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Synthesis, characterization and antimicrobial study of oxobutanoate

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ABSTRACT

Various sulfonamide derivatives on reaction with ethylactoacetate furnished different ethyl-3-oxo-2-(2-(3-(N-alkyl sulfamoyl) phenyl) hydrazono) butanoates **(2(a-j))**. All the novel synthesised compounds **(2(a-j))** were characterized by spectral studies. The compounds showed significant antimicrobial activity against various bacteria and fungi.

KEYWORDS

Oxobutanoate;
Spectral studies;
Antimicrobial.

INTRODUCTION

Sulpha drugs are bacteriostatic and are also referred to as antibacterials. The sulphonamides are synthetic antimicrobial agents with a wide spectrum encompassing most Gram-positive and many Gram-negative organisms. These drugs were the first efficient treatment to be employed systematically for the prevention and cure of bacterial infections. The another compound say,oxobutyrate is an efficient cathodic inhibitor[1]. Ethyl 2-arylhydrazono-3-oxobutyrates showed significant antimicrobial activity[2]. The hydrazone products, ethyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-3-oxobutyrate and methyl 2-[(3,5-dimethylpyrazole-4-yl)hydrazono]-4-methoxy-3-oxobutanoate showed inhibition against *M. tuberculosis*, respectively[3]. The oxobutanoate derivatives gives many heterocyclic compounds[4-9]. Hence the present paper comprises the synthesis and characterization of novel 3-oxo-butanoate derivatives shown in schemes 1.

EXPERIMENTAL

All chemicals used were of laboratory grade. Various sulfonamide derivatives **(1(a-j))** were prepared by reported method.[10] Melting points were determined in open capillary tubes and were uncorrected. IR spectra were recorded in KBr pellets on a Nicolet 760D spectrometer. ^{1}H NMR and ^{13}C NMR spectra were recorded in DMSO with TMS as internal standard on a Bruker spectrometer at 400 MHz and 100 MHz, respectively. LC-MS of selected samples taken on LC-MSD-Trap-SL_01046 instrument.

Ethyl 3-oxo-2-(2-(3-sulfamoylphenyl) hydrazono) butanoate (2a)

3-aminobenzenesulfonamide **(1a)** (0.01mole) was dissolved in a mixture of HCl (8ml) and water (6ml) and cooled to 0°C in ice bath. To it a cold aqueous solution of sodium nitrate (0.03mole) was added. The diazonium salt solution was filtered into a cooled solution of ethyl actoacetate (0.01mole) and sodium acetate (0.12mole) in ethanol (50ml). The resulting solid was washed with water and recrystallized from EtOH/MeOH. Yield 84%; m.p.166-168°C. IR [ν,cm^{-1},KBr]:3034-3086(C-Haromatic),2920,1465 (CH_3, CH_2),1290(C-N),1725-1765 (C=O), 1148(C-O),1325(SO_2),905(S-N), 3369(N-H), 1695-1540 (C=N), 706-585(C-S). ^{1}H NMR [400MHz,δ, ppm,

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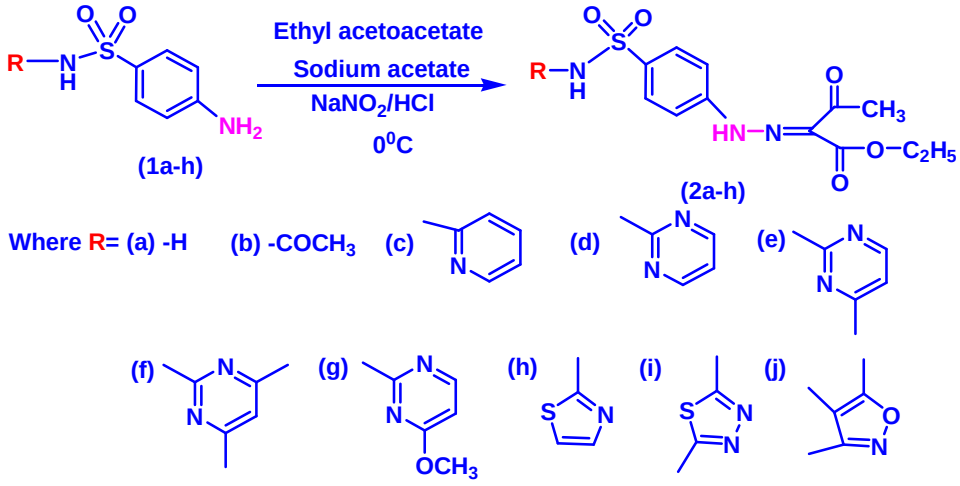

Schemes 1

DMSO-d_6]:1.34 (t,3H,CH_3), 4.29 (q,2H, $COCH_2$), 2.35(s,3H,$COCH_3$),6.90-7.67(m,4H,ArH),11.62(s,1H,NH),7.42(s, 2H,NH).^{13}CN-MR [100MHz, δ, *ppm*, DMSO]: 114.8 -143.6(Ar-C),14.2,26.9(CH_3), 61.4(CH_2), 165.4, 195.4 (CO). LC-MS:*m/z*321(M^+).*Anal.* Calcd for $C_{12}H_{15}N_3O_5S$ (313): C, 46.00; H, 4.83; N, 13.41; S, 10.23. Found: C, 45.9; H, 4.8; N, 13.4; S, 10.2.

Ethyl 2-(2-(3-(N-acetylsulfamoyl) phenyl) hydrazono) -3- oxobutanoate (2b)

N-(3-aminophenylsulfonyl)acetamide **(1b)** (0.01mole) was dissolved in a mixture of HCl (8ml) and water (6ml) and cooled to 0°C in ice bath. To it a cold aqueous solution of sodium nitrate (0.03mole) was added. The diazonium salt solution was filtered into a cooled solution of ethyl actoacetate (0.01mole) and sodium acetate (0.12mole) in ethanol (50ml). The resulting solid was washed with water and recrystallized from EtOH/MeOH. Yield 81%;m.p.156-158°C.IR[ν,cm^{-1},KBr]: 3034-3086(C-Haromatic), 2920, 1465 (CH_3, CH_2),1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2),905(S-N),3369(N-H), 1695-1540 (C=N), 706-585(C-S). ^{1}H NMR [400MHz,δ,ppm, DMSO- d_6] :1.34 (t, 3H,CH_3), 4.29 (q, 2H,$COCH_2$), 2.37(s, 6H,$COCH_3$),6.90-7.67 (m, 4H,ArH), 11.62 (s, 1H,NH),7.45(s, 1H,NH).^{13}C N-MR [100 MHz, δ, *ppm*, DMSO]: 114.8-143.6(Ar-C),14.2,22.3,26.9 (CH_3),61.4(CH_2),165.4,192.4, 195.4(CO). LC-MS: *m/z* 367(M^+). *Anal.* Calcd for $C_{14}H_{17}N_3O_6S$ (355): C, 47.32; H, 4.82; N, 11.82; S, 9.02. Found C, 47.3; H, 4.8; N, 11.8; S, 8.9.

Ethyl 3-oxo-2-(2-(3-(N-pyridin-2-ylsulfamoyl) phenyl) hydrazono) butanoate (2c)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 76%; m.p.173-175°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic), 2920, 1465 (CH_3, CH_2), 1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2),905(S-N),3369(N-H), 1695-1540 (C=N), 706-585(C-S).^{1}H NMR [400MHz, δ,ppm, DMSO- d_6] : 1.34(t, 3H,CH_3), 4.29 (q, 2H, $COCH_2$),2.35 (s,3H, $COCH_3$), 6.90-7.72(m, 8H,ArH),11.62 (s,1H,NH),7.54(s,1H,NH). ^{13}CN-MR [100MHz, δ, *ppm*, DMSO] : 114.8-154.6(Ar-C),14.2,26.9(CH_3), 64.8(CH_2), 165.4, 195.4 (CO).LC-MS:*m/z* 402 (M^+). *Anal.* Calcd for $C_{17}H_{18}N_4O_5S$ (390): *C, 52.30; H, 4.65; N, 14.35;S, 8.21*. Found: *C, 52.2; H, 4.6; N, 14.3; S, 8.1.*

Ethyl 3-oxo-2-(2-(3-(N-pyrimidin-2-ylsulfamoyl) phenyl) hydrazono) butanoate (2d)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 78%; m.p.148-149°C. IR [ν,cm^{-1},KBr]:3034-3086(C-Haromatic),2920,1465 (CH_3, CH_2),1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2),905(S-N),3369(N-H), 1695-1540 (C=N), 706-585(C-S). ^{1}H NMR [400MHz, δ,ppm, DMSO- d_6] : 1.34 (t, 3H,CH_3), 4.29 (q, 2H, $COCH_2$), 2.35(s, 3H,$COCH_3$),6.90-7.73(m, 7H,ArH),11.62 (s, 1H,NH),7.42(s, 1H,NH). ^{13}C N-MR [100 MHz, δ, *ppm*, DMSO] : 114.8-170.6(Ar-C), 14.2,26.9 (CH_3), 61.4 (CH_2), 165.4, 195.4 (CO).LC-MS:*m/z* 406 (M^+).

Anal. Calcd for $C_{16}H_{17}N_5O_5S$ (391): *C, 49.10; H, 4.38; N, 17.89; S, 8.19*. Found: *C, 49.0; H, 4.3; N, 17.8; S, 8.1*.

Ethy l2-(2-(3-(N-(4-methylpyrimidin-2-yl)sulfamoyl)phenyl)hydrazono)-3-oxobutanoate (2e)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 77%; m.p.143-145°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic), 2920,1465 (CH_3, CH_2),1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2), 905 (S-N),3369(N-H),1695-1540 (C=N), 706-585(C-S). ^{1}H NMR [400MHz, δ,ppm, DMSO- d_6] :1.34(t,3H,CH_3),4.29 (q, 2H,$COCH_2$), 2.35 (s, 3H, $COCH_3$), 6.90-8.30(m, 6H,ArH),11.62(s,1H,NH),7.44(s,1H,NH),2.34(s,3H,CH_3). ^{13}C NMR [100MHz, δ, *ppm*, DMSO] : 114.8-170.6(Ar-C),14.2,24.5,26.9 (CH_3),61.4, (CH_2), 165.4, 195.4 (CO).LC-MS:*m/z* 413 (M^+). *Anal.* Calcd for $C_{17}H_{19}N_5O_5S$ (405): *C, 50.36; H, 4.72; N, 17.27; S, 7.91*. Found: *C, 50.3; H, 4.7; N, 17.2; S, 7.9*.

Ethyl 2-(2-(3-(N-(4,6-dimethylpyrimidin-2-yl)sulfamoyl)phenyl)hydrazono)-3-oxobutanoate (2f)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 76%; m.p.145-147°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic), 2920,1465 (CH_3, CH_2),1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2),905(S-N),3369(N-H), 1695-1540 (C=N) 706-585(C-S). ^{1}H NMR [400MHz,δ,ppm,DMSO-d_6]: 1.34 (t,3H,CH_3), 4.29(q, 2H,$COCH_2$),2.35(s, 3H, $COCH_3$), 6.90-8.30(m, 5H,ArH),11.62(s, 1H,NH),7.44(s, 1H, NH), 2.34 (s, 6H,CH_3). ^{13}C N-MR [100 MHz, δ, *ppm*, DMSO] : 114.8-170.6(Ar-C), 14.2, 24.5,24.7, 26.9 (CH_3), 61.4,(CH_2), 165.4, 195.4 (CO). LC-MS:*m/z* 427(M^+). *Anal.* Calcd for $C_{18}H_{21}N_5O_5S$ (419): C, 51.54; H, 5.05; N, 16.70;S, 7.64. Found: C, 51.5; H,4.9; N, 16.6;S, 7.6.

Ethyl 2-(2-(3-(N-(4-methoxypyrimidin-2-yl)sulfamoyl)phenyl)hydrazono)-3-oxobutanoate (2g)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 76%; m.p.147-149°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic),2920,1465 (CH_3, CH_2), 1290(C-N),1725-1765(C=O),1148(C-O),1325(SO_2),905(S-N),3369(N-H), 1695-1540 (C=N), 1380(C-O) 706-585(C-S).^{1}H NMR [400MHz, δ,ppm, DMSO- d_6] : 1.34(t, 3H,CH_3), 4.29 (q, 2H,$COCH_2$), 2.35(s,3H,$COCH_3$),6.90-7.67(m,6H,ArH),11.62(s,1H,NH),7.42 (s,1H,CH_3), 3.92(s, 3H,CH_3). ^{13}C N-MR [100 MHz, δ, *ppm*, DMSO] : 114.8-167.6(Ar-C),14.2, 26.9,50.8 (CH_3), 61.4(CH_2), 165.4, 195.4 (CO). LC-MS:*m/z* 436(M^+). *Anal.* Calcd for $C_{17}H_{19}N_5O_6S$ (422): *C, 48.45; H, 4.54; N, 16.62; S, 7.61*. Found: *C, 48.4; H, 4.5; N, 16.6; S, 7.6*.

Ethyl 3-oxo-2-(2-(3-(N-thiazol-2-ylsulfamoyl) phenyl) hydrazono) butanoate (2h)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 78%; m.p.141-143°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic),2920,1465 (CH_3, CH_2), 1290(C-N), 1725-1765(C=O),1325(SO_2),905(S-N),3369(N-H),1695-1540 (C=N),706-585(C-S). ^{1}HNMR [400 MHz,δ,ppm,DMSO- d_6] : 1.34(t, 3H,CH_3), 4.29 (q, 2H,$COCH_2$),2.35(s, 3H,$COCH_3$), 6.90-7.50(m, 6H,ArH),11.62 (s, 1H,NH), 7.42 (s, 1H, NH). ^{13}C N-MR [100 MHz, δ, *ppm*, DMSO] :114.8-171.8(Ar-C),14.2,26.9(CH_3),61.1(CH_2),165.4,195.4(CO).LC-MS:*m/z* 408 (M^+). *Anal.* Calcd for $C_{15}H_{16}N_4O_5S_2$ (396): C, 45.44; H, 4.07; N, 14.13; S, 16.18. Found: C, 45.4; H, 3.9; N, 14.1; S, 16.1.

Ethyl 2-(2-(3-(N-(5-methyl-1,3,4-thiadiazol-2-yl) sulfamoyl) phenyl) hydrazono)-3-oxo butanoate (2i)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 81%; m.p.142-144°C. IR [ν,cm^{-1},KBr]: 3034-3086(C-Haromatic),2920, 1465(CH_3, CH_2), 1290(C-N), 1725-1765(C=O),1325(SO_2),3369(N-H),1695-1540(C=N), 706-585(C-S). ^{1}HNMR [400MHz, δ,ppm, DMSO- d_6] : 1.34(t, 3H,CH_3), 4.29 (q, 2H,$COCH_2$), 2.35 (s, 3H,$COCH_3$), 6.90-7.50(m, 4H,ArH),11.62 (s, 1H,NH),7.42 (s, 1H,NH), 2.66(s, 3H, CH_3). ^{13}C N-MR [100 MHz,δ, *ppm*, DMSO] :114.8-174.8(Ar-C), 14.2,19.3,26.9 (CH_3), 61.1(CH_2),165.4,195.4(CO).LC-MS:*m/z* 423 (M^+). *Anal.* Calcd for $C_{15}H_{17}N_5O_5S_2$ (411): *C, 43.79; H, 4.16; N, 17.02; S, 15.59*. Found: *C, 43.7; H, 4.1; N,*

16.9; S, 15.5.

Ethyl 2-(2-(3-(N-(3,4-dimethylisoxazol-5-yl)sulfamoyl) phenyl) hydrazono)-3-oxobutanoate (2j)

Prepared as per the procedure mentioned for compound **(2a)** and **(2b)**. Yield 83%; m.p.139-141°C. IR [ν,cm^{-1},KBr]:3034-3086(C-Haromatic), 2920,1465 (CH_3, CH_2), 1290(C-N), 1725-1765(C=O),1325(SO_2),3369(N-H), 1695-1540 (C=N), 1040(O-N),706-585(C-S).^{1}HNMR [400M Hz, δ,ppm, DMSO- d_6] : 1.34(t, 3H,CH_3), 4.29 (q, 2H,$COCH_2$), 2.35(s,3H,$COCH_3$), 6.90-7.50(m,4H,ArH),11.62(s,1H,NH),7.42(s,1H,NH), 2.25(s, 6H,CH_3). ^{13}C N-MR [100 MHz, δ, *ppm*, DMSO] : 114.8-162.8(Ar-C),9.5,11.8,14.2,26.9 (CH_3),61.1 (CH_2), 165.4,195.4(CO).LC-MS:*m/z* 416 (M^+). *Anal.* Calcd for $C_{17}H_{20}N_4O_6S$ (408) : C, 49.99; H, 4.94; N, 13.72; S,7.85. Found: C, 49.9; H, 4.9; N, 13.7; S, 7.8.

RESULTS AND DISCUSSION

The synthesis of **(1a-h)** has been performed based on the method reported[10]. From these compounds the novel compounds **(2a-h)** have been synthesized. All the compounds were confirmed on the basis of the elemental analysis and spectroscopic investigation. IR spectroscopic investingation of **(2a-h)** reveals bands at 1640-1596(C=N) and ^{1}H NMR δ 11.62(s, 1H,NH). The examination of these data reveals that the IR band and ^{1}H NMR signals are appropriate to the correspond structure of compound. The final structure of all compounds was confirmed by ^{13}C NMR and LC- MS data, i.e. The compounds **(2a)** shows the molecular ion peak *m/z* 326 give the molecular weight of **2a** i.e. 313. All these facts confirm the structures **(2(a-j))**.

Antibacterial activities

Antibacterial activities of all the compounds were studied against Gram–positive Bacteria (*Bacilus subtilis* and *Staphyllococcus aureus*) and Gram-negative Bacteria (*E.coil, Salmonella typhi* and *Klebsiella promioe*) at a concentration of 50μg/ml by Agar cup plate method. Methanol system was used as control in this method. Under similar condition using sulphonamide as a standard for comparison carried out control experiment. The area of inhibition of zone measured in mm. Compound **(2e)** and **(2f)** found more active against the above microbes. Other compounds were found more active against the above microbes. The antibacterial activities all compounds are shown in TABLE 1.

TABLE 1 : Antibacterial activity of ethyl-3-oxo-2-(2-(3-(N-alkyl sulfamoyl)phenyl) hydrazono)butanoates 2(a-j)

Compounds	Zone of Inhibition(mm) (Activity Index)^{std}				
	Gram+ve		Gram–ve		
	Bacillus Subtilis	*Staphylococcus Aureus*	*Kllebsiella promioe*	*Salmonella typhl*	*E.coil*
2a	53 (0.62)	46 (0.83)	66 (0.80)	61 (0.88)	67 (0.93)
2b	46 (054)	50 (0.90)	75 (0.91)	63 (0.91)	65 (0.90)
2c	80 (0.94)	46 (0.83)	76 (0.92)	64 (0.92)	62 (0.86)
2d	81 (0.95)	49 (0.89)	74 (0.90)	61 (0.88)	67 (0.93)
2e	84 (0.98)	54 (0.98)	80 (0.97)	67 (0.97)	70 (0.97)
2f	82 (0.96)	52 (0.94)	78 (0.95)	65 (0.94)	69 (0.95)
2g	78 (0.91)	49 (0.89)	74 (0.90)	60 (0.86)	66 (0.91)
2h	80 (0.94)	48 (0.87)	76 (0.92)	63 (0.91)	64 (0.88)
2i	50 (0.90)	46 (054)	75 (0.91)	63 (0.91)	62 (0.86)
2j	76 (0.92)	46 (0.83)	80 (0.94)	64 (0.92)	65 (0.90)
Sulphonamide	85	55	82	69	72

(Activity Index) ^{std} = Zone of Inhibition of the sample/ Zone of Inhibition of the standard

CONCLUSION

The present study reports the synthesis of novel oxobutyrate from the corresponding sulfonamide derivatives **(2(a-j))**. The antimicrobial activity of ethyl-3-oxo-2-(2-(3-(N-alkyl sulfamoyl) phenyl) hydrazono)

butanoates **(2(a-j))** was carried out against some strain bacteria. The results show that the synthesized compounds were toxic against the bacteria. The investigation of antibacterial screening reveals that the compounds **(2e)** and **(2f)** have exhibited good antibacterial activity comparable to the standard drugs, while compounds **(2e)** and **(2f)** displayed better antifungal activity.

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