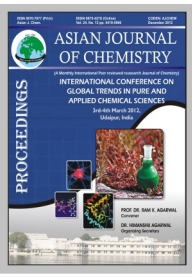
Asian Journal of Chemistry; Vol. 24, No. 12 (2012), 5592-5596

ASIAN JOURNAL OF CHEMISTRY

www.asianjournalofchemistry.co.in



Microwave Assisted Synthesis of New Heterocyclic Compounds: 1,2,3-Triazoles and Tetrazoles and Study of Their Biological Activity†

ADNAN I. MOHAMMED[1,*], ASHOUR H. DAWOOD[1], KHALID F. ALI[2] and MOHSEN AL-MOSAWI[3]

[1]Department of Chemistry, College of Science, University of Kerbala, Kerbala, Iraq
[2]Department of Chemistry, College of Education-Ibn Al-Haitham, University of Baghdad, Baghdad, Iraq
[3]College of Applied Medical Science, University of Kerbala, Kerbala, Iraq

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

AJC-11704

The work includes synthesis of 1,2,3-triazoles *via* click conditions and using the microwave irradiation starting from two synthesized azides: 2,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranosyl azide (**5**) and perfluorobutylethyl azide (**10**) and different terminal alkynes. It also includes microwave enhanced synthesis of tetrazoles *via* the reaction of two synthesized azides *i.e.*, perfluorobutylethyl azide (**10**) and 1,5-diazidopentane (**13**) with benzoyl cyanide. Most of the prepared compounds have been characterized by: TLC, FT-IR, ^{1}H NMR, ^{13}C NMR, LC-MS and microelemental analysis.

Key Words: Microwave synthesis, 1,2,3-Triazoles, Click chemistry, Tetrazoles, D-mannitol.

INTRODUCTION

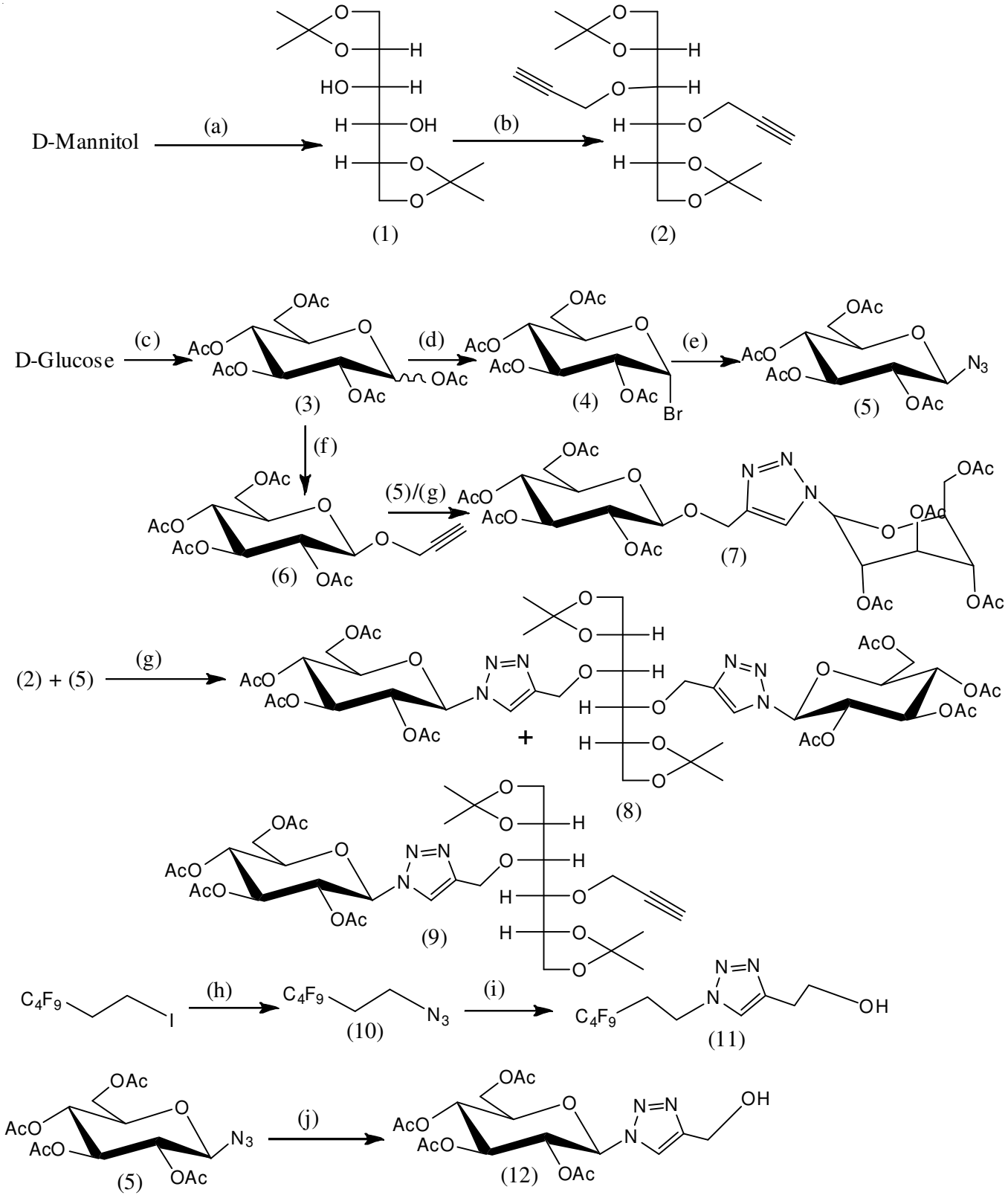
Copper-catalyzed reaction was reported at the same time and individually by the groups of Meldal *et al.*[1] and Sharpless *et al.*[2] and has been called click reaction. It converts organic azides and terminal acetylenes completely into the corresponding 1,4-disubstituted 1,2,3-triazoles. Since the innovation of the click reaction, this method has found use in varied areas of chemistry such as dendrimers and polymers[3], drug[4], materials[5], bioconjugation[6], antibiotic[7], anticancer[8] and HIV protease inhibitors[9]. The pharmaceutical importance of triazoles has prompted the design and synthesis of various triazolo nucleosides. Recently, A. Mohammed[10] synthesized new sugar based triazoles and bistriazoles starting from D-glucose. Chiral macrocycles containing the sucrose skeleton were prepared by a click chemistry route[11]. Stereoisomers of 1,2,3-triazole-functionalized, conformationally restricted β- or γ-amino esters with a cyclopentane skeleton were efficiently synthesized[12]. A novel type of receptors based on 1,2,3-triazole glycyrrhetinic acid derived from natural triterpenoid molecules has been synthesized *via* click chemistry and they showed high selectivity and affinity for Hg^{2+} ion by both the 1,2,3-triazole rings and aldehyde groups[13]. Tetrazoles are a class of heterocycles with a wide range of applications and they are receiving considerable attention. This functional group is regarded as biologically equivalent to the carboxylic acid in medicinal chemistry. The most widely used method of preparation for 5-substituted 1-*H* tetrazoles is [2+3] cycloaddition of azide anion to organic nitriles[14]. High-density energetic salts that contain nitrogen-rich cations and the 5-(tetrazol-5-ylamino)tetrazolate ($HBTA^{-}$) or the 5-(tetrazol-5-yl)tetrazolate (HBT^{-}) anion were readily synthesized by the metathesis reactions of sulfate salts with barium compounds[15].

EXPERIMENTAL

Chemical reagents and starting materials were obtained from Ajax and Sigma-Aldrich Chemical. Infrared spectra were recorded using AVATAR 320 FT-IR. ^{1}H and ^{13}C NMR spectra were recorded using 300 MHz Bruker DPX spectrometers. Microelemental analysis was performed with elemental analyzer EA-300 eurovector. Mass spectra were recorded using Waters 996 Micromass at the University of New South Wales, Sydney, Australia. Silica TLC plates were used with an aluminum backing (0.2 mm, 60 F_{254}). All microwave enhanced reactions have been done using biotage microwave initiator 2.5. All the prepared compounds have been purified by flash chromatography.

Synthesis of 2,3,4,6-*tetra*-*O*-acetyl-β-D-glucopyranosyl azide (5): Into a (20 mL) process vial equipped with a stirring bar sodium azide (0.195 g, 3.0 mmol) was added to the solution of compound (0.41 g, 1.0 mmol) in DMF (5 mL). The vial

†Presented at International Conference on Global Trends in Pure and Applied Chemical Sciences, 3-4 March, 2012; Udaipur, India



Reagents and conditions: (a) Acetone,$ZnCl_2$ rt 3hrs; (b) propargyl bromide, NaOH, DMF rt 24 h;(c) Ac_2O, pyridine rt 16 h; (d) 33% HBr/AcOH 0-rt 1 h; (e) NaN_3, DMF, MW, 80°C, 10 min; (f) propargyl alcohol, $SnCl_4$, 0-rt, 1.5 h; (g) CuI, Et_3N, DMSO, MW, 100°C, 2 h; (h) NaN_3, DMSO, MW, 100°C, 1h; (i) 3-butyn-1-ol, CuI, Et_3N, DMSO, MW, 100°C, 2 h; (i) propargyl alcohol, CuI, Et_3N, DMSO, MW, 100°C, 2 h.

Scheme-I: Microwave assisted synthesis of 1,2,3-triazoles

was sealed by capping with a Teflon septum fitted in an aluminum crimp top. The mixture was pre-stirred for 1 min then irradiated with microwave for 10 min at 80 ºC then left to cool to room temperature. The reaction was quenched with water (10 mL) and extracted with ether (3 × 20 mL), the combined organic layers washed with brine (20 mL), water (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure to give compound (**5**) (0.36 g, 96 %) as a white crystalline solid, m.p. 102-104 ; $[\alpha]^D$ -18(c 0.5 in $CHCl_3$).

Synthesis of perfluorobutylethyl azide (10): Compound (**10**) were synthesized according to the procedure of azide (**5**), using DMSO as solvent and irradiation time 1 h at 100 ºC, (1.15 g, 80 %) based on (5 mmol) of the starting material, pale yellow oil.

Synthesis of triazoles (7, 8, 9, 11 and 13): Into a (20 mL) process vial equipped with a stirring bar are placed alkyne (2 mmol), triethylamine (278 mL, 2 mmol), CuI (0.2 mmol) and DMSO (4.0 mL). The mixture was stirred for 1 min and then azide (2.2 mmol or 4.2 mmol) in a small amount of DMSO (2 mL) was added. The vial was sealed by capping with a Teflon septum fitted in an aluminum crimp top. The mixture was irradiated with microwave for 2 h at 100 ºC then left to cool to room temperature. The contents of the vial are poured on water (20 mL) and extracted with EtOAc (3 × 25 mL), the combined organic layers washed with NaCl saturated solution (20 mL), water (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography of the residue (silica, 3:1 ether, light petroleum) produced the targeted triazoles.

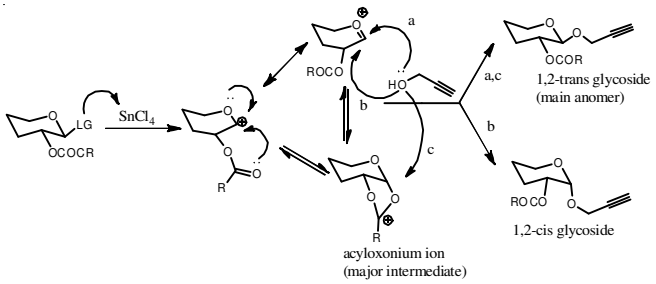
Synthesis of tetrazoles (14 and 15): Into a (10 mL) process vial equipped with a stirring bar are placed benzoyl cyanide (1.0 mmol), azide (1.0 mmol or 0.5 mmol) and DMF (5.0 mL). The vial was sealed by capping with a Teflon septum fitted in an aluminum crimp top. The mixture was pre-stirred for 1 min then irradiated with microwave for 5 h at 163 ºC then left to cool to room temperature. The contents of the vial are poured on water (20 mL) and extracted with EtOAc (3 × 25 mL), the combined organic layers washed with NaCl saturated solution (20 mL), water (20 mL), dried over Na_2SO_4 and evaporated under reduced pressure. Flash chromatography of the residue (Silica, 3:1 EtOAc, light petroleum) produced the targeted tetrazoles. The physical properties and microanalysis of these compounds are given in Table-1

RESULTS AND DISCUSSION

We follow click strategy to synthesize the 1,2,3-triazoles because this route give only one 1,4-disubstituted 1,2,3-triazoles. The overall route of synthesis of 1,2,3-triazoles outlined in the following **Scheme-I**:

The work commenced by the reaction of D-mannitol with anhydrous acetone in the presence of zinc chloride as an acidic catalyst to give the diacetonemannitol (**1**)[16], Williamson etherification of compound (**1**) using propargyl bromide and crushed sodium hydroxide in DMF at room temperature yielded compound (**2**)[10].

Conversion of D-glucose to 1,2,3,4,6-penta-*O*-acetyl-β-D-glucopyranose (**3**)[16] using the traditional acetylaing agent acetic anhydride and sodium acetate to give the β-anomer only in very good yield. The treatment of compound (**3**) with HBr/HOAc in dry conditions for 45 min produced acetobromoglucose (**4**)[17] also in very good yield. Microwave assisted S_N2 reaction of glycosyl bromide (**4**) with sodium azide in DMF for 10 min gave glycosyl azide (**5**) in quantitative yield due to the nucleophile strength (N_3^-) and the neighboring group participation of acetate in position **2** of the sugar. Glycosidation of glucose penaacetate (**3**) with propargyl alcohol in the presence of stannic chloride afforded the glycoside (**6**) in very good yield. $SnCl_4$ plays a great role in activation of the anomeric acetate beside the acetate group in position **2** as shown in the **Scheme-II** below[17]:



Scheme-II: Mechanism of formation of the glycoside bond (the role of $SnCl_4$ and the neighboring group participation)

Microwave assisted Cu(I) catalyzed 1,3-dipolarcycloaddition of azide (**5**) to alkyne (**6**) afforded triazoles (**7**) in good yield.

Microwave assisted cycloaddition of glycosyl azide (**5**) to the diacetylene (**2**) using click conditions in DMSO at 100 ºC for 2 h afforded the two triazoles (**8**) and (**9**). The other compound produced from the above cycloaddition is compound (**9**). Microwave assisted S_N2 reaction of perfluorobutylethyl iodide with sodium azide in DMSO at 100 ºC for 1 h gave perfluorobutylethyl azide (**10**) in an excellent yield. Microwave enhanced cycloaddition of azide (**10**) to the 3-butyn-1-ol using click conditions in DMSO at 100 ºC for 2 h afforded the two triazoles (**11**). Microwave assisted cycloaddition of glycosyl azide (**5**) to propargyl alcohol using click conditions in DMSO at 100 ºC for 2 h gave triazoles (**12**) **(Scheme-III)**.

The reaction of 1,5-dibromopentane with sodium azide in DMF as solvent using microwave irradiation at 80 ºC for 2 h afforded 1,5-diazidopentane (**13**) in an excellent yield.

Microwave enhanced 1,3-dipolarcycloaddition reaction of benzoyl cyanide with azides (**10**) and (**13**) afforded the tetrazoles (**14**) and (**15**) respectively.

Biological activities: The biological activity of the prepared compounds were carried out by two different methods:

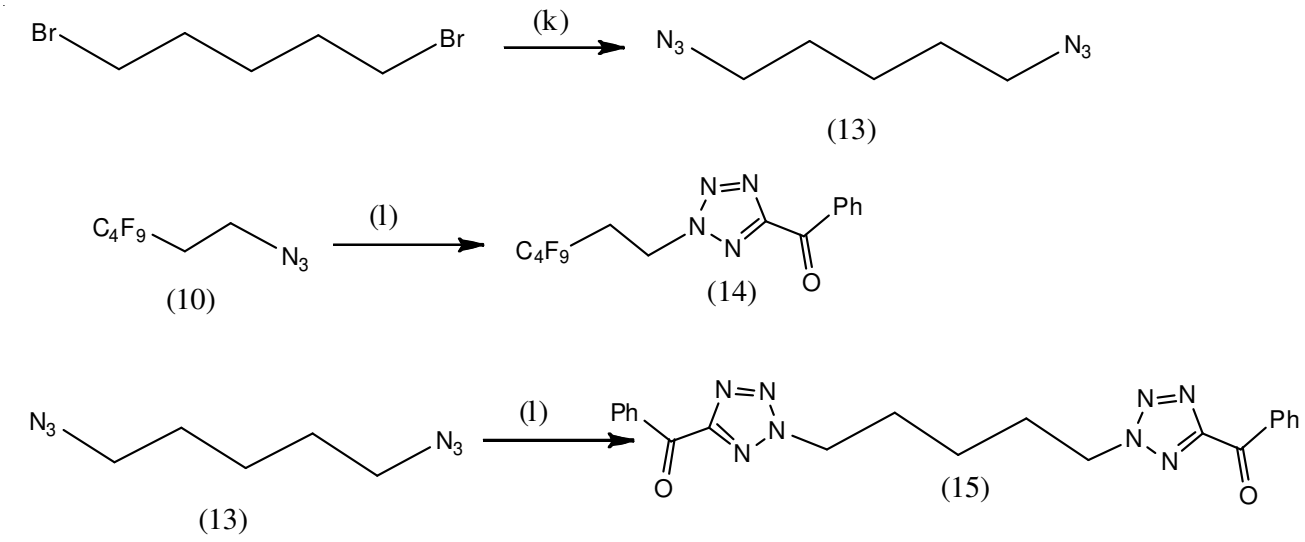
Nutrient agar diffusion procedure (Wells method): Dissolved 28 g from nutrient in one litter of distilled water then heated to dissolve completely; the agar and the petri dishes were sterilized by autoclave for 15 min at 120 ºC with (G^+) as *Staphylococcus* and (G^-) as *Escherichia coli* for 24 h at 37 ºC, the inhibition zone was measured.

Nutrient Broth technique: The nutrient broth prepared of bacteria by putting the nutrient broth in two tubes, then added to the first tube *Bacillus Subtllis* as (G^+) type and the other added *Escherichia coli* as (G^-) type for 24 h at 37 ºC.

The results of biological activity of inhibition zone radii appeared the bacteria growth area. Table-2 summarized the

TABLE-1
PHYSICAL PROPERTIES AND MICROANALYSIS OF THE TARGET COMPOUNDS

Comp.	Yield	Physical state	Melting point (ºC)	R_f Eluent	Name	Microelemetal analysis (Found)		
						C (%)	H (%)	N (%)
7	0.70 g, 92%	White solid	199-202	0.31 1:2(hexane/ EtOAc)	1-(2,3,4,6-*tetra-O*-acetyl-β-D-glucopyranosyl)-4-[(2,3,4,6-*tetra-O*-acetyl-β-D-glucopyranosyl) oxymethyl]1*H*-1,2,3-triazole	49.01	5.44	5.53
						(48.79)	(5.28)	(5.42)
8	0.50 g, 56%	White solid	141-143	0.30 1:3(hexane/ EtOAc)	2-(Acetoxymethyl)-6-(4-((1,2-*bis*-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-((1-(3,4,5-triacetoxy-6-(acetoxymethyl)tetrahydro-2*H*-pyran-2-yl)-1*H*-1,2,3-triazol-4-yl)methoxy)ethoxy)methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate	50.92	5.95	7.75
						(50.80)	(5.77)	(7.49)
9	0.39 g, 43%	White solid	127-129	0.36 1:3(hexane/ EtOAc)	2-(Acetoxymethyl)-6-(4-((1,2-*bis*-(2,2-dimethyl-1,3-dioxolan-4-yl)-2-(prop-2-yn-1-yloxy)ethoxy) methyl)-1*H*-1,2,3-triazol-1-yl)tetrahydro-2*H*-pyran-3,4,5-triyl triacetate	54.00	6.37	5.90
						(53.78)	(6.25)	(5.83)
11	0.32 g 89%	White solid	207-209	0.32 1:3(hexane/EtOAc)	4-(2-Hydroxyethyl)-1-(2-perfluorobutylethyl)-1*H*-1,2,3-triazole	33.44	2.81	11.70
						(33.12)	(2.66)	(11.51)
12	0.40 g 93%	White solid	187-190	0.31 1:3(hexane/EtOAc)	4-[Hydroxymethyl]-1-(2,3,4,6-tetra-O-acetyl-beta-D-glucopyranosyl)1*H*-1,2,3-triazole	47.55	5.40	9.79
						(47.29)	(5.25)	(9.63)
14	0.30 g 71%	White solid	215-218	0.33 1:3(hexane/EtOAc)	5-Benzoyl-2-(2-perfluorobutylethyl)-2*H*-tetrazole	40.01	2.16	13.33
						(39.93)	(1.98)	(13.11)
15	0.28 g 67%	White solid	200-203	0.34 1:3(hexane/EtOAc)	(2,2'-(Pentane-1,5-diyl)-*bis*-(2*H*-tetrazole-5,2-diyl))-*bis*-(phenylmethanone)	60.57	4.84	26.91
						(60.33)	(4.78)	(26.69)



Reagents and conditions: (k) NaN_3, DMF, MW, 80ºC, 2h; (l) benzoyl cyanide, DMF, MW, 163ºC, 5 h.

Scheme-III: Microwave assisted synthesis of Tetrazoles

TABLE-2
BACTERIA GROWTH IN THE NUTRIENT AGAR DIFFUSION 10^{-3} M

Compound	Inhibition zone radii	
	G^+ *Staphylococcus*	G^- *Escherichia coli*
7	++	+
8	+++	+
9	-	++
11	++	-
12	++	+
14	++	+
15	++	++

High active = +++ (more than 20 mm inhibition zone), Medium active = ++ (11-20 mm inhibition zone), Low active= + (8-10 mm inhibition zone), Inactive=-(less than 7 mm inhibition zone)

bacteria growth in the first method (nutrient agar diffusion) and Table-3 summarized the bacteria growth in the second method respectively.

TABLE-3
BACTERIA GROWTH IN THE NUTRIENT BROTH TECHNIQUE 10^{-3} M

Compound	G^+ *Bacillus Subtllis*	G^- *Escherichia coli*
7	+	+
8	+	+
9	+	+
11	+	-
12	-	+
14	+	+
15	-	+

ACKNOWLEDGEMENTS

Thanks to the Iraqi Ministry of Higher Education and Scientific Research, Research and Development Department for the financial support.

REFERENCES

1. C.W. Tornoe, C. Christensen and M. Meldal, *J. Org. Chem.*, **67**, 3057 (2002).
2. V. Rostovtsev, L. Green, V. Fokin and K.B. Sharpless, *Angew. Chem., Int. Ed.*, **41**, 2596 (2002).
3. W. Binder and R. Sachsenhofer, *Macromol. Rapid. Commun.*, **28**, 15 (2007).
4. H.C. Kolb and K.B. Sharpless, *Drug Disc. Today*, **8**, 1128 (2003).
5. R. Evans, *Aust. J. Chem.*, **60**, 384 (2007).
6. P. Wu and V.V. Fokin, *Aldrichim. Acta*, **40**, 7 (2007).
7. K. Rathwell, J. Sperry and M. Brimble, *Tetrahedron*, **66**, 4002 (2010).
8. Q. Wan, J. Chen, G. Chen and S.J. Danishefsky, *J. Org. Chem.*, **71**, 8244 (2006).
9. M. Whiting, J.C. Tripp, Y.-C. Lin, W. Lindstrom, A.J. Olson, J.H. Elder, K.B. Sharpless and A.V. Fokin, *J. Med. Chem.*, **49**, 7697 (2006).
10. A. Mohammed and Al-Mustansiryah, *J. Sci.*, **22**, 2, 51 (2011).
11. S. Jarosz, B. Lewandowski and A. Listkowski, *Synthesis*, 913 (2008).
12. L. Kiss, E. Forro, R. Sillanpaa and F. Fulop, *Tetrahedron*, **66**, 3599 (2010).
13. J. Hu, M. Zhang, L. Yua and Y. Ju, *Bioorg. Med. Chem. Lett*., **20**, 4342 (2010).
14. Y. Zhou, C. Yao, R. Ni and G. Yang, *Syn. Communn.*, **40**, 2624 (2010).
15. Y. Guo, G. Tao, Z. Zeng, H. Gao, D. Parrish and J. Shreeve, *Chem. Eur. J.*, **16**, 3753 (2010).
16. I. Vogel, in eds.: B.S. Furniss, A.J. Hannaford, P.W.G. Smith and A.R. Tatchell, Vogel's Text Book of Practical Organic Chemistry, Longman Ltd., Harlow, UK, edn. 5, p. 645 (1989).
17. A.I. Mohammed and R.S. Jwad, *J. Kerbala Univ.*, **9**, 42 (2011).