International Journal of ChemTech Research
CODEN (USA): IJCRGG, ISSN: 0974-4290, ISSN(Online):2455-9555
Vol.10 No.4, pp 89-96, 2017

Characterization, Synthesis and Study of Biological Activity of new Derivatives of Sulphadiazine

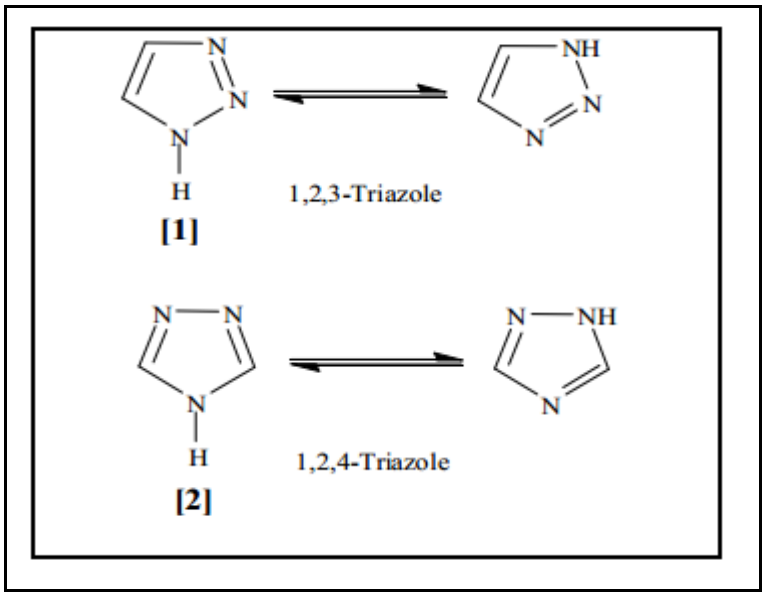
[1]Ezat H. Zmam, *[2]Ahmed W. Radh, [3]Farked W. Salman

[1,3]Department of Chemistry, College of Science, Kufa University, Najf-Iraq
[2]Department of Chemistry, College of Pharmacy, Kufa University, Najf-Iraq

Abstract : Sulphadiazine converted to 2-chloro-*N*-(4-(*N*-pyrimidin-2-yl sulfamoyl) phenyl) acetamide (A) as a result of reacation through chloroacetyl chloride is going to be responded through sodium azide towards form 2-azido-*N*-(4-(*N*-pyrimidin-2-yl-sulfamoyl) phenyl acetamide (B). 1,2,3-triazoline derivatives (S1-S7) were made through cycloaddition responses among substance (B) which includes chalcones. Ready substances were being stamped by T.L.C. , C.H.N.S. explanations, F.T.I.R spectra together with ^{1}H-NMR range. 1,2,3-triazoline derivatives were checked for antibacterial activity.
Keywords : 1,2,3-triazoline, azide,anti bacterial activityandSulphadiazine.

Introduction

Sulfonamides compounds have many kinds of biological activities and agents of this category of pharmacological agents are often utilized in clinics as antithyroid [1], antibacterial [2], hypoglycaemic [3], diuretic [4, 5] and anti-carbonic anhydrase [6,7]. In 1950s Stevens [8] found that Sulfadiazine an antibiotic and Sulfadiazine derivatives were known to show substantial antitumor action [9,10].Barbiturates have been widely used in the past because of their biological properties. Acting on the central nervous system, barbiturates lead to anxiolytics, hypnotics or anticonvulsants. On the other hand, facing the addiction potential of these drugs and the high risk of overdose, this type of compounds started to be replaced.Among these research, studies can be read on new concepts of hypnotics and antiepileptic drugs,[11]fluorinated barbituricacids,[12] and developments of barbiturates in the control of intracranial hypertension or their effects on the GABA receptors[10] (a class of receptors responding to the chief neurotransmitter in the vertebrate central nervous system. Barbiturate by-produccts are key predecessors for preparing biologically active compounds [13].They've been noted to have different pharmacological functions like ant tubercular, antimicrobial, antitumor, anti-inflammatory and anticonvulsant activities [14,15]. 1,2,3- Triazole components present in different compounds show varied biological properties like antibacterial [16], activity against gram positive bacteria [17], anti-fungal [18] , anti-viral activity against many viruses [19] .Triazoles happen to be 5 membered heterocyclic substances possessing 3 nitrogen atoms [20]. Triazoles will be involving 2 forms 1,2,3-triazole as well as 1,2,4-triazole [21]. 1,2,3-Triazole is definitely one associated with 2 isomeric chemical type (1) plus (2) along with molecular formulation $C_2H_3N_3$ that possess 5 representative band regarding 2 carbon atoms as well as 3 nitrogen atoms, 1,2,4-Triazoles that can be generally fragrant heterocyclic these are planer fragrant techniques possessing 6π-electrons having distortion of 6π-system caused inside annular nitrogen.Triazoles of small molecular weights are drugs available for treating anti-inflammatory [22].The present study reports the preparationnew derivatives of sulphadiazine, characterization by C.H.N.S. explanations , F.T.I.R spectra as well as^{1}H-NMR rangeand study biological activity of prepared compounds.



Methods and Materials

Melting points are measured making use of Electronica heat burning stage equipment. F.T.I.R spectra measured by bruker F.T.I.R spectrophotometer, Kufa University. ^{1}H-NMR were measured by Bruker spectrometer, (400MHZ) with DMSO-*d6* because solvent, University of Kashan in Iran.

Synthesis of 2-chloro-*N*-(4-(*N*-pyrimidin-2-yl sulfamoyl) phenyl) acetamide (A)

(0.01 mol) of Sulfadiazine and (1.6 ml) triethylamine in DMF as solvent, (0.01 mol) chloroacetyl chloride was introduced drop by drop. The mixture of reaction was shaken with (Three or more hours.) plus in the direction of this conclusion associated with this effect; this solvent vaporized. Ultimately this product was re-crystallized and filtered from ethanol and dried.

T.L.C. (benzene : ethanol 4:1) (R*f*, 0.59) (m.p. 220-222, yield 87%)

Anal. Calc. for $C_{12}H_{11}ClN_4O_3S$; H%3.39; N% 17.15; S% 9.81, C% 44.11

Found N% 16.98, H% 3.88 S% 9.78, C% 43.92

I.R spectra; Amide (N-H) str. (3440)cm^{-1} , Sulfone(N-H) str. (3375)cm^{-1}**,** (C=O) (1680)cm^{-1}, Aromatic ring (1400-1620)cm^{-1}, (C=N) str. Pyrimidine ring (1530) cm^{-1} and (C-Cl) (760) cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) (Ar-H) (6.82-7.88), (HC=N) pyrimidine ring (8.79), Sulfone(N-H) (11.25) and Amide (N-H) (10.12)

Synthesis of 2-azido-*N*-(4-(*N*-pyrimidin-2-yl-sulfamoyl) phenyl acetamide (B)

(0.01 mol) of Sodiumazide was added to (0.01 mol) a fix associated with 2- chloro-*N*-(4-(*N*-pyrimidin-2 ylsulfamoyl) phenyl) acetamide [A] inside (11ml) DMF as solvent. Reaction combination had been after that refluxed on (90 ^{0}C) with regard to about (7 hours.) while moving. This solvent vaporized, The product had been precipitated, filtered and washed thoroughly with diethyl ether. Then, the product was re-crystallized through deride and ethanol.

Produce (75 %), m.p. (118-120 ^{0}C) and R*f*(0.56) (benzene : ethanol, 4:1).

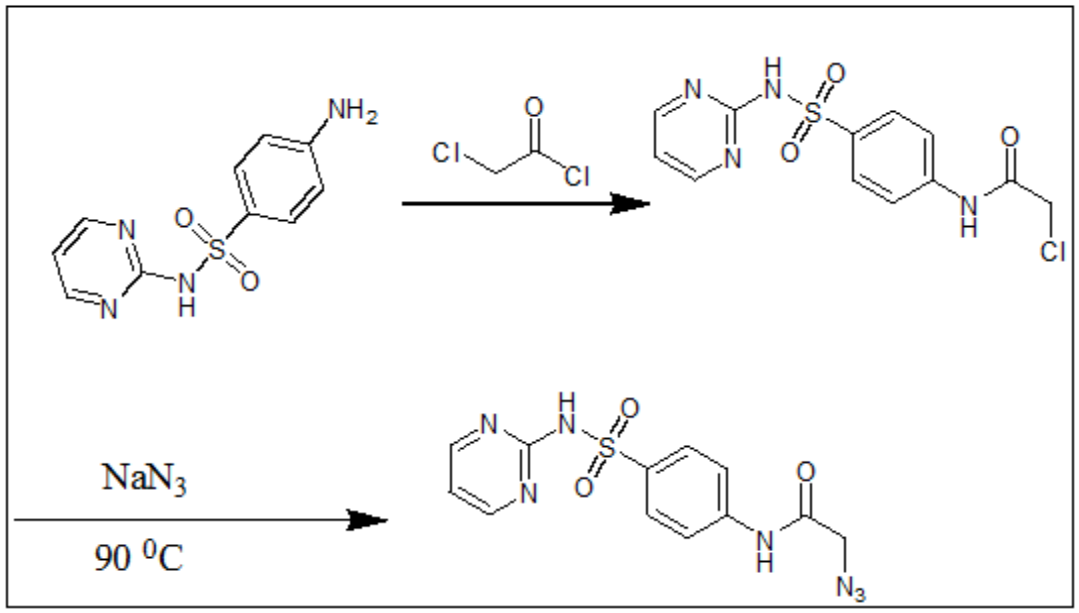
Anal. Calc. for $C_{12}H_{11}N_7O_3S$; H% 3.33; N% 29.41; S% 9.62, C% 43.24

Found N% 29.07, H% 3.25, S% 9.56,C% 43.16

I.R spectra: Amide(N-H) str. (3450)cm^{-1} , Sulfone(N-H) str. (3345)cm^{-1}, (N_3) str. (2117) cm^{-1}

,(C=O) (1685)cm^{-1}, Aromatic ring(1400-1620)cm^{-1} and (C=N) str. Pyrimidine ring (1525) cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) (Ar-H) (6.75-7.79), (HC=N) pyrimidine ring (8.82), Sulfone(N-H) (11.22), Amide (N-H) (10.13)



Scheme (1)

Forming of 1,2,3-triazoline derivatives (S1-S7)

1,2,3-triazoline derivatives were made by reaction between (0.02 mol) 2-azido-*N*-(4-(*N*-pyrimidin-2-yl-sulfamoyl) phenyl acetamide (B) had been blended within DMF as solvent (50 ml) and chalcons were synthesized in our previous study [23] (0.01 mol) was introduced into the solution. This mixture is then refluxed at 110 ^oC for about 24 hrs. This solvent seemed to be evaporated. This item had been brought on, filtered as well as laundered thoroughly through diethyl azure. Finally product was re-crystallized through ethanol and deride.

- 1,3-bis(oxomethylene)bis(5-(4-(dimethylamino)phenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(*N*-(4-(*N*-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S1)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.43) , (m.p. 212-214, yield 71%)

Chemical Formula: $C_{54}H_{56}N_{18}O_{11}S_2$

Anal. Calc. H%, 4.71; N%, 21.06, S%5.36,C%, 54.17

Found. H % 4.62; N%19.796; S% 5.216,C% 54.01

I.R spectra: Amide (N-H) str. ((3410)cm^{-1} , Sulfone(N-H) str. (3330)cm^{-1}(C-Har., 3060) cm^{-1}, (C-Hal., 2970 cm^{-1}, Amide (C=O 1666) cm^{-1}, (C=N) str. Pyrimidine ring(1530) cm^{-1}, (Aromatic ring (1420-1610)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.702), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.23), ((6H) (N-(C<u>H</u>$_3$)$_2$ 3.2),(CO-C<u>H</u>$_2$-) 3.36), (HC=N) pyrimidine ring (8.82),Amide (N-H) (10.31),Sulfone(N-H) (11.20) , ((Ar-H)) 6.577-7.893))

- 1,3-bis(oxomethylene)bis(5-(4-bromophenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S2)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.44) , (m.p. 277-279, yield 76%)

Chemical Formula: $C_{50}H_{44}Br_2N_{16}O_{11}S_2$

Anal. Calc. H%, 3.50; N%, 17.66; S%, 5.05, C%,47.33

Found : H % 3.432; N%16.87, S%, 4.98,C% 47.17

I.R spectra: I.R spectra:(C-Har., 3060) cm^{-1}, (C-Hal., 2976 cm^{-1}, Amid (C=O 1680) cm^{-1}, Amide (N-H) str. ((3380)cm^{-1} , (C=N) str. Pyrimidine ring (1550) cm^{-1} ,(C-Br ,720) cm^{-1}, (Aromatic ring (1420-1620)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.703), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.31),(CO-CH_2-) 3.34), (HC=N) pyrimidine ring (8.82),Amid(N-H) (10.29) , Sulfone(N-H) (11.22) , ((Ar-H)) 6.62-7.889),.

- 1,3-bis(oxomethylene)bis(5-(3-hydroxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S3)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.50) , (m.p. 176-179, yield 80%)

Chemical Formula:$C_{50}H_{46}N_{16}O_{13}S_2$

Anal. Calc. H%, 4.06; N%, 19.60, S%, 5.61,C%, 52.53

Found: N%18.89, H% 3.98); S%, 5.44,C% 52.34

I.R spectra:(O-H ,3360) cm^{-1} , (C-Har., 3060) cm^{-1}, (C-Hal., 2965)cm^{-1},Amid (C=O 1685) cm^{-1}, Amide (N-H) str. ((3360)cm^{-1} , (C=N) str. Pyrimidine ring (1540) cm^{-1}, (Aromatic ring) (1420-1600)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.703), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.22),(CO-CH_2-) 3.34), ((1H) (O<u>H</u>)8.68)), (HC=N) pyrimidine ring (8.83), Amid(N-H) (10.32), Sulfone(N-H) (11.28) , ((Ar-H)) 7.21-8.021)

- 1,3-bis(oxomethylene)bis(5-(4-nitrophenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S4)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.42) , (m.p. 234-236, yield 83%)

Chemical Formula:$C_{50}H_{44}N_{18}O_{15}S_2$

Anal. Calc.H%, 3.69; N%, 20.99, S%, 5.34C%, 50.00

Found :N% 20.49, H%3.49; S%, 5.221,C% 49.82

I.R spectra:(C-Har., 3073) cm^{-1}, (C-Hal., 2977)cm^{-1}, Amid (C=O 1660) cm^{-1}, (N-H) str. ((3370)cm^{-1} , (C=N) str.Pyrimidine ring(1540) cm^{-1} (NO_2,1355) cm^{-1}, (Aromatic ring) (1427-1598)cm^{-1}

^{1}H-NM R spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.703), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.22),(CO-CH_2-) 3.33), (HC=N) pyrimidine ring(8.84) , Amid (N-H) (10.30),Sulfone (N-H) (11.22), ((Ar-H)) 7.223-8.232))

- 1,3-bis(oxomethylene)bis(5-(4-hydroxy-3-methoxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S5)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.47) , (m.p. 288-290 , yield 82%)

Chemical Formula: $C_{52}H_{50}N_{16}O_{15}S_2$

Anal. Calc. H%, 4.19; N%, 18.63, S%, 5.33,C%, 51.91

Found: N% 18.42, H% 3.981 ;S%, 5.22,C% 51.58

I.R spectra:(O-H ,3380) cm^{-1} , (C-Har., 3070) cm^{-1}, (C-Hal., 2978)cm^{-1}, Amide (C=O1678) cm^{-1}, Amide (N-H) str. ((3380)cm^{-1} , (C=N) str. Pyrimidine ring(1546) cm^{-1}, (Aromatic ring) (1425-1600)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.703), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.21),(CO-C<u>H</u>$_2$-) 3.34), ((3H) (O-C<u>H</u>$_3$) 3.36), ((1H) (O<u>H</u>)8.51)), (HC=N) pyrimidine ring (8.843), Amide (N-H) (10.32),Sulfone (N-H) (11.24), ((Ar-H)) 7.043-8.34)

- 1,3-bis(oxomethylene)bis(5-(4-hydroxyphenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S6)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.49) , (m.p. 266-268, yield 80%)

Chemical Formula:$C_{50}H_{46}N_{16}O_{13}S_2$

Anal. Calc. H%, 4.06; N%, 19.60, S%,5.61,C%, 52.53

Found: N%19.43, H% 4.01; S%, 5.49,C% 52.29

I.R spectra:(O-H ,3380) cm^{-1} , (C-Har., 3060) cm^{-1}, (C-Hal., 2970)cm^{-1}, Amide (C=O 1660) cm^{-1}, Amide (N-H) str. ((3380)cm^{-1} , (C=N) str. Pyrimidine ring (1545) cm^{-1}, (Aromatic ring) (1420-1610)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.702), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.203),(CO-C<u>H</u>$_2$-) 3.36), ((1H) (O<u>H</u>)8.83)), (HC=N) pyrimidine ring(8.85),Amide (N-H) (10.33), Sulfone(N-H) (11.32) , ((Ar-H))7.212-8.211)

- 1,3-bis(oxomethylene)bis(5-(4-chlorophenyl)-4,5-dihydro-1,2,3-triazoline-4,1(diyl))bis(N-(4-(N-pyrimidin-2-ylsulfamoyl)phenyl)acetamide)Veronal (S7)

T.L.C. (benzene : methanol, 4:1) (R*f*, 0.43) , (m.p. 199-201, yield 80%)

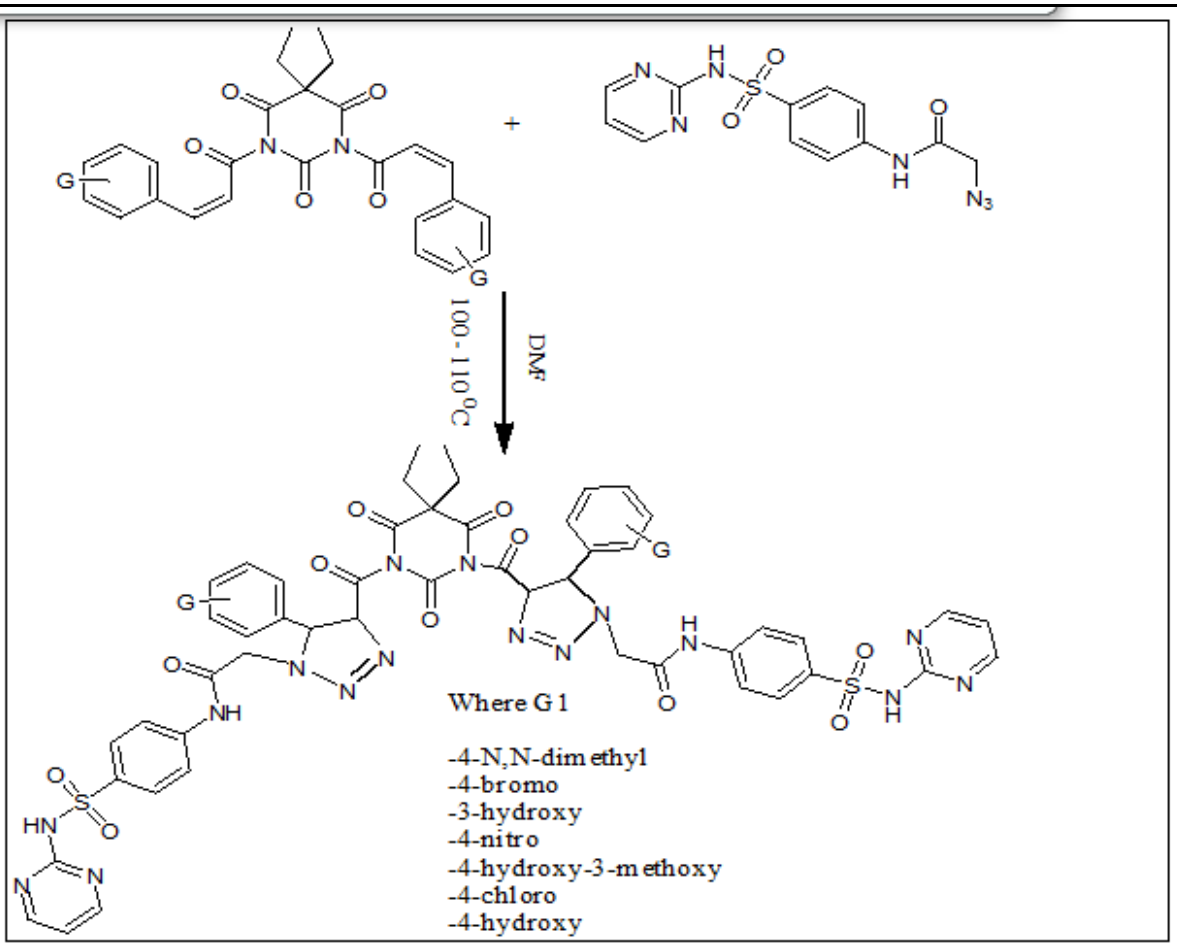
Chemical Formula: $C_{50}H_{44}C_{l2}N_{16}O_{11}S_2$

Anal. Calc. H%, 3.76; N%, 18.99, S%, 5.43,C%, 50.89

Found:N% 18.43, H% 3.29; S%, 5.31,C% 50.63

I.R spectra: (C-Har., 3056) cm^{-1}, (C-Hal., 2978)cm^{-1},Amid (C=O 1660) cm^{-1}, Amid (N-H) str. ((3390)cm^{-1} , (C=N) str. Pyrimidine ring(1530) cm^{-1}, (C-Cl, 686) cm^{-1}, (Aromatic ring) (1420-1606)cm^{-1}

^{1}H-NMR spectrum, (δ ppm), (DMSO-*d6*) ((6H) (-C<u>H</u>$_3$) 0.702), ((4<u>H</u>), (-C<u>H</u>$_2$-) 2.33),(CO-C<u>H</u>$_2$-) 3.33), (HC=N) pyrimidine ring (8.84),Amid (N-H) (10.33), Sulfone(N-H) (11.34), ((Ar-H)) 7.063-8.122))



Scheme(2)

Results and Discussion

In the present research the synthesis of some new 1,2,3-triazoline derivatives were achieved fromSulphadiazine.Sulphadiazine was converted to 2-chloro-*N*-(4-(*N*-pyrimidin-2-yl sulfamoyl) phenyl) acetamide (A) through reacting by using chloroacetyl chlorideas well astriethylamineinside the DMF as solvent. 2-azido-*N*-(4-(*N*-pyrimidin-2-yl-sulfamoyl) phenyl acetamide (B) through reacting (A) having sodium azide. This (C.H.N.S) analysis of synthesized compound (A) and (B) was accepted agreement with the calculated percentage of elements. The F.T.I.R spectra of this compound and ^{1}H-NMR spectrum good evidence for formatted compounds (scheme 1).

Chalcones compounds [23] were synthesized in our previous study condense with 2-azido-*N*-(4-(*N*-pyrimidin-2-yl-sulfamoyl) phenyl acetamide (B) to give 1,2,3-triazoline derivatives(S1-S7). The [C.H.N.S] analysis of synthesized compounds] were accepted agreement with the calculated percentage of elements. The F.T.I.R spectra of these compounds and ^{1}H-NMR spectrum consider good evidence for formatted our compounds (scheme 2).

Antibacterial activity test

Sulphadiazine derivatives (S1-S7) were screened with regard to antiseptic action in opposition to Pseudomonas aeruginosa, Escherichia coli as well as Staphylococcus aureusin Muller Hinton agar. [24] by measuring the inhibition zone in (mm). Azithromycin (250 µg/ µL) was the chosen standard drug for antibacterial activity. Each bacteria isolate was inoculated on to the Muller-Hinton Agar [sterilize in autoclave] by dipping a cotton swab in to the suspension and streaking over the surface of the agar plates. Then, in the solidified medium, four holes were made (6 mm). These holes were filled with (0.5 ml) of the prepared

compounds ((250 µg/ µL) of the compound dissolved in 1ml of DMSO solvent). These plates were incubated at 37 ^{0}C and measured of zone inhibition after 48 hours. The results are presented in Table 2.

Table 1 Antibacterial activities of compound

Comp. No.	Escherichia coli		Staphylococcus aureus		Pseudomonas aeruginosa	
	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition
S1	35	175	35	185.5	30	100
S2	45	275	35	185.5	0	0
S3	50	250	25	132.5	35	116.67
S4	20	100	30	159	20	66.6
S5	35	175	0	0	30	100
S6	25	125	30	159	20	66.6
S7	40	200	35	185.5	30	100
S.T.	20	100	28	100	30	100

St., standard (Azithromycin

When we show the data of (inhibition zone %) of all compounds in Table 2 we noticed some key results:Compounds (S1-S7) showed good activity against Escherichia coli. But (S5) showed nil activity against Staphylococcus aureus, whereas the other compounds showed good activity against Staphylococcus aureus. Also we showed compounds (S1,S3,S4,S5,S6 and S7) have good activity against Pseudomonas aeruginosa.

References

1. J. Drews, Science; 287 (2000) 1960–1964.
2. C.W. Thornber; Chem. Soc. Rev.; 8 (1979) 563–580.
3. C.T. Supuran, A. Scozzafava; Exp. Opin. Ther. Patents; 10 (2000) 575–600.
4. T.H. Maren; Annu. Rev. Pharmacol. Toxicol.; 16 (1976) 309–327.
5. A.E. Boyd 3rd, Diabetes; 37 (1988) 847–850.
6. C.T. Supuran, A. Scozzafava; Curr. Med. Chem. Immunol. Endocr.Metabol. Agents; 1 (2001)61–97.
7. C.D. Stevens, P.M. Quinlin, M.A. einken, Science (1950) 112:561.
8. F. Zunino and G. Savi; Inorganica ChimicaActa;80(1983) 99-102.
9. V. A. Yadrovskaya, G. V.Bornovalova, E. P. Savina, I. Ispenkova and V. G. Skvortsov; Pharmaceutical Chemistry Journal; 22(1988)532.
10. N. Moussier,L. Bruche, F.Viani, M. Zanda, Curr. Org. Chem.2003, 7 (10), 1071-1080
11. H. M.Shapiro, Br. J. Anaesth. 1985; 57 (1), 82-95.
12. R. G.; Sans, M. G.Chozas, Pharmazie 1988, 43 (12), 827-9.
13. A.A.El-Tombary, S.A.M. El-Hawash, N.S.Habiba, R. Soliman, L.M. El-Ashmawy and O.G. Shaaban,Med.Chem., 9(2013)1099-1112.
14. D.S. Badiger, R.S. Hunoor, B.R. Patil, R.S.Vadavi, C.V. Mangannavar, I.S. Muchchandi,Y.P. Patil, M. Nethaji, and K.B. Gudasi, Inorganica Chem. Acta. 384(2012)197-203.
15. O.M.I. Adly and A.A.A.Emara, SpectrochimicaActc Part a-Molecular Biomol. Spectrosc.132(2014) 91-101.
16. H.B. Ghodasara, A.R. Trivedi, V.B. Kataria, B.G. Patel and V.H. Shah, Med.Chem. Res.22(2013)6121-6128.

17. V.D. Bock, H. Hiemstra and J.H. Maarseveen,Eur. J. Org. Chem. ,51(2006) 456-462.
18. Li Z. X., xue P., Ysunt H., Williams D., Sharpless K.B., Fokin V.V. and Jia G. ; J. Am. Chem., Soc; 127(2005) 15998-15999.
19. M. Al-Amin and M. Rabiul Islam; Bangladesh J Pharmacol; 1(2006), 21-26.
20. D.R. Buckle, C.J. Rockell, H.Smith,and B.A. Spicer, J. Med. Chem. 29(1986) 2262 -2267.
21. R. Alvarez , S.Velazquez, A.San-Felix , S. Aquaro,E. D. Clercq, C.F. Perno,A. Karlsson,J. Balzarini, andM.J.Camarasa, J. Med. Chem. , 37 (1994) 4185- 4194.
22. E. D. Clercq Nature Rev. Drug Discovery , 1(2002) 13-25.
23. W. R. Ahmed, Der Pharmacia Lettre, 8 (19) (2016), 450-456.
24. S. J. Wadher , M. P. Pulanik , N. A. Karande and P. G .Yeole ; Int. J. Pharm Tech Res.; 1(1) (2009) P. 22-33 .

*****