Novel Synthesis and Antibacterial Activity of Some Pyridazine Derivatives

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Various pyridazin-3(2H)-ones, 3-chloropyridazines and pyridazin-3(2H)-thiones were synthesized and treated with the sulpha drug (knowing by sulphamethoxazole). All the new compounds were evaluated for their antibacterial activity. They showed significant antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Gram + ve) and *E. coli, Pseudomonas aeruginosa* and *Yersinia enterocolitica* (Gram - ve) bacteria by agar plate diffusion method.

All proposed structures were confirmed by IR, ^{1}H NMR, Mass spectra and Elemental analysis.

Keywords: Pyridazin-3(2H)-one; Antibacterial activity.

INTRODUCTION

As a part of our research program directed to the selection of new heterocycles as analogues to useful drugs,[1-2] we have previously described the synthesis and chemotherapeutic activity of pyridazine derivatives.[3-9] Our interest in the field of organosulphur compounds[10] and the fact added by Bailey (1993) and Karen et. al., (1997),[11-12] that the combination of trimethoprim and sulphamethoxazole is more effective in delaying the emergence of bacterial resistance which prevents bacterial division and is also bactericidal, opens a new target for conversion of these pyridazines to their sulpha derivatives and leads to investigation of their potential activity on some (Gram + ve) bacteria and (Gram - ve) bacteria pathogens and non pathogens.

EXPERIMENTAL

Melting points are not corrected. I.R. spectra in KBr were recorded on a Pye Unicom SP 1200 spectrophotometer. ^{1}H NMR spectra were recorded on a EMNMR spectrometer 200 MHZ PMR using DMSO as a solvent and TMS as internal reference (Chemical shifts in δ ppm). Mass spectra and analysis were carried out by the Microanalytical Laboratory of Cairo University.

Synthesis of 4-(3,4,5-trimethoxybenzyl)-6-methyl-3-chloropyridazine 2_a

A suspension of 4-(3,4,5-trimethoxybenzyl)-6-methylpyridazin-3(2H)-one (**1**$_a$) (0.01 mol) in phosphorus oxychloride (5 mL), was heated under reflux for 3 hrs, then poured into crushed ice containing sodium hydroxide (10%). The solid product formed was washed with water, collected by filtration, and recrystallized to give (**2**$_a$).

Synthesis of 4-(3,4,5-trimethoxybenzyl)-6-methylpyridazin-3(2H)-thione 3_a

A solution of (**2**$_a$) (0.015 mol) in ethanol (50 mL) and thiourea (0.12 mol) was heated under reflux for 3 hrs. The solid product formed was collected by filtration and recrystallized to give (**3**$_a$).

Synthesis of 4-aroyl-6-aryl-pyridazin-3(2H)-ones 4_{a-c} and 4-aroyl-6-aryl-pyridazin-3(2H)-thiones 5_{a-c}

A mixture of (**1**$_{a-c}$) or (**3**$_{a-c}$) (0.01 mol) and (0.01 mol) seleniumdioxide was heated under reflux in acetic acid (20 mL) for 3 hrs; the reaction mixture was poured into crushed ice. The solid product formed in each case was washed with water, collected by filtration and recrystallized to give the title compounds.

Synthesis of 4-(sulphamethoxazole)-aryl-6-aryl-pyridazin-3(2H)-ones 6_{a-c} and 4-(sulphamethoxazole)-aryl-6-aryl-pyridazine-3(2H)-thiones 7_{a-c}

A mixture of (**4**$_{a-c}$) or (**5**$_{a-c}$) (0.01 mol) and sulphamethaxazole (0.01 mol) was heated under reflux in ethanol (20 mL) for 24 hrs. The reaction mixture evaporated, the solid product formed and recrystallized to give (**6**$_{a-c}$) and (**7**$_{a-c}$).

Synthesis of N-methyl-4-[(sulphamethoxazole)-(o-methoxyphenyl)]-6-phenylpyridazin-3(2H)-one 8_b and N-methyl-4-[(sulphamethoxazole)-(o-methoxyphenyl)]-6-tolylpyridazin-3(2H)-thione 8_c

a) Dimethylsulphate (0.01 mol) was added to ethanolic solution 6_c or 7_b (0.01 mol) in 20% NaOH solution (50 mL)

and the reaction mixture warmed in a water bath for 6 minutes and left to cool. The solid product was filtered off and recrystallized to give (8_b or 8_c).

b) A mixture of (**9_b**) or (**9_c**) (0.01 mol) and sulphomethoxazole (0.01 mol) was heated under reflux in ethanol (20 mL) for 24 hrs; the reaction mixture was evaporated. The solid product formed was recrystallized to give (**8_b**) or (**8_c**).

Synthesis of N-methyl-4-(o-methoxybenzoyl)-6-phenylpyridazinone 9_b and N-methyl-4-(o-methoxybenzoyl)-6-p-tolylpyridazin-3(2H)-thione 9_c

Dimethyl sulphate (0.01 mol) was added to an ethanolic solution of (**4_c**) or (**5_b**) (0.01 mol) in 20% NaOH solution (50 mL), and the reaction mixture was warmed on a water bath for 10 minutes and left to cool. The solid product was filtered off and recrystallized to give (**9_b**) or (**9_c**).

Synthesis of 4-aryl-6-aryl-pyridazine-3-sulphamethoxazole $10_{a\text{-}c}$

A mixture of (**$2_{a\text{-}c}$**) (0.01 mol) and sulphamethoxazole (0.01 mol) was heated under reflux in ethanol (20 mL) for 24 hrs. The reaction mixture evaporated, a solid product formed and was recrystallized to give (**$10_{a\text{-}c}$**).

RESULTS AND DISCUSSION

This is in continuation of our previous investigation on 6-aryl-4-(aryl methyl)pyridazin-3(2H)-ones (**$1_{a\text{-}c}$**) and in an attempt to obtain 4,6-disubstituted pyridazin-3(2H)-thiones (**$3_{a\text{-}c}$**) using a new methodolgy for thiation.[7] These key starting materials were prepared by the reaction of 4,6-disubstituted pyridazin-3(2H)-one (**$l_{a\text{-}c}$**) with phosphorus oxychloride to give 3-chloropyridazines (**$2_{a\text{-}c}$**), followed by treatment with thiourea in refluxing ethanol to give (**$3_{a\text{-}c}$**) via the thioronium salt formation as shown in Scheme I.

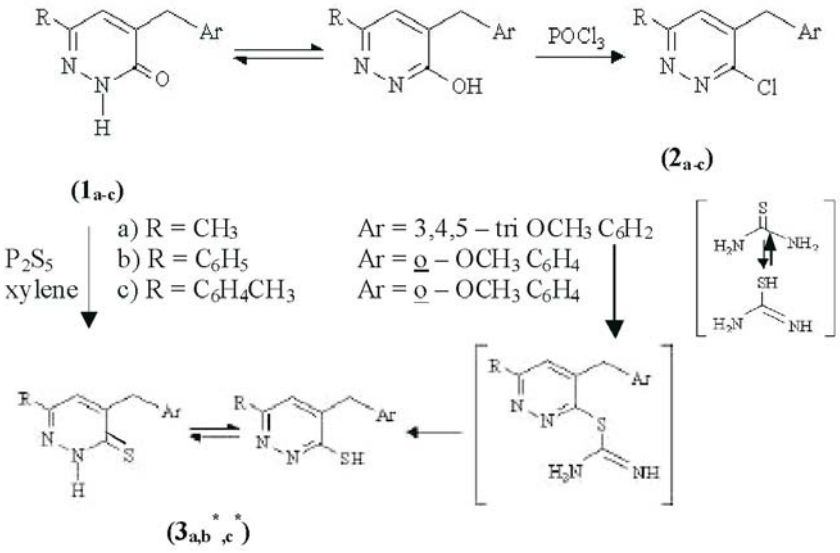
These compounds were also obtained in a similar yield as a one pot reaction of phosphorus pentasulphide in boiling xylene with 4,6-disubstituted pyridazin-3(2H)-one (**$1_{a\text{-}c}$**).

The oxidation of pyridazin-3(2H)-ones with selenium dioxide in refluxing acetic acid for three hours occurs with formation of the ketonic derivatives.

Initially we oxidized both (**$1_{a\text{-}c}$**) and (**$3_{a\text{-}c}$**) with selenium dioxide to give the corresponding 6-aryl-4-aroyl pyridazin-3(2H)-one (**$4_{a\text{-}c}$**) and 6-aryl-4-aroyl pyridazin-3(2H)-thione (**$5_{a\text{-}c}$**). The ^{1}H NMR and GC/Ms data showed evidence for the formation of all products as shown in experimental part.

As an extension to those investigations, we examined the reaction of 6-aryl-4-aroyl pyridazin-3(2H)-one (**$4_{a\text{-}c}$**) and 6-aryl-4-aroyl pyridazin-3(2H)-thione (**$5_{b,c}$**) with an equivalent mole of sulphamethoxazole-[4-amino-N-(5-methyl-3-isoxazolyl)benzenesulphonamide], in refluxing ethanol for 24 hrs; we obtained new sulpha products (**$6_{a\text{-}c}$**) and (**$7_{b,c}$**) in good yield which reacted with dimethylsulphate in the presence of sodium hydroxide to give the N-methyl derivatives (**$8_{b,c}$**). Also compounds (**$8_{b,c}$**)\were prepared by reaction of

Scheme I

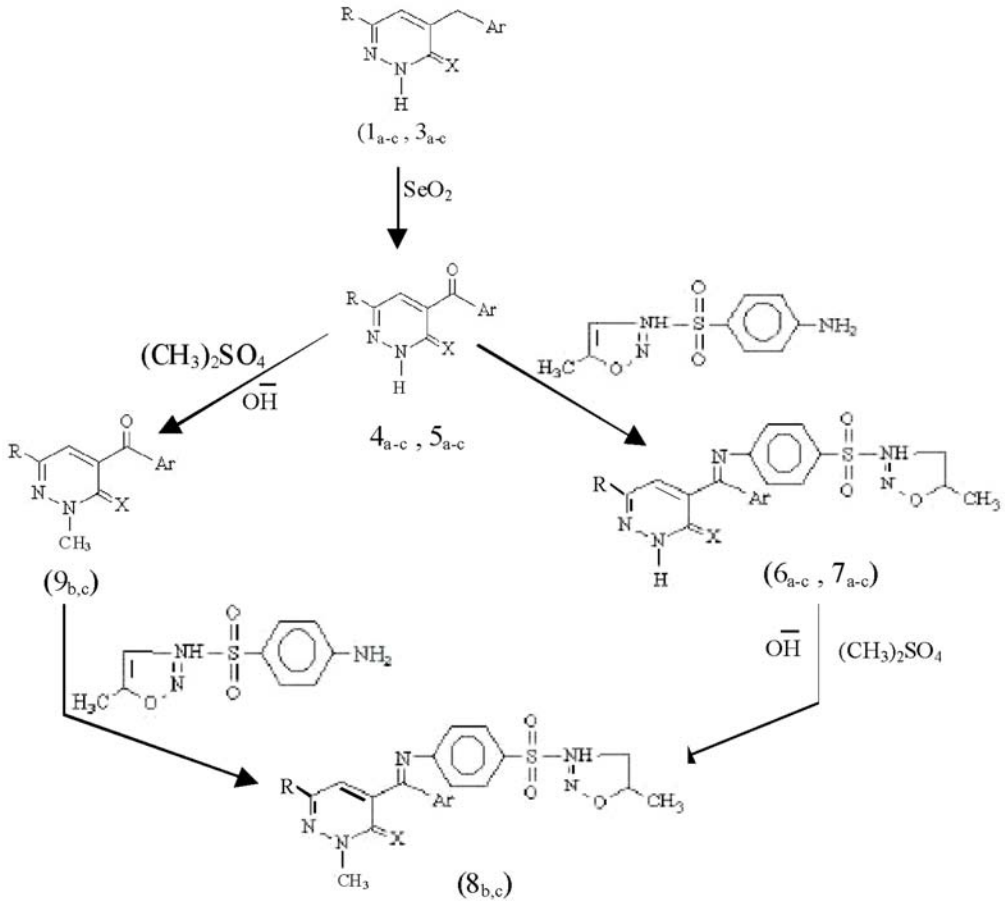


3b* , 3c* Ref. [7]

(**4**$_c$,**5**$_b$) with dimethylsulphate in the presence of sodium hydroxide to give the N-methyl derivatives (**9**$_{b,c}$), which reacted with an equivalent mole of sulphamethoxazole, in refluxing ethyl alcohol for 24 hrs; forming sulpha derivatives (**8**$_{b,c}$) as shown in Scheme II.

Also, the reaction of chloro derivatives (**2**$_{a-c}$) with an

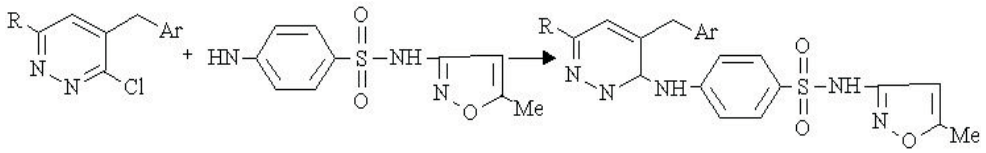
Scheme II



1) x = O 3) x = S 4) x = O 8$_b$) X = S 9$_b$) X = S
5) x = S 6) x = O 7) x = S 8$_c$) X = O 9$_c$) X = O

a)R= CH_3 Ar =3,4,5 – tri $OCH_3C_6H_2$
b)R= C_6H_5 Ar =o – $OCH_3C_6H_4$
c)R=$C_6H_4CH_3$ Ar =o – $OCH_3C_6H_4$

Scheme III



* The only non pathogens bacteria in this study.

Table 1. Biological activity of some new compounds on some bacteria in (mm/iml bore) of 10^{-4} mol in 20 mL acetone

No	*Staphylococcus aureus*	*E. coli*	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Yersinia enterocolitica*
Sulfamet-hoxazole (10^{-4} mol in 20 mL acetone)	50	1	- ve	- ve	- ve
3$_a$	- ve	1	- ve	- ve	> 90
4$_a$	- ve	1	- ve	- ve	> 90
5$_a$	- ve	1	- ve	- ve	> 90
5$_b$	> 90	1	- ve	- ve	- ve
5$_c$	- ve	- ve	- ve	- ve	> 90
6$_a$	> 90	20	15	- ve	- ve
6$_b$	45	- ve	- ve	- ve	15
6$_c$	- ve	- ve	- ve	- ve	> 90
7$_b$	> 90	- ve	- ve	- ve	25
8	15	10	20	10	> 90
10$_a$	- ve	- ve	- ve	- ve	> 90
10$_b$	25	- ve	10	- ve	35
10$_c$	- ve	20	20	25	> 90

Table 2. Physical data of compounds **1-10**

Comp.	M.P.	Yield; Colour	Molecular Formula	Analysis (%) (Calcd/Found)				
				C	H	N	Cl	S
1$_a$	130-131	68% White	$C_{15}H_{18}N_2O_4$	62.07 62.50	6.21 6.45	9.66 10.10		
2$_a$	150-151	69% White	$C_{15}H_{17}N_2O_3Cl$	58.35 57.91	5.51 5.20	9.08 8.88	11.51 11.97	
3$_a$	185-186	57% Yellow	$C_{15}H_{18}N_2O_3S$	58.82 59.42	5.88 5.62	9.15 9.50		10.46 10.91
4$_a$	176-177	50% White	$C_{15}H_{16}N_2O_5$	59.21 58.73	5.26 4.91	9.21 9.63		
5$_a$	73-75	49% Brown	$C_{15}H_{16}N_2O_4S$	56.25 56.83	5.00 5.10	8.75 9.17		10.00 9.72
5$_b$	89-91	51% Pale brownish Yellow	$C_{18}H_{14}N_2O_2S$	67.08 66.78	4.35 4.19	8.70 8.30		9.94 10.21
5$_c$	78-80	47% Brown	$C_{19}H_{16}N_2O_2S$	67.86 67.55	4.76 4.93	8.33 7.90		9.52 9.27
6$_a$	148-150	72% Pale yellow	$C_{25}H_{25}N_5O_7S$	55.66 56.05	4.64 4.31	12.99 13.17		5.94 6.23
6$_b$	138-140	76% Beige	$C_{28}H_{23}N_5O_5S$	62.11 61.87	4.25 4.52	12.94 13.21		5.91 6.21
6$_c$	144-146	74% White	$C_{29}H_{25}N_5O_5S$	62.70 62.45	4.50 4.23	12.61 12.20		5.77 5.30
7$_b$	120-122	80% Reddish Brown	$C_{28}H_{23}N_5O_4S_2$	60.32 59.91	4.13 4.47	12.57 12.13		11.49 11.10
7$_c$	140-142	79% Orange	$C_{29}H_{25}N_5O_4S_2$	60.95 61.25	4.38 4.10	12.26 12.50		11.21 10.83
8$_a$	222-224	77% Yellow	$C_{25}H_{27}N_5O_6S$	57.14 56.83	5.14 4.91	13.33 13.62		6.10 5.83
8$_b$	168-170	75% Beige	$C_{28}H_{25}N_5O_4S$	63.76 64.08	4.74 4.42	13.28 12.98		6.07 6.47
8$_c$	130-132	73% White	$C_{29}H_{27}N_5O_4S$	64.33 64.00	4.99 5.13	12.94 13.25		5.91 6.23
9$_b$	110-112	43% Beige	$C_{19}H_{16}N_2O_2S$	67.86 68.00	4.76 5.01	8.33 8.00		9.52 9.99
9$_c$	207-209	45% Beige	$C_{20}H_{18}N_2O_3$	71.86 72.18	5.39 5.12	8.38 8.76		
10$_b$	133-135	47% Brown	$C_{29}H_{25}N_5O_4S_2$	60.95 61.32	4.38 4.52	12.26 12.02		11.21 11.65
10$_c$	181-183	49% Yellow	$C_{30}H_{27}N_5O_5S$	63.27 63.68	4.75 4.52	12.30 12.52		5.62 5.43

Table 3. Spectroscopic data of compounds **1-10**

Compd. No	IR spectra (ν_{max} in cm^{-1})	^1H NMR (δ in ppm), Mass spectra
1_a	3140 (NH), 2937.2 (CH_3), 2492.3 (CH_2), 1651 (C=O), 1603 (C=N).	δ 1.928 (s, 3H, CH_3), δ 3.84-3.93 (s, 9H, $3OCH_3$ of CH_3O-Ar), δ 4.14 (s, 2H, CH_2), δ 6.47 (s, 1H, CH hetero), δ 7.09-7.26 (m, 2H, Ar-H), δ 12.07 (s, 1H, NH), M.S: *m/z* (290).
2_a	2904 (CH_3), 2483.1 (CH_2), 1592 (C=N)	M.S: *m/z* (308.5)
3_a	3146.3 (NH), 2924.5 (CH_3), 2427.2 (CH_2), 1593.4 (C=N).	δ 2.32 (s, 3H, CH_3), δ 3.82-3.86 (s, 9H, $3OCH_3$ of CH_3O-Ar), δ 4.08 (s, 2H, CH_2), δ 6.59 (s, 1H, CH hetero), δ 7.26-7.42 (m, 2H, Ar-H), δ 12.59 (s, 1H, NH), M.S: *m/z* (306).
4_a	3141.6 (NH), 2939.3 (CH_3), 1651 (C=O), 1605.6 (C=N).	M.S: *m/z* (304)
5_a	3055-3093 (NH), 2941.9 (CH_3), 1639.8 (C=O), 1586.2 (C=N), 1110 (C=S).	δ 2.8 (s, 3H, CH_3), δ 3.72-3.93 (s, 9H, $3OCH_3$ of CH_3O-Ar), δ 6.45 (s, 1H, CH hetero), δ 7.79-7.93 (m, 2H, Ar-H), δ 12.23 (s, 1H, NH), M.S: *m/z* (320).
5_b	3056.4 (NH), 1656.5 (C=O), 1595.9 (C=N), 1158.3 (C=S).	δ 3.65 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.25 (s, 1H, CH hetero), δ 7.32-7.99 (m, 9H, 2Ar-H), δ 11.92 (s, 1H, NH), M.S: *m/z* (322).
5_c	3143.3 (NH), 2922.5 (CH_3), 1660.1 (C=O), 1597.8 (C=N), 1184.3 (C=S).	δ 2.72 (s, 3H, CH_3), δ 3.55 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.31 (s, 1H, CH hetero), δ 7.35-7.87 (m, 8H, 2Ar-H), δ 12.01 (s, 1H, NH), M.S: *m/z* (336).
6_a	3155.8-3230.3 (NH), 2935.7-2967.4 (CH_3), 1598.2-1605.5 (C=N), 1324.2 (SO_2).	δ 2.19-2.35 (s, 6H, $2CH_3$ hetero), δ 3.59-3.87 (s, 9H, $3OCH_3$ of CH_3O-Ar), δ 6.20-6.63 (s, 2H, 2CH hetero), δ 7.26-7.62 (m, 6H, 2Ar-H), δ 8.04 (s, 1H, NH), δ 10.92 (s, 1H, NH pyridazine), M.S: *m/z* (539).
6_b	3140.5-3260 (NH), 2893.1 (CH_3), 1595-1621 (C=N), 1381.2 (SO_2).	δ 2.34 (s, 3H, CH_3 hetero), δ 3.81 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.55-6.60 (s, 2H, 2CH hetero), δ 7.26-7.69 (m, 13H, 3Ar-H), δ 11.30 (s, 1H, NH), δ 12.14 (s, 1H, NH pyridazine), M.S: *m/z* (541).
6_c	3134.6-3209.7 (NH), 2902.2-2966.2 (CH_3), 1592.7-1607.6 (C=N), 1324.1 (SO_2).	δ 2.27 (s, 3H, CH_3 hetero), δ 2.81 (s, 3H, CH_3), δ 3.77 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.27-6.53 (s, 2H, 2CH hetero), δ 7.13-7.84 (m, 12H, 3Ar-H), δ 10.57 (s, 1H, NH), δ 11.94 (s, 1H, NH pyridazine), M.S: *m/z* (538).
7_b	3068-3210.3 (NH), 2965.8 (CH_3), 1596.1-1620.4 (C=N), 1313.4 (SO_2), 1158 (C=S).	δ 2.33 (s, 3H, CH_3 hetero), δ 3.73 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.56-6.61 (s, 2H, 2CH hetero), δ 7.36-7.60 (m, 13H, 3Ar-H), δ 8.21 (s, 1H, NH), δ 11.9 (s, 1H, NH pyridazine), M.S: *m/z* (556).
7_c	3100-3220 (NH), 2920-2960 (CH_3), 1550-1600 (C=N), 1318 (SO_2), 1130 (C=S).	δ 2.22 (s, 3H, CH_3 hetero), δ 2.61 (s, 3H, CH_3), δ 3.52 (s, 3H, OCH_3 of CH_3O-Ar), δ 6.38-6.52 (s, 2H, 2CH hetero), δ 7.32-7.71 (m, 12H, 3Ar-H), δ 8.42 (s, 1H, NH), δ 12.1 (s, 1H, NH pyridazine), M.S: *m/z* (570).
8_b	3056.4 (NH), 2967.5 (CH_3), 1446.8-1598.9 (C=N), 1384.3 (SO_2), 1158.9 (C=S), 1023.5 (N-CH_3).	δ 2.34 (s, 3H, CH_3 hetero), δ 3.88 (s, 3H, OCH_3 of CH_3 O-Ar), δ 4.05 (s, 3H, N-CH_3), δ 6.2-6.57 (s, 2H, 2CH hetero), δ 7.3-7.85 (m, 13H, 3Ar-H), δ 9.87 (s, 1H, NH), M.S: *m/z* (571).
8_c	3214 (NH), 2929.6-2965.6 (CH_3), 1655.1 (C=O), 1499.4-1600.8 (C=N), 1312.7 (SO_2), 1094.7 (N-CH_3).	δ 2.29 (s, 3H, CH_3 hetero), δ 2.51 (s, 3H, CH_3), δ 3.79 (s, 3H, OCH_3 of CH_3 O-Ar), δ 4.10 (s, 3H, N-CH_3), δ 6.10-6.62 (s, 2H, 2CH hetero), δ 7.12-7.58 (m, 12H, 3Ar-H), δ 10.93 (s, 1H, NH), M.S: *m/z* (569).
9_b	1658.4 (C=O), 1521-1598.9 (C=N), 1158.9 (C=S), 1070.2 (N-CH_3).	δ 2.36 (s, 3H, CH_3), δ 3.67-3.74 (s, 3H, OCH_3 of CH_3 O-Ar), δ 3.97 (s, 3H, N-CH_3), δ 6.89 (s, 1H, CH hetero), δ 7.27-7.56 (m, 8H, 2Ar-H) M.S: *m/z* (336).
9_c	2967.5 (CH_3), 1642-1670 (C=O), 1554-1583 (C=N), 1100.7 (N-CH_3).	M.S: *m/z* (334).
10_a	3147.1-3180.2 (NH), 2938.2-2975.1 (CH_3), 2584.5 (CH_2), 1544.6-1607 (C=N), 1331.6 (SO_2).	δ 2.14-2.2 (s, 6H, $2CH_3$ hetero), δ 3.54-3.77 (s, 9H, $3OCH_3$ of CH_3 O-Ar), δ 4.26 (s, 2H, CH_2), δ 6.17-6.71 (s, 2H, 2CH hetero), δ 7.61-7.88 (m, 6H, 2Ar-H), δ 9.71 (s, 1H, NH hetero), δ 11.41 (s, 1H, NH), M.S: *m/z* (524).
10_b	3134.2-3205.1 (NH), 2958.6 (CH_3), 2370 (CH_2), 1602.3-1650.3 (C=N), 1366.3 (SO_2).	δ 2.25 (s, 3H, CH_3 hetero), δ 3.47 (s, 3H, OCH_3 of CH_3 O-Ar), δ 4.15 (s, 2H, CH_2), δ 6.25-6.69 (s, 2H, 2CH hetero), δ 7.23-7.9 (m, 13H, 3Ar-H), δ 9.82 (s, 1H, NH hetero), δ 11.85 (s, 1H, NH), M.S: *m/z* (527).
10_c	3170.3-3200 (NH), 2915-2990 (CH_3), 2410 (CH_2), 1595-1610 (C=N), 1315 (SO_2).	δ 2.39 (s, 3H, CH_3 hetero), δ 2.75 (s, 3H, CH_3), δ 3.51 (s, 3H, OCH_3 of CH_3 O-Ar), δ 4.27 (s, 2H, CH_2), δ 6.16-6.58 (s, 2H, 2CH hetero), δ 7.17-7.83 (m, 12H, 3Ar-H), δ 10.03 (s, 1H, NH hetero), δ 12.00 (s, 1H, NH), M.S: *m/z* (541).

equivalent mole of sulphamethaxazole, in refluxing ethyl alcohol for 24 hrs; formed sulpha derivative (**10**$_{a-c}$) as shown in Scheme III.

All the synthesized target compounds have been tested for their antibacterial activity against *Staphylococcus aureus* and *Bacillus subtilis* (Gram + ve) and *E. coli, Pseudomonas aeruginosa* and *Yersinia enterocolitica* (Gram - ve) bacteria by agar plate diffusion method. The results of antibacterial activity indicate variable results as shown in Table 1.

All these novel structures were confirmed by IR, ^{1}H NMR, Mass spectra and Elemental analysis.

The new compounds were screened for their antibacterial activity against some (Gram + ve) bacteria (*Staphylococcus aureus* and **Bacillus subtilis*) and (Gram - ve) bacteria (*E. coli, Pseudomonas aeruginosa* and *Yersinia enterocolitica*) pathogens and non pathogens as shown in Table 1.

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