



Synthesis, characterization and antimicrobial study of oxobutanoate

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ABSTRACT

Various sulfonamide derivatives on reaction with ethylactooacetate 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.

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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-oxobutyrate 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.

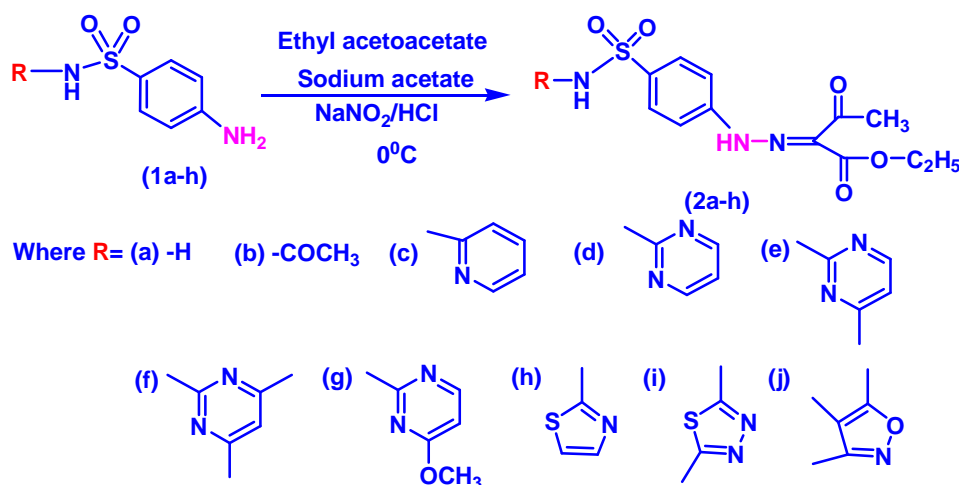
EXPERIMENTAL

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. ¹H NMR and ¹³C 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-Trip-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 actooacetate (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 (CH₃,CH₂),1290(C-N),1725-1765 (C=O), 1148(C-O),1325(SO₂),905(S-N), 3369(N-H), 1695-1540 (C=N), 706-585(C-S). ¹H NMR [400MHz, δ , ppm,



Schemes 1

DMSO-*d*₆]: 1.34 (t, 3H, CH₃), 4.29 (q, 2H, COCH₂), 2.35 (s, 3H, COCH₃), 6.90-7.67 (m, 4H, ArH), 11.62 (s, 1H, NH), 7.42 (s, 2H, NH). ¹³CN-MR [100MHz, δ, ppm, DMSO]: 114.8-143.6 (Ar-C), 14.2, 26.9 (CH₃), 61.4 (CH₂), 165.4, 195.4 (CO). LC-MS: *m/z* 321 (M⁺). *Anal.* Calcd for C₁₂H₁₅N₃O₅S (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-aminophenylsulfonamide) (1b) (0.01 mole) 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 acetoacetate (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-H aromatic), 2920, 1465 (CH₃, CH₂), 1290 (C-N), 1725-1765 (C=O), 1148 (C-O), 1325 (SO₂), 905 (S-N), 3369 (N-H), 1695-1540 (C=N), 706-585 (C-S). ¹H NMR [400MHz, δ, ppm, DMSO-*d*₆]: 1.34 (t, 3H, CH₃), 4.29 (q, 2H, COCH₂), 2.37 (s, 6H, COCH₃), 6.90-7.67 (m, 4H, ArH), 11.62 (s, 1H, NH), 7.45 (s, 1H, NH). ¹³C N-MR [100 MHz, δ, ppm, DMSO]: 114.8-143.6 (Ar-C), 14.2, 22.3, 26.9 (CH₃), 61.4 (CH₂), 165.4, 192.4, 195.4 (CO). LC-MS: *m/z* 367 (M⁺). *Anal.* Calcd for C₁₄H₁₇N₃O₆S (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-H aromatic), 2920, 1465 (CH₃, CH₂), 1290 (C-N), 1725-1765 (C=O), 1148 (C-O), 1325 (SO₂), 905 (S-N), 3369 (N-H), 1695-1540 (C=N), 706-585 (C-S). ¹H NMR [400MHz, δ, ppm, DMSO-*d*₆]: 1.34 (t, 3H, CH₃), 4.29 (q, 2H, COCH₂), 2.35 (s, 3H, COCH₃), 6.90-7.72 (m, 8H, ArH), 11.62 (s, 1H, NH), 7.54 (s, 1H, NH). ¹³CN-MR [100MHz, δ, ppm, DMSO]: 114.8-154.6 (Ar-C), 14.2, 26.9 (CH₃), 64.8 (CH₂), 165.4, 195.4 (CO). LC-MS: *m/z* 402 (M⁺). *Anal.* Calcd for C₁₇H₁₈N₄O₅S (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-H aromatic), 2920, 1465 (CH₃, CH₂), 1290 (C-N), 1725-1765 (C=O), 1148 (C-O), 1325 (SO₂), 905 (S-N), 3369 (N-H), 1695-1540 (C=N), 706-585 (C-S). ¹H NMR [400MHz, δ, ppm, DMSO-*d*₆]: 1.34 (t, 3H, CH₃), 4.29 (q, 2H, COCH₂), 2.35 (s, 3H, COCH₃), 6.90-7.73 (m, 7H, ArH), 11.62 (s, 1H, NH), 7.42 (s, 1H, NH). ¹³C N-MR [100 MHz, δ, ppm, DMSO]: 114.8-170.6 (Ar-C), 14.2, 26.9 (CH₃), 61.4 (CH₂), 165.4, 195.4 (CO). LC-MS: *m/z* 406 (M⁺).

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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.

Ethyl 12-(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 [$\nu, \text{cm}^{-1}, \text{KBr}$]: 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). ^1H NMR [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), 6.90-8.30 (m, 6H, ArH), 11.62 (s, 1H, NH), 7.44 (s, 1H, NH), 2.34 (s, 3H, CH_3). ^{13}C NMR [100 MHz, 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 [$\nu, \text{cm}^{-1}, \text{KBr}$]: 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). ^1H NMR [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), 6.90-8.30 (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 [$\nu, \text{cm}^{-1}, \text{KBr}$]: 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). ^1H NMR [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), 6.90-7.67 (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-yl)sulfamoyl)phenyl)hydrazono)butanoate (2h)

Prepared as per the procedure mentioned for compound (2a) and (2b). Yield 78%; m.p. 141-143°C. IR [$\nu, \text{cm}^{-1}, \text{KBr}$]: 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). ^1H NMR [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-oxobutanoate (2i)

Prepared as per the procedure mentioned for compound (2a) and (2b). Yield 81%; m.p. 142-144°C. IR [$\nu, \text{cm}^{-1}, \text{KBr}$]: 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). ^1H NMR [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, 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 [$\nu, \text{cm}^{-1}, \text{KBr}$]: 3034-3086 (C-H aromatic), 2920, 1465 ($\text{C-H}_3, \text{C-H}_2$), 1290 (C-N), 1725-1765 (C=O), 1325 (SO_2), 3369 (N-H), 1695-1540 (C=N), 1040 (O-N), 706-585 (C-S). $^1\text{H NMR}$ [400 MHz, $\delta, \text{ppm}, \text{DMSO-d}_6$]: 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). $^{13}\text{C NMR}$ [100 MHz, $\delta, \text{ppm}, \text{DMSO}$]: 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 $\text{C}_{17}\text{H}_{20}\text{N}_4\text{O}_6\text{S}$ (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 investigation of (2a-h) reveals bands at 1640-1596 (C=N) and $^1\text{H NMR}$ δ 11.62 (s, 1H, NH). The examination of these data reveals that the IR band and $^1\text{H NMR}$ signals are appropriate to the correspond structure of compound. The final structure of all compounds was confirmed by $^{13}\text{C NMR}$ 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 (*Bacillus subtilis*

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	
	<i>Bacillus Subtilis</i>	<i>Staphylococcus Aureus</i>	<i>Klebsiella promioe</i>	<i>Salmonella typhl</i>	<i>E.coil</i>
2a	53 (0.62)	46 (0.83)	66 (0.80)	61 (0.88)	67 (0.93)
2b	46 (0.54)	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 (0.54)	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

and *Staphylococcus aureus*) and Gram-negative Bacteria (*E.coil*, *Salmonella typhi* and *Klebsiella promioe*) at a concentration of 50 $\mu\text{g/ml}$ 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.

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)

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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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