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FACILE SYNTHESIS OF THREE AZETIDINE DERIVATIVES USING SOME CHEMICAL STRATEGIES

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ABSTRACT
There are reports which show the preparation of several azetidine derivatives using different protocols; however, some methods use reagents that can be dangerous and require specific conditions. The aim of this study was to synthesize three azetidine derivatives using some chemical tools. The chemical structure of azetidine derivatives was confirmed through both ^{1}H and ^{13}C-NMR spectra.In conclusion, in this study is reported a facile synthesis of three azetidine derivatives using reagents that are not expensive and are easy to handle.

KEYWORDS. Azetidine, derivatives, nitrobenzoyl,azide.

INTRODUCTION
For several years, researchers in the area of chemical and pharmacy sciences have shown interest in the preparation of derivatives of substituted heterocycles using several protocols[i,ii]. For example, a study showed the synthesis aziridines and azetidines from N-(ω-haloalkyl) imines[iii]. Other data have shown the asymmetric cyclization of 1,3-amino alcohols in the presence of carbonyldiimidazole to form some 2,3-disubstituted azetidines[iv]. In addition, other report indicates the synthesis of α-carbonylated azeditines via nucleophilic addition/ring contraction of α-bromopyrrolidinones[v]. Moreover, a studyshowed the cyclization of aniline with 1,3-dichloropropane to form a *N*-phenyl-azetidine derivative[vi]. Also, some azetidine-pyrimidine derivatives were prepared from (+)-diethyltartrate and NaN_3[vii]. Other report

showed the cyclization of some γ-amino alcohols in the presence of 1,1′-carbonyldiimidazole to form several cis-substituted azetidines[viii]. Recently, some (+)- and(-)-Azetidine-2-carboxylic Acid were prepared from 3-Bromo-propan-1-ol and 1-Phenyl-ethylamine[ix]. All these reports showed the preparation of several azetidine derivatives using different protocols; however, some of these methods use reagents that can be expensive, dangerous and require specific conditions. Therefore, the aim of this study was synthetizing a three azetidine derivatives using some chemical strategies

EXPERIMENTAL

2.1 General methods

All the reagents used in this study were purchased from Sigma-Aldrich Sigma-Aldrich Co., Ltd. The melting point for compounds was evaluated on an Electrothermal (900 model). Infrared spectra (IR) were determined using KBr pellets on a Perkin Elmer 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 MHz (megahertz) in $CDCl_3$ (deuterated chloroform) using TMS (tetramethylsilane) as an internal standard. EIMS (electron impact mass spectroscopy) spectra were determined using a Finnigan Trace Gas Chromatography Polaris Q-Spectrometer. Elementary analysis data were determined from a Perkin Elmer Ser. II CHNS/02400 elemental analyzer.

2.2 Chemical Synthesis

N-(3-Ethynyl-phenyl)-benzamide (2)

A solution of 3-ethynylanyline (100 mg, 0.85 mmol), benzoic acid (105 mg, 0.86 mmol) and boric acid (55 mg, 0.89 mmol) in 5 ml of methanol was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (4:1) system.; yielding 68 %; m.p. 62-64 ^{o}C; IR (V_{max}, cm^{-1}) 2122 and 1642: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 2.94 (s, 1H), 7.20-7.90 (m, 9H), 8.16 (broad, 1H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 78.20, 84.00, 119.50, 123.92, 124.40, 127.54, 128.00, 129.12, 129.90, 132.44, 136.24, 138.24, 165.82 ppm. EI-MS m/z: 221.08. Anal. Calcd. for $C_{15}H_{11}NO$: C, 81.43; H, 5.01; N, 6.33; O, 7.23. Found: C, 81.40; H, 5.00.

N-[3-(3-Benzoylamino-phenyl)-1-cyclohexyl-4-cyclohexylimino-azetidin-2-ylidene]-4-nitro-benzamide (3)

A solution of compound **2** (200 mg, 0.95 mmol), *N,N′*-diciclohexylcarbodiiimide (196 mg, 0.95 mmol), *p*-nitrobenzoylazide (180 mg, 0.94 mmol)and Copper(II) chloride anhydrous (130 mg, 0.97 mmol) was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (4:1:1) system; yielding 48 %; m.p.157-159^{o}C; IR (V_{max}, cm^{-1}) 3320, 1642 and 1480: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 1.06-1.36 (m, 10H), 1.40-3.28 (m, 12H), 5.46 (m, 1H), 6.40-7.54 (m, 7H), 7.86-8.08 (m, 6H), 8.20 (broad, 1H), 8.40 (m, 2H) ppm. ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 23.02, 24.42, 25.43, 26.06, 26.32, 29.61, 55.70, 58.32, 59.10, 115.81, 117.32, 124.19, 124.48, 127.00, 128.00, 129.14, 130.90, 132.44, 133.36, 135.14, 135.32, 137.80, 142.62, 152.50, 164.90, 165.82, 175.82 ppm. EI-MS m/z: 591.28. Anal. Calcd. for $C_{35}H_{37}N_5O_4$: C, 71.05; H, 6.30; N, 11.84; O, 10.82. Found: C, 71.00; H, 6.28.

N-[1-Cyclohexyl-4-cyclohexylimino-3-(hydroxy-phenyl-methyl)-azetidin-2-ylidene]-4-nitro-benzamide (5)

A solution of 1-phenyl-2-propyn-1-ol (120 µl, 0.99 mmol), *N,N′*-diciclohexylcarbodiiimide (196 mg, 0.95 mmol), *p*-nitrobenzoylazide (180 mg, 0.94 mmol)and Copper(II) chloride anhydrous (130 mg, 0.97 mmol) was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:water (5:1) system; yielding 56 %; m.p.210-212^{o}C; IR (V_{max}, cm^{-1}) 3400, 3320 and

1482: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H: 1.06-1.36 (m, 10H), 1.40-3.19 (m, 12H), 3.22 (m, 1H), 4.96 (m, 1H), 5.34 (broad, 1H), 7.30-8.40 (m, 9H), ^{13}C NMR (300 MHz, Chloroform-*d*) δ_C: 23.02, 24.40, 25.42, 26.02, 26.30, 29.60, 57.90, 58.64, 59.84, 74.22, 124.22, 128.34, 128.94, 129.92, 131.11, 137.70, 140.22, 141.80, 152.52, 167.44, 175.93ppm. EI-MS m/z: 502.25. Anal. Calcd. for $C_{29}H_{34}N_4O_4$: C, 69.30; H, 6.82; N, 11.15; O, 12.73. Found: C, 69.28; H, 6.80.

4-[1-Cyclohexyl-2-cyclohexylimino-4-(4-nitro-benzoylimino)-azetidin-3-yl]-butyric acid(7)

A solution of 5-hexynoic acid (110 µl, 0.99 mmol),*N*,*N*′-diciclohexylcarbodiiimide (196 mg, 0.95 mmol), *p*-nitrobenzoylazide (180 mg, 0.94 mmol) and Copper(II) chloride anhydrous (130 mg, 0.97 mmol) was stirring for 72 h at room temperature. The mixture obtained was dried under reduced pressure and purified by crystallization using the methanol:hexane:water (4:2:1) system.; yielding 56 %; m.p.185-187^{o}C; IR (V_{max}, cm^{-1}) 3322, 1712, 1642 and 1482: ^{1}H NMR (300 MHz, Chloroform-*d*) δ_H:1.06-1.36 (m, 10H), 1.40-1.64 (m, 10H), 1.76-2.44 (m, 6H), 3.10-3.20 (m, 2H), 5.16 (m, 1H), 8.02-8.08 (m, 4H), 9.92 (broad, 1H) ppm.^{13}C NMR (300 MHz, Chloroform-*d*) δ_C:22.70, 23.00, 24.42, 25.40, 26.02, 26.30, 28.00, 29.60, 34.54, 51.62, 57.90, 58.64, 124.20, 131.12, 139.22, 142.16, 152.52, 168.93, 175.98, 178.32ppm. EI-MS m/z: 482.57. Anal. Calcd. for $C_{26}H_{34}N_4O_5$: C, 64.71; H, 7.10; N, 11.61; O, 16.58. Found: C, 64.70; H, 7.08.

Physicochemical parameters

The theoretical electronic properties, such as HOMO (Highest Occupied Molecular Orbital), LUMO (Lowest Unoccupied Molecular Orbital) energy, and HBD (hydrogen bond donor groups) and HBA (Hydrogen Bond Acceptor groups) and) were evaluated using both SPARTAN'06 and LigandScoutprograms[x,xi].

RESULTS AND DISCUSSION

In this investigation, three azetidine derivatives were using several strategies; the first stage was achieved via synthesis of a N-(3-Ethynyl-phenyl)-benzamide; here, it is important to mention that several benzamide derivatives have been prepared via hydrolysis of aromatic nitriles, interconversions of carboxylic acid derivatives[xii], rearrangement of oximes[xiii], addition[xiv], and other ways. However, some protocols involve expensive reagents that require special conditions for handling. In this investigation, N-(3-Ethynyl-phenyl)-benzamide was prepared from 3-ethynylanyline and benzoic acid in the presence of boric acid; it is noteworthy that the catalyst has been used as catalyst to synthesis of some amide derivatives[xv].

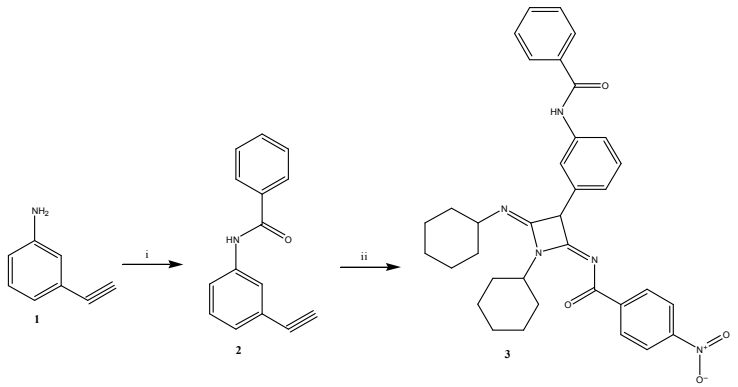

Figure 1. Synthesis of N-[3-(3-Benzoylamino-phenyl)-1-cyclohexyl-4-cyclohexylimino-azetidin-2-ylidene]-4-nitro-benzamide(**3**). Reaction of 3-ethynylanyline (**1**) with benzoic acid (i) to form N-(3-Ethynyl-phenyl)-benzamide (**2**). Then, **3** was prepared fromcompound **2,** *N*,*N*′-diciclohexylcarbodiiimide and *p*-nitrobenzoylazide (ii).

The ^{1}H NMR spectrum of **2**showed several signals at 2.94 ppm for alkyne group; at 7.20-7.90 ppm for phenyl groups; at 8.16 ppm for amide group. ^{13}C NMR spectra showed chemical shifts at 78.20-84.00 ppm for alkyne group; at 119.50-138.24 ppm for phenyl groups; at 165.82 ppm for amide group. Finally, the mass spectrum from **2**showed a molecular ion (m/z) 221.08.

Preparation of azetidine derivatives

There are studies that show the preparation of several azetidine derivatives using different reagents as catalyst such as chloroacetyl chloride[xvi], sodium bis(trimethylsilyl)amide[xvii], 1,4-diazabicyclo[2.2.2]octane[xviii], $Mn(OAc)_2$[xix], CuI[xx], (tert.Butylimino)tris(pyrrolidino)-phosphorane[xxi] and others. In this study, anazetidine derivative (**3**) was prepared using the three components system (compound **2**, N´N-diciclohexylcarbodiimideand *p*-nitrobenzoylazideusingCopper(II) chloride as catalyst (Figure 1). Reaction mechanism to formation of **3** involves a 2 +2 addition as intermediary product (Figure 2).

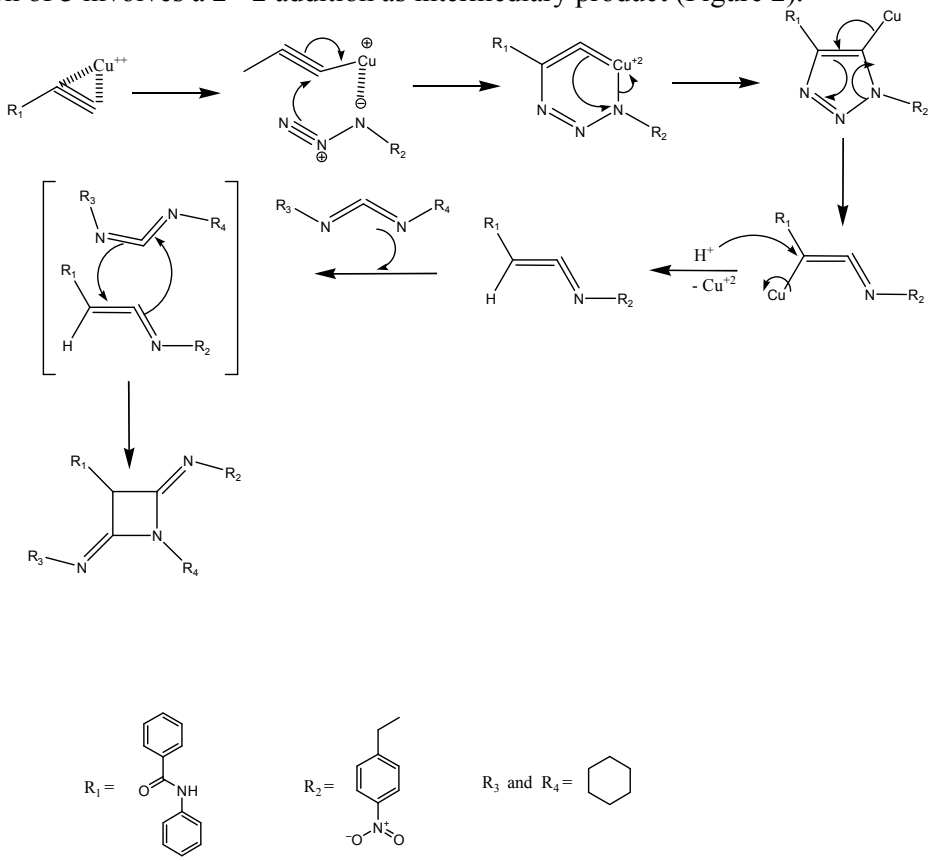

Figure 2. Reaction mechanism involved in the synthesis of an azetidine derivative.

In addition, the ^{1}H NMR spectrum of**3**showed several signals at 1.06-3.28 ppm for both cyclohexane rings; at 5.46 ppm for azetidine ring; at 6.40-8.08 and 8.40 ppm for phenyl groups; at 8.20 ppm for amino group. ^{13}C NMR spectra showed chemical shifts at 23.02-29.61 and 58.32-59.10 ppm for both cyclohexane rings; at 57.70, 135.14 and 164.90 ppm for azetidine ring; at 115.81-133.36, 135.36-152.50 ppm for phenyl groups; at 165.82-175.82 ppm for amide groups. In addition, the mass spectrum from **3**showed a molecular ion (m/z) 591.28.

On the other hand, a second azetidine derivative (compound **5**) was developed using the multicomponent system (1-Phenyl-prop-2-yn-1-ol, N´N-diciclohexylcarbodiimideand*p*-nitrobenzoylazide) in the presence of Copper(II) chloride (Figure 3).

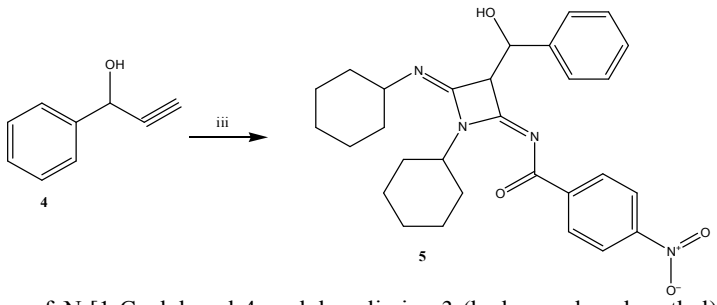

Figure 3. Preparation of N-[1-Cyclohexyl-4-cyclohexylimino-3-(hydroxy-phenyl-methyl)-azetidin-2-ylidene]-4-nitro-benzamide (**5**) from 1-phenyl-2-propyn-1-ol, *N′*-diciclohexyl- carbodiiimide and *p*-nitrobenzoylazide (iii) in presence of Copper(II).

The ^{1}H NMR spectrum of **5**showed some signals at 1.06-3.19 ppm for both cyclohexane rings; at 3.22 ppm for azetidine ring; at 4.96 ppm for methylene bound to both hydroxyl and phenyl groups; at 5.34 ppm for hydroxyl group; at 7.30-8.40 ppm for phenyl groups.^{13}C NMR spectra showed chemical shifts at23.02-58.64 ppm for cyclohexane rings; at 59.84, 137.70 and 167.44 ppm for azetidine ring; at 74.22 ppm for methylene bound to both hydroxyl and phenyl groups; at 124.22-131.11 and 140.22-152.52 ppm for phenyl groups; at 175.93 ppm for amide group. In addition, the mass spectrum from **5**showed a molecular ion (m/z) 502.25.

Finally, a third azetidine derivative (compound **7**) was prepared via the three component system (Hex-5-ynoic acid, *N′N*-diciclohexylcarbodiimide and *p*-nitrobenzoylazideusingCopper(II) chloride as catalyst in mild conditions (Figure 4).

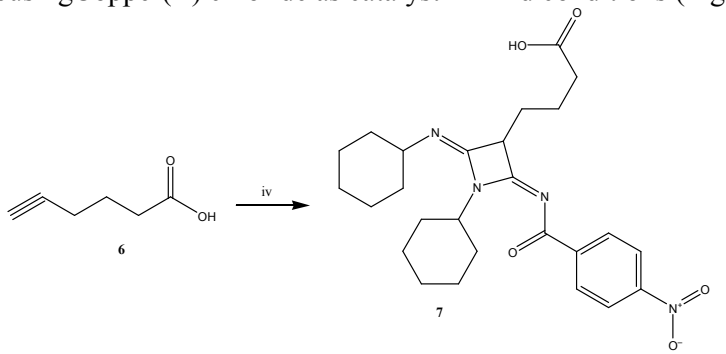

Figure 4.Synthesis of 4-[1-Cyclohexyl-2-cyclohexylimino-4-(4-nitro-benzoylimino)-azetidin-3-yl]-butyric acid (**7**) from5-hexynoic acid,*N*,*N′*-diciclohexylcarbodiiimideand *p*-nitrobenzoylazide (iv) using Copper(II) as catalyst.

The ^{1}H NMR spectrum of **7**showed several signals at 1.06-1.64 and, 3.10-3.20 ppm for both cyclohexane rings; at 1.76-2.44 ppm for arm bound to both carboxyl group and azetidine ring; at 5.16 ppm for azetidine ring; at 8.02-8.08 ppm for phenyl groups; at 9.92 ppm for carboxyl group.^{13}C NMR spectra showed chemical shifts at 22.70, 28.00 and 34.54 ppm for arm bound to both carboxyl group and azetidine ring; at 23.00-26.30, 29.60 and 57.90-58.64 ppm for both cyclohexane rings; at 51.62, 139.22 and 168.93 ppm for azetidine ring; at 124.20-131.12 and 142.16-152.52 ppm for phenyl groups; at 175.98 ppm for amide group; at 178.32 ppm for carboxyl group. Additionally, the mass spectrum from **7**showed a molecular ion (m/z) 482.57.

Theoretical evaluation of physicochemical parameters **of compounds 3**, **5** and **7.**There are reports that indicate that frontier orbitals (HOMO-LUMO) may be related to biological

activity exerted by some compounds on several cells target[xxii-xxiv]; therefore, in this study, HOMO LUMO orbitals were determinate using Spartan 0´6 program[x]. The results are shown in the Figure 5 and Table 1 indicate differences in both HOMO and LUMO values for compounds **3**, **5** and **7**.

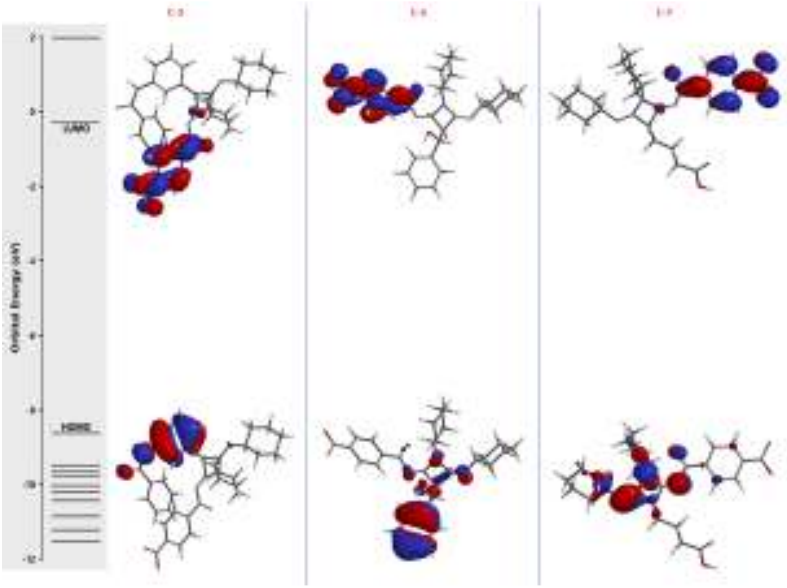

Figure 5. Electronic parameters (HOMO and LUMO) of the compounds **3**(C-3), **5**(C-5) and **7**(C-7) using the Spartan 0´6 model.

Table 1. Theoretical evaluation of physicochemical parameters involved in the chemical structure of compounds **3**(C-3), **5** (C-5) and **7**(C-7) usingSPARTAN'06 software.

Parameters	C-3	C-5	C-7
Polarizability (cm^3)	86.46	78.91	76.71
PSA	49.71	40.12	62.02
LogP	7.42	6.08	5.28
Dipole moment (debyte)	7.44	4.68	3.97
HBD	1	1	1
HBA	5	4	4
HOMO (eV)	-8.49	-8.61	-9.12
LUMO (eV)	2.35	2.36	2.17

HBD (hydrogen bond donors); HBA (hydrogen bond acceptors); PSA (polar surface area).

In addition, to evaluate the different electro-donation ability of compounds **3**, **5** and **7**, some electronic parameters such as HBD (hydrogen bond donors) and HBA (hydrogen bond acceptors) were determinate using a previously method reported[x]; the results indicated that compound **3** has a different electron-donation ability compared with **5** and **7**(Table 1).Analyzing these results and other reports which suggest that these physicochemical parameters may be related to lipophilicity degree; in this study, the lipophilicity degree of compounds **3**, **5** and **7** was determined using a previously reported method[xxv-xxvii]. The results showed a higher LogP value for the compound **3** compared with **5** and **7** which is translated as higher lipophilicity degree.

Pharmacophore ligand model

Several chemical models have been used to determine the three-dimensional orientation adopted by the functional groups of a molecule to predict its interaction with several biomolecules[xxviii]; for example, the use of a pharmacophore model which can furnish a new

insight to design novel molecules that can enhance or inhibit the function of a biological target which can be useful in new drug discovery. Analyzing this premise in this study, the LigandScoutsoftware[xi] was used to develop a pharmacophore model for compounds **3**,**5** and**7**(Figure 6). The results showed that functional groups involved in the compounds **3**,**5** and**7**could interact via hydrophobic contacts or as hydrogen bond acceptors or as hydrogen bond donor with some biomolecules.

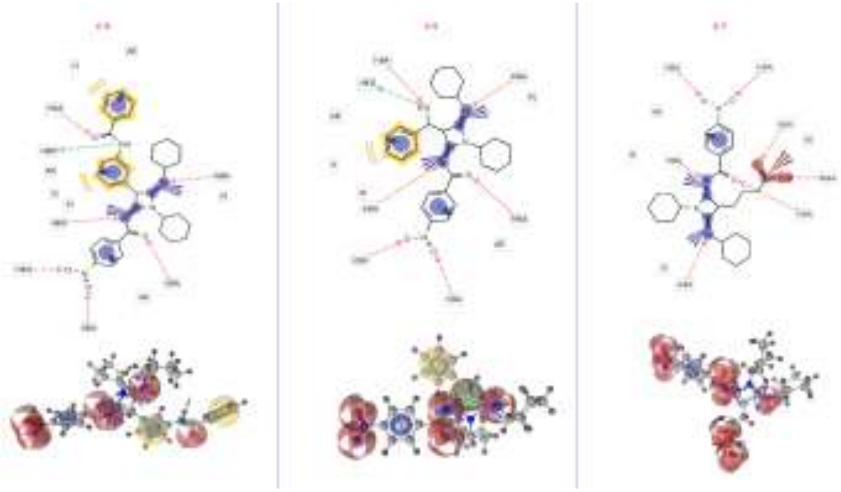

Figure 6 Determination of physicochemical parameters: HBD (hydrogen bond donors); HBA (hydrogen bond acceptors) involved in the chemical structure of compounds **3**(C-3), **5**(C-5) and **7**(C-7) using LigandScout program.

CONCLUSIONS

In this study, the preparation of three azetidine derivatives using some chemical strategies is reported. The protocols used include reagents that are not dangerous and do not require special conditions.

CONFLICTS OF INTEREST

None

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