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FACILE SYNTHESIS OF TWO ADAMANTYL DERIVATIVES USING SOME CHEMICAL STRATEGIES.

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ABSTRACT
There are several reports for synthesis of adamantyl derivatives using some protocols; however, these methods use some reagents which could be dangerous and require special conditions. The aim of this investigation was to synthesize two new adamantyl derivatives (**7** or **8**) from 1-Adamantyl bromomethyl ketone using some chemical strategies. The chemical structure was determinate through NMR spectroscopic analysis. The results showed a higher yield from **7** compared with **8**. In conclusion in this study, a facile method for preparation of either **7** or **8** is reported.

KEYWORDS: Adamantyl, imidazole, Copper(II).

INTRODUCTION
For several years, some adamantyl derivatives have been synthesized using different methods[i-v]; for example, the preparation of *N*-acyl adamantane-1-carbohydrazide from 1-adamantanecarbonyl chloride and carboxylic acid hydrazide[vi]. Besides, and adamantyl acetate was synthesized via reaction of 1-adamantanol with acetic anhydride in the presence of zinc chloride[vii]. Other data showed the preparation of an adamantane-1-carbaldehyde from adamantanemethanol and Oxalyl chloride[viii]. In addition, a study display the reaction of 5-adamantyl-4-amino-3-mercapto-1,2,4-triazole with phosphorus oxychloride to form the compound 6-methyl-3-(tricyclo[3,3,1,13,7]decan-1-yl)-1,2,4-triazolo[3,4-b][1,3,4]thia-diazole[ix]. Besides, a 5-(1-Adamantyl)-4-phenyl-2- (4-substituted piperazine-1-ylmethyl)-1,2,4-triazoline-3-thione were prepared from 5-(1-adamantyl)-4-phenyl-1,2,4-triazoline-3-thione (compound 5) and 1-substituted piperazines/formaldehyde[x]. Other study showed the binding

of an adamantyl derivative to fullerene (60) in the presence of iodide and 1,8-diazabicyclo[5.4.0]undec-7-ene[xi]. Recently, a 1-Adamantylcarbonylamino)-2-aryl-4-thiazolidinone was synthesized via reaction of an arylideneamino derivative with mercaptoacetic acid in benzene[xii]. All these data show various protocols which use some reagents that can be dangerous and require special conditions such as differences in pH and higher temperatures. Therefore, the aim of this study was to prepare two adamantyl derivatives (compounds **7** and **8**) were prepared using some chemical strategies.

EXPERIMENTAL

General methods

The compound (*E*)-N1-(1- phenylethylidene)ethane-1,2-diamine was prepared using a previously method reported[xiii]. Besides, starting materials were purchased from commercial suppliers (Sigma-Aldrich). NMR spectra were recorded on a Varian VXR300/5 FT apparatus (300 MHz/$CDCl_3$) using tetramethylsilane as an internal standard. Electron Ionization mass spectrometry (EIMS) was recorder on a Finnigan PolarisQ ion trap mass spectrometer. Melting-point (m.p.) was determinate on an electrothermal-900 model apparatus. The infrared spectrum (IR) was determinate on a thermo-scientific iSOFT/IR device. Elemental analysis was determined using a PerkinElmer apparatus (Ser. II CHNS / 02400).

Chemical synthesis

Preparation of 1-(1-adamantyl)-2-imidazol-1-yl-ethanone (3)

In a round bottom flask (10 ml), 1-Adamantyl bromomethyl ketone (200 mg, 0.78 mmol), imidazole (55 mg, 80 mmol), Copper(II) chloride (105 mg, 0.78 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 68% of product; m.p. 260-262 ^{0}C; IR (V_{max}, cm^{-1}) 3168, 3080 and 1712: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.76-1.88 (m, 6H), 1.96-2.00 (m, 6H), 2.04-2.12 (m, 3H), 5.50 (s, 2H), 7.52 (d, 1H, J = 1.60 Hz), 7.56 (d, 1H, J = 1.60 Hz), 8.82 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 29.34, 34.45, 38.86, 46.94, 54.66, 120.52, 124.90, 137.85, 207.40 ppm. EI-MS m/z: 244.15. Anal. Calcd. for $C_{15}H_{20}N_2O$. C, 73.74; H, 8.25; N, 11.47, O, 6.55. Found: C, 73.72; H, 8.22.

Preparation of 1-(1-adamantyl)-2-(2-methylimidazol-1-yl)ethanone (4)

In a round bottom flask (10 ml), 1-Adamantyl bromomethyl ketone (200 mg, 0.78 mmol), 2-methylimidazole (65 mg, 80 mmol), Copper(II) chloride (105 mg, 0.78 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 56% of product; m.p. 238-240 ^{0}C; IR (V_{max}, cm^{-1}) 3168, 3080, 1710 and 1470: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 1.60-1.88 (m, 12H), 2.22 (m, 3H), 2.70 (s, 3H), 7.00-7.64 (m, 2H), 8.22 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 15.30, 29.44, 35.24, 41.00, 41.22, 117.74, 130.62, 148.72, 175.12 ppm. EI-MS m/z: 258.17. Anal. Calcd. for $C_{16}H_{22}N_2O$. C, 74.38; H, 8.58; N, 10.84, O, 6.19. Found: C, 74.35; H, 8.56.

Synthesis of 1-(1-adamantyl)-2-[(4R,5R,6S)-5-(hydroxymethyl)-10,12-diazatricyclo [7.3.0.04,6]dodeca-1(9),11-dien-10-yl]ethenone (5)

In a round bottom flask (10 ml), compound **3** (200 mg, 0.82 mmol), (1*R*,8*S*,9*s*)-Bicyclo[6.1.0]non-4-yn-9-ylmethanol (120 mg, 0.80 mmol), Copper(II) chloride (110 mg, 0.81 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was

evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 53% of product; m.p. 176-178 ^{0}C; IR (V_{max}, cm^{-1}) 3400, 3166, 3080, 1712 and 1467: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.88-1.30 (m, 3H), 1.36-1.44 (m, 6H), 1.62 (m, 2H), 1.64 (m, 3H), 1.68 (m, 2H), 1.70-1.94 (m, 6H), 2.40-2.52 (m, 4H), 3.30-3.50 (m, 2H), 4.68 (s, 2H), 5.12 (broad, 1H), 6.70 (s, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 15.60, 20.26, 2056, 26.80, 27.82, 30.06, 30.62, 31.87, 36.66, 38.60, 47.44, 54.93, 62.50, 120.40, 139.80, 144.42, 206.82 ppm. EI-MS m/z: 368.24. Anal. Calcd. for $C_{23}H_{32}N_2O_2$. C, 74.96; H, 8.75; N, 7.60, O, 8.68. Found: C, 74.92; H, 8.74.

Preparation of 1-(1-adamantyl)-2-[(4R,5R,6S)-5-(hydroxymethyl)-11-methyl-10,12-diazatricyclo[7.3.0.04,6]dodeca-1(9),11-dien-10-yl]ethenone (6)

In a round bottom flask (10 ml), compound **4** (200 mg, 0.77 mmol), (1*R*,8*S*,9*s*)-Bicyclo[6.1.0] non-4-yn-9-ylmethanol (120 mg, 0.80 mmol), Copper(II) chloride (110 mg, 0.81 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 45% of product; m.p. 76-78 ^{0}C; IR (V_{max}, cm^{-1}) 3400, 3166, 3080 and 1712:: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.88-1.30 (m, 3H), 1.36-1.44 (m, 6H), 1.62 (m, 2H), 1.64 (m, 3H), 1.68 (m, 2H), 1.70-1.94 (m, 6H), 2.34 (s, 3H), 2.46-2.56(m, 4H), 3.30-3.50 (m, 2H), 4.68 (s, 2H), 5.12 (broad, 1H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 13.68, 15.60, 20.26, 2056, 26.80, 27.32, 27.82, 30.06, 30.62, 32.40, 36.66, 38.60, 47.44, 54.72, 62.50, 119.56, 139.70, 144.02, 206.60 ppm. EI-MS m/z: 382.26. Anal. Calcd. for $C_{24}H_{34}N_2O_2$. C, 75.35; H, 8.96; N, 7.32, O, 8.36. Found: C, 75.32; H, 8.94.

Synthesis of [(4S,5R,6R)-12-[(E)-C-(1-adamantyl)-N-[2-[(Z)-1-phenylethylideneamino] ethyl]car-bonimidoyl]-11-methyl-10,12-diazatricyclo[7.3.0.04,6]dodeca-1(9),10-dien-5-yl]me-thanol (7)

In a round bottom flask (10 ml), compound **5** (200 mg, 0.54 mmol), (E)-N^1-(1-phenylethylidene)ethane-1,2-diamine (90 mg, 0.55 mmol), boric acid (40 mg, 0.65 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 72% of product; m.p. 110-112 ^{0}C; IR (V_{max}, cm^{-1}) 3400, 3162, 3080 and 1710: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.88 (m, 2H), 1.24 (m, 3H), 1.30 (m, 1H), 1.60 (m, 6H), 1.62 (m, 2H), 1.66 (m, 3H), 1.68 (m, 2H), 2.04 (m, 3H), 2.24 (s, 3H), 2.44-2.52 (m, 4H), 3.30-3.50 (m, 2H), 3.74-3.76 (m, 4H), 4.34 (s, 2H), 5.12 (broad, 1H) ppm. 7.36-7.60 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 14.82, 15.32, 19.80, 20.20, 26.92, 30.06, 30.54 30.64, 31.86, 32.62, 37.24, 40.76, 49.22, 51.90, 52.60, 62.50, 120.20, 127.55, 127.90, 128.16, 132.74, 141.46, 142.52, 160.78, 183.54 ppm. EI-MS m/z: 512.35. Anal. Calcd. for $C_{33}H_{44}N_4O$. C, 77.30; H, 8.65; N, 10.93, O, 3.12. Found: C, 77.28; H, 8.62.

Preparation of [(4S,5R,6R)-12-[(E)-C-(1-adamantyl)-N-[2-[(Z)-1-phenylethylidene-amino]ethyl]carbonimidoyl]-11-methyl-10,12-diazatricyclo[7.3.0.04,6]dodeca-1(9),10-dien-5-yl]methanol (8)

In a round bottom flask (10 ml), compound **6** (200 mg, 0.52 mmol), (E)-N^1-(1-phenylethylidene)ethane-1,2-diamine (90 mg, 0.55), boric acid (40 mg, 0.65 mmol) and 5 ml of methanol were stirred at room temperature for 72 h. Then, the solvent was evaporated under reduced pressure and following the product was purified via crystallization using the methanol:hexane:water (4:2:1) system; yielding 54% of product; m.p. 132-134 ^{0}C; IR (V_{max}, cm^{-1}) 3402, 3164, 3080, 1712 and 1465: ^{1}H NMR (300 MHz, $CDCl_3$-*d*) δ_H: 0.88 (m, 2H), 1.24 (m, 3H), 1.30 (m, 1H), 1.60 (m, 6H), 1.62 (m, 2H), 1.66 (m, 3H), 1.68 (m, 2H), 2.04 (m, 3H), 2.24 (s, 3H), 2.34 (s, 3H), 2.50-2.58 (m, 4H), 3.30-3.50 (m, 2H), 3.74-3.76 (m, 4H), 4.34 (s,

2H), 5.12 (broad, 1H) ppm. 7.36-7.60 (m, 5H) ppm. ^{13}C NMR (300 Hz, $CDCl_3$) δ_C: 13.42, 14.82, 15.34, 19.80, 20.20, 27.42, 30.06, 30.54 30.64, 32.36, 32.62, 37.24, 40.76, 47.02, 51.90, 52.60, 62.50, 119.30, 127.55, 127.90, 128.16, 141.46, 142.52, 146.64, 160.78, 184.32 ppm. EI-MS m/z: 526.36. Anal. Calcd. for $C_{34}H_{46}N_4O$. C, 77.52; H, 8.80; N, 10.64, O, 3.04. Found: C, 77.50; H, 8.77.

Results and Discussion

There are several reports on methods for the synthesis of adamantyl derivatives[i-xii]; However, these protocols use different reagents that are difficult to handle and require special conditions such as differences in pH and higher temperatures. Analyzing these data in this investigation two adamantyl derivatives (compounds **7** and **8**) were prepared as follows.

3.1 Synthesis of an imidazole-adamantyl derivative (3)

Several studies[xiv, xv], have been published on the N-alkylation of azoles with halo ketones; for example, the synthesis of 1-(1-adamantyl)-2-(1-imidazolyl)ethanone via reaction of imidazole with 1-adamantyl bromomethyl ketone in the presence of dimethylformamide at 0 ^{o}C for 7 days[xvi]. Analyzing this data in this study, the 1-(1-adamantyl)-2-(1-imidazolyl)ethenone (compound **3**) was prepared using different conditions. In this way, the imidazole reacted with 1-Adamantyl bromomethyl ketone using Copper(II) chloride as catalyst at room temperature to form the compound **3**. It is noteworthy that both ^{1}H and ^{13}C, NMR signals for this compound were in similar manner to signals previously reported for 1-(1-adamantyl)-2-(1-imidazolyl)ethanone[xvi] as follows: The ^{1}H NMR for compound **3** showed several signals at 1.76-2.12 ppm for adamantane fragment; at 5.50 ppm for methylene bound to both imidazole ring and ketone group; at 7.52-8.82 ppm for imidazole ring. The ^{13}C NMR spectra display chemical shifts at 29.34-46.94 ppm for adamantane fragment; at 54.66 ppm for methylene group bound to both imidazole ring and ketone group; at 120.52-137.85 for imidazole ring; at 207.40 ppm for ketone group. Besides, the mass spectrum from **3** showed a molecular ion (m/z) 230.14.

On the other hand, in an alternative experimental, 2-methylimidazol reacted with 1-Adamantyl bromomethyl ketone using boric acid in the presence of boric acid to synthesis of compound **4**. The H NMR for compound **4** showed several signals at 15.30 ppm for methyl group; at 1.76-2.12 ppm for adamantane fragment; at 5.50 ppm for methylene bound to both imidazole ring and ketone group; at 7.52-8.82 ppm for imidazole ring. The ^{13}C NMR spectra display chemical shifts at 12.82 ppm for methyl group; at 29.34-46.94 ppm for adamantane fragment; at 53.92 ppm for methylene group bound to both imidazole ring and ketone group; at 120.52-137.85 for imidazole ring; at 207.23 ppm for ketone group. In addition, the mass spectrum from **4** showed a molecular ion (m/z) 244.15.

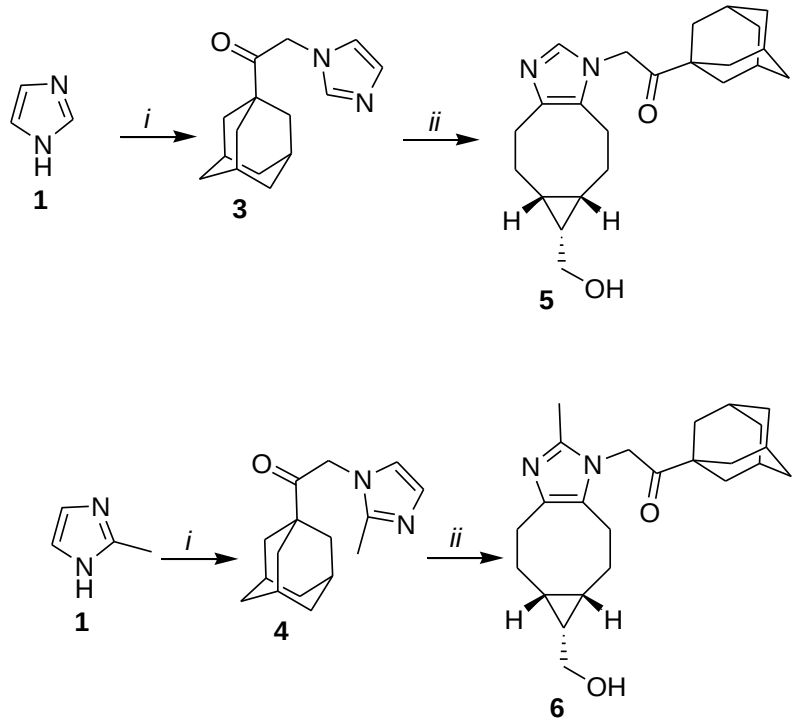

Figure 1. Synthesis of adamantyl-diazatricyclo derivatives (**5** or **6**). *Reagents and conditions i* = 1-Adamantyl bromomethyl ketone, Copper(II) chloride. MeOH, rt, 72 h. *ii* = Copper(II) chloride, MeOH, rt 72 h. rt = room temperature.

Synthesis of two adamantyl-diazatricyclo derivatives

It is important to mention that several methods have been used for the synthesis of diazatricyclo analogs; these protocols use some reagents such as sodium cyanoborohydride[xvii], phthalic acid dichloride[xviii], Mn(III)[xix], $CO/CO_2(CO)_8$[xx], and others. In this study two adamantyl-diazatricyclo derivatives were prepared via reaction of either compounds **3** or **4** with 1*R*,8*S*,9*s*)-Bicyclo[6.1.0]non-4-yn-9-ylmethanol in the presence of Copper(II) chloride to form **5** or **6**. The ^{1}H NMR for compound **5** showed several signals at 0.88-1.30, 1.62, 1.68 and 2.40-2.52 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 1.36-1.44, 1.64 and 1.70-1.94 ppm for adamantane fragment; at 3.30-3.50 ppm for methylene bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 4.68 ppm for methylene group bound to both imidazole ring and ketone group; at 5.12 ppm for hydroxyl group; at 6.70 ppm for imidazole ring. The ^{13}C NMR spectra display chemical shifts at 15.60-26.80 and 30.06-31.87 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 27.82 and 36.66-47.44 ppm for adamantane fragment; at 54.93 ppm for methylene group bound to both imidazole ring and ketone group; at 62.50 ppm for methylene group bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 120.40 and 144.42 ppm for imidazole ring; at 206.82 ppm for ketone group. Besides, the mass spectrum from **5** showed a molecular ion (m/z) 368.24.

On the other hand, the ^{1}H NMR for compound **6** showed several signals at0.88-1.30, 1.62, 1.68 and 2.46-2.56 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 1.36-1.44, 1.64 and 1.70-1.94 ppm for adamantane fragment; at 2.34 ppm for methyl group; at 3.30-3.50 ppm for methylene bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 4.68 ppm for methylene group bound to both imidazole ring fragment and ketone group; at 5.12 ppm for hydroxyl group. The ^{13}C NMR spectra display chemical shifts at 13.68 ppm for methyl group; at 15.60-27.32 and 30.06-32.40 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 27.82 and 36.66-47.44 ppm for adamantane fragment; at 52.72 ppm for methylene bound to both imidazole ring

fragment and ketone group; at 62.50 ppm for methylene group bound to both for Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 119.56-144.02 ppm for imidazole ring; at 206.60 ppm for ketone group. Additionally, the mass spectrum from **6** showed a molecular ion (m/z) 382.26.

Preparation of two imino derivatves

There are several reports in the literature on the synthesis of some imine analogs[xxi-xxiii]. In this study, the synthesis of compounds **7** or **8** were prepared via reaction of either compound **5** or **6** with (E)-N^1-(1- phenylethylidene)ethane-1,2-diamine using boric acid as catalyst.

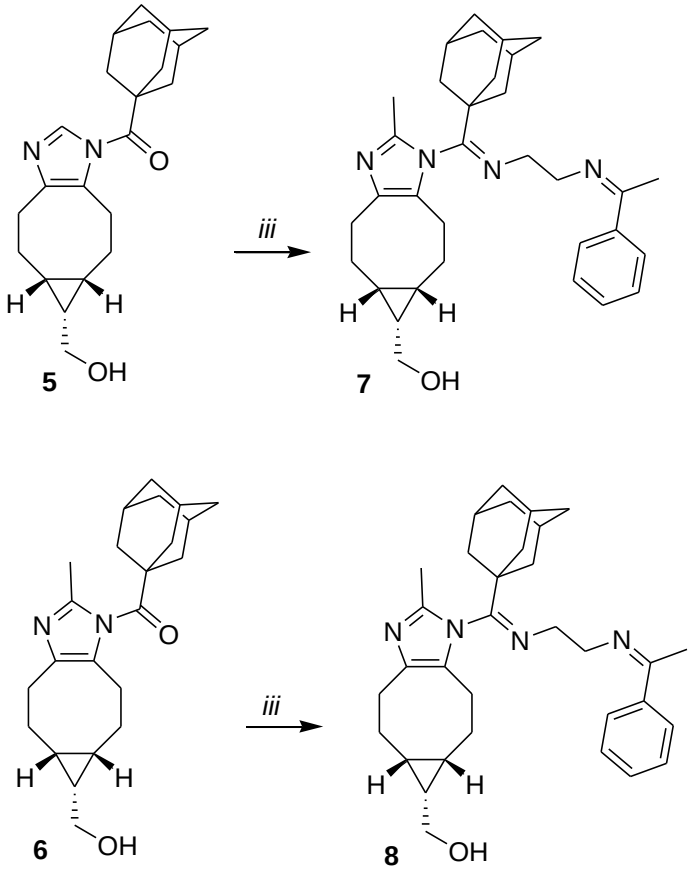

Figure 2. Synthesis of two imino derivatives (**7** or **8**). *Reagents and conditions: iii* = (E)-N^1-(1-phenylethylidene)ethane-1,2-diamine, boric acid, MeOH, rt, 72 h. rt = room temperatures

The ^{1}H NMR for compound **7** showed several signals at 0.88, 1.30, 1.62, 1.68 and 2.44-2.52 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 1.24, 1.60, 1.66 and 2.04 ppm for adamantane fragment; at 2.24 ppm for methyl group; at 3.30-3.50 ppm for methylene bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 3.74-3.76 ppm for methylene bound to both imino and amino groups; at 4.34 ppm for methylene group bound to both imidazole ring and imino group; at 5.12 ppm for hydroxyl group; at 7.36-7.60 ppm for phenyl group. The ^{13}C NMR spectra display chemical shifts at 14.82, 19.80-30.06 and 30.64-31.86 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 15.32 ppm for methyl group; at 30.54 and 32.62-40.76 ppm for adamantane fragment; at 49.22 for methylene bound to both imidazole ring and imino group; at 51.90-52.60 ppm for methylene groups bound to both amino and imino groups; at 62.50 ppm for methylene group bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 120.20 and 132.74-141.46 ppm for imidazole ring; at 127.55-128.16 and 142.52 ppm for phenyl group; at 160.78-183.54 ppm for imino groups. Besides, the mass spectrum from **7** showed a molecular ion (m/z) 512.35.

Finally, The ^{1}H NMR for compound **8** showed several signals at 0.88, 1.30, 1.62, 1.68 and 2.50-2.58 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 1.24, 1.60, 1.66 and 2.04 ppm for adamantane fragment; at 2.24 ppm for methyl bound to both imino and phenyl groups; at 2.34 ppm for methyl group bound to imidazole ring; at 3.30-3.50 ppm for methylene bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 3.74-3.76 ppm for methylene groups bound to both amino and imino groups; at 4.34 ppm for methylene group bound to both imidazole ring and imino group; at 5.12 ppm for hydroxyl group; at 7.36-7.60 ppm for phenyl group. The ^{13}C NMR spectra display chemical shifts at 13.42 ppm for methyl bound to imidazole ring; at 14.62, 19.80-30.06 and 30.64-32.36 ppm for Bicyclo[6.1.0]non-4-ene fragment; at 15.34 ppm for methyl bound to both imino and phenyl groups; at 30.54 and 32.62-40.76 ppm for adamantane fragment; at 47.02 ppm for methylene group bound to both imidazole ring and imino group; at 51.90-52.60 ppm for methylene groups bound to both imino and amino groups; at 62.50 ppm for methylene group bound to both Bicyclo[6.1.0]non-4-ene fragment and hydroxyl group; at 119.30, 141.46 and 146.64 ppm for imidazole ring; at 127.55-128.16 and 142.52 ppm for phenyl group; at 160.78-184.32 ppm for imino groups. Besides, the mass spectrum from **8** showed a molecular ion (m/z) 526.36.

CONCLUSIONS

In this research reported a facile synthesis of two adamantyl derivatives (compounds **7** and **8**) using various chemical strategies; it is important to mention that the reagents used in this method are easy to handle and do not require specific conditions. Besides, it is worth mentioning that analyzing the chemical structure of these compounds, it could be interesting to evaluate their biological activity in some biological model.

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