ISSN: 0975 -8542

Journal of Global Pharma Technology

Available Online at: www.jgpt.co.in

RESEARCH ARTICLE

Antibacterial Activity of New Synthesized Derivatives 3-Substituted Imidazo Benzothiazole from 2- amino- benzothiazole

Zainab Amer

Department of Chemistry, College of Science, University of Baghdad, Iraq.

Abstract

In this study, bromophenyl phencyl bromide was activated with 2-amino-benzothiazole to prepare 2-bromophenylimidazo (1, 2-a) benzothiazole [1]. Then prepare 2-bromophenyl imidazo (1,2-a) benzothiazol-3-carbaldyhade [2] of the interaction of 2-bromophenyl imidazo (1,2-a) benzothiazol [1] with the presence of $POCl_3$, DMF and CH_3Cl. After that I attended derivatives of Schiff bases [A_1-A_3] were synthesized from the reaction of 2-bromo phenyl imidazo (1, 2-a) benzothiazole-3-carpaldehyde [2] with different primary aromatic amines. New derivatives of oxazepine [B_1-B_3] were prepared from the interaction of amino compounds [A_1-A_3] with malic anhydride. The amino compounds [A_1-A_3] were then reacted with phenyliso cyanide to prepare new beta-lactam compounds [C_1-C_3]. At last, Schiff bases [A_1-A_3] were reduced to prepare new amino derivatives of imidazo (1, 2-a) benzothiazole [D_1-D_3]. All prepared compounds were characterized by melting point and FT-IR. Some of them characterized by ^{1}H-NMR and^{13}C-NMR spectra. Also, antibacterial activities to some prepared derivatives were studied by using different bacteria.

Keywords: *2-amino-benzothiazole, Schiff bases, Oxazepine, Beta-Lactam, Reduction, Antibacterial activity.*

Introduction

Benzothiazole derivatives are bicyclic ring system, having a wide spectrum of biological activities like antimicrobial [1], anthelmintic [2], antifungal [3], antibiofilms [4], anti-urease [5], anti-inflammatory [6] and schistosomicidal activity [7]. Schiff base is can be easily synthesis by condensation reaction of a primary amine with active carbonyl compound [8].

This compound has the importance to prepare because to used as ligand [9] and show biological activities including antimicrobial [10], antibacterial [11] and anticancer activity [12]. Oxazepine is a seven member hetrocyclic, contain two hetro atom (O and N).

It has some important biological properties such as antibacterial [13], analgesic [14], anticoagulant [15] and anticancer [16].ß-Lactam is four-membered hetrocyclic. It is appear interest worldwide in synthesis of enzymes, amino acids and drugs [17-19].

Reduction of azomethine bond by using sodium borohydride was appeared the biological activity of reduced compounds [20].

Preparation Methods

Preparation of 2-bromophenylimidazo (1, 2-a) benzothiazole [1] [21]

Equimolar quantity (0.01 mole) of 2-amino-benzothiazole, bromophenyl phencyl bromide and sodium bicarbonate respectively were dissolved in ethanol (30 ml). The mixture was refluxed for 6 hrs. Then, was added (5 %) of sodium hydroxide to a mixture to made the PH=10. The solid compound product was filtered and recrystallized from ethanol.

Preparation of 2-bromophenylimidazo (1, 2-a) benzothiazole-3-carbaldyhade [2] [22]

(0.01 mole) of phosphourous oxychloride ($POCl_3$) was added drop wise with stirring to dim ethyl form amide (DMF) (0.01 mole) in the flask contain on (20 ml) chloroform in temperature kept aqt (0-5) C^0.

Then, phenyl 2-bromophenylimidazo (1, 2-a) benzothiazole [1] was added to mixture with stirring. This reaction was refluxed for 3 hrs. The obtain solid compound was filtered and purified from ethanol. Tables (1) show all physical properties.

Preparation of Schiff bases [A_1-A_3] [23]

2-bromophenylimidazo (1, 2-a) benzothiazole-3-carbaldyhade [2] (0.01 mole) was dissolved in (30 ml) of absolute ethanol contain (2 ml) of glacial acetic acid, then (0.01 mole) of aromatic primary amines were added. The reaction mixture was refluxed for (5-6) hours. This reaction was allowed to cooled, filtered and recrystallized from ethanol. Table (1) indicates to physical properties and FT.IR of compounds [A_1-A_3]

Preparation of 1, 3-Oxazepine Derivatives [B_1-B_3] [24]

A mixture of equimolar amounts (0.003 mole) of Schiff bases [A_1-A_3] and succinic anhydride in (20 ml) of dry benzene were refluxed for (8 hours). Then, the colour crystal solid was formed and recrystallized with dioxin.

Preparation of β-lactam Derivatives [C_1-C_3] [25]

A mixture of equimolar amounts (0.005 mole) of Schiff bases [A_1-A_3] and phenyl isocyanate in (30 ml) of chloroform was refluxed for (6 hours). Then, the colour crystal solid was formed and recrystallized with ethanol.

Preparation of Aminomethyle Imidazo Benzothiazole Derivatives [D_1-D_3] [26]

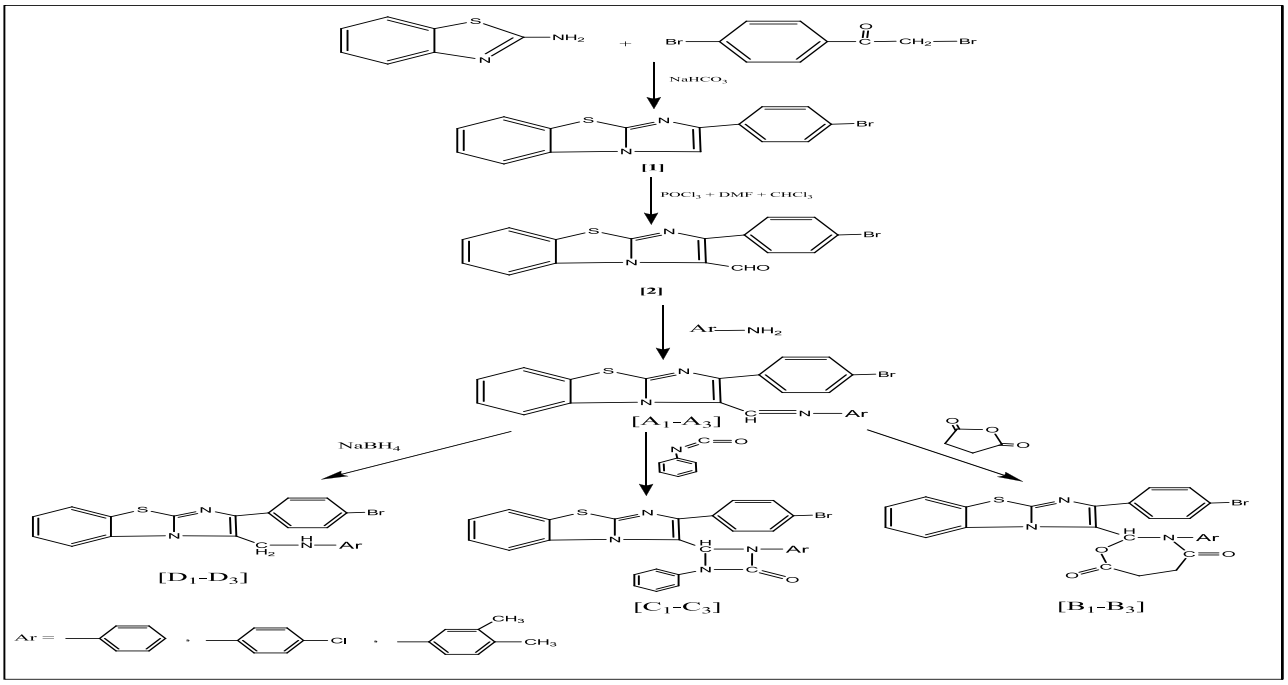
A methanolic solution of Schiff base [A_1-A_3] (0.002 mole) was added to sodium borhydride (0.03 mole) at (0-5) C^0 with stirring for (30 min). Then, this solution was leaved over night at room temperature. The crystal solid was filtered and purified from ethanol.Table (2) indicates to physical properties and FT.IR of compounds [B_1-B_3], [C_1-C_3] and [D_1-D_3].

Biological Activity [27]

By well diffusion method which used to know antibacterial activity for some new prepared compounds in vitro against Gram negative bacteria (*klebsilla pneumonia*) and Gram positive bacteria (*staphylococcus aureus*). Bacteria isolate on to the Muller-Hinton Agar (MHA) by sopping small cotton on a short thin stick and spotting over the surface of plates. Then, five holes were made and putting (0.5 ml) of the synthesized compounds. These plates were incubating at 37 ^{0}C and calculate of zone inhibition after 24 hours.

Results and Discussion

In this prepare, compounds were synthesized from the reaction of 2-bromo phenyl imidazo (1, 2-a) benzothiazole -3- carbaldyhade [2] with three different aromatic amines to produced new Schiff bases [A_1-A_3]. These new compounds [A_1-A_3] reacted with succinic anhydride to prepared new oxazepine derivatives [B_1-B_3], reacted with phenyl isocyanate to prepared new ß-lactam [C_1-C_3] and reduced by sodium borhydride to prepared new derivatives [D_1-D_3] respectively as shown in Scheme (1).



Scheme 1: Synthesis of all compounds

FTIR spectrum of compound [1] showed absorption at [3035, 1575, 1578 and 721] cm^{-1} were belong to the ν(C-H) aromatic, ν(C=C), ν(C=N) imidazo and ν(C-Br) respectively. FTIR spectrum of compound [2] appeared bands at [1691, 1793, 1591, 725] cm^{-1} were due to the ν(C=O), ν(C-H) aldyhede, ν(C=N) imidazo and ν(C-Br). FTIR spectra of compound [A_1-A_3] showed disappearance of absorption band at (1691) cm^{-1} was due to the ν(C=O) and appearance of absorption band at (1618-1636) cm^{-1} was due to ν(C=N) Schiff base, other data were shown in Table [1]. FTIR spectra of oxazepine compounds [B_1-B_3] were appeared bands at (1661-1677) cm^{-1} and (1635-1642) cm^{-1} were attributed to ν(C=O) lactone and ν(C=O) lactam, other data were shown in table [2].

^{1}H-NMR of compound [B_1] showed signals at δ (7.6-8) ppm due to aromatic proton, signal at δ (8.9) ppm belong to proton of oxazepine and signal at δ (2.4) ppm attributed to (CH_2) group. ^{13}C-NMR of oxazepine compound [B_1] appeared signals at δ (109-131) ppm due to aromatic carbon, δ (147) ppm belong to (C-N), δ (159) ppm attributed to (C=O) and δ (130) ppm attributed to (C-S), Table [3] shown other data. FTIR spectra of ß-lactam [C_1-C_3] were observed band at (1700-1712) cm^{-1} due to ν(C=O) lactam group, other data were shown in table [2]. ^{1}H-NMR of ß-lactam [C_3] observed signals at δ (7.6-8.2) ppm due to aromatic proton, δ (6.9) ppm attributed to (CH-N) and δ(2.5) ppm belong to (CH_3) group. ^{13}C-NMR of ß-lactam derivative [C_3] shown signals at δ(110-130) ppm due to aromatic carbon, δ(157) ppm belong to (C-N) and δ(131) ppm attributed to (C-S), Table [3] shown other data. FTIR spectra of reduction Schiff bases [D_1-D_3] showed appearance of absorption band at (3342-3367) cm^{-1} belong to ν (N-H), other data were shown in table [2]. ^{1}H-NMR of compound [D_2] showed signals at δ (7.5-8) ppm due to aromatic proton, signal at δ (8.9) ppm belong to (N-H) and δ(4.3) ppm attributed to (CH_2-N). ^{13}C-NMR of compound [D_2] observed at δ (109-130) ppm belong to aromatic carbon, δ (135) ppm due to (C-N) and δ (137) ppm attributed to (C-S), Table [3] shown other data.

Antibacterial Activity

The prepared compounds [1, 2, A_3, B_1, C_2 and D_3] were examined for antibacterial activity against *staphylococcus aureus* (gram positive) and *Klebsilla pneumonia* (gram negative) by well diffusion method. The results were showed that compounds (1 and 2) inactive against *S. aureus* while compounds (A_3, C_2 and D_3) showed moderately active against *S. aureus* and compound (B_1) was exhibited highly active against these bacteria. Compounds (1, 2, A_3 and C_2) were appeared moderately active against *K. pneumonia* while Compounds (B_1 and D_3) showed highly active against these bacteria. Table [4] showed these result.

Table 1: Physical properties and FTIR spectra data of compounds [1, 2] and [A_1- A_3]

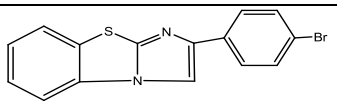
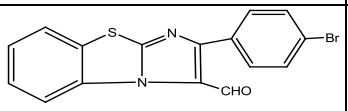
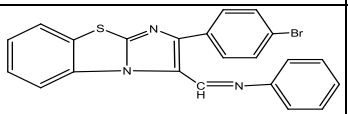
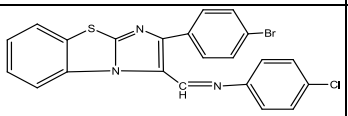
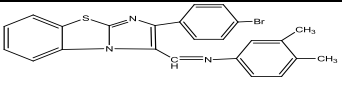
Comp. No.	Compound Structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions cm^{-1}				
					υ(C-H) aromatic	υ(C=N) Imidazo	C=C) υ(aromatic	υ(C-Br)	Others
1		152-155	76	Brown	3035	1587	1575	721	-
2		204-206	96	Green	3010	1591	1578	725	υ(C-H)aldyhede=2793 υ(C=O)=1691
A_1		118-120	54	Off white	3053	1581	1573	746	υ(C=N)Schiff=1636
A_2		115-117	69	yellow	3091	1589	1545	748	υ(C=N)Schiff=1620 υ(C-Cl)= 830
A_3		112-116	52	Off white	3062	1600	1571	740	υ(C-H) aliphatic=2891 υ(C=N)Schiff=1618

Table 2: Physical properties and FTIR spectra data of compounds [B_1-B_3], [C_1-C_3] and [D_1-D_3]

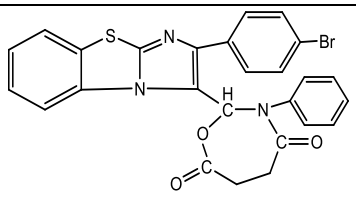
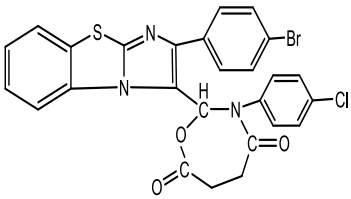
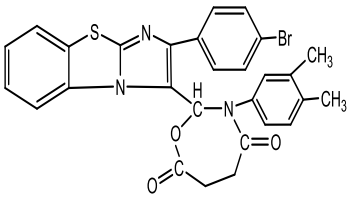
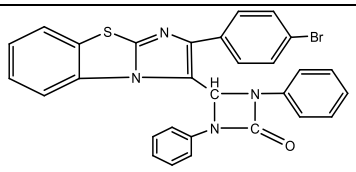
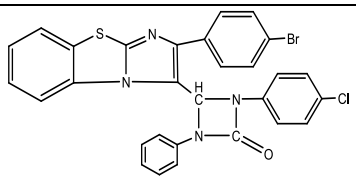
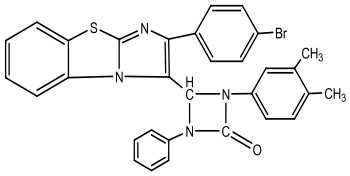
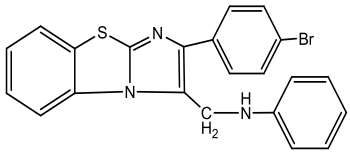
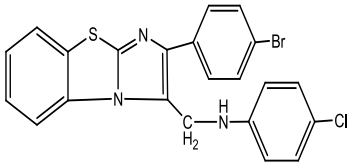
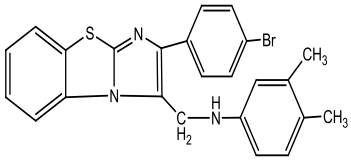
Comp. No.	Compound Structure	M.P. ^{0}C	Yield %	Color	Major FTIR Absorptions cm^{-1}				
					υ(C-H) aromatic	υ(C=N) Imidazo	C=C) υ(aromatic	υ(C-Br)	Others
B_1		100-102	60	Brown	3055	1593	1585	746	υ(C=O)lacton=1676 υ(C=O)lactam=1635
B_2		138-140	80	Brown	3049	1597	1579	752	υ(C=O)lacton=1661 υ(C=O)lactam=1637 υ(C-Cl)=835
B_3		oily	85	Brown	3062	1598	1580	754	υ(C=O)lacton=1677 υ(C=O)lactam=1642 υ(C-H) aliphatic=2900
C_1		oily	70	Off white	3055	1590	1578	748	υ(C=O)ß-lactam=1708
C_2		102-104	55	Off white	3031	1592	1580	739	υ(C=O)ß-lactam=1700 υ(C-Cl)=850
C_3		oily	60	Brown	3063	1589	1578	749	υ(C=O)ß-lactam=1712 υ(C-H) aliphatic=2920
D_1		135-137	70	Brown	3058	1590	1579	740	υ(N-H)sym=3344 υ(N-H)asym=3284
D_2		110-112	65	Brown	3013	1600	1578	746	υ(N-H)sym=3367 υ(N-H)asym=3288 υ(C-Cl)=843
D_3		118-120	40	Brown	3066	1599	1570	729	υ(N-H)sym=3342 υ(N-H)asym=3271 υ(C-H) aliphatic=2898

Table 3: ^{1}HNMR data and ^{13}C-NMR data for compounds [B_1, C_3 and D_2]

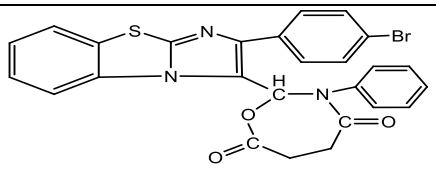
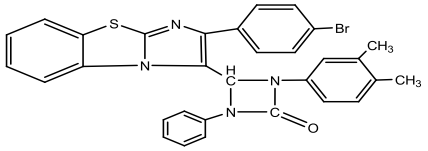
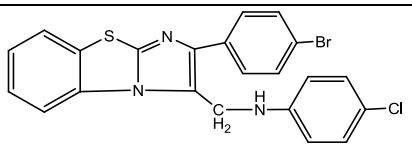
Comp. No.	Compound structure	^{1}H-NMR spectral data δ ppm	^{13}C-NMR spectral data δ ppm
B_1		(7.6-8) aromatic proton, (8.9) H of oxazepine ring and (2.4) CH_2 mehtyl group	(109-131) aromatic carbon, (147) C-N, (157) C=N, (130) C-S and (159) C=O
C_3		(7.6-8.2) aromatic proton , (6.9) CH-N and (2.5) CH_3 group	(110-130) aromatic carbon, (157) C-N, (158) C=N, (131) C-S, (70) CH-N, (158) C=O and (18) CH_3
D_2		(7.5-8) aromatic proton, (8.9) NH and (4.3) CH2 –N	(109-131) aromatic carbon, (135) C-N, (158) C=N, (38) CH2 –N and (137) C-S

Table 4: Antibacterial activity of some prepared compounds

Bacteria / Comp. No.	*Staphylococcus aureus*	*Klebsilla pneumonia*
1	-	10
2	-	12
A_3	11	12
B_1	15	18
C_2	9	10
D_3	10	17

Acknowledgement

I want to thank Dr. Mohanad Masadin Ahl-Albate Universityat Jordan for to examine ^{1}H-NMR and ^{13}C-NMR measurements.

References

1. Rajeeva B, Srinivasulu N, Shantakumar SM (2009) Synthesis and antimicrobial activity of some new 2-substitutedbenzothiazole derivatives. E-J. Chem., (6):775–779.
2. Gaware VM, Dhamak KB, Kotade KB (2016) synthesis and evaluation of benzothiazole derivatives for anthelmintic activity. Ejpmr., 3(5): 454-459.
3. Alessia C, Alessia C, Ivana D, Marilena M, Antonio C, Françoise VB, Antonio R, Filomena C and Carlo F (2013) 2-Amino benzothiazole derivatives: Search for new antifungal agents. European Journal of Medicinal Chemistry, (64):357-364.
4. Ghaneya SH, Fadi M A, Mohamed TS, Ahmed OE and Loah RH (2015) Synthesis of some benzothiazole derivatives evaluated as antimicrobials and antibiofilms. J. Chem. Pharm. Res., 7(7):1125-1143.
5. Yasmeen G, Nasir R, Mnaza N, Faiz HN, Asma Y, Shazia K, Umer R, Iftikhar H, Muhammad Z and Saiful I (2013) Efficient synthesis of 2-amino-6-arylbenzothiazoles via Pd (0) Suzuki cross coupling reactions: potent urease enzyme inhibition and nitric oxide scavenging activities of the products. Molecules, (18):8845-8857.
6. Venkatesh P and Pandeya SN (2009) Synthesis, characterization and anti-inflammatory activity of some 2-aminobenzothiazole derivatives. Int. J. Chem. Tech. Res, 1(4):1354-1358.
7. Mona AM, Samia W, Fatem R, Amira MS (2007) Synthesis and in vitro evaluation of new benzothiazole derivatives as schistosomicidal agents. Molecules, (12):622-633.
8. Mostafa YN, Ibrahim SA, Hasssan AD, Sobhia SA (2018) Synthesis and characterization of some Schiff base complexes derived from 2, 5-dihydroxyacetophenone with transition metal ions and their biological activity. J. Bas. & Environ. Sci., (5):60-71.
9. Jonathan C, Vania A, Mauricio F, Paul H, Carolina M, Jean H, David C (2018) Pentacoordinated chloro-iron (III) complexes with unsymmetrically substituted N_2O_2 quadridentate Schiff-base ligands: syntheses, structures, magnetic and redox properties. Inorganics, 6(5):2-16.

10. Alwan SM, Al-Kaabi J, Hashim R (2014) Synthesis and preliminary antimicrobial activity of new Schiff bases of pyrido [1,2-a] pyrimidine derivatives with certain amino acids. Med. Chem., (4): 635-639.

11. Sahar S, Hoda P, Naser F, Mehran D and Fereshteh M (2018) Cobalt (II) complexes with Schiff base ligands derived from terephthalaldehyde and ortho-substituted anilines: synthesis, characterization and antibacterial activity. Appl. Sci., (8):2-12.

12. Muhammad AA and Karamat MA (2011) Synthesis, Characterization and Biological activity of Schiff bases. International proceedings on Chemical, biological and enviromental engineering, (10):1- 7.

13. Zena G, Redhab AJ and Suaad MH (2017) Synthesis and identification of some new derivatives of oxazpine, thiazinone and hydroquinazoline and evaluation of antibacterial activity. Iraqi Journal of Science. (58):1565-1579.

14. Sawant R, Bhangale L, Wadekar J and Gaikwad P (2012) Substituent selection for design and synthesis of antimicrobial 1, 3 oxazines. A Topliss Modified Approach, (60):32-39.

15. Ramesh LS, Mahesh SM and Jyoti BW (2012) Anticoagulant potential of schiff bases of 1, 3-oxazines. International Journal of Pharmacy and Pharmaceutical Sciences, 4(4):320-323.

16. Ouberai M, Asche C, Carrez D, Croisy A, Dumy P and Demeunynck M (2006) 3,4-DihydroH[1,3] oxazino [4,5c]acridines as a new family of cytotoxic drugs. Bioorganic and Medicinal Chemistry Letters, (16): 4641-4643.

17. Anushree K and Iwao O (2012) Advances in the chemistry of ß-lactam and its medicinal applications. Tetrahedron, (68):10640-10664.

18. Girija SS and Siji S (2014) Advances in synthesis of monocyclic ß-lactams. Arkivoc. 337-385.

19. Rana AA, Zainab Amer, Entesar O Al-Tamimi1 (2018) Synthesis and characterization of substituted 1, 2, 4-triazole and their derivatives on poly ethylene. Journal of Pharmaceutical Sciences and Research, 10(5): 1079-1084.

20. Padmavathi PP, Sushant SP, Rahul ND, Panneer TS, Syed A (2012) Synthesis and antimicrobial activity of novel 2-amino Benzothiazole derivatives. Journal of Pharmacy Research, 5(7): 3830-3833.

21. Rana AA (2018) Preparation, Characterization and Biological Activity of New Derivatives of 3-Cyclic Oxazepine, 3-Cyclic Lactam and 3-Aminomethyl Imidazo (1, 2-a) Benzthiazol. Journal of Global Pharma Technology, 10(06): 80-87.

22. Naeemah Al-Lami, Zainab A, Rana AA (2018) Pryparation, Characterization And Biological Activity of New Derivatives of 2-Biphenyl-3-Aminomethylimidazo (1, 2- a) Pyrimidine. Journal of Pharmaceutical Sciences and Research, 10(12):3344-3350

23. Zainab A (2010) Synthesis and Characterization of New 1, 3-Oxazepine Derivatives and Study of the Biological Activity of Some of these Compounds. M. Sc. Thesis. College of Science, University of Kufa.

24. Zainab A and Hasan Th G (2018) Synthesis and Identification of New Oxazepine Derivatives bearing Azo group in their structures. Iraqi Journal of Science, 59(1A):1-8.

25. Ahmed WN and Atheer MM (2015) Synthesis of some new sulfonamide derivatives based on 1, 3, 4-oxadiazole. J. Chem. Pharm. Res., 7(3):300-306.

26. June SB, More RM, Kadam AB, Mamidwar SU, Kandharkar KB, Kulkarni PA (2012) Direct reductive amination of Shiff bases using sodium borohydride possessing antibacterial activity. Journal of Pharmacy Research, 5(8):4379-4381.

27. Vaca ML, Silva PG, Laciar AL (2009) Comparison of microplate agar drop and well diffusion plate methods for evaluating hemolytic activity of Listeria monocytogenes African Journal of Microbiology Research, 3(6): 319-324.

