07 and 3.67 ppm for cyclohexyl ring group; at 2.61 and 2.81 ppm for hydrogen's involved in the spacer arm between the nucleus steroid and glibenclamide fragment were found. In addition, several signals at 2.65, 2.76 and 3.75 ppm for arm bound to phenyl ring of steroid; at 2.86 and 3.48 ppm for protons involved in the arm bound to both phenyl and amide groups were shown. Finally, the spectrum contains other signals at 3.95 ppm for methoxy group; at 5.79 ppm for amide, amino and hydroxyl groups; at 6.52-7.84 ppm for phenyl groups. It is important to mention that the ^{1}H NMR spectra of the secondary amides are usually more complex than the primary amides due to the presence of a substituent bonded to the amide nitrogen atom. These substituents produce a much wider range of chemical shifts for the amide proton, which may, in addition, display coupling to aliphatic groups bonded to it. The chemical shifts of aliphatic groups bonded to the carbonyl group are similar to those observed for the primary amides, while those groups bonded to the nitrogen resonate at slightly lower field than the corresponding amines[25].

On the other hand, the ^{13}C NMR spectrum of **5** contains peaks at chemical shifts of 11.3 ppm for methyl group of steroid fragment; at 23.53, 26.07-27.71, 37.34-38.45, 43.60-44.62, 50.52, 81.82-112.50, 123.75-128.18, 134.73, 137.16 and 154.75 ppm; at 24.59-25.47, 33.56, 47.28 ppm for cyclohexyl ring. In addition, other signals at 28.05 and 30.05 ppm for spacer arm between both amide and phenyl groups; at 36.06 and 40.03 ppm for arm bound to both amide and phenyl groups; at 41.57, 45.30 and 53.32 ppm for arm bond to phenyl group of steroid fragment were found. Other chemical

shifts at 55.20 for methoxy group; at 112.87-120.65, 128.98-130.11, 136.17 and 141.41-147.41 ppm for phenyls groups; at 163.68 and 168.57 ppm for amide groups; at 172.25 and 172.62 ppm were display. Finally, the presence of **6** was further confirmed from mass spectrum which showed a molecular ion at m/z 474.50.

Evaluation of physicochemical parameters: For several years, physicochemical parameters such as log P and *p* have been used to measure the electronic and lipophilicity properties of many compounds[26]. 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[27]. 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[28]. Therefore, in this work, the log P and π parameters were calculated by the method reported by Mannhold and Waterbeemd[29]. The results (Table-1) showed an increase in log P and π values in compounds **5** with respect to **1** and **3**. This phenomenon is conditioned mainly by the contribution of all substituent atoms involved in the chemical structure of the different compounds (Tables 2-4). These results showed that aliphatic carbons in compound **5** contribute to the high lipophilicity in comparison with **1** and **3**. Additionally, other results showed that the lipophilicity of **1** is high in comparison with **3**. This phenomenon is due to the presence of both methyl and methylene groups and aromatic carbon involved in chemical structure of **3**. All these data suggest that different functional groups involved in the chemical structure of compound studied induce changes in the degree of lipophilicity. Nevertheles, it is important to mention that there are other physicochemical parameters that can be relate with the degree of lipophilicity such as molar volume (V_m) and molar refractivity (R_m), which are steric constants. In addition these options 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 work, V_m and molar refractivity R_m were calculated using ACD/Chem Sketch algorithms[30]. The results showed an increase in both R_m and V_m values for **5** in comparison with **1** and **3**. These data indicate that steric impediment, conformational preferences and internal rotation of **6** 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),

TABLE-1
PHYSICOCHEMICAL PARAMETERS
log P OF COMPOUNDS **1**, **3** AND **5**

Program	Compounds		
	1	**3**	**5**
ALOGPs	2.99	2.45	4.79
AC logP	3.08	2.89	5.49
ALOGP	3.21	3.06	6.19
MLOGP	1.57	1.70	3.09
KOWWIN	3.67	3.49	6.91
XLOGP2	3.65	3.21	7.00
XLOGP3	3.83	3.25	6.92
Average *logP*	3.14 (± 0.76)	2.86 (± 0.61)	5.77 (± 1.45)

TABLE-2
PHYSICOCHEMICAL PARAMETERS
log K_{ow} AND π OF COMPOUND **1**

log K_{ow} Fragment	Contribution
-CH_3 [aliphatic	0.5473
-CH_2- [aliphatic carbon]	3.4377
-CH [aliphatic carbon]	0.3614
-NH- [aliphatic attach]	-4.4886
Aromatic Carbon	3.5280
-OH [hydroxy, aromatic attach]	-0.4802
-O- [oxygen, one aromatic attach]	-0.4664
-C(=O)N [aromatic attach]	0.1599
-SO_2-N [aromatic attach]	-0.2079
-NC(=O)N- [urea]	1.0453
Equation Constant	0.2290
log K_{ow}	3.6655
π	-1.1245

TABLE-3
PHYSICOCHEMICAL PARAMETERS
log K_{ow} AND π OF COMPOUND **3**

log K_{ow} Fragment	Contribution
-CH_3 [aliphatic carbon]	0.5473
-CH_2- [aliphatic carbon]	4.4199
-CH [aliphatic carbon]	0.3614
-NH- [aliphatic attach]	-4.4886
Aromatic carbon	3.5280
-O- [oxygen, one aromatic attach]	-0.4664
-COOH [acid, aliphatic attach]	-0.6895
-C(=O)O [ester, aliphatic attach]	-0.9505
-C(=O)N [aromatic attach]	0.1599
-SO_2-N [aromatic attach]	-0.2079
-NC(=O)N- [urea]	1.0453
Equation constant	0.2290
log K_{ow}	3.4879
π	-0.1771

TABLE-4
PHYSICOCHEMICAL PARAMETERS
log K_{ow} AND π OF COMPOUND **5**

log K_{ow} Fragment	Contribution
CH_3 [aliphatic carbon]	1.0946
-CH_2- [aliphatic carbon]	8.8398
-CH - [aliphatic carbon]	1.8070
-NH_2- [aliphatic attach]	-1.4148
-NH- [aliphatic attach]	-5.9848
Aromatic carbon	5.2920
-OH- [hydroxy, aromatic attach]	-0.4802
-O- [oxygen, one aromatic attach]	-0.4664
-C(=O) O [ester, aliphatic attach]	-1.9010
-C(=)N [aromatic attach]	0.1599
-SO_2-N [aromatic attach]	-0.2079
-NC(=O) N- [urea]	1.0453
-*tert* Carbon [3 or more carbon attach]	0.2676
Fused aliphatic ring unit correction	-1.3684
Equation constant	0.2290
log K_{ow}	6.9117
π	3.4238

which are cumulative effects of the different intra-and inter-molecular forces involved in the structural chemistry of some compounds[31,32]. Therefore, in this study P_c and S_t were also evaluated. The results indicate that both values of P_c and S_t for **5** were high in comparison with **1** and **3** (Table-5). These data

TABLE-5
PHYSICOCHEMICAL PARAMETERS OF COMPOUNDS **1**, **3** AND **5**

Compound	R_m (cm^3)	V_m (cm^3)	P_c (cm^3)	I_r (cm^3)	S_f (dyne/cm)	Density (g/cm^3)	Polarizability (10^{-24} cm^3)
1	123.60 ± 0.4	348.90 ± 5.0	993.4 ± 6.0	1.626 ± 0.03	85.70 ± 5.0	1.36 ± 0.1	48.99 ± 0.5
3	144.09 ± 0.4	412.70 ± 5.0	1184 ± 6.0	1.615 ± 0.03	67.80 ± 5.0	1.39 ± 0.1	57.12 ± 0.15
5	241.06 ± 0.4	672.1 ± 5.0	1932.0 ± 6.0	1.636 ± 0.03	68.20 ± 5.0	1.34 ± 0.1	95.56 ± 0.5

R_m = molar refractivity; V_m = molar volume; P_c = parachor; I_r = index of refraction; S_f = surface tension

indicate that these physicochemical parameters can also modify the degree of lipophilicity of **5**.

In conclusion, all theoretical data suggest that:

(1) The compound **5** have higher degree of lipophilicity in comparison with the compounds **1** and **3**.

(2) There are a relationship between the physicochemical descriptors evaluated in this study with the degree of lipophilicity of compound **5**.

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