ISSN 1112-9867

Available online at http://www.jfas.info

SYNTHESIS OF BENZIMIDAZOLE-CYCLOHEXANONE DERIVATIVES

N. Belkheiri[1,*], Z. Belkacem[1], M. Derdour[1], F. Mechrouh[1], R.M. Bachar[1], M. Fodili[1], M. Amari[1,2], P. Hoffmann[3]

[1]Laboratoire de Chimie Organique et des Substances Naturelles, Université Ziane Achour, Djelfa, Algérie

[2] Faculté de Chimie – USTHB – BP32, El-Alia, 16111 Bab Ezzouar, Alger, Algérie

[3]Laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, UMR 5068, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse, Cedex 4, France

Received: 08 December 2017 / Accepted: 14 April 2018 / Published online: 01 May 2018

ABSTRACT

This work reports the synthesis and characterization of new benzimidazole-cyclohexanone derivatives **3a-d, 4a-d** and **5a-d** under different reaction conditions. The intermediates and final compounds were purified and their chemical structures were elucidated using ^{1}H-NMR, ^{13}C-NMR and mass spectral data.

Keywords: Benzimidazole, Cyclohexanone, NMR, Reaction intermediates

Author Correspondence, e-mail: belkheirinadji@yahoo.fr

doi: http://dx.doi.org/10.4314/jfas.v10i2.15

1. INTRODUCTION

Benzimidazole derivatives are of wide interest because of their diverse biological activity and clinical applications, the benzimidazole ring is present in some clinically used drugs, such as proton pump inhibitors, the antiviral enviroxime and the antihistaminic astemizole, but it may also display antimycobacterial, antimicrobial, anticonvulsant, analgesic, anti-inflammatory, anti-diabetic, antiprotozoal, antipsychotic, antioxidant and antitumoral properties[1].

Some of them like thiabendazole, mebendazole or albendazole are widely used asantihelmintic drugs [2], due to their ability to bind selectively with high affinity to the β-

subunit of helminthmicrotubule protein [3]. Benzimidazolone derivatives also cover a broad range of biological activities, including opioid receptor antagonistic [4] or antinociceptive [5] effects, and potassium channel activation [6].

The benzimidazolone and benzimidazolothione ring structures possess a number of interesting biologically properties and constitute a constrained ring system with two nitrogen atoms linked by an ethylene bridge, as diazoles ring system [7,8].

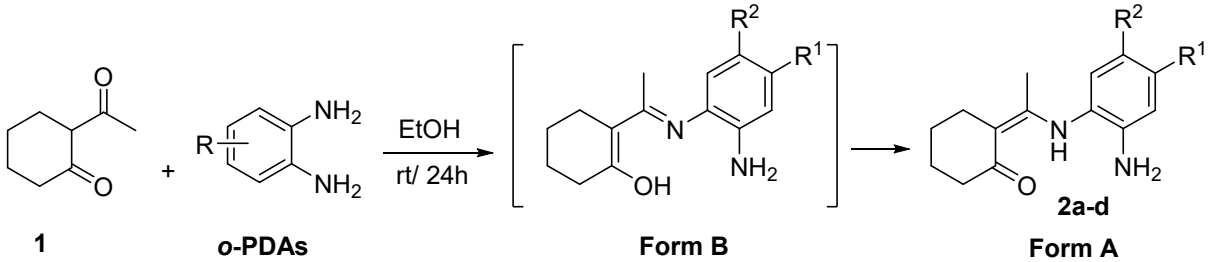
Cyclohexanone-analogous, which designed based on the curcumin corestructure, have been discovered as potential EGFR inhibitors [9], drugs for the treatment of ER-negative breast cancer [10].

2. RESULTS AND DISCUSSION

From this point of view, in the present study, new Benzimidazole-cyclohexanone derivatives were synthesized. We used two-step procedure with different reagents for synthesis of twelve benzimidazole derivatives.

In the first step, A similar procedure involving the addition of *o*-PDAs to 2-acetylbutyrolactone and analogues, was recently used by our group to access benzimidazole-butyrolactone derivatives [11].

By examining a variety of reaction conditions, we have found that the process is usually most efficient using an equimolar mixture of 2- acetylcyclohexanone **1** and *o*-PDAs in ethanol at room temperature. Under these conditions all the intermediates were obtained in good yields(60–80%) and readily isolated by simple recrystallization (Scheme 1). The structures of all these synthons **2a–d** have been established on the basis of ^{1}H and ^{13}C NMR.



a. $R^1 = R^2 = H$ b. $R^1 = CH_3$, $R^2 = H$

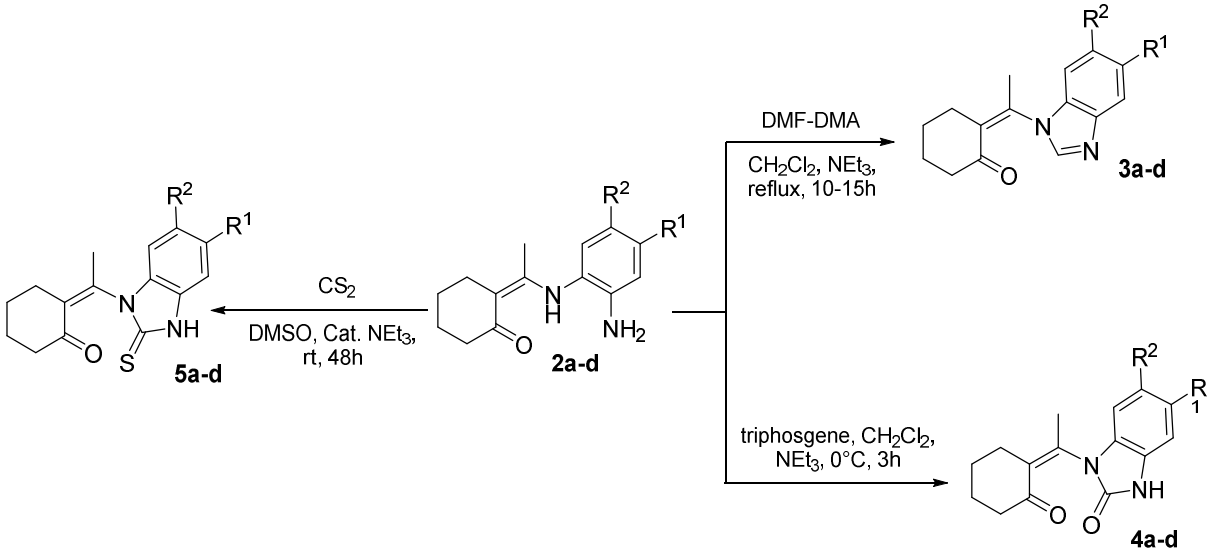
c. $R^1 = Cl$, $R^2 = H$ d. $R^1 = H$, $R^2 = NO_2$

Scheme 1. Synthesis of aminophenylaminoethylidenecyclohexanones **2a-d**

Table 1. Conditions of formation and physical data of **2a-d** in ethanol at 25 °C

Compounds	R^1	R^2	Time(h)	Yield (%)	mp (°C)	Nature and color
2a	H	H	24	60	191-193	Brown powder
2b	CH_3	H	24	65	195-197	Yellow powder
2c	Cl	H	24	73	204-206	White powder
2d	H	NO_2	24	80	207-209	Yellow powder

The next step consisted in the preparation of the benzimidazole ring by treating the isolated (Z)-2-(1-aminoethylidene)cyclohexanones **2a–d** either with *N,N*-dimethylformamide, dimethylacetal (DMF–DMA) in refluxing CH_2Cl_2 in the presence of catalytic amounts of NEt_3 lasting from 10 to 15 h, triphosgene in CH_2Cl_2 and allowed to stir for 3 h starting from 0°C up to room temperature, carbon disulfide in DMSO at room temperature of NEt_3, respectively, benzimidazole **3a–d**, benzimidazolone **4a–d**, or benzimidazole-2-thione **5a–d** attached to a cyclohexanone moiety via a 1-aminoethylidene moiety(Scheme 2)[11].



Scheme 2. Synthesis of benzimidazoles **3a-d**, benzimidazolones **4a-d** and benzimidazolothiones **5a-d**

All compounds **3-5** were characterized by the various spectroscopic methods.

Their physical properties are summarized in table 2.

Table 2. Conditions of formation and physical data of **3-5**

Compounds	R^1	R^2	Temperature	Solvent	Time(h)	Yield (%)	mp (°C)	Nature and color
3a	H	H	reflux	CH_2Cl_2	10	85	173-175	Yellow powder
3b	CH_3	H	reflux	CH_2Cl_2	12	90	202-204	Yellow powder
3c	Cl	H	reflux	CH_2Cl_2	15	75	207-209	Off white powder
3d	H	NO_2	reflux	CH_2Cl_2	12	65	213-215	Yellow powder
4a	H	H	0°C	CH_2Cl_2	3h	90	223-225	Grey powder
4b	CH_3	H	0°C	CH_2Cl_2	3h	70	229-230	Brown powder
4c	Cl	H	0°C	CH_2Cl_2	3h	88	235-236	Yellow powder
4d	H	NO_2	0°C	CH_2Cl_2	3h	90	242-243	White powder
5a	H	H	rt	DMSO	48h	95	225-226	Orange powder
5b	CH_3	H	rt	DMSO	48h	85	234-235	Yellow powder
5c	Cl	H	rt	DMSO	48h	50	231-232	Brown powder
5d	H	NO_2	rt	DMSO	48h	60	242-244	White powder

3. EXPERIMENTAL

All chemicals were obtained from Aldrich. Melting points were taken on a Thomas Hoover apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained with a Bruker AC 300 at 300 MHz (^{1}H) or 75 MHz (^{13}C). The chemical shifts are reported in ppm(δ-scale) relative to internal TMS and coupling constants are reported in Hertz (Hz). High-resolution mass spectrometry HRMS spectra were obtained with a GC TOF Waters and Waters Q / TOF Ultima.

General procedure for synthesis of 2a-d

In 20 mL ethanol, a 2-acetylcyclohexanone (1 mL, 0.01 mol) was reacted with *o*-phenylenediamines (1.08 g, 0.01 mol).The mixture was stirred at room temperature 24 hours under magneticstirring, the compounds precipitate in the reaction media. After filtration under reduced pressure, the corresponding compounds **2a-d** were purified by recrystallization from ethanol.

General procedure for synthesis of 3a-d

An equimolar amount of (Z)-2-(2 Aminophenylamino) ethylidene) cyclohexanones **2a-d** (1.8 mmol) and DMF DMA (1.8 mmol) was allowed to stir under refluxing dichloromethane (20 mL) for 10 to 15 h (the reactions are monitored by TLC) in the presence of few drops of triethylamine. The precipitating products were removed by evaporation and treatment with diethyl ether. The pure compounds **3a-d** were recrystallized from ethanol.

General procedure for synthesis of 4a-d

A mixture of (Z)-2-(2 Aminophenylamino) ethylidene) cyclohexanones **2a-d** (0.02 mol) and trimethylamine (0.04 mol) in dichloromethane (40 mL) was placed in an ice/water bath under constant magnetic stirring. Triphosgene (6.6 mmol) was gradually added over a period of 3 h. The reaction was quenched in ice/water and the product was extracted using dichloromethane (3 x 40 mL). The organic fraction was dried over anhydrous sodium sulfate. Solid products of **4a-d** were obtained upon evaporation of the dichloromethane solution.

General procedure for synthesis of 5a-d

A mixture of (Z)-2-(2 Aminophenylamino) ethylidene) cyclohexanones **2a-d** (2 mmol) and thiosulfide (2 mmol) in DMSO (30 mL) was stirred at room temperature for 48 h in the presence of a few drops of NEt_3. The reaction mixture was then slowly versed in ice/water under stirring. Compounds **5a-d** were precipitated, collected by filtration and washed with water.

(Z)-2-[1-(2-Aminophenylamino)ethylidene)]cyclohexanone 2a

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.60-1.70 (m, 4H, CH_2), 1.76 (s, 3H, CH_3), 2.26 and 2.36 (2t, *J* 3.7 Hz, 4H, CH_2), 3.75 (s, 2H, NH_2), 6.80-7.30 (m, 4H, Harom), 9.26 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.5 (CH_3), 22.8, 26.5, 27.4 and 41.0 (4 x CH_2), 99.5 (CO-**C**=C), 119.3, 124.5, 126.5, 127.6, 128.4 and 142.8 (Carom), 155.1 [=*C*(CH_3)-NH], 202.4 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{14}H_{18}N_2O+Na]^+$: 253.1330; found: 253.1215.

(Z)-2-[1-(2-Amino-4-methylphenylamino)ethylidene]cyclohexanone 2b

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.64-1.76 (m, 4H, CH_2), 1.15 and 1.72 (2s, 6H, CH_3), 2.20 and 2.26 (2t, *J* 3.7 Hz, 4H, CH_2), 2.95 (s, 2H, NH_2), 7.10-7.80 (m, 3H, Harom), 8.80 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.6 and 24.2 (2 x CH_3), 22.5, 26.4, 27.4 and 40.0 (4 x CH_2), 100.1 (CO-**C**=C), 116.5, 119.2, 122.4, 128.7, 139.1 and 143.4 (Carom), 156.3 [=*C*(CH_3)-NH], 200.8 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{15}H_{20}N_2O+Na]^+$: 267.1550; found: 267.1346.

(Z)-2-[1-(2-Amino-4-chlorophenylamino)ethylidene]cyclohexanone 2c

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.60-1.70 (m, 4H, CH_2), δ 1.80 (s, 3H, CH_3), 2.25 and 2.37 (2t, *J* 4.1 Hz, 4H, CH_2), 3.98 (s, 2H, NH_2), 6.60-7.10 (m, 3H, Harom), 9.16 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.3 (CH_3), 22.5, 26.6, 27.5 and 41.2 (4 x CH_2), 201.4 (CO-**C**=C), 115.6, 118.5, 123.4, 129.8, 134.1 and 145.7 (Carom), 157.3 [=*C*(CH_3)- NH], 201.8 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{14}H_{17}ClN_2O$+Na]$^+$: 287.0908; found: 287.0917.

(Z)-2-[1-(2-Amino-5-nitrophenylamino)ethylidene]cyclohexanone 2d

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.64-1.75 (m, 4H, CH_2), 2.10 (s, 3H, CH_3), 2.24 and 2.37 (2t, *J* 3.6 Hz, 4H, CH_2), 4.00 (s, 2H, NH_2), 6.80-7.70 (m, 3H, Harom), 9.40 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.8 (CH_3), 23.0, 26.2, 27.6 and 39.8 (4 x CH_2), 99.0 (CO-**C**=C), 114.2, 126.1, 125.5, 125.6, 136.1 and 152.6 (Carom), 156.4 [=*C*(CH_3)-NH], 200.5 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{14}H_{17}N_3O_3$+Na]$^+$: 298.1210; found: 298.1140.

(Z)-2-[1-(1*H*-Benzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 3a

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.69-1.74 (m, 4H, CH_2), 1.85 (s, 3H, CH_3), 2.39 and 2.40 (2t, *J* 3.9 Hz, 4H, CH_2), 6.60-7.30 (m, 4H, Harom), 9.30 (s, 1H, N=CH-N); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.5 (CH_3), 22.7, 26.4, 27.3 and 41.2 (4 x CH_2), 100.6 (CO-**C**=C), 115.5, 119.1, 124.4, 126.6, 128.2 and 142.8 (Carom), 153.5 (N=CH-N), 157.0 [=C(CH_3)-N<], 198.9 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{16}N_2O$+Na]$^+$: 263.1214; found: 263.1109.

(Z)-2-[1-(5-Methyl-1*H*-benzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 3b

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.20 and 1.83 (2s, 6H, CH_3), 1.68-1.75 (m, 4H, CH_2), 2.41 and 2.43 (2t, *J* 3.8 Hz, 4H, CH_2), 6.55-7.20 (m, 3H, Harom), 9.32 (s, 1H, N=CH-N); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.2 and 23.6 (2 x CH_3), 22.5, 26.3, 27.1 and 40.6 (4 x CH_2), 99.7 (CO-**C**=C), 115.8, 119.2, 124.5, 126.5, 129.0 and 143.0 (Carom), 153.4 (N=CH-N), 156.5 [=C(CH_3)-N<], 199.8 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{16}H_{18}N_2O$ +Na]$^+$: 277.1302; found: 277.1256.

(Z)-2-[1-(5-Chloro-1*H*-benzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 3c

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.66-1.73 (m, 4H, CH_2), 1.80 (s, 3H, CH_3), 2.40 and 2.42 (2t, *J* 3.9 Hz, 4H, CH_2), 6.52-6.98 (m, 3H, Harom), 9.25 (s, 1H, N=CH-N); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.6 (CH_3), 22.6, 26.5, 27.2 and 41.4 (4 x CH_2), 99.6 (CO-**C**=C), 116.6, 119.6, 123.1, 129.8, 134.7 and 145.2 (Carom), 153.3 (N=CH-N), 156.9 [=C(CH_3)-N<], 199.7 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{15}ClN_2O$+Na]$^+$: 297.0856; found: 297.0804.

(Z)-2-[1-(5-Nitro-1H-benzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 3d

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.70-1.76 (m, 4H, CH_2), 2.10 (s, 3H, CH_3), 2.42 and 2.43 (2t, *J* 3.8 Hz, 4H, CH_2) , 6.52-7.03 (m, 3H, Harom), 9.20 (s, 1H, N=CH-N); ^{13}C NMR (75 MHz, DMSO-d^6): δ 15.2 (CH_3), 22.9, 26.7, 27.5 and 40.5 (4 x CH_2), 99.8 (CO-**C**=C), 113.7, 123.5, 125.1, 125.7, 135.3 and 152.5 (Carom), 153.3 (N=CHN). 156.2 [=C(CH_3)-N], 200.4 (C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{15}N_3O_3$+Na]$^+$: 308.1055; found: 308.0908.

(Z)-1-[1-(2-oxocyclohexylidene)ethyl]-1*H*-benzo[*d*]imidazol-2(3*H*)-one 4a

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.66-1.75 (m, 4H, CH_2), 2.45 (s, 3H, CH_3), 2.28 and 2.44 (2t, *J* 3.8 Hz, 4H, CH_2), 7.10-7.62 (m, 4H, Harom), 9.32 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 19.2 (CH_3), 22.5, 26.3, 27.4 and 40.7 (4 x CH_2), 102.8 (CO-**C**=C), 108.7, 109.5, 121.0, 121.3, 128.4 and 129.2 (Carom), 138.1 [=C(CH_3)- N], 149.8 and 198.9 (2 x C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{16}N_2O_2$+Na]$^+$: 279.1127; found: 279.1093.

(Z)-5-Methyl-1-[1-(2-oxocyclohexylidene)ethyl]-1*H*-benzo[*d*]imidazol-2(3*H*)-one 4b

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.19 and 2.35 (2s, 6H, CH_3), 1.62-1.73 (m, 4H, CH_2), 2.30 and 2.46 (2t, *J* 3.9 Hz, 4H, CH_2), 6.80-7.77 (m, 3H, Harom), 9.29 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 18.7 and 19.2 (2 x CH_3), 22.5, 26.2, 27.4 and 40.9 (4 x CH_2), 100.8 (CO-**C**=C), 109.0, 109.3, 120.5, 121.4, 128.8 and 129.7 (Carom), 138.9 [=C(CH_3)-N], 148.2 and 203.3 (2 x C=O); HRMS (ESI$^+$): m/z calcd for [$C_{16}H_{18}N_2O_2$+Na]$^+$: 293.1304; found: 293.1264.

(Z)-5-Chloro-1-[1-(2-oxocyclohexylidene)ethyl]-1*H*-benzo[*d*]imidazol-2(3*H*)-one 4c

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.64-1.73 (m, 4H, CH_2), 2.15 (s, 3H, CH_3), 2.28 and 2.41 (2t, *J* 3.9 Hz, 4H, CH_2), 7.20-7.82 (m, 3H, Harom), 9.20 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 19.6 (CH_3), 22.5, 26.2, 27.5 and 41.0 (4 x CH_2), 99.6 (CO-**C**=C), 108.2, 110.2, 120.2, 122.0, 128.3 and 129.8 (Carom), 142.3 [=C(CH_3)- N], 151.8 and 198.8 (2 x C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{15}ClN_2O_2$+Na]$^+$: 313.0708; found: 313.0680.

(Z)-6-Nitro-1-[1-(2-oxocyclohexylidene)ethyl]-1*H*-benzo[*d*]imidazol-2(3*H*)-one 4d

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.63-1.75 (m, 4H, CH_2), 2.18 (s, 3H, CH_3), 2.25 and 2.46 (2t, *J* 3.9 Hz, 4H, CH_2), 7.50-8.61 (m, 3H, Harom), 9.32 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 19.9 (CH_3), 22.6, 26.5, 27.1 and 40.6 (4 x CH_2), 99.8 (CO-**C**=C), 108.6, 109.5, 120.6, 121.5, 128.1 and 128.8 (Carom), 142.4 [=C(CH_3)-N], 152.0 and 198.9 (2 x C=O); HRMS (ESI$^+$): m/z calcd for [$C_{15}H_{15}N_3O_4$+Na]$^+$: 324.1040; found: 324.0923.

(Z)-2-[1-(2-Thioxo-2,3-dihydrobenzo[*d*]imidazol-1- yl) ethylidene]cyclohexanone 5a

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.62-1.74 (m, 4H, CH_2), 2.23 (s, 3H, CH_3), 2.24 and 2.47 (2t, *J* 3.7 Hz, 4H, CH_2), 6.68- 6.98 (m, 4H, Harom), 12.76 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.5 (CH_3), 22.6, 26.5, 27.5 and 40.8 (4 x CH_2), 100.4 (CO-**C**=C), 110.7, 111.5, 123.7, 127.4, 131.6 and 132.5 (Carom), 141.3 [=C(CH_3)- N], 165.2 (C=S), 199.6 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{15}H_{16}N_2OS+Na]^+$: 295.0920; found: 265.0502.

(Z)-2-[1-(5-Methyl-2-thioxo-2,3-dihydrobenzo[*d*]imidazol-1yl)ethylidene]cyclohexanone 5b

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.64-1.77 (m, 4H, CH_2), 2.42 and 2.50 (2s, 6H, CH_3), 2.25 and 2.36 (2t, *J* 3.8 Hz, 4H, CH_2), 6.60-7.52 (m, 3H, Harom), 11.76 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 16.9 and 17.2 (2 x CH_3), 22.6, 26.5, 27.5 and 41.0 (4 x CH_2), 99.8 (CO-**C**=C), 104.4, 110.1, 122.6, 124.5, 138.2 and 143.1 (Carom), 141.0 [=C(CH_3)-N],165.8 (C=S), 200.1 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{16}H_{18}N_2OS+Na]^+$: 303.1029; found: 303.0908.

(Z)-2-[1-(5-Chloro-2-thioxo-2,3-dihydrobenzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 5c

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.62-1.74 (m, 4H, CH_2), 2.23 (s, 3H, CH_3), 2.31 and 2.39 (2t, *J* 3.7 Hz, 4H,CH_2), 6.52-7.26 (m, 3H, Harom), 12.29 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.7 (CH_3), 22.5, 26.3, 27.5 and 41.1 (4 x CH_2), 99.1 (CO-**C**=C), 101.8, 107.5, 119.2, 121.2, 125.3 and 131.6 (Carom), 142.0 [=C(CH_3)-N], 166.2 (C=S); 200.6 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{15}H_{15}ClN_2OS+Na]^+$: 329.0540; found: 329.0204.

(Z)-2-[1-(6-Nitro-2-thioxo-2,3-dihydrobenzo[*d*]imidazol-1-yl)ethylidene]cyclohexanone 5d

^{1}H NMR (300 MHz, DMSO-d^6): δ 1.65-1.76 (m, 4H, CH_2), 2.25 (s, 3H, CH_3), 2.35 and 2.47 (2t, J 3.7 Hz, 4H, CH_2), 6.90-7.14 (m, 3H, Harom), 11.35 (s, 1H, NH); ^{13}C NMR (75 MHz, DMSO-d^6): δ 17.6 (CH_3), 22.7, 25.8, 26.9 and 39.8 (4 x CH_2), 99.6 (CO-**C**=C), 105.3, 107.5, 120.3, 127.2, 131.9 and 140.6 (Carom), 142.1 [=C(CH_3)- N], 166.8 (C=S), 201.7 (C=O); HRMS (ESI$^+$): m/z calcd for $[C_{15}H_{15}N_3O_3S+Na]^+$: 340.0712; found: 340.0744.

4. CONCLUSION

A new series of benzimidazole-cyclohexanone **3a-b**, **4a-b** and **5a-b** were synthesized by the reaction of (Z)-2-(1-aminoethylidene)cyclohexanones with different electrophilic reagents as DMF-DMA, triphosgene and carbon disulfide. All these compounds were obtained in moderate-to good yields under mild operating conditions. The determination of the structural features of these intermediates was first performed by solution ^{1}H, ^{13}C NMR and HRMS.

5. ACKNOWLEDGEMENTS

The authors would like to think the Department of Organic Chemistry. Laboratoire de Chimie Organique et des Substances Naturelles, Université Ziane Achour, Djelfa, Algerie, the Faculté de Chimie – USTHB – BP32, El-Alia, 16111 Bab Ezzouar, Alger, Algerie and the laboratoire de Synthèse et Physico-Chimie de Molécules d'Intérêt Biologique, UMR 5068, Université Paul Sabatier, 118 route de Narbonne, 31062 Toulouse, Cedex 4, France

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How to cite this article:
Belkheiri N, Belkacem Z, Derdour M, Mechrouh F, Bachar RM, Fodili M, Amari M, Hoffmann P.Synthesis of benzimidazole-cyclohexanone derivatives. J. Fundam. Appl. Sci., 2018, *10(2), 213-221.*