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RESEARCH ARTICLE

SYNTHESIS, CHARACTERIZATION AND STUDY BIOLOGICAL ACTIVITY OF NEW 1, 2, 3-TRIAZOLINE DERIVATIVES OF SULFADIAZINE

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ABSTRACT

In this study, Sulfadiazine reacted with ($NaNO_2$)and (HCl) to form diazonum salt was converted to 4-azido-*N*-(pyrimidin-2-yl)phenylsulfonamid (An) by reaction with sodium azide. 1,2,3-triazoline derivatives (B1-B10) were synthesized viaclick reaction, Huisgen 1,3-dipolar cycloadditionbetween compound (An) with chalcones and unsaturated compound like maleicanhydride, acrylamide, p-benzoquinone and cinnamylalcohol in presence cuprous chloride and sodium ascorbate.Identification of products by elemental analysis C.H.N.S., FT-IR spectra and ^{1}H-NMR spectrum. 1,2,3-triazoline derivatives compounds were screened for antibacterial activity.

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INTRODUCTION

4-amino-*N*-pyrimidin-2-yl-benzenesulfonamide Sulfadiazine, is a sulfonamide group of antibiotic which has been used in veterinary and human therapy over 60 years (Al-Abachi and Al-Talib, 1995), sulfadiazine compounds have applied as standard topical therapy for patients with partial-thickness burns. (Miller *et al*., 2012) Heterocyclic compounds play an important role in antibacterial and biological activity particularly. (Chen *et al*., 2014) Five member ring contain nitrogen atomheterocycles have important in biological activity (Anand *et al*., 2009). Triazoles possess a different biological properties, such as antibacterial, anti-fungal (Buckle *et al*., 1986), antituberculosis agents (Bagihalli *et al*., 2008; Karthikeyan *et al*., 2006; Dabak *et al*., 2003; Shanmugavelan *et al*., 2011; Joshi *et al*., 2004; Kai *et al*., 2012), antiviral compounds against many viruses (Holla *et al*., 2003) anticancer compounds (Wamhoff *et al*., 1984), anti-HIV (Tiew *et al*., 2012), neuraminidase inhibitors (Turan-Zitouni *et al*., 1999) and plant growth regulators (He *et al*., 2012). 1,2,3 –triazoles and 1,2,3 –triazoline were synthesized by Huisgen 1,3-dipolar cycloadditionclick reactions between azideswith alkynes to prepare 1,2,3 –triazoles or with alkenes to prepare 1,2,3 –triazolines in found cuprous chloride or cuprous iodide and sodium ascorbate. (Oh *et al*., 2012; Guezguez *et al*., 2006; Rostotsev *et al*., 2002; Tornøe *et al*., 2002; Chan *et al*., 2004) The other method, 1,2,3–triazoles and 1,2,3–triazolinesformation requires vigorous conditions, that is, longer reaction timesand high temperature, they could take from 12 to 48 hours at high temperatures (~110 C°) (Fu *et al*., 2005).

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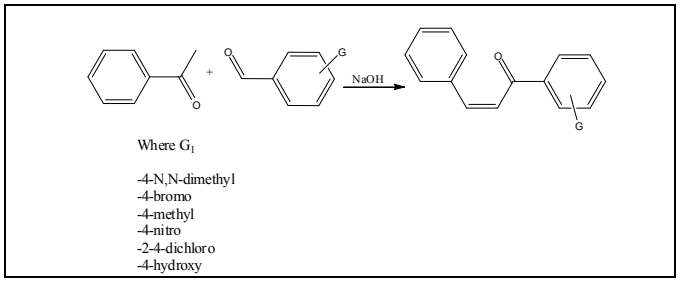
MATERIALS AND METHODS

All solvents used were redistilled. I.R spectra were recorded on Schimadzu I.R- 408 spectrophotometer. Elemental analysis was performed using a Perkin- Elmer 204E Instrument. ^{1}HNMR spectrum were recorded on Bruker 300MHz. Thin layer chromatography (T.L.C) were performed on a silica- gel SG- 40 (Merck) and developed with the solvents mentioned, spots were visualized with Iodine vapor.

General procedure for synthesis chalcones

To a stirred mixture of (60 mmol) of acetophenon(60mmol) of aromatic aldehydes in (15 mL) ethanol at room temperature, 25% NaOH aqueous solution was added droop wise which stirring was continued for further(30-50) mint. Then, the reaction was completed depended on TLC technique (hexane: ethylacetate, 4:1). The color precipitate formed was filtered and washed with 3% aqueous HCl, then with distilled water and re-crystallized from ethanol.



Scheme (1)

Synthesis4-azido-*N*-(pyrimidin-2-yl)phenylsulfonamid (An)

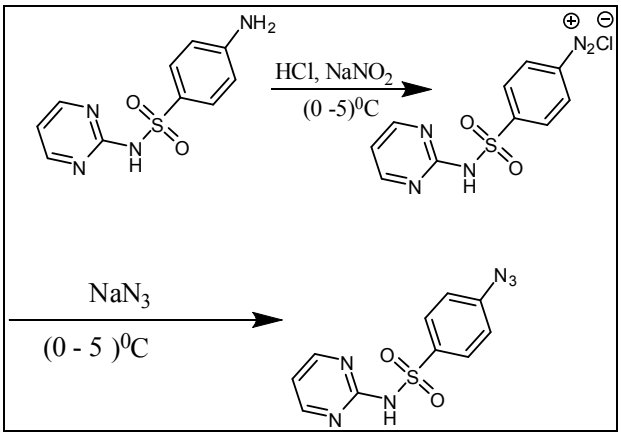
Sulfadiazine (80 mmole) was dissolved in (1.7ml) of concentrated hydrochloric acid and (10 ml) of distilled water. The mixture was cooled at (0-5 ^{0}C) in ice-water bath. Then a solution of sodium nitrite (0.01mol) was dissolved in (5 ml) of distilled water then it will be cooled at (0-5 ^{0}C). This solution was added a drop wise to the mixture with stirring. The diazonum salt solution was added portion wise to solution of (80 mmol) of sodium azideand controlled temperature at (0-5^{0}C). The mixture was stirred for 30 mint. The mixture was left over night. The product was separated by filtration, washed with distilled water several times and re-crystallized from ethanol.

Chemical Formula: $C_{10}H_8N_6O_2S$

Elemental Analysis:

Calculate: C% 43.47; H% 2.92; N%30.42; S% 11.61
Found: C% 43.299, H% 2.898, N% 30.223, S% 11.441)
(m.p. 223-225, yield 87%)

IR (KBr disc, cm^{-1}): 3432 (N-H sulfonamide Str), 3077 (Aryl C-H), 1537 (C=N str), 1312 (SO_2sulfonamide sym.)1147 (SO_2Asym.str.), 1426-1633(Aromatic ring), 1129 cm^{-1} (N_3str).



Scheme (2)

Synthesis of 1,2,3-triazoline derivatives (B1-B10)

(1,1 mmo) l of 4-azido-*N*-(pyrimidin-2-yl) phenylsulfonamid (A) and(1,1 mmol) of chalcones, maleicanhydride, acrylamide, p-benzoquinone and cinnamylalcohol were dissolved in DMF (20ml). To this mixture was added CuCl(0.2 mmol) and sodium ascorbate (0.4 mmol). The solution was stirred at (60-70 ^{0}C) until T.L.C. indicated the reaction was completed and consumption of the azide. The mixture was diluted with diethyl ether and water. The organic phase was separated, and the water phase was extracted tow times with diethyl ether. The organic phase were dried over MgSO4. Removal of the solvent and recrystallized from hexanes -chloroform.

- 4-(4-(4-(dimethylamino)benzoyl)-5-phenyl-4,5-dihydro-1-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide (B1)

Chemical Formula: $C_{27}H_{25}N_7O_3S$

Elemental Analysis:

Calculate: C, 61.47; H, 4.78; N, 18.58; S, 6.08

Found: C, 61.261; H, 4.687; N, 18.454; S, 6.021
m.p. 140-142, yield 81%

IR (KBr disc,cm^{-1}): 3352 (N-Hsulfonamide Str), 3070 (Aryl C-H),2960,2843 (Alkyl C-H),1661 (C=O amidstr), 1537 (C=N str), 1312 (SO_2sulfonamide sym.)1147 (SO_2Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*):11.321 (SO_2-NH), 8.724 (HC=Npyrimidine ring), 4.003 (C-Htriazoline ring),8.615-6.625 (Aryl C-H),3.19 (N-$(CH3)_2$.

- 4-(4-(4-bromobenzoyl)-5-phenyl-4,5-dihydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B2)

Chemical Formula: $C_{25}H_{19}BrN_6O_3S$

Elemental Analysis, Calculate: C, 53.29; H, 3.40; N, 14.92; S, 5.69

Found: C, 53.099; H, 3.310; N, 14.832; S, 5.498
m.p. 202-204, yield 78%
IR (KBr,cm^{-1}): 3350 (N-HStr),3090 (Aryl C-H),,1660 (C=O str), 1545 (C=N str), 1159 (SO_2Asym.str.), 1423-1600 (Aromatic ring), 780 (C-Br).

^{1}HNMR (δ ppm), (DMSO-*d6*): 11.221 (SO_2-NH), 8.744 (HC=N pyrimidine ring), 4.013 (C-Htriazoline ring), 8.415-6.635 (Aryl C-H).

- 4-(4-(4-methylbenzoyl)-5-phenyl-4,5-dihydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B3)

Chemical Formula: $C_{26}H_{22}N_6O_3S$

Elemental Analysis:

Calculate: C, 62.64; H, 4.45; N, 16.86; S, 6.43
Found : C, 62.489; H, 4.397; N, 16.776; S, 6.333
m.p. 166-168, yield 80%
IR (KBr disc, cm^{-1}): 33542 (N-HsulfonamideStr), 3077 (Aryl C-H), 2940, 2840 (Alkyl C-H),1670 (C=O amidstr), 1537 (C=N str), 1320 (SO_2sulfonamide sym.)1140 (SO_2Asym.str.), 1425-1600 (Aromatic ring).
^{1}HNMR (δ ppm), (DMSO-*d6*): 11.22 (SO_2-NH), 8.778 (HC=N pyrimidine ring) , 4.111 (C-Htriazoline ring), 8.44-6.4 (Aryl C-H), 2.678 (CH_3).

- 4-(4-(4-nitrobenzoyl)-5-phenyl-4,5-dihydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B4)

Chemical Formula: $C_{25}H_{19}N_7O_5S$

Elemental Analysis:

Calculate : C, 56.70; H, 3.62; N, 18.52; S, 6.06
Found : C, 56.661; H, 3.611; N, 18.42; S, 6.011
m.p. 134-136, yield 84%

IR (KBr disc, cm^{-1}): 3333 (N-HsulfonamideStr), 3077 (Aryl C-H), 1676 (C=O amid str), 1548 (C=N str), 1327(SO_2 sulfonamide sym.)1140 (SO_2Asym.str.), 1425-1600 (Aromatic ring), 1490 (NO_2Str sym.) 1330(NO_2StrAsym).

^{1}HNMR (δ ppm), (DMSO-*d6*): 11.21 (SO_2-NH), 8.646 (HC=N pyrimidine ring), 4.223 (C-Htriazoline ring), 8.66-6.636 (Aryl C-H).

- 4-(4-(2,4-dichlorobenzoyl)-5-phenyl-4,5-dihydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B5)

Chemical Formula: $C_{25}H_{18}Cl_2N_6O_3S$

Elemental Analysis:

Calculate : C, 54.26; H, 3.28; N, 15.19; S, 5.79

Found : C, 54.122; H, 3.18; N, 15.019; S, 5.619

m.p.199-201 , yield 74%
IR (KBr disc,cm^{-1}): 3354 (N-HsulfonamideStr),3070 (Aryl C-H),1687 (C=O amid str),1540 (C=N str), 1333 (SO_2sulfonamide sym.) 1136 (SO_2Asym.str.), 1425-1600 (Aromatic ring), 670 (C-ClStr).

^{1}HNMR (δ ppm), (DMSO-*d6*): 11.301 (SO_2-NH), 8.743(HC=N pyrimidine ring), 4.131 (C-Htriazoline ring), 8.677-6.676 (Aryl C-H).

- 4-(4-(4-hydroxybenzoyl)-5-phenyl-4,5-dihydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B6)

Chemical Formula: $C_{25}H_{20}N_6O_4S$

Elemental Analysis:

Calculate: C, 59.99; H, 4.03; N, 16.79;S, 6.41
Found : C, 59.889; H, 4.012; N, 16.679;S, 6.331
m.p. 187-189, yield 72%
IR (KBr disc, cm^{-1}):3420 (O-HStr), 3343 (N-HsulfonamideStr), 3066 (Aryl C-H), 1671 (C=O amidStr), 1566 (C=N str), 1341 (SO_2sulfonamide sym.),1130(SO_2 Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*): 11.311 (SO_2-NH), 8.79 (HC=N pyrimidine ring), 4.213 (C-Htriazoline ring), 8.611-6.434 (Aryl C-H), 8.321 (OH).

- 4-(4,7-dioxo-3,4,7,7-tetrahydro-1-benzo-1,2,3triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B7)

Chemical Formula: $C_{16}H_{12}N_6O_4S$

Elemental Analysis:

Calculate : C, 50.00; H, 3.15; N, 21.86;S, 8.34

Found : C, 49.98; H, 3.005; N, 21.776;S, 8.214
m.p. 144-146, yield 77%
IR (KBr disc, cm^{-1}):3329 (N-HsulfonamideStr), 3090 (Aryl C-H), 1690 (C=O amid Str), 1560 (C=Nstr), 1328 (SO_2 sulfonamide sym.), 1141(SO_2 Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*): 11.233 (SO_2-NH), 8.88 (HC=N pyrimidine ring), 3.887 (C-Htriazoline ring), 8.75-6.875 (Aryl C-H), 6.52 (CH=CH) P-benzoqunone.

- 4-(4,6-dioxo-3,4,6,6-tetrahydro-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B8)

Chemical Formula: $C_{14}H_{10}N_6O_5S$

Elemental Analysis:

Calculate : C, 44.92; H, 2.69; N, 22.45;S, 8.57

Found : C, 44.782; H, 2.499; N, 22.345;S, 8.447
m.p. 168-170, yield 78%
IR (KBr disc, cm^{-1}):3344 (N-HsulfonamideStr) ,3082 (Aryl C-H), 1688 (C=O amid Str), 1549 (C=N str), 1320 (SO_2 sulfonamide sym.), 1131(SO_2Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*) : 11.201 (SO_2-NH), 8.694 (HC=N pyrimidine ring) , 4.213 (C-Htriazoline ring), 8.64-6.33 (Aryl C-H).

- 1-(5-carboxamyl)-1,2,3-triazole-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B9)

Chemical Formula: $C_{13}H_{13}N_7O_3S$

Elemental Analysis:

Calculate: C, 44.95; H, 3.77; N, 28.23;S, 9.23

Found : C, 44.775; H, 3.667; N, 28.123;S, 9.133
m.p. 188-190 , yield 82%

IR (KBr disc, cm^{-1}):3377 (N-HsulfonamideStr), 3300 (NH_2 Str), 3088(Aryl C-H),1660 (C=O amidStr) ,1544 (C=N str), 1309 (SO_2sulfonamide sym.),1122(SO_2Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*) : 11.44 (SO_2-NH), 8.66 (HC=N pyrimidine ring) , 3.892 (C-Htriazoline ring), 8.233-6.78(Aryl C-H),2.919 (CH_2-OH), 4.399 (CH_2-OH).

- 4-(5-(hydroxymethyl)-4-phenyl-1,2,3-triazol-1-yl)-N-(pyrimidin-2-yl)benzenesulfonamide(B10)

Chemical Formula: $C_{19}H_{18}N_6O_3S$

Elemental Analysis:

Calculate : C, 55.60; H, 4.42; N, 20.48; S, 7.81
Found: C, 55.498; H, 4.322; N, 20.38; S, 7.771
m.p. 178-180 , yield 80%

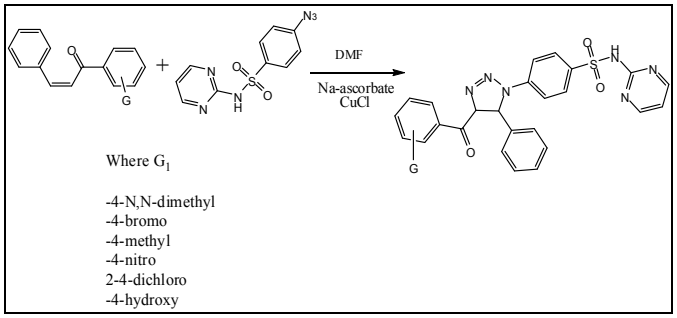
IR (KBr disc,cm^{-1}):3340 (N-HsulfonamideStr), 3416 (OHStr), 3070(Aryl C-H), 2942,2830 (Alkyl C-H),1540 (C=N str), 1333

Table 1. Antibacterial activities of compounds (B1-B10)

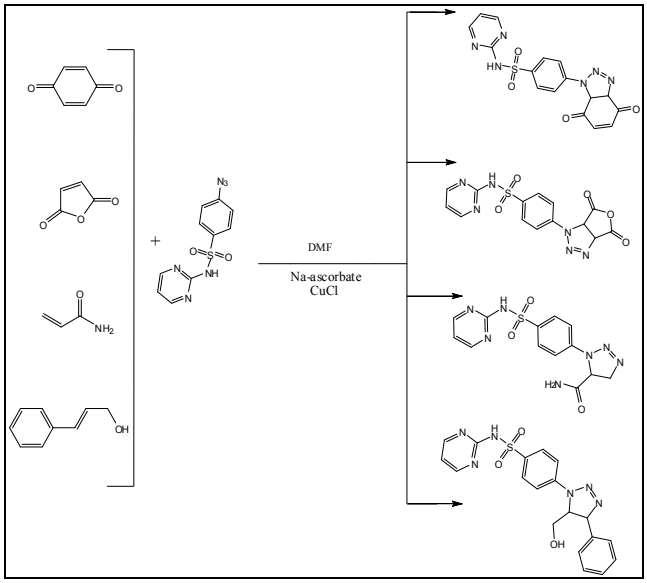
Comp. No.	Escherichia coli		Staphylococcus aureus		Pseudomonas aeruginosa	
	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition	Zone of inhibition (mm)	% Inhibition
B1	10	50	0	0	34	133.33
B2	35	175	35	185.5	0	0
B3	45	225	0	0	35	116.67
B4	5	25	30	159	0	0
B5	0	0	25	132.5	30	100
B6	0	0	30	159	20	60
35	175	225	25	132.5	40	133
B8	20	100	28	100	30	100
B9	10	50	20	120	5	16.6
B10	15	75	30	159	10	33

(SO_2 sulfonamide sym.), 1132(SO_2Asym.str.), 1425-1600 (Aromatic ring).

^{1}HNMR (δ ppm), (DMSO-*d6*) : 11.387 (SO_2-NH), 8.884 (HC=N pyrimidine ring) , 4.117 (C-Htriazoline ring), 8.415-6.787 (Aryl C-H), 7.178 (CO-NH_2).



Scheme (3)



Scheme (4)

RESULTS AND DISCUSSION

In this paper, synthesized of some new 1,2,3-triazoline derivatives were achieved from Sulfadiazine which converted to 4-azido-*N*-(pyrimidin-2-yl)phenylsulfonamid was prepared in previous study. (Ahmed, 2016) Chalcones are prepared viareaction between acetophenone and aromatic benzaldehydein found sodium hydroxide as catalyst, followed by dehydration to yield the desire chalcones. The products was accepted and agreement with theliterature. (Ezhilarasi *et al*., 2015) 1,2,3-triazoline derivatives(B1-B10) were synthesized by click reaction between Chalcones and unsaturated compounds like (maleicanhydride, acrylamide, p-benzoquinone and cinnamylalcohol) and 4-azido-N-(pyrimidin-2-yl) phenylsulfonamid (An)in found sodium ascorbate and cuprous chloride as catalyst. The [C.H.N.S] analysis of synthesized compounds were accepted agreement with the calculated percentage of elements. The F.T.I.R spectra appears consumption of the azide of 4-azido-*N*-(pyrimidin-2-yl)phenylsulfonamid and disappears band at 2130 cm^{-1}due to azide group.^{1}H-NMR spectrum considergood evidence for formatted our compounds (scheme 3).

Antibacterial activity test

All synthesized compounds (B1-B10) were screened for biological activity (antibacterial) against some types of bacteria such as Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa. Muller Hinton agar method (Wadher et al., 2009) was used to measuring the inhibition zone in (mm). The results are presented in Table 1.

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