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Design and Synthesis of a Diaza-bicyclo-naphthalen-oxiranyl-methanone Derivative. Theoretical Analysis of Their Interaction with Cytochrome P450-17A$_1$

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ABSTRACT

Several agents have been used for the treatment of prostate cancer such as flutamide, galeterone, abiraterone and others; however, some of these drugs can produce some secondary effects. The aim of this study was to synthesize a diaza-bicyclo-naphthalen-oxiranyl-methanone derivative using some chemical tools. The structure of all compounds involved in this study was confirmed by spectroscopy and spectrometry data. In addition, the theoretical interaction of diaza-bicyclo-naphthalen-oxiranyl-methanone derivative with the cytochrome P450-17A$_1$ enzyme (3RUK) was evaluated in a docking model using some drugs such as galeterone and abiraterone as controls. The results showed that diaza-bicyclo-naphthalen-oxiranyl-methanone could interact with different types of amino acid residues involving 3RUK protein surface as compared to both galeterone and abiraterone. This phenomenon may be due to the differences in the chemical structure of compounds. All these data indicate that diaza-bicyclo-naphthalen-oxiranyl-methanone derivative could change the biological activity of cytochrome P450-17A$_1$ enzyme which may be translated as good candidates for prostate cancer.

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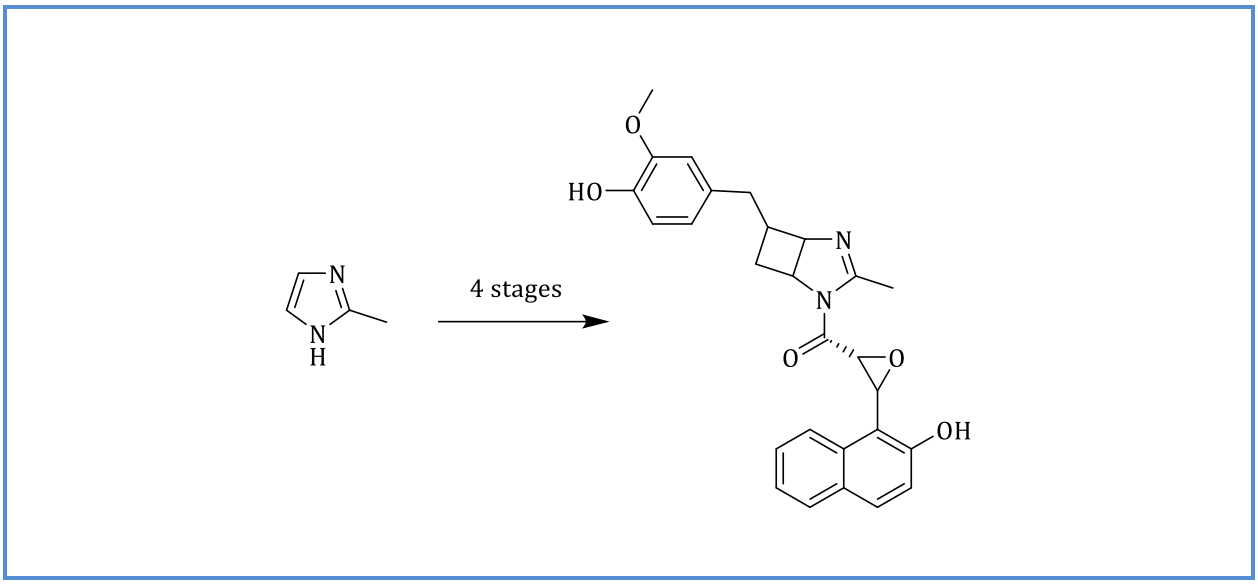
Graphical Abstract



Introduction

Several reports indicate that prostate cancer is one of the main health problems in men [1, 2]; there are some drugs for treatment of this clinical pathology such as flutamide [3], apalutamide [4], bicalutamide [5], abiraterone [6], leuprolide [7], gosereline [8] and others; however, some of these drugs can cause several adverse effects. In the search of some pharmacological alternatives for treatment of prostate cancer, several compounds have been synthesized; for example, the preparation of an antiandrogen through the reaction of benzoazole with 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene [9]. Another study showed the preparation of a cytochrome P450-17A_1 antagonist *via* oximation of abiraterone as prostate cancer inhibitor [10]. Also, a report indicates the preparation of a schiff base *via* reaction of copper with quinoline-2 carboxaldehyde as proteasome inhibitors in human prostate cancer cells [11]. Another report showed the synthesis of an inhibitor of prostate cancer (17-azolyl-steroid derivative) by the reaction of 3β-acetoxy-17-chloro-16-formylandrosta-5,16-diene with an azolyl group as nucleophile [12]. In addition, a study showed the preparation of prostate cancer inhibitor *via* acetylation of galeterone [13]. All these data indicate that several compounds can inhibit the prostate cancer; however, the site of interaction with some cell targets is not very clear, so more studies are needed on this phenomenon. Analysing, this hypothesis, in this study a diaza-bicyclo-naphthalen-oxiranyl-methanone derivative was synthesized, and their theoretical interaction with cytochrome P450-17A_1 enzyme was evaluated using a docking model.

Experimental

Chemical synthesis

All the reagents used in this study were purchased from Sigma-Aldrich Co., Ltd. Infrared spectra (IR) were determined using KBr pellets on a PerkinElmer Lambda 40 spectrometer.^{1}H and ^{13}C NMR (nuclear magnetic resonance) spectra were recorded on a Varian VXR300/5 FT NMR spectrometer at 300 and 75.4 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as an internal standard. EIMS (electron impact mass spectroscopy) spectra were determined using a Finnegan trace gas chromatography Polaris Q-spectrometer. Elementary analysis data were determined from a PerkinElmer Ser. II CHNS/02400 elemental analyser.

2-methoxy-4-(3-methyl-2,4-diaza-bicyclo[3.2.0]hept-3-en-6-ylmethyl)-phenol (2)

A solution of 2-methylimidazol (80 mg; 0.87 mmol), eugenol (140 µL; 0.90 mmol) 5 mL of methanol was stirring to reflux for 12 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol: water (4:1) system. Yielding 54%; IR (V_{max}, cm^{-1}) 3400, 3330 and 2815: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 0.84-1.56 (m, 3H), 1.94 (s, 3H), 2.66-2.72 (m, 2H), 3.86 (s, 3H), 3.92-4.30 (m, 2H), 6.74-6.90 (m, 3H), 7.02 (broad, 2H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C: 20.62, 28.93, 35.80, 40.50, 55.86, 58.40, 69.80, 114.30, 115.32, 123.84, 131.88, 144.50, 147.70, 153.62 ppm. EI-MS m/z: 246.13. Anal. Calcd. for $C_{14}H_{18}N_2O_2$: C, 68.27; H, 7.37; N, 11.37; O, 12.99. Found: C, 68.20; H, 7.32.

2-chloro-1-(2-methyl-imidazol-1-yl)-ethanone (3)

A solution of **2** (100 mg, 0.41 mmol), chloroacetyl chloride (64 µL; 0.80 mmol), triethylamine (112 µL; 0,8 mmol), and 5 mL of methanol was stirring to reflux for 12 h. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol: hexane: water (4:2:1) system. Yielding 54%; IR (V_{max}, cm^{-1}) 3332, and 1638: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 2.66 (s, 3H), 4.40 (m, 2H), 6.70-7.79 (m, 2H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C: 15.32, 40.62, 116.95, 134.54, 145.24, 165.22. EI-MS m/z: 158.58. Anal. Calcd. for $C_6H_7ClN_2O$: C, 45.44; H, 4.45; Cl, 22.36; N, 17.66; O, 10.09. Found: C, 45.40; H, 4.40.

2-chloro-1-[6-(4-hydroxy-3-methoxy-benzyl)-3-methyl-2,4-diaza-bicyclo[3.2.0]hept-3-en-2-yl]-ethanone (4)

A solution of **3** (100 mg, 0.63 mmol chloroacetyl chloride (64 µL; 0.80 mmol), triethylamine (112 µL; 0.80 mmol) and 5 mL of methanol was stirring to reflux for 12 h. The mixture obtained was

dried under reduced pressure and purified by crystallization using the methanol: water (4:1) system. Yielding 54%; IR (V_{max}, cm^{-1}) 3402, 3330 and 2814: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.14-1.19 (m, 3H), 1.74 (s, 3H), 2.66-2.74 (m, 2H), 3.86 (s, 3H), 4.10-4.14 (m, 2H), 4.76-4.82 (m, 2H), 5.46 (broad, 1H), 6.74-6.90 (m, 3H) ppm. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C: 19.76, 26.02, 36.02, 40.50, 41.76, 51.07, 55.86, 68.32, 114.30, 115.35, 123.86, 132.15, 144.53, 147.70, 151.36, 166.20 ppm. EI-MS m/z: 322.79. Anal. Calcd. for $C_{16}H_{19}ClN_2O_3$: C, 59.54; H, 5.93; Cl, 10.98; N, 8.68; O, 14.67. Found: C, 68.20; H, 7.32.

[6-(4-hydroxy-3-methoxy-benzyl)-3-methyl-2,4-diaza-bicyclo[3.2.0]hept-3-en-2-yl]-[3-(2-hydroxy-naphthalen-1-yl)-oxiranyl]-methanone (5)

A solution of **4** (200 mg, 0.61 mmol), 1-(2-Hydroxy-naphthalen-1-yl)-ethanone(100 mg, 0.58 mmol) and sodium hydroxide (30 mg, 0.75 mmol) and 5 mL of methanol was stirred to reflux for 12 h. The obtained mixture was dried under reduced pressure and purified by crystallization using the methanol: water (4:2) system. Yielding 54%; IR (V_{max}, cm^{-1}) 3400, 3332, 2815, and 1640: ^{1}H NMR (300 MHz, $CDCl_3$) δ_H: 1.14-1.22, 1.74 (s, 3H), 2.66-2.74 (m, 2H), 3.86 (s, 3H), 4.28-4.46 (m, 2H), 4.50-4.80 (m, 2H), 6.74-7.22 (m, 4H), 7.30 (broad, 2H), 7.34-7.90 (m, 5H) pp. ^{13}C NMR (300 MHz, $CDCl_3$) δ_C: 19.76, 26.02, 36.02, 40.50, 52.84, 53.47, 53.90, 55.87, 68.32, 114.30, 115.35, 118.85, 121.45, 122.58, 123.43, 123.86, 126.81, 127.86, 129.2, 130.35, 132.15, 134.66, 144.53, 147.70, 153.06, 153.92, 164.82 ppm. EI-MS m/z: 458.51. Anal. Calcd. for $C_{27}H_{26}N_2O_5$: C, 70.73; H, 5.72; N, 6.11; O, 17.45. Found: C, 68.20; H, 7.32.

Theoretical evaluation of lipophilicity degree involved in the compounds 2-5

The LogP and π values for **2-5** were carried out using KOWWING program [14]. In addition, both Vm and Rm values for compound **2-5** were determinate using ACD/labs 8.0 software [15].

Electronic parameters evaluation (HOMO and LUMO)

The molecular orbitals HOMO and LUMO for all compounds were theoretically evaluated with SPARTAN'06 software package (Wave Function Inc. Irvine, CA, 2000), using hartree-fock method at 321-G level [16].

Interaction between compounds 2-5 with cytochrome P450-17A_1

Theoretical analysis of interaction of compounds **1-4** on androgen receptor (3L3Z) [17], and cytochrome P450-17A_1 enzyme (3RUK) [18], was carried out using a docking program (docking server) [19]. In addition, flutamide and abiraterone were used as controls.

Result and Discussion

For several years the development of new drugs for the treatment of prostate cancer has increased [9-13]; however, the site of interaction with some cell target is not very clear, so more studies are needed on this phenomenon. The aim of this study was synthesizing a diaza-bicyclo-naphthalen-oxiranyl-methanone derivative to evaluate their interaction with androgen receptor or cytochrome P450-17A_1 enzyme.

First stage

Preparation of a diaza-bicyclo derivative (2)

There are several reports which showed the preparation of some diazabicyclo analogs using some reagents such as I_2 [20], dimethylpiperazine [21], rodhium [22], H_2SO_4 [23] and others; however, some of these reagents are difficult to handle require and special conditions. Therefore, in this work the 2-methylimidazol was reacted with eugenol using copper(II) as catalyst m (Figure 1).

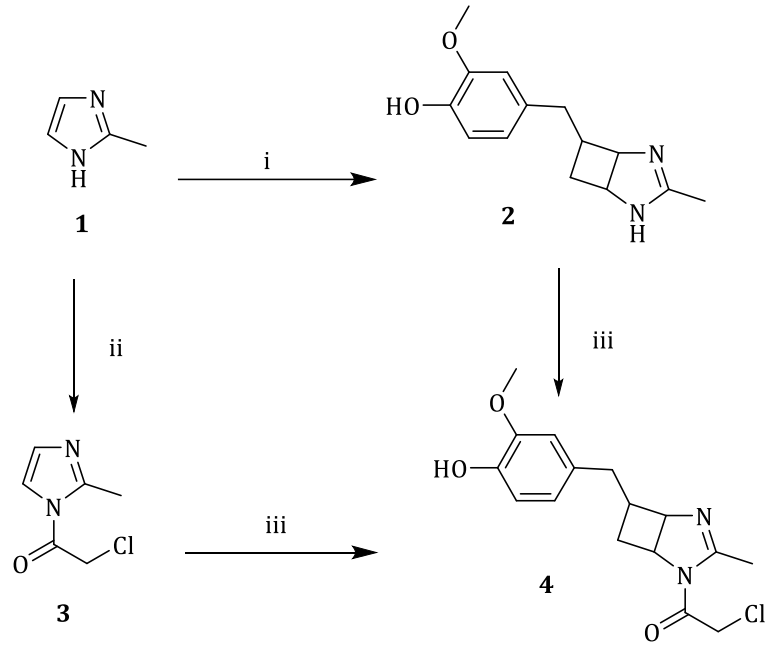


Figure 1. Synthesis of a chloroamide derivative (4). The first sage was achieved by preparation of a 2-methoxy-diaza-bicyclo-phenol analog (2) by reaction of 2-methylimidazol (1) with eugenol (i). Then, 2 was reacted with chloroacetyl chloride (ii) to synthesis of a chloroamide derivative (4). The second stage was achieved by formation of 2-chloro-1-(2-methyl-imidazol-1-yl)-ethanone (3) via reaction of 1 with chloroacetyl chloride (iii). Finally, 3 was reacted with eugenol to form 4 (iv)

The results of ^{1}H NMR spectrum of **2** showed several signals at 0.82-1.56 and 3.92-4.30 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 1.94 ppm for methyl group bound to 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 2.66-2.72 ppm for methylene group bound to both phenyl group and 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 3.86 ppm for methoxy group; at 3.90-4.30 ppm for

2,4-diaza-bicyclo[3.2.0]hept-3-ene; at 6.74-6.90 ppm for phenyl group; at 7.02 for both amino and hydroxyl groups.

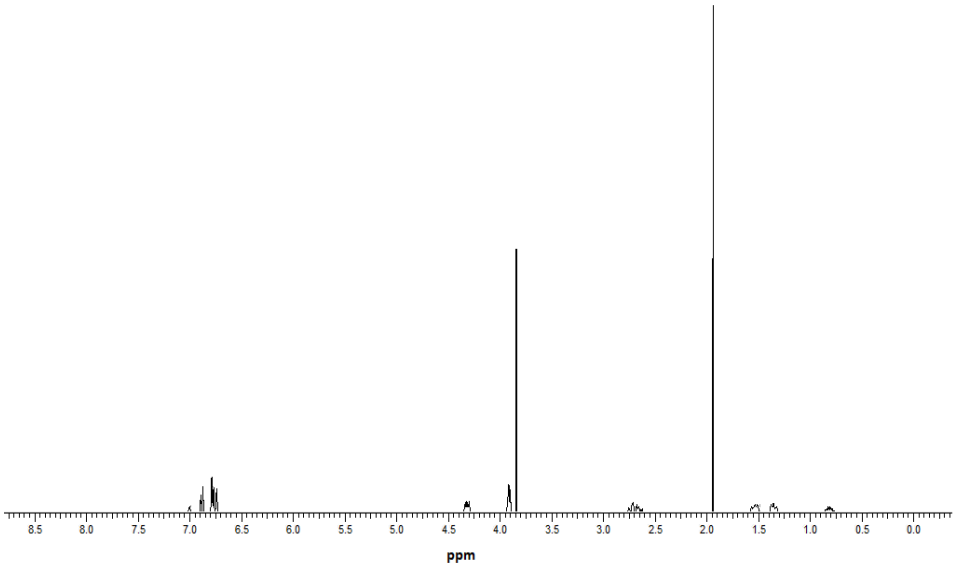


Figure 2. The scheme shown ^{1}H NMR spectrum of 2. Analysed with a varian VXR300/5 FT NMR apparatus at 300 MHz in $CDCl_3$

The ^{13}C NMR spectra displays chemical shifts at 20.62 ppm for methyl bound to 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 28.93-35.80, 58.40-69.40 and 153.63 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 40.50 for methylene group bound to both phenyl group and 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 55.86 ppm for methoxy group; at 114.30-147.70 ppm for phenyl group. In addition, the mass spectrum from **2** showed a molecular ion (m/z) at 246.13.

Synthesis of an imidazole-chloroamide derivative (3)

There are some studies which showed the preparation of chloroamides using some reagents such as trichloroisocyanuric acid [24], *N*-chlorobenzotriazole [25], chloroacetyl chloride [26-28]. Therefore, in this study, 2-methylimidazole (**1**) was reacted with chloroacetyl chloride (Figure 1) to form a chloroamide derivative (**2**). ^{1}H NMR spectrum of **3** showed several signals at 2.66 ppm for methyl group; at 4.40 ppm for methylene group of chloroamide; at 6.70-7.79 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring. The ^{13}C NMR spectra displays chemical shifts at 15.32 for methyl group; at 40.62 ppm for methylene group of chloroamide; at 116.95-145.24 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 165.22 for amide group. Additionally, the mass spectrum from **3** showed a molecular ion (m/z) at 158.58.

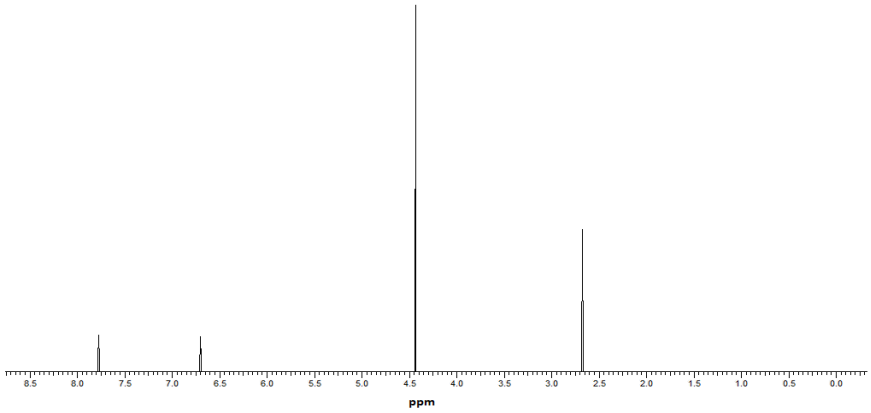


Figure 3. ^{1}H NMR spectrum of 3. Analysed with a varian VXR300/5 FT NMR apparatus at 300 MHz in $CDCl_3$

Preparation of a diaza-bicyclo-chloroamide derivative (4)

The compound **2** reacted with chloroamide in mild conditions to form the compound **4** (Figure 1). ^{1}H NMR spectrum of **4** showed several signals at 1.14-1.22 and 4.76-4.82 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 1.74 ppm for methyl group bound to 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 2.66-2.74 ppm for methylene group bound to both phrnyl and 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 3.86 ppm for methoxy group; at 4.10-4.14 ppm for methylene of chloroamide; at 6.74-6.90 ppm for phenyl group; at 5.46 for hydroxyl group.

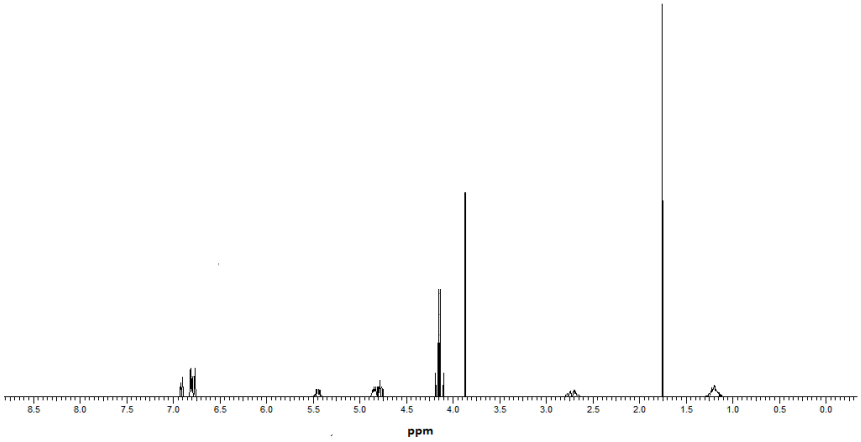


Figure 4. The scheme shown ^{1}H NMR spectrum of 4. Analysed with a varian VXR300/5 FT NMR apparatus at 300 MHz in $CDCl_3$

The ^{13}C NMR spectra displays chemical shifts at 19.76 ppm for methyl group bound to 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 26.02-36.02. 51.07, 68.32 and 151.36 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 40.50 ppm for methylene bound to both phenyl group and 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 41.76 ppm for methylene group of chloroamide; at 55.86 ppm for methoxy group; at 114.30-147.70 ppm for phenyl group. Finally, the mass spectrum from **4** showed a molecular ion (m/z) at 322.79.

Synthesis of a diaza-bicyclo-naphthalen-oxiranyl-methanone derivative (5)

There are several data for the preparation of oxirane derivatives using a different protocol; nevertheless, expensive reagents and special conditions are required [29-35]. For example, the most widely practiced methods employ some reagents such as Co(III) and Cr(III) [36, 37].

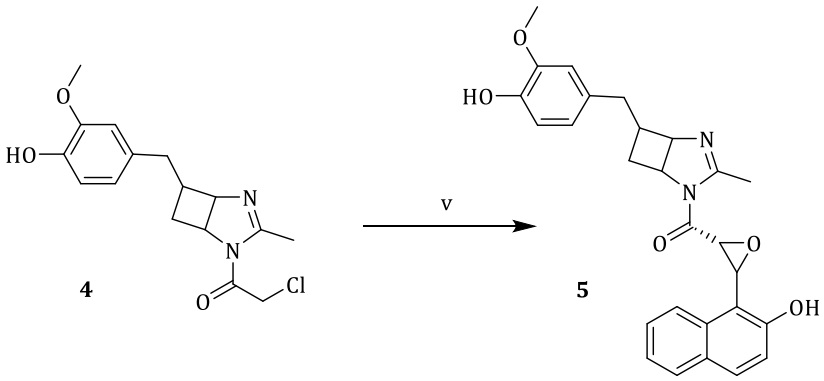


Figure 5. Synthesis of diaza-bicyclo-naphthalen-oxiranyl-methanone derivative (**5**). Reaction of chloroamide derivative (**4**) with 1-(2-Hydroxy-naphthalen-1-yl)-ethanone (v) to form **5**

Therefore, in this study the compound **5** was prepared by the reaction of **4** with 2-hydroxy-1-naphthaldehyde in basic conditions (Figure 2).

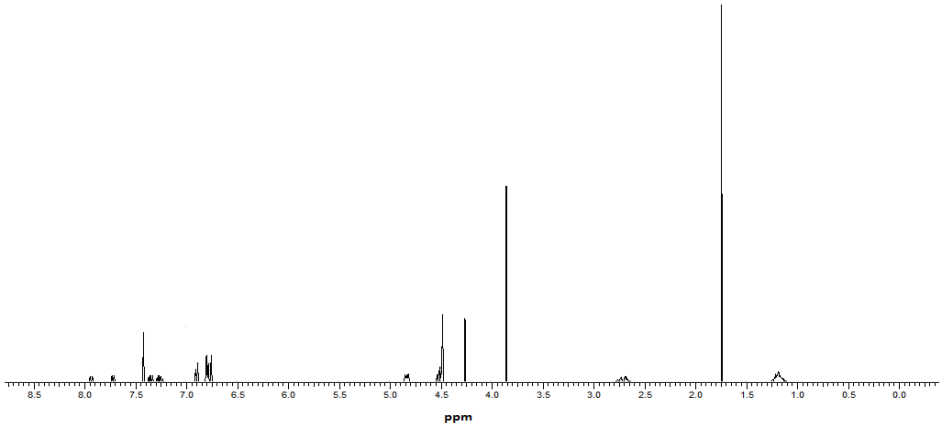


Figure 6. The scheme shown ^{1}H NMR spectrum of 5. Analysed with a varian VXR300/5 FT NMR apparatus at 300 MHz in $CDCl_3$

The ^{1}H NMR spectrum of **5** showed several signals at 1.14-1.22 and 4.50-4.80 ppm for 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 1.74 ppm for methyl group bound to 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 2.66-2.74 ppm for methylene group bound to both phenyl group and 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring; at 3.86 ppm for methoxy group; at 4.28-4.46 ppm for oxirane ring; at 6.74-7.22 and 7.34-7.90 ppm for phenyl groups; at 7.30 ppm for hydroxyl groups. The ^{13}C NMR spectra displays chemical shifts at 26.02-36.02, 58.84, 63.32 and 153.06 ppm for 2,4-diaza-

bicyclo[3.2.0]hept-2-ene ring; at 40.50 ppm for methylene group bound to both 2,4-diaza-bicyclo[3.2.0]hept-2-ene ring and phenyl group; at 53.47-53.90 for oxirane ring; at 55.87 ppm for methoxy group; at 114.30-147.70 and 153.92 ppm for phenyl groups; at 164.82 ppm for amide group. In addition, the mass spectrum from **5** showed a molecular ion (m/z) at 458.51.

Physicochemical parameters of compound 2-5

To delineate the structural chemical requirements of the compounds 2-5 some parameters such as the descriptors logP and π were determinate. It is important to mention that 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 [14] and this premise is supported by following data [38]:

$$Kow = c_o^{equil}/c_w^{equil}$$

Where:

c_o^{equil}=concentration of the compound under consideration (analyte A) in 1-octanol in the equilibrium.

c_w= concentration of the analyte in water in the equilibrium

It is noteworthy that logKow values are typically between-3 (very hydrophilic)and +10 (extremely hydrophobic).

Table 1. Physicochemical parameters involved in the chemical structure of compounds **2** and **3**

2	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	0.9822
	-CH [aliphatic carbon]	1.0842
	-C [aliphatic carbon-No. H, not tert]	0.9723
	-NH-[aliphatic attach]	-1.4962
	Aromatic Carbon	1.7640
	-OH [hydroxyl, aromatic attach]	-0.4802
	-O [oxygen, one aromatic attach]	-0.4664
	-N=C [aliphatic attach]	-0.0010
	Fused aliphatic ring unit correction	-0.3421
	Ring reaction -> alkyloxy ortho to- OH	-0.2560
	-C-N=C-N-C [cyclic] structure correction	0.6000
	Equation Constant	0.2290
	Π	1.9439
	Log Kow	2.4844
3	$-CH_3$ [aliphatic carbon]	0.5473
	$-CH_2-$ [aliphatic carbon]	0.4911
	-Cl [chlorine, aliphatic attach]	0.3102
	Aromatic Carbon	0.8820
	-C(=O)- [carbonyl, one aromatic attach]	-0.8667
	Aromatic Nitrogen [5-member ring]	-1.0524
	Equation Constant	0.2290
	π	
	Log Kow	0.5405

It is important to mention that the differences between the substituted and unsubstituted logP values are conditioned by the π value for a particular substituent. Therefore, in this study, logP and π parameters were calculated using a previously method reported [14]. The results showed that logKow and π were higher for compound **5** compared to **2**-**4**, which translates to more lipophilicity (Tables 1 and 2).

This phenomenon may be conditioned by other factors chemical such as volume molar (V_m) and molar refractivity (R_m) which are two physicochemical parameters which are involved in several changes in some biological models [39]. The values determinate showed that V_m and R_m were higher for **5** compared to **2**-**4** (Table 3), this phenomenon could condition difference in the biological activity of **5** in relation to compounds **2**-**4**.

Table 2. Physicochemical parameters involved in the chemical structure of compounds **3** and **4**

4	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	1.4733
	-CH [aliphatic carbon]	1.0842
	C [aliphatic carbon - No H, not tert]	0.9723
	-N< [aliphatic attach]	-1.8323
	Cl [chlorine, aliphatic attach]	0.3102
	Aromatic Carbon	1.7640
	-OH [hydroxyl, aromatic attach]	-0.4802
	-O- [oxygen, one aromatic attach]	-0.4664
	-C(=O)N [aliphatic attach]	-0.5236
	-N=C [aliphatic attach]	-0.0010
	Mono-halo acetamide [-N-CO-C-halo]	0.3263
	Fused aliphatic ring unit correction	-0.3421
	Ring reaction -> alkyloxy ortho to -OH	-0.2560
	Equation Constant	0.2290
	π	0.8679
	LogKow	3.3523
5	$-CH_3$ [aliphatic carbon]	1.0946
	$-CH_2-$ [aliphatic carbon]	0.9822
	-CH [aliphatic carbon]	1.8070
	C [aliphatic carbon - No H, not tert]	0.9723
	-O- [oxygen, aliphatic attach]	-1.2566
	-N< [aliphatic attach]	-1.8323
	Aromatic Carbon	4.7040
	-OH [hydroxyl, aromatic attach]	-0.9604
	-O- [oxygen, one aromatic attach]	-0.4664
	-C(=O)N [aliphatic attach]	-0.5236
	-N=C [aliphatic attach]	-0.0010
	Fused aliphatic ring unit correction	-0.3421
	Ring reaction -> alkyloxy ortho to -OH	-0.2560
	Aryloxy (or -C-O)-C-C(=O)NH- correction	0.4874
	-O-C-C(-O-)-C(=O)- structure correction	1.0000
	Equation Constant	0.2290
	π	2.2858
	LogKow	5.6381

However, analyzing this hypothesis, it is important to mention that also another physicochemical descriptor such as topological polar surface area (TPSA) also could condition the biological activity of these compounds. Therefore, TPSA was determinate for compounds **2**-**5**; the results showed that TPSA was higher for **5** compared with **2**-**4**. All these data suggest that compound **5** could have a high probability of interacting with some biological molecule due to its lipophilic characteristics, which could result in some specific effect such as, occurs with other compounds [40].

Table 3. Physicochemical parameters of compounds **2**-**5**

Parameter	C-2	C-3	C-4	C-5
V_m(cm^3)	67.39	121.60	228.70	314.20
R_m (cm^3)	183.90	39.92	82.96	123.66
Polarizability	59.65	50.58	64.24	76.45
Dipole moment (debyte)	3.53	3.47	4.47	4.64
PSA (Å^2)	46.74	21.79	48.97	71.36
Energy ($^{\Phi}$Hartree)	-794.66	-870.12	-1402.47	-1512.12
HOMO (eV)	-7.86	-8.95	-7.97	-7.58
LUMO (eV)	4.02	2.30	3.23	2.28
Gap energy, eV (HOMO LUMO)	-11.88	-11.25	-11.20	-9.86
$^{\varpi}$HBD	1	0	1	2
^{6}HBA	3	3	4	6

$^{\Phi}E_h$ = 4.359 744 650(54)×10^{-18} J = 27.211 386 02(17) eV [41].
$^{\varpi}$HBD (hydrogen bond donors); ^{6}HBA (hydrogenbond acceptors).

Electronic parameters

Molecular orbitals (HOMO and LUMO) for the compounds **2**-**5** were theoretically determinate using spartan´06 software package. The results showed that HOMO and LUMO values were lower for **5** compared with the compound **2**-**4** (Table 3, Figure 3); these results suggest that **5** have a strong electro donating ability in comparison with **2**-**4**.

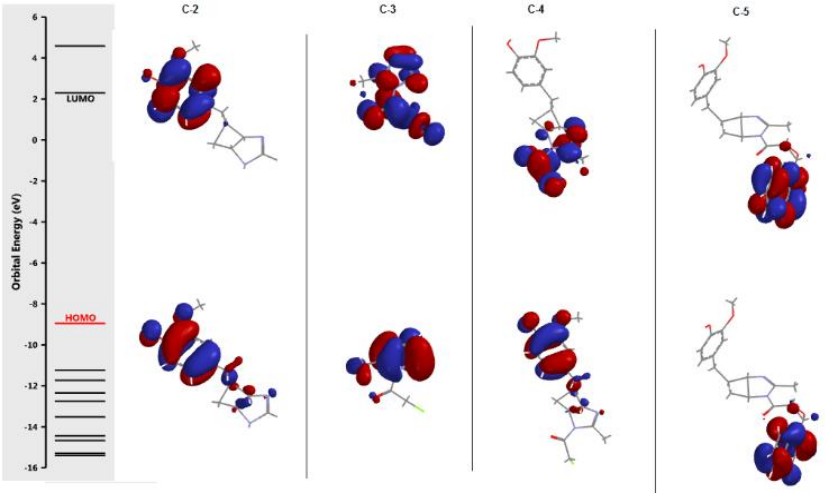


Figure 3. Molecular orbitals (HOMO and LUMO) involved in the compounds **2**-**5** (C-2, C-3, C-4 and C5). Visualized with SPARTAN'06 software

Theoretical analysis of interaction of compounds 2-5 with cytochrome P450-17A$_1$ enzyme (3RUK)

There are some reports which indicate the interaction between molecule-protein and protein-protein as they are involved in several biological processes such as signal transduction, physiological regulation, gene transcription, and enzymatic reactions [42]. It is important to mention that several drugs can induce changes biological activity of some biological system *via* interactions with either specific protein or enzyme; therefore, several theoretical models have been developed to predict the interaction of drugs with different proteins or enzymes [43].

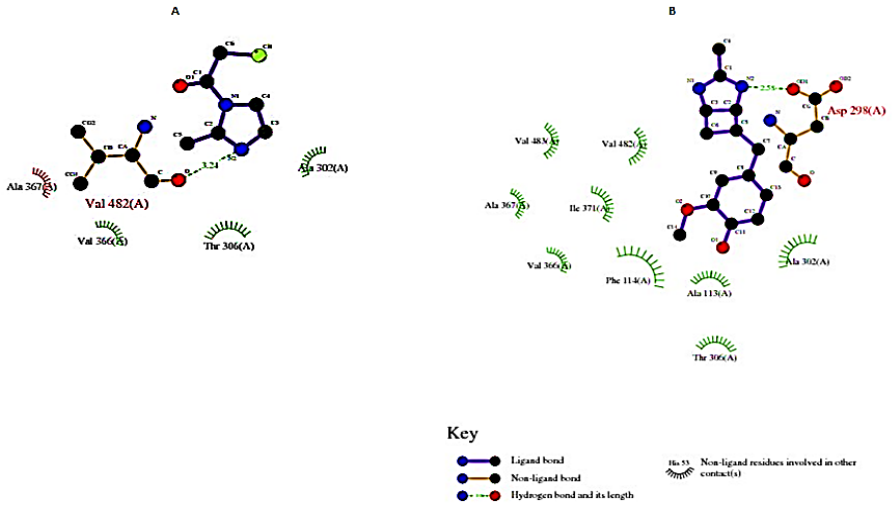


Figure 4. The scheme showed the binding site of amino acid residues involved in the interaction of cytochrome P450 17A$_1$ enzyme (3RUK) with the compound**2 (A)** and **3 (B)**. Visualized with GL mol viewer, dockingserver

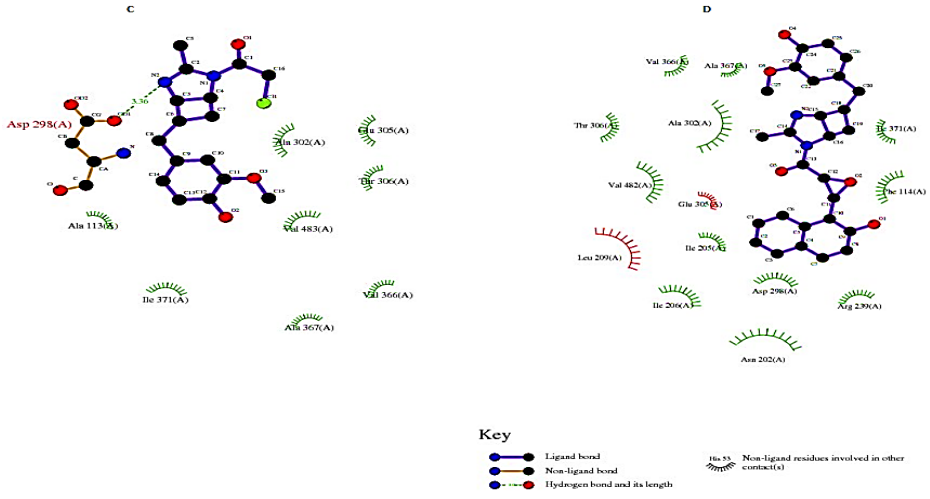


Figure 5. The scheme showed the binding site of amino acid residues involved in the interaction of cytochrome P450 17A$_1$ enzyme (3RUK) with the compound**4 (C)** and **5 (D)**. Visualized with GL mol viewer, dockingserver

Analysing these data, in this study, was carried out using a theoretical analysis on interaction of compounds **2-5** with cytochrome P450-17A_1 enzyme (3RUK) using galeterone and abiraterone as control. The results showed the interaction of compounds **2-5** with different types of amino acid residues involving 3RUK protein as compared to abiraterone and galeterone (Figure 4-5; Table 5 and 6, in red).

Table 4. Aminoacid residues involved in the interaction between abiraterone e and compounds **2-5** on cytochrome P450-17A_1 enzyme (3RUK). Similar aminoacid residues to abiraterone

	Abiraterone	**C-2**	**C-3**	**C-4**	**C-5**
Amioacid Residues	Ala_{113} Tyr_{201} Asn_{202} Ile_{205} Asp_{298} Ala_{302} Thr_{306} Val_{366} Ala_{367} Val_{482}	Ala_{302} Thr_{306} Val_{366} Ala_{367} Val_{482}	Ala_{113} Phe_{114} Asp_{298} Ala_{302} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{482} Val_{483}	Ala_{113} Asp_{298} Ala_{302} Glu_{305} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{483}	Phe_{114} Asn_{202} Ile_{205} Ile_{206} Leu_{209} Arg_{239} Asp_{298} Ala_{302} Glu_{305} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{482}

Table 5. Amino acid residuesinvolved in the interaction between abiraterone and compounds **2-5** on cytochrome P450-17A_1 enzyme (3RUK). Similar aminoacid residues to galeterone

	Galeterone	**C-2**	**C-3**	**C-4**	**C-5**
Aminoacid Residues	Ala_{113} Phe_{114} Asn_{202} Ile_{205} Leu_{209} Ala_{302} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{482}	Ala_{302} Thr_{306} Val_{366} Ala_{367} Val_{482}	Ala_{113} Phe_{114} Asp_{298} Ala_{302} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{482} Val_{483}	Ala_{113} Asp_{298} Ala_{302} Glu_{305} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{483}	Phe_{114} Asn_{202} Ile_{205} Ile_{206} Leu_{209} Arg_{239} Asp_{298} Ala_{302} Glu_{305} Thr_{306} Val_{366} Ala_{367} Ile_{371} Val_{482}

This phenomenon may due to differences in the chemical structure of compounds; however, to validate this premise, other types of factors must be evaluated, such as some thermodynamic parameters.

Thermodynamic parameters

There are some reports which indicate that some thermodynamic factors could be involved in the interaction drug-protein [44]; therefore, in this study some thermodynamic parameters involved in the interaction of compounds **2**-**5** with cytochrome P450-17A_1 enzyme (3RUK) were evaluated using galeterone or abiraterone as control. It is noteworthy that thermodynamic parameters were the following; 1) free energy of binding which determinate the energy value that require a molecule to interact with a protein in a water environment. 2). Electrostatic energy that is the product of electrical charge and electrostatic potential, which are involved in the ligand-protein system [44]; 3) total intermolecular energy and 4) van der waals (vdW) + hydrogen bond (Hbond) + desolvation energy (which have an influence on the movement of water molecules into or out of the ligand-protein system).

Table 6. Thermodynamic parameters involved in the interaction of abiraterone and compounds **1**-**4** on cytochrome P450-17A_1 enzyme (3RUK)

Compound	Est. Free Energy of Binding (kcal/mol)	Est. Inhibition Constant, (Ki)	vdW + Hbond + desolv. Energy (kcal/mol)	Electrostatic Energy (kcal/mol)	Total Intermol. Energy (kcal/mol)	Interact. Surface
Abiraterone	-11.43	4.18	-12.08	0.01	-12.06	594.799
Galeterone	-12.53	659.07	-12.86	0.03	-12.83	634.905
2	-5.03	204.89	-5.44	0.11	-5.33	342.040
3	-6.54	16.07	-6.40	-0.93	-7.33	493.670
4	-8.02	1.33	-8.25	-0.13	-8.38	569.890
5	-7.46	3.40	-9.56	-0.27	-9.83	688.886

The results showed in the Table 6. indicate that the energy requirements involved in the interaction of compounds **4** or **5** with the 3RUK protein surface were higher compared to compounds **2** and **3** (Table 4). In addition, the inhibition constant (Ki) values were lower for both compounds **4** and **5** compared with galeterone or abiraterone and compounds **1**-**3**.

All these data suggested that differences in the energy levels and Ki between the interactions of the compounds studied with the 3RUK protein may be translated as different changes in the biological activity of cytochrome P450-17A_1 enzyme in the presence of **5** in comparison with the compounds **2**-**4**.

Conclusion

All the theoretical results indicate that compound **5** has a higher affinity for the 3RUK protein, which may result in changes in the biological activity of the cytochrome P450-17A1 enzyme.

However, it is important to mention that to validate this hypothesis, it is necessary to carry out studies in some biological model.

References

[1] Collins A.T., Berry P.A., Hyde C., Stower M.J., Maitland N.J. *Cancer Res.*, 2005, **65**:10946

[2] Ortelli L, Spitale A., Mazzucchelli L., Bordoni A. *BMC Cancer*, 2018, **18**:733

[3] Rezaeifar Z., Rounaghi G.H., Es'haghi Z., Chamsaz M. *Mater. Sci. Eng. C*, 2018, **91**:10

[4] Rachner T., Tsourdi E., Hofbauer L., *N. Engl. J. Med.*, 2018, **378**:2541

[5] Beebe J., Ruterbusch J., Bylsma L., Gillezeau C. *Adv. Ther.*, 2018, **1**:14

[6] Bono J.S., Logothetis C.J., Molina A., Fizazi K., North S., Chu L., Chi K.N., Jones R.J., Goodman O.B., Saad F., Staffurth J.N., Mainwaring P., Harland S., Flaig T.W., Hutson T.E., Cheng T., Patterson H., Hainsworth J.D., Ryan C.J., Sternberg C.N., EllardS.L., Fléhon A., Saleh M., Scholz M., Efstathiou E., Zivi A., Bianchini D., Loriot Y., Chieffo N., Kheoh T., Haqq C.M., Scher H.I. *N. Engl. J. Med*, 2011, **364**:1995

[7] Saltzstein D., Shore N., Moul J., Chu F., Concepcion R., Motte S. *Ther. Adv. Urol.*, 2017, **10:**43

[8] Meani D., Solarić M., Visapää H., Rosén R., Janknegt R., Soče M. *Ther. Adv. Urol*., 2017 **10**:51

[9] Handratta V.D., Vasaitis T.S., Njar V.C.O., Gediya L.K., Kataria R., Chopra P., Newman D., Farquhar R., Guo Z., Qiu Y., Brodie A.M.H. *J. Med. Chem.*, 2005, **48**:2972

[10] Fehl C., Vogt C.D., Yadav R., Li K., Scott E.E., Aubé J. *J. Med. Chem.*, 2018, **61**:4946

[11] Adsule S., Barve V., Chen D., Ahmed F., Dou Q.P., Padhye S., Sakar F.H. *J. Med. Chem.*, 2006, **49**:7242

[12] Njar V.C.O., Kato K., Nnane I.P., Grigoryev D.N., Long B.J., Brodie A.M.H. *J. Med. Chem.*, 1998, **41**:902

[13] Purushottamachar P., Godbole A.M., Gediya L.K., Martin M.S., Vasaitis T.S., Kwegyir-Afful A.K., Ramalingam S., Ates-Alagoz Z., Njar V.C.O. *J. Med. Chem.*, 2013, **56**:4880

[14] Figueroa-Valverde L., Díaz-Cedillo F., Rosas-Nexticapa M., García-Cervera E., Pool-Gómez E., López-Ramos M., Hau-Heredia L., Sarabia-Alcocer B. *Monats. FürChem.*, 2010, **141**:373

[15] Schnackenberg L.K., Beger R.D. *J. Chem. Inf. Mod.*, 2005, **45**:360

[16] Fisher R., Guhathakurta M. *Astroph. J. Lett.*, 1995, **447:**139

[17] Kuzikov A.V., Dugin N.O., Stulov S.V., Shcherbinin D.S., Zharkova M.S., Tkachev Y.V., Timofeev V.P., Veselovsky A.V., Shumyantseva V.V., Misharin A.Y. *Steroids*, 2014, **88**:66

[18] Macindoe G., Mavridis L., Venkatraman V., Devignes M.D., Ritchie D.W. *Nucleic acids Res.*, 2010, **38**: W445

[19] Ramírez E., López, J., Chacón, P. *Bioinformatics*, 2016, **32**:2386

[20] Kumar Y., Kuila B., Mahajan D., Singh P., Mohapatra M., Bhargava G. *Tetraedron Lett*, 2014, **55**:2793

[21] Mann F.G., Mukherjee D.P. *J. Chem. Soc.*, 1949, **1:**2298

[22] Angelovski G., Eilbracht P., *Tetrahedron*, 2003, **59**:8265

[23] Curtis P., Bunnelle H., Pagano G., Gopalakrishnan M., Faghi R. *Syn. Com*, 2006, **36**:321

[24] Hiegel G.A., Hogenauer T.J., Lewis J.C. *Synthet. Communicat.*, 2005, **35**:2099

[25] Katritzky A., Majumder S., Jain R. *Arkivo*, 2003, **2003**:74

[26] Sibi J., Jacob G., *Orient J. Chem.*, 2013, **29**:565

[27] Harte A.J., Gunnlaugsson T. *Tetraedron Lett.*, 2006, **47**:6321

[28] Katke S., Amrutkar S., Bhor R., Khairnar M. *Int. J. Pharm. Sci. Res.*, 2011, **2**:148

[29] Borredon E., Clavellinas F., Delmas M., Gaset A., Sinisterra J.V. *J. Org. Chem.*, 1990, **55**:501

[30] Machida S., Isoda Y., Kunieda M., Tamiaki H. *Tetraedron Lett.*, 2012, **53**:6277

[31] Rawal V.H., Newton R.C., Krishnamurthy V. *J. Org. Chem.*, 1990, **55**:5181

[32] Xie M., Wang Z., Zhao Y. *J. Polym. Sci*., 2001, **39**:2799

[33] Bhat B.A., Dhar K.L., Puri S.C., Saxena A.K., Shanmugavel M., Qazi G.N. *Bioorg. Med. Chem. Lett.*, 2005, **15**:3177

[34] Park K.K., Surh Y.J., Stewart B.C., Miller J.A. *Biochem. Biophys. Res. Comm.,* 1990, **169**:1094

[35] Figueroa-Valverde L., Díaz-Cedillo F., Rosas-Nexticapa M., Maldonado-Velazquez G., García-Cervera E., Pool-Gomez E., Jarquin-Barberena H., Lopez-Ramos M., Rodriguez-Hurtado F., Chan-Salvador M. *Lett. Org. Chem.*, 2015, **12**:394

[36] Schaus S.E., Brandes B.D., Larrow J.F., Tokunaga M., Hansen K.B., Gould A.E., Furrow M.E., Jacobsen E.N. *J. Am. Chem. Soc.*, 2002, **124**:1307

[37] Martinez L.E., Leighton J.L., Carsten D.H., Jacobsen E.N. *J. Am. Chem. Soc.*, 1995, **117**:5897

[38] Cumming H., Rücker C. *ACS Omega*, 2017, **2**:6244

[39] Figueroa-Valverde L., Diaz-Cedillo F., Ramos M. Cervera E. *Med. Chem. Res.*, 2011, **20**:847

[40] Figueroa-Valverde L., Rosas-Nexticapa M., Mateu-Armand V., Herrera-Meza S., Lopez-Ramos M. *Bioinerfase Res. Appl. Chem*., 2018, **8**:3161

[41] Mohr P., Taylor, B., Newell, D. *J. Phys. Chem. Reference Data*. 2008, **80**: 633.

[42] Andersson C.D., Thysell E., Lindström A., Bylesjö M., Raubacher F., Linusson A. *J. Chem. Inf. Model*, 2007, **47**:1673

[43] Elokely K.M., Doerksen R.J. *J. Chem. Inf. Model*, 2013, **53**:1934

[44] Mandell J.G., Roberts V.A., Pique M.E., Kotlovyi V., Mitchell J.C. *Protein Eng.*, 2001, **14**:105

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