Asian Journal of Chemistry; Vol. 28, No. 4 (2016), 895-898

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2016.19545

Synthesis, Characterization and Biological Activity of Some New Acetohydrazide Derivatives *via* 3,3'-Dimethylbenzidine

MAYSOON T. TAWFIQ[1,*] and ZAINAB A. JABARAH[2]

[1]Department of Chemistry, College of Education for Pure Science/Ibn-Al-Haitham, University of Baghdad, Baghdad, Iraq
[2]Division of Basic Science, College of Agriculture, University of Baghdad, Baghdad, Iraq

*Corresponding author: E-mail: maysoontariqwaleed@yahoo.com

Received: 1 August 2015; *Accepted*: 1 October 2015; *Published online*: 30 December 2015; AJC-17711

Schiff base (**1**): 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetic acid was obtained by condensation of 3,3'-dimethylbenzidine with glyoxalic acid in ethanol. The esterfication of **1** with ethanol in presence of sulfuric acid gave the ester (**2**): diphenyl-2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetate, then converted this ester to the acid hydrazide by reaction with hydrazine hydrate in ethanol to gave (**3**): 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetohydrazide,which was reacted with substituted aldehydes in ethanol to give the corresponding Schiff bases (**4 a,b,c**): 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidine)*bis*(*N*'-(3-alkyl-4-hydroxybenzylidene)acetohydrazide). The prepared compounds were characterized by spectral methods and Schiff bases were screened for antibacterial activity.

Keywords: Heterocyclic compounds, Schiff bases, 3,3'-Dimethylbenzidine, Glyoxylic acid, Acid hydrazide, Acetohydrazide.

INTRODUCTION

Hydrazides have been considerable interest in the development of novel compounds and used as intermediates in synthesis as functional groups in metal carbonyls [1,2], in organic compounds [3] and in particular in hydrazine Schiff base ligands (A) and (B) [4-6],which are among others employed in dinuclear catalysts [7]. Hydrazides and their condensation products have displayed diverse range of biological properties such as bactericidal [8-10], antifungal [11], anticonvulsant [12,13], antitumor [14-18], antileprotic [19], antimalarial [20], anticancer [21], antidepressant [22], anti-HIV [23], analgesic-anti-inflammatory [24], leishmanicidal [25], vasodilator activities [26].

Schiff bases are the compounds containing azomethine group (-HC=N-).They are condensation products of ketones or aldehydes with primary amines. Formation of Schiff base generally takes place under acid or base catalysis or with heat. Schiff bases are considered as an important class of organic compounds and have a wide application in many biological aspects, proteins, visual pigments, enzymatic aldolization and decarboxylation reactions [27]. Moreover, some Schiff-bases were exhibits antibiotic, antiviral and antitumor agents because of their specific structure [28,29]. An interesting application of Schiff bases is their use as an effective corrosion inhibitor, which is based on their ability to spontaneously form a monolayer on the surface to be protected. Many commercial inhibitors include aldehydes or amines, but presumably due to the C=N bond the Schiff bases function more efficiently in many cases [30]. The aim of this work is to synthesize and characterize new Schiff bases and to study their spectral and biological activities against some of microorganisms.

EXPERIMENTAL

All melting points are uncorrected in degree centigrade and determined on Gallenkamp electric melting point apparatus. FT-IR spectra were recorded (KBr disk) on a SHIMADZU FT-IR 8300 spectrophotometer in the range (4000-400) cm^{-1}. UV/visible spectra were recorded on UV/visible varian UV-Cary-100 spectrophotometers in DMSO as solvent. ^1H NMR spectra were determined on a BRUKER-400 MHz operating 300 MHz spectrometer with tetramethylsilane (TMS) as an internal standard and the chemical shifts are in δ ppm using deuterated dimethyl sulfoxide (DMSO-d_6) as a solvent, measurements were made at Chemistry Department, AHL-Al- Bayt University, Jordan. The reactions progress was monitored by thin-layer chromatography (TLC) using Fertigfollen precoated sheets type polygram silg and the plates were developed with iodine vapour. The biological activity was performed by Environmental Laboratory, Baghdad University, Baghdad, Iraq.

Synthesis of 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*-(azan-1-yl-1-ylidene)diacetic acid (1) [31,32]: A solution of 3,3'-dimethylbenzidine (0.01 mol, 2.12 g) in absolute ethanol (20 mL) was slowly added to a solution of glyoxalic acid (0.02 mol, 1.48 g) + 2 drops of glacial acetic acid in absolute ethanol (15 mL). After stirring for 1 h, the mixture was refluxed for 3-4 h. After cooling the mixture was filtered and washed with cold ethanol and recrystallized from ether.

Synthesis of diphenyl-2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-idene)diacetate (2) [33,34]: 2,2'-(3,3'-Dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetic acid (**1**) (0.005 mol, 1.62 g) was refluxed with 25 mL of absolute ethanol and few drops of conc. sulfuric acid for 5-6 h. The mixture was left to cool and filtered to give crystals; recrystallized from ethanol.

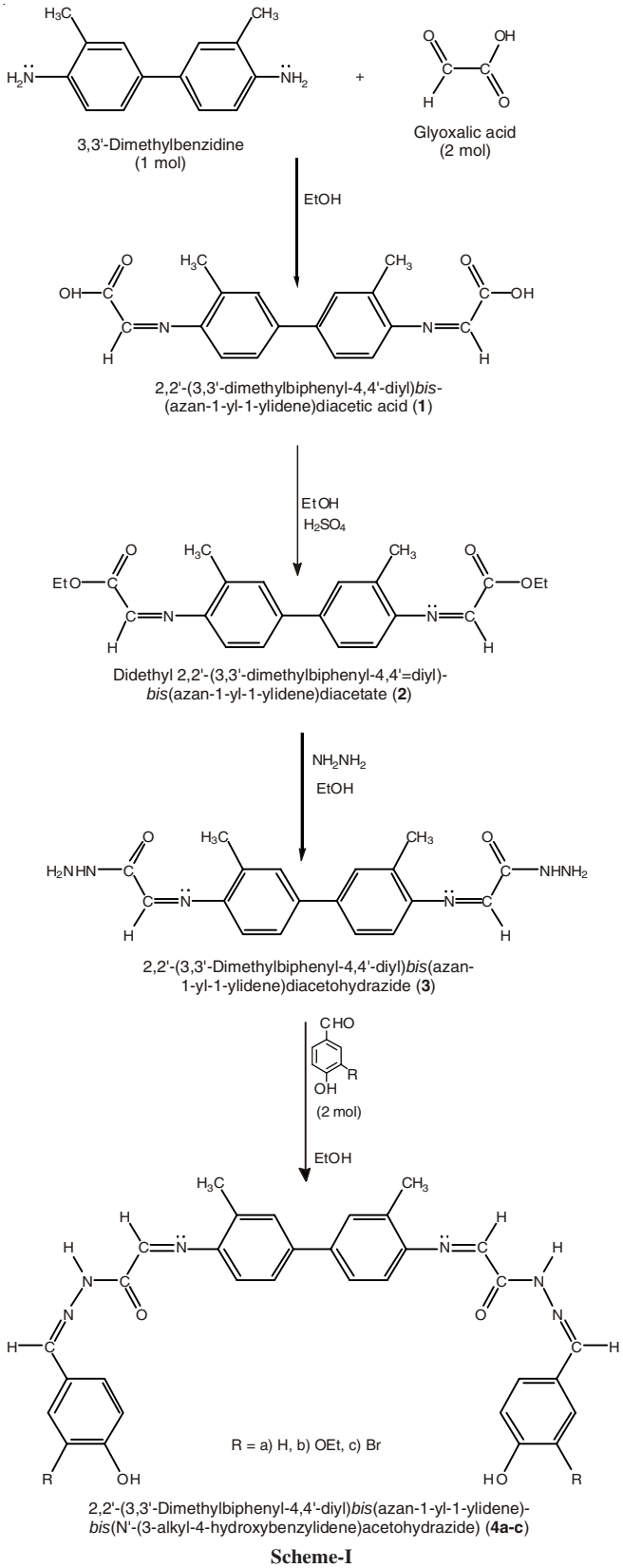
Synthesis of 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*-(azan-1-yl-1-lidene)diacetohydrazide (3) [35,36]: To a solution of (0.005 mol, 1.9 g) of diphenyl-2,2'-(3,3'-dimethyl-biphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetate (**2**) in absolute ethanol (20 mL) was added (0.01 mol, 0.5 g, 0.5 mL) of hydrazine hydrate (90 %). The mixture was refluxed under anhydrous conditions for 12 h. Excess solvent was distilled off. The resulting solid was then separated out on cooling filtered and recrystallized from ethanol. The compound was separated as shining yellow needle shaped crystals.

Synthesis of 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*-(azan-1-yl-1-ylidine)*bis*(*N*'-(3-alkyl-4-hydroxybenzylidene)-acetohydrazide) (4 a, b, c) [37-40]: A mixture of 2,2'-(3,3'-dimethyl biphenyl-4,4'-diyl)*bis*(azan-1-yl-1-lidene)diaceto-hydrazide (**3**) (0.002 mol), appropriate aromatic aldehyde namely 4-hydroxybenzaldehyde, 3-ethoxy-4-hydroxy benzal-dehyde and 3-bromo-4-hydroxybenzaldehyde (0.004 mol) in (20 mL) absolute ethanol was stirring for 1 h and the mixture was refluxed for 7-8 h. The formed precipitate after cooling was filtered, dried and re-crystallized from benzene and ethanol (1:1) to give compounds (**4a,b,c**), respectively (**Scheme-I**).

RESULTS AND DISCUSSION

The infrared study of the important methods in identification of absorbed peaks of the resulting functional groups effective and which are found within the structural formula of the compounds prepared. The difference in the intensity of the main functional groups of absorption peaks is an indication of the occurrence of interaction. The first step involved synthesis of imine as starting material: 2,2'-(3,3'-dimethylbiphenyl-4,4'-diyl)*bis*(azan-1-yl-1-ylidene)diacetic acid (1)from condensation reaction of 3,3'-dimethylbenzidineandglyoxalic acid.

The mechanism of this reaction is known [41]. This imine was identified by m.p. and FT-IR, (Tables 1 and 2). From FT-IR spectrum can clearly see the disappearance bands of (-NH_2) of amine group at ν(3410-3356) cm^{-1} and ν(C=O) of aldehyde group at 1669 cm^{-1} and appearance of sharp medium stretching absorption in the range of 1619 cm^{-1} due to imine group ν(-C=N-) and strong bands at 1726, 1657 cm^{-1} are due to ν(C=O) of carboxylic group. Compound **1** was converted to ester (**2**) by reaction with absolute ethanol in presence of H_2SO_4 drops by (esterfication reaction) [41,42].The product was characterized by physical properties and FT-IR spectroscopy (Tables 1 and 2).



Scheme-I

The mechanism of this condensation is known and is acid catalyzed [43,44]. The FT-IR spectrum of compounds **2** showed disappearance of (OH) and (C=O) of acidic group band, this proves the occurrence of esterification reaction.

The reaction of hydrazine hydrate with ester is one of the most common reaction to synthesize the acid hydrazide, it is a

TABLE-1
PHYSICAL PROPERTIES OF THE PREPARED COMPOUNDS

Comp. No.	m.f.	m.w. (g/mol)	Yield (%)	m.p. (°C)	Colour
1	$C_{18}H_{16}O_4N_2$	324	85	216-218	Yellow light
2	$C_{22}H_{24}O_4N_2$	380	77	119-121	Light brown
3	$C_{18}H_{20}O_2N_6$	352	74	134-136	Yellow
4a	$C_{32}H_{28}O_4N_6$	560	63	195-197	Light yellow
4b	$C_{36}H_{36}O_6N_6$	648	67	183-185	Light yellow
4c	$C_{32}H_{26}O_4N_6Br_2$	718	56	201-204	Light brown

TABLE-2
FT-IR SPECTRAL DATA OF THE PREPARED COMPOUNDS

Comp. No.	ν(CH) aro.	ν(CH) ali.	ν(OH) acid	ν(C=O) acid	ν(C=N) imine	ν(C=O) ester	ν(NH_2), NH	ν(NH_2) Amide II	ν(O-H) phenol	Other
1	3050	2931	3172	1726, 1657	1619	–	–	–	–	1267 ν(C-O) acid
2	3056	2924, 2897, 2884	–	–	1585	1773-1736	–	–	–	1270 ν(C-O) ester
3	3027	2965	–	–	1583	–	3431-3326	1663-1679	–	–
4a	3035	2963	–	–	1643	–	3342	1686	3419	–
4b	3034	2916, 2865	–	–	1622	–	3359	1689	3421	1195 ν(C-O) ether
4c	3063	2970	–	–	1636	–	3350	1658	3407	521 ν(C-Br)

tetrahedral nucleophilic substitution reaction [45-47]. FT-IR spectrum of the hydrazide derivative (**3**) showed the appearance of the characteristic absorption band in the region 3431-3323 cm^{-1} due to the asymmetric and symmetric stretching vibration of the(-HN-NH_2) group and disappearance of absorption bands at 1773-1736 cm^{-1} due to the stretching vibration of carbonyl group of ester, while showed appearance of absorption band at 1663-1679 cm^{-1} of the compound **3** due to stretching vibration of amide II band [40,45,48] (Table-2).

The mechanism of this reaction is already reported [45,47]. The treatment of acid hydrazides with different aromatic aldehydes in refluxing ethanol and no acid catalyst were used during the synthesis of all compounds afforded the corresponding acetohydrazide derivatives that was identified as compound (**4a,b,c**) on the basis of its spectral data [49,50].

Compounds **4** were characterized by physical properties, FT-IR (Tables 1 and 2) and ^{1}H NMR for compound **4a**. FTIR spectra showed the disappearance of (NH_2) stretching vibration present in the spectrum of acid hydrazides and showed a broad peak for (NH) group at (3421-3342) cm^{-1} which was overlap with absorption of phenol group (OH), (1689-1658) cm^{-1} due to (C=O) amide II group and (1643-1622) cm^{-1} due to (C=N) of Schiff base. The mechanism of this reaction is already reported [46,47,50].

^{1}H NMR spectrum of compound **4a** shows the following characteristic chemical shifts: protons of (-CH_3) groups at δ 2.45 ppm, protons of (-N=CH) groups at δ 3.39 and 4.36 ppm, respectively, protons of aromatic rings appeared at the ranges δ 6.67-6.94 and 7.6-7.77 ppm, respectively, proton of (-OH) group at δ 9.73 ppm and proton of (-NH) group at δ 10.38 ppm.

UV-visible spectra of compounds (**4a**, **4b** and **4c**) showed intense maxima at (243-367 nm) referring to $\pi\rightarrow\pi^*$ and $n\rightarrow\pi^*$ electronic transition, respectively (Table-3).

Antibacterial activity: The antibacterial test was performed according to the disc diffusion method. Compounds (**4a**, **4b** and **4c**) were assayed for their antimicrobial activity *in vitro* against two strains of Gram-negative and positive bacteria (*Escherichia coli* and *Staphococcus aureus*).

TABLE-3
UV-VISIBLE SPECTRAL DATA OF PREPARED COMPOUNDS

Compound No.	λ_{max} (nm)
4a	292, 319
4b	336, 367
4c	243

Prepared agar and Petri dishes were sterilized by autoclaving for 15 min at 121 °C. The agar plates were surface inoculated uniformly from the broth culture of the tested microorganisms. In the solidified medium suitably spaced apart holes were made all 6 mm in diameter. These holes were filled with 0.1 mL of the prepared compounds (10 mg of the compound dissolved in 1 mL of DMSO solvent), DMSO was used as a solvent. These plates were incubated at 37 °C for 24 h for bacteria. The inhibition zones caused by the various compounds were examined. The results of the preliminary screening tests are:

For *Staphococcus aureus* (Gram-positive), compound **4b** showed highest activity, while compound **4a** showed no activity on these bacteria. Compound **4c** showed slightly activity.

For *E. coli* (Gram-negative), compound **4c** have no effect on this bacteria because this bacteria is highly resistant to a wide range of antibiotic because of the slim polysaccharides in cell wall which blocked antibiotics from bacteria and also there are genetic factor. While compounds **4a**, **4b** have effect on this bacteria (Table-4).

TABLE-4
ANTIBACTERIAL ACTIVITIES OF SOME OF THE SYNTHESIZED COMPOUNDS

Compound No.	*Escherichia coli*	*Staphococcus aureus*
4a	+	–
4b	+	++
4c	–	+

– = No inhibition = inactive; + = 5-10 mm = slightly active;
++ = 11-20 mm = moderately active.

REFERENCES

1. F. Armbruster, U. Klingebiel and M. Noltemeyer, *Z. Naturforsch.*, **61b**, 225 (2006).
2. O.S. Senturk, S. Sert and U. Ozdemir, *Z. Naturforsch.*, **58b**, 1124 (2003).
3. H. Mohrle and G. Keller, *Z. Naturforsch.*, **58b**, 885 (2003).
4. J. Chakraborty, R.K.B. Singh, B. Samanta, C.R. Choudhury, S.K. Dey, P. Talukder, M.J. Borah and S. Mitra, *Z. Naturforsch.*, **61b**, 1209 (2006).
5. C.T. Zeyrek, A. Elmali and Y. Elerman, *Z. Naturforsch.*, **61b**, 237 (2006).
6. C. Janiak, P.G. Lassahn and V. Lozan, *Macromol. Symp.*, **236**, 88 (2006).
7. M. Mohan, M.P. Gupta, L. Chandra and N.K. Jha, *Inorg. Chim. Acta*, **151**, 61 (1988).
8. Z.H. Chohan and S.K.A. Sherazi, *Synth. React. Inorg. Met.-Org. Chem.*, **29**, 105 (1999).
9. T. Jeeworth, H.L.K. Wah, M.G. Bhowon, D. Ghoorhoo and K. Babooram, *Synth. React. Inorg. Met.-Org. Chem.*, **30**, 1023 (2000).
10. I.A. Tossidis, C.A. Bolos, P.N. Aslanidis and G.A. Katsoulos, *Inorg. Chim. Acta*, **133**, 275 (1987).
11. R.C. Aggarwal, N.K. Singh and R.P. Singh, *Inorg. Chim. Acta*, **20**, 2794 (1981).
12. A. Maiti and S. Ghosh, *Indian J. Chem.*, **29B**, 980 (1989).
13. J.R. Dimmock, S.C. Vashishtha and J.P. Stables, *Eur. J. Med. Chem.*, **35**, 241 (2000).
14. N. Dharmaraj, P. Viswanathamurthi and K. Natarajan, *Transition Met. Chem.*, **26**, 105 (2001).
15. C.H. Colins and P.M. Lyne, Microbial Methods, University Park Press, Baltimore, p. 422 (1970).
16. L. Savini, L. Chiasserini, A. Gaeta and C. Pellerano, *Bioorg. Med. Chem.*, **10**, 2193 (2002).
17. J.A. Anten, D. Nicholis, J.M. Markpoulos and O. Markopoulou, *Polyhedron*, **6**, 1075 (1987).
18. K. Andelkovic, D. Sladic, A. Bacchi, G. Pelizzi, N. Filipovic and M. Rajkovic, *Transition Met. Chem.*, **30**, 243 (2005).
19. R.M. Silverstein, G.C. Bassler and T.C. Morrill, Spectrometric Identification of Organic Compounds, Wiley, New York, edn 4 (1981).
20. T. Haack, R. Fattori, M. Napoletano, F. Pellacini, G. Fronza, G. Raffaini and F. Ganazzoli, *Bioorg. Med. Chem.*, **13**, 4425 (2005).
21. G. Strappaghetti, C. Brodi, G. Giannaccini and L. Betti, *Bioorg. Med. Chem. Lett.*, **16**, 2575 (2006).
22. F. Al'-Assar, K.N. Zelenin, E.E. Lesiovskaya, I.P. Bezhan and B.A. Chakchir, *Pharm. Chem.*, **36**, 598 (2002).
23. H.L. Singh and A.K. Varshney, *Bioinorg. Chem. Appl.*, **2006**, 1 (2006).
24. R.P. Jain and J.C. Vederas, *Bioorg. Med. Chem. Lett.*, **14**, 3655 (2004).
25. A. Scozzafava, L. Menabuoni, F. Mincione, G. Mincione and C.T. Supuran, *Bioorg. Med. Chem. Lett.*, **11**, 575 (2001).
26. A.M. Elsome, J.M.T. Hamilton-Miller, W. Brumfitt and W.C. Noble, *J. Antimicrob. Chemother.*, **37**, 911 (1996).
27. S.K. Sahoo, R.K. Bera, M. Baral and B.K. Kanungo, *J. Photochem. Photobiol. Chem.*, **188**, 298 (2007).
28. H.M. Parekh and M.N. Patel, *Russ. J. Coord. Chem.*, **32**, 431 (2006).
29. N. Raghav, A. Suman, M. Singh, R. Kaur and A. Rohilla, *Int. J. Appl. Biol. Pharm. Technol*., **2**, 193 (2011).
30. S.S. Li, H. Chen, S. Lei, H. Ma, R. Yu and D. Liu, *Corros. Sci.*, **41**, 1273 (1999).
31. D. Chiarino, F. Ferrario, F. Pellacini and A. Sala, *J. Heterocycl. Chem.*, **26**, 589 (1989).
32. L. Szilagyi and Z. Gyorgydeak, *J. Am. Chem. Soc.*, **101**, 427 (1979).
33. W.N. Ahamed, T.G. Hassan and M.A. Abid Allah, *J. Univ. Anbar Pure Sci.*, **4** (2010).
34. L. John and L. Barry, Advanced Practical Organic Chemistry, CRC Press, edn 3 (2013).
35. S. Ghammamy, R. Shakeri, B. Shaabani, K. Mehrani and S. Rajaei, *Afr. J. Pure Appl. Chem.*, **5**, 145 (2011).
36. O.W. Salawu and A.O. Abdulsalam, *Der Pharma Chemica*, **3**, 298 (2011).
37. L.M. Matz and H.H. Hill Jr., *Anal. Chim. Acta*, **457**, 235 (2002).
38. B.S. Furnis, A.J. Hannaford, P.W. Gsmith and A.R. Tatchell, Text Book of Practical Organic Chemistry, London (2005).
39. B. Mahesha, S.L. Belagali, M. Murali and K.N. Amruthesh, *Int. J. Chem. Phys. Sci.*, **3**, 82 (2010).
40. R.M. Mohammed, M.Sc. Thesis, Islamic University of Gaza, Deanery of Higher Studies Faculty of Science, Gaza, Palestine (2013).
41. K.J. Ibtisam, Ph.D. Thesis, Baghdad University, Baghdad, Iraq (2001).
42. I.V. Arthur, Practical Organic Chemistry, edn 3, London (1973).
43. W.B. Kantlehnerin, M. Trost and I. Fleming, Strategy and Efficiency in Modern Organic Chemistry, Pergamon Press, Inc., Elmsford, New York, vol. 6, pp. 485-599 (1991).
44. E.K. Eurantoin and S. Patai, The Chemistry of Carboxylic Acids and Esters, Wiley Interscience, New York (1969).
45. J. Hamdi, Ph.D. Thesis, Al-Mustansiria University, Baghdad, Iraq (1999).
46. S. Özbey, F.B. Kaynak, H. Göker and C. Kus, *J. Chem. Crystallogr.*, **34**, 851 (2004).
47. H. Abdel-Aziz, T. Elsaman, M. Attia and A. Alanazi, *Molecules*, **18**, 2084 (2013).
48. D.Y. Curtin, R.C. Fuson, C.K.F. Hermann, T.C. Morrill and R.L. Shriner, The Systematic Identification of Organic Compounds, John Wiley & Sons, New York, edn 8 (2004).
49. M.M. Rafat, H.F. Daisy and K.S. Ola, *Molecules*, **16**, 16 (2011).
50. A.J. Mahrath, S.A. Aowda and S.N. Kamil, *J. Babylon Univ. Pure Appl. Sci.*, **21**, 206 (2013).