Sys Rev Pharm 2020; 11(3): 490 – 494
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

Synthesis and Biological Activity of Some New Thiazolidinone Derivatives

Kawther A.Alheety[1], Nebras M. Jamel[1] and Jumbad H. Tomma[1]
[1]Dept. of Chemistry/College of Education For Pure Science-Ibn Al-Haitham/University of Baghdad/Iraq
Corresponding author:
Kawther A.Alheety
E-mail: kawtheralheety67@gmail.com

Article History: *Submitted: 25.01.2020* *Revised: 24.02.2020* *Accepted: 19.03.2020*

ABSTRACT
The compound [G1] was prepared from the reaction of thiosemicarbazide with para-hydroxyphenylmethyl ketone in ethanol as a solvent. Then by sequence reactions prepared [G2] and [G3] compounds. The compound [G4] reaction with ethyl acetoacetoneto synthesized compound [G6] and acetyl acetone to synthesized compound [G5]. Reaction the [G3] with two different types of aldehydes in the present of pipredine to form new alkenes compounds [G7]and [G8].The compound [G3] reacted with hydrazine hydrate to formation[G4] with present the hydrazine hydrade 80% in (10) ml of absolute ethanol. Latter the compound [G4]reacted with different aldehydes with present the glacial acetic acid and the solvent was ethanol to formed the Schiff bases compounds[G9] and [G10]. All the prepared compounds were characterized by FT-IR, ^{1}H-NMR spectra, also biologically activity evaluated, the synthesized derivatives have been screened for their two species of bacteria were used in this study as tested organisms. These are *Escherichia Coli* (Gram negative) and *staphylococcus* (Gram positive).
Key words: Thiazoledinones, alkenes, pyrazoles, Schiff bases, antibacterial activity.
Correspondence:
Kawther A. Alheety
Department of Chemistry, College of Education for Pure Science – Ibn Al – Haitham, University of Baghdad, Iraaq
E-mail: kawtheralheety67@gmail.com
DOI: 10.5530/srp.2020.3.62

INTRODUCTION

Heterocyclic compounds are considered an important branch of organic compounds due to their application in drugs, agricultural fertilizers and industrial studies (1) a variety of atoms, such as N, O, S, P, Si and as can be incorporated into the ring structures (2). The most common heterocyclic are those with five- or six membered rings (3). Heterocyclic compound containing atom other than carbon in their ring, have long been proven to have vivid biological activities. The biological activities of heterocyclic rings, such as triazoles, indoles, pyrones, morpholines, pyridines, and pyrazoles, have been reviewed widely (4,5). The 4-thiazolidinone is one of class represent an important analogue to thiazolidine heterocyclic compounds (6). The cyclization reaction for synthesis of thiazolidin-4-one compounds was carried out by conventional (7-12) or microwave irradiation techniques (13-15). Thiazolidinone is another heterocyclics have biological important which contain of sulfur atom at position 1, nitrogen atom of at position 3, and a carbonyl group at the 2, 4, or 5 positions. The various derivatives: 2-thiazolidinone or 4-thiazolidinone or 5-thiazolidinone or 2-thioxo-4-thiazolidinone and thiazolidine-2,4-dione are associated with number of pharmacological properties. The 2-thiazolidinones have been recently examined as BRD4 bromodomain inhibitors, and 5-thiazolidinone compounds have a good applications in the dyes chemistry. Whereas 2-thioxo-4-thiazolidinone compound (rhodanine) is an important type of numerous drug-like compounds. The 4-thiazolidinone moiety is a magic part (wonder nucleus), which has been known to possess a wide spectrum of biological activities, such as antimicrobial, anti-inflammatory, antitubercular, antidiabetic and antiviral. The biological behaviour which shown by 4-thiazolidinone have been reported in the references (16,17).

The aim of this work

It is synthesis new compounds derived from imidazoliden-4-one derivatives and studying the biological activity of them.

EXPERIMENTAL

MATERIALS AND METHODS

Materials

All chemical materials were obtained from BHD, Ltd and Fluk companies.

Instruments

FTIR spectra (using KBr disc) were determined by on a Shimadzo (8300), ^{1}HNMR spectra were determined by company: Bruker (model: ultra shield 300 MHz), origin: Switzerland (in solvent DMSO), ppm(δ), uses internal standard (TMS). Gallen Kamp melting point apparatus was used for determined uncorrected melting points.

General Experimental Procedures

The reaction sequence leading to the formation of new compounds [IX] and [X] are outlined in Scheme 1.

Synthesis of 4-(1-(4-hydroxyphenyl)ethylidene)hydrazine-1-carbothioamide [G1]

A mixture of 4- hydroxyacetophenone(1.36g ,0.01mol), thiosemicarbazide (0.91g , 0.01mol) in ethanol (20mL) was refluxed for 5hrs. It cool and filters the precipitate until it dried and recrystallized from ethyl acetate. (18)

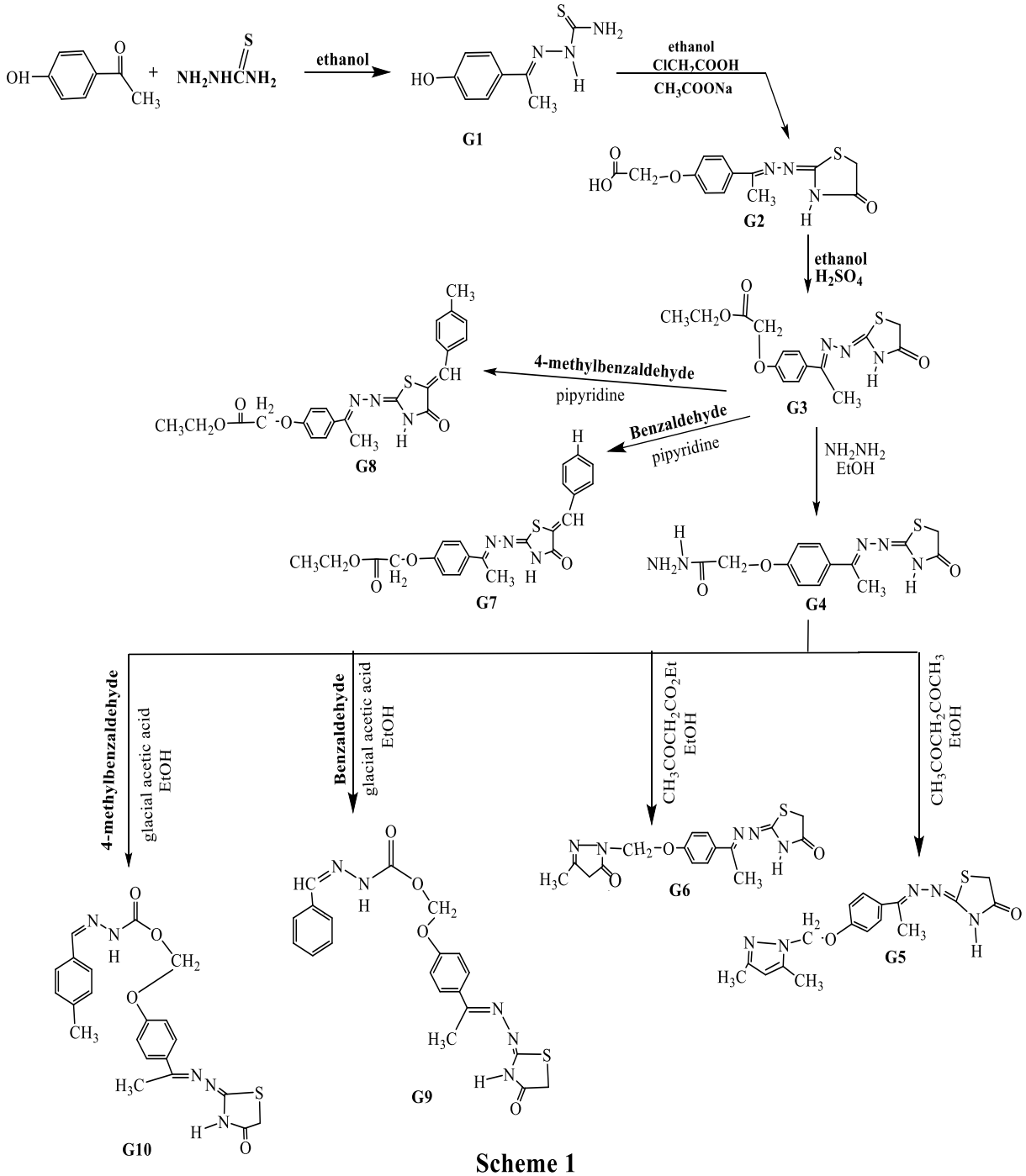
Synthesis of (4-{1-[(4-oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid [G2]

A mixture of compound [G1] (0.001mol) with (0.003mol) for sodium acetate and the (0.003mol) of mono

chloroacetic acid in (5) ml of absolute ethanol was refluxed for 8hrs. in ice water. Then poured the result reaction in to ice water, the formed solid was filtered off and recrystallized from ethanol (19).

Synthesis of (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid ethyl ester [G3]
A mixture compound [G2] (0.001 mol) with 40 ml absolute ethanol, 5 ml of concentrated sulfuric acid was added, the mixture refluxed for (8h.), the end of reaction checked by TLC. Ester was separated by extracted it with water [G3] then the solid formed filtered, drying then recrystallization by using ethanol (20)

Synthesis of (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid hydrazide [G4]
A mixture of compound [G3] (0.01mol) with (0.14mole) hydrazine hydrate 80% in (10) ml of absolute ethanol was refluxed for 3h. After cooling, the formed solid was filtered off and recrystallized ethanol (21).



Scheme 1

Synthesis of (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid hydrazide [G5] and 6-Synthesis of (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazonoethyl}-phenoxy)-acetic acid hydrazide [G6]
A mixture of compound [G4] (0.028 mol) and $CH_3COCH_2COCH_3$ or $CH_3COCH_2CO_2Et$ (0.028 mol) in EtOH (40mL) was heated for 3hrs. The reaction mixture was cooled and the powder solid was filtered off, the recrystallization of new pyrazoles [G5] and pyrazoline [G6] was carried from ethanol (22)

Synthesis of (4-{1-[(5-Benzylidene-4-oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid ethyl ester [G7] and [4-(1-{[5-(4-Methyl-benzylidene)-4-oxo-thiazolidin-2-ylidene]-hydrazono}-ethyl)-phenoxy]-acetic acid ethyl ester [G8].

A mixture of compound [G3] (0.01mole) with (0.025mol) 4-methylbenzaldehyde or banzealdehyde in (1 ml) of pipredine was refluxed for 4hrs. After cooling, the formed solid in R.T.pour the result reaction on ice water the to formed solid, filttered off and recrystallized from ethanol (18)

Synthesis (Schiff bases) of (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazonoethyl}-phenoxy)-acetic acid hydrazide–G9 and (4-{1-[(4-Oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid hydrazide–G10
A mixture of compound [G4] (o.oo6 mol) with (10 ml) ethanol and added (0.006 mol) from benzaldehyde to formed compound [G9] (4-methylbenzaldehyde to formed [G10]) with 3drops of glacial acetic acid, the mixture was refluxed for 3hrs.,after completing the reaction, the solid filtered [G9 , G10] then recrystallized ethanol.

Table 1: Physical properties of the compound

Comp.. No.	Name of structure	Yield %	Melting Points°c	Color
G1	4-(1-(4-hydroxyphenyl) ethylidene) hydrazine-1-carbothioamide	78	219-221	Wight
G2	(4-{1-[(4-oxo-thiazolidin-2-yl-idene)-hydrazono]-ethyl}-phenoxy)-acetic acid	65	240-242	white
G3	(4-{1-[(4-oxo-thiazolidin-2-yl-idene)-hydrazono]-ethyl}-phenoxy)-acetic acid ethyl ester	88	138-140	yellow
G4	(4-{1-[(4-oxo-thiazolidin-2-yl-idene)-hydrazono]-ethyl}-phenoxy)-acetic acid hydrazide	72	202-204	Brown
G5	2-({1-[4-(3,5-dimethyl-4,5-di-hydro-pyrazol-1-yl-methoxy)-phenyl]-ethylidene}-hydrazono)-thiazolidin-4-one	77	248 dec.	yellow
G6	2-({1-[4-(5-Methyl-3-oxo-pyrazolidin-1-yloxymethoxy)-phenyl]-ethylidene}-hydrazono)-thiazolidin-4-one	60	243 dec.	Gray
G7	(4-{1-[(5-Benzylidene-4-oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxy)-acetic acid ethyl ester	75	170	yellow
G8	[4-(1-{[5-(4-Methyl-benzylidene)-4-oxo-thiazolidin-2-ylidene]-hydrazono}-ethyl)-phenoxy]-acetic acid ethyl ester	98	120	yellow
G9	N'-Benzylidene-hydrazinecarboxylic acid 4-{1-[(4-oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxymethyl ester	98	160	yellow
G10	N'-(4-Methyl-benzylidene)-hydrazinecarboxylic acid 4-{1-[(4-oxo-thiazolidin-2-ylidene)-hydrazono]-ethyl}-phenoxymethyl ester	88	202	yellow

RESULTS AND DISCUSSION

The Table: 2 shows the values of the IR spectral absorption stretching bands of all compounds.
Compound [G1] was prepared from reaction of 4-hydroxyacetophenone and thiosemicarbazide in ethanol and diagnosed by the FT-IR spectrum of compound [G1] showed two bands in the field (3363-3178) cm^{-1} due to NH_2, NH and OH stretching and a good band for C=N at 1631 cm^{-1}, stretching band at 1600cm^{-1} for C=C Finally, a sharp peak around 1224 cm^{-1} is attributed of υ C=S stretching.
The compound [G2] was synthesized from the refluxing compound [G1] with sodium acetate and mono chloroacetic acid in absolute ethanol .this compound was diagnosed by the infrared spectrum which appearance new a broad band OH group at 3399 cm^{-1} and at 3323 cm^{-1} for NH stretching. Also showed a good stretching band at 1670 for C=O group. The ^{1}HNMR spectrum (in DMSO-d

as a solvent) of compound [G2] exhibited the following characteristics chemical shifts: (s, 1H, OH)at δ 11.86 ppm and (s, 1H,NH) at δ 9.83ppm, δ(6.80-7.71) ppm for aromatic protons, for protons of CH_2O and CH_2 of cyclic appeared at δ3.03ppm and three protons for CH_3.

The compound [G3] synthesized by esterification of acid compound [G2]in the absolute ethanol and sulfuric acid. The IR spectrum appeared two bands for C=O at (1741 cm^{-1}) and (1271cm^{-1}) it is for ester moiety. The ^{1}HNMR spectrum(in DMSO-d as a solvent) of compound [G3] exhibited the following characteristics chemical shifts: NH appearance at δ(12.02)ppm (s, 1H), aromatic protons at δ(6.80-7.71) ppm, (m, 2H,$\underline{CH_2}$Me) at δ(3.84)ppm, (s, 2H,CH_2) at δ (4.15)ppm for the cyclic moiety, (s, 2H, CH_2) at δ (3.73)ppm for CH_2-CO group, (s,3H,CH_3) at δ (2.31)ppm for N=C-CH_3 group. Finally, three protons of CH_3 terminal group appeared at δ(1.3)ppm.

The compound [G**4**] synthesized by a mixture of [G3] with Hydrazine hydrate 80% in absolute ethanol. Infrared spectrum appearance a new band for NH_2 and NH group in (3319 - 3200)cm^{-1} at the same time disappeared bands for C-O and C=O stretching bands. The compound [G5] and [G6] were synthesized by reflux a mixture of [G4] with CH3COCH2COCH3 or CH3COCH2CO2Et in abs. EtOH for 3hrs. The infrared spectral data were given in Table no. (2). The ^{1}HNMR spectrum (in DMSO-d as a solvent) of compound [G6] exhibited the following characteristics chemical shifts**:** (s,1H,NH) at δ (9.81) ppm, four aromatic protons at δ(6.71-7.76), (s,4H,CH_2-O and CH_2 of thiazolidinone ring) at δ (3.74)ppm, Three protons of CH_3 at pyrazole ring with three protons of C=N-CH_3 appeared as singlet type at δ (2.24)ppm, and for pyrazoline cyclic (s,2H ,CH_2) at δ (1.96)ppm.

A compound [G3] mixting with banzealdehyde or 4-metrhylbenzaldehyde in pipredine under reflux to give compounds [G7] and [G8], respectively. Infrared spectroscopy appeared alkene group for them at the region (1610 -1608) cm^{-1}. The ^{1}HNMR spectrum (in DMSO-d as a solvent) of compound [G7] exhibited the following characteristics chemical shifts: (s,1H,NH) δ(10.1) ppm, (m ,10H, Ar-H and CH for alkene) δ (7.04–7.82)ppm, (s,2H,O-CH_2) δ (3.55)ppm, (s,2H,CH_2C=O) δH=(4.4)ppm, (s,3H,CH_3-C=N) δ(2.45)ppm, (t, 3H, terminal CH_3) δ(1.4)ppm. The ^{1}HNMR spectrum (in DMSO-d as a solvent) of compound [G8] exhibited the following characteristics chemical shifts: (t, 3H, $\underline{CH_3}CH_2$) δ(1.6)ppm, (s, 3H, CH_3C=N) at δ (2.24)ppm, (s ,3H,CH_3ph) at δ(2.31)ppm. (s,4H,CH_2CO and O-CH_2) at δ (3.59)ppm, (m, 4H, Ar. and CH alkene) δ (7.52-7.93)ppm, (s,1H,NH) δ (10.4)ppm.

The Schiff bases [G9] and [G10] produce from the reaction of compound [G4] with aromatic aldehydes in ethanol and glacial acetic acid (3drops). The compound [G9] was diagnosed via infrared spectrum by appeared methine group(-CH=N-) at the region (1620) cm^{-1} at the same time disappeared NH_2 bands. The compound [G10]] was diagnosed via infrared spectrum which was appeared imine group(-CH=N-) at the region (1618) cm^{-1}. The ^{1}HNMR spectrum (in DMSO-d as a solvent) of compound [G10] exhibited the following characteristics chemical shifts: (s,1H,NH) at δ (12. 6)ppm, (s, 1H,-CH=N) at δ (8.74)ppm, (m,8H,Ar-H) at δ(6.85-7.82)ppm, (s,4H,CH_2O and CH_2 cyclic) δH =3.7ppm, (s,3H,CH_3Ph) δH =2.98ppm., (s, CH_3-C=N) δ2.27ppm.

Table 2: Characteristic bands of FT-IR spectrum (cm^{-1}) of compounds

COM. NO.	υNH	υ CH arom.	υ CH aliph.	υC=O	υC=N	υC=C arom.	υ C-S	Others
G1	Overlap with NH2	3020	2972-2933	-	1631	1570	-	υ C=S 1224
G2	3323	3074	2804-2800	1670	1608	1512	791	υ OH : 3394
G3	3188	3054	2985-2858	1691	1641,1601	1514	789	ester: υ C=O, 1741 υ C-O: 1271
G4	Overlap with NH_2	3076	2989-2844	1708	1678,1645	1500	779	υNH2 : 3325 – 3319
G5	3402	3018	2987-2931	1662	1603,1600	1514	785	
G6	3402	3010	2939-2929.	1662	1603	1520	777	
G7	3018	3016	2924-2846	1774	1604,1600	1515	775	υ C=C: 1610
G8	3016	3021	2846-2796	1697	1662, 1608	1504	767	υ C=C 1608
G9	3413	3051	2999-2856	1670	1620	1574	812	
G10	3408	3064	2993-2935	1680	1618	1510	779	

Biological activity

Using diffusion method on the agar plate for new compounds were screened in bacterial activity against gram positive such as *Staphylococcus aureas.* Gram negative such as *Escherichia coli* species (23), The screening results given in the following Table 3.

Table 3: Biological Activity Bacteria of the compounds

COM. NO.	Staphylococcus Aureus (G +)	Escherichia coli (G -)
G1	20	25
G2	11	12
G3	-	12
G4	20	26
G5	11	12
G7	11	12
G8	17	-
G9	13	11
G10	-	11
Control DMSO	-	-

CONCLUSION

In this research, synthesis of new compounds with good results via the available methods and materials. As for the biological study, it gave medium results for positive bacteria are better than negative.

REFERENCES

1. R. O. C. Norman, "Principles of Organic Synthesis", John Wiley & Sons, Inc. New York, 313 (1974).
2. H. L. Yalc and K. Losee. *J. Med. Chem.,* 9, 478 (1966).
3. R.K. Bansal, "Heterocyclic Chemistry" 4th edition, New Age international (P) Limited,Publishers, New Delhi, 2005.
4. A. Guzman-Perez, R. T. Webster, M. C. Allen, J. A. Brown, A. R. Buchholz, E. R. Cook, W. W. Day, E. S. Hamanaka, S. P. Kennedy, D. R. Knight, P. J. Kowalczyk, R. B. Marala, C. J. Mularski, W. A. Novomisle, R. B. Ruggeri, W. R. Tracy, R. J. Hill, *Bioorg Med Chem Lett,* 11, 803(2001).
5. A. E. Amr, N. A. Abdel-Latif, M. M. Abdalla, *Bioorg Med Chem.,* 14, 373 (2006).
6. DA. Horton, GT. Bourne, ML. Smyth, *ChemRev*, 103, 893 (2003).
7. S. G. Kucukguzel, E. E. Oruc, S. Rollas, F. Sahin, A. Ozbek, *Eur. J.Med. Chem*., 37, 197-206 (2002).
8. S. K. Bhati, A. Kumar, *Eur. J. Med. Chem*., 43, 2323-2330 (2008).
9. M. L. Barreca, A. Chimirri, L. De Luca, A. M. Monforte, P. Monforte, , A. Rao, M. Zappalà, J. Balzarini, E. De Clercq, C. Pannecouque, M. Witvrouw, *Bioorg. Med. Chem. Lett*., 11, 1793-1796 (2001).
10. V. Murugesan, Y. S. Prabhakar, B. KattiS., *J. Mol. Graph. Model.*, 27, 735-743 (2009) .
11. J. Blanchet, J. Zhu, *Tetrahedron Letters*, 45, 4449-4452 (2004).
12. J. Balzarini, B. Orzeszko-Krzesinska, J. K. Maurin, *Eur. J. Med. Chem.*, 44, 303-311 (2009).
13. C. Saiz, C. Pizzo, E. Manta, P. Wipf, S. G. Mahler, *Tetrahedron.Lett.*, 50, 901-904 (2009).
14. J. Wrobel, J. Jetter, W. Kao, J. Rogers, L. Di, J. Chi, M. C. Perez, G. C. Chen, E. S. Shen, *Bioorg. Med. Chem. Lett.*, 14, 5729-5741(2006).
15. R. Ottana, R. Maccari, M.L. Barreca, G. Bruno, A. Rotondo, A. Rossi, G. Chiricosta, R. Di-Paola, L. Sautebin, S. Cuzzocrea, M.G. Vigorita, *Bioorg. Med. Chem.*, 13, 4243-4252 (2005).
16. A. Verma, S. K. Saraf, *Eur J Med Chem.,* 43, 897 (2008).
17. A. K. Jain, A. Vaidya, V. Ravichandran, S. K. Kashaw, R. K. Agrawal, *Bioorg Med Chem*., 20, 3378 (2012).
18. A. N. Ayyash, H. J. Jaffer, J. H. Tomma, *American Journal of Organic Chemistry,*4(2), 52-62 (2014).
19. N. M. Jamel, M. T. Tawfiq, I. Y. majeed, J. H. Tomma, *J. Pharm. Sci. & Res.,* 11(9), 3339-3343 (2019).
20. I. Vogel, "A textbook of practical organic chemistry", 3rd Ed Longman Group Ltd., London (1974).
21. Kh. F. Ali, K. M. Lazim, J. H. Tomma, *Ibn Al-Haitham Jour. for Pure & Appl. Sci.,* 27 (3), 422-432 (2014).
22. A. El-masry, H. Fahmy, S. Abdelwahed, *Molecules*, 5, 1429-1438 (2000).
23. B. Al-Zaidi, M. Hasson, M. Ismail, *Journal of Applied Pharmaceutical Science*, 9(04), 045-057 (2019).
24. Chandy, A. Acute aorto-iliac artery occlusion: A rare complication of mitral stenosis (2015) Journal of Cardiovascular Disease Research, 6 (2), pp. 104-105. DOI: 10.5530/jcdr.2015.2.11