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Synthesis and evaluation of some novel heterocyclic compounds containing Pyrimidine and Thiazolidinone rings and their Derivatives as an antimicrobial agents

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ABSTRACT

A series of (4, 6-disubstituted phenyl) pyrimidine and their derivatives are known for their biological importance**.** In present research work, we have attempted both Conventional to synthesize 1- (4, 6-disubstituted phenyl) pyrimidin-2yl-2-(4methoxyphenyl) thiazolidine-4-one. A wide spectrum of biological activities like anti-diabetic, anti-bacterial, antifungal, anti-oxidant and anti-inflammatory activities are found to be associated with pyrimidine nucleus. Chalcones were synthesized by claisen-schmidt reaction using aromatic aldehydes and ketones. Then reacting with guanidine hydrochloride the resultant pyrimidine compounds are synthesized. Again its Schiff's base reaction is carried out and then cycloaddition reaction is done, so (4, 6-disubstituted phenyl) pyrimidin-2 yl-2-(4methoxyphenyl) thiazolidine-4-one derivatives are prepared by using thioglycolic acid. All the synthesized compounds were characterized by IR were recorded for all compounds, ^{1}H-NMR and Elemental Analysis was carried out for prototype of compounds. All the compounds were evaluated for antibacterial (*S. aureus* and *E. coli*) activity and antifungal (*A. niger and C. albicans*) activity at the concentration of 100 µg/mL by using cup-plate agar diffusion method. The activity was measured in terms of zone of inhibition and compared with standard drug Ciprofloxacin for antibacterial activity and Griseofulvin for antifungal activity.

Keywords: Pyrimidine, Anti-diabetic, Antimicrobial screening, Anti-oxidant and Anti- inflammatory.

INTRODUCTION

Pyrimidines derivatives occur vary widely in the living organisms and are among the first compounds to have been studied by the organic chemist. The barbiturates, valuable soporific and hypnotic drugs, and a number of useful antibacterial and antimalerial drugs also contain pyrimidine nucleus. Vitamins B1 and B2 also contains pyrimidines moiety [1].

Pyrimidines are the class of drugs, known to possess various biological activities. They are also shown to possess anticancer activity. Some of the derivatives of pyrimidines like trimethoprim, methotrexate and pyrimethamine have shown to exhibit antimicrobial, anticancer and antimalarial activities respectively. Some recent studies have shown that pyrimidines also possess anti-inflammatory activity. Pyrimidine, being an integral part of DNA and RNA, imparts to diverse pharmacological properties as effective bactericide and fungicide [2,3]. Certain pyrimidine derivatives were also known to exhibit antimalarial [4], antifilarial [5], antioxidant [6, 7] and anti-HIV activities [8] Some of the 3,4-dihydropyrimidines (DHPM) have emerged as integral backbones of several calcium channel blockers, antihypertensive agents, adrenergic and neuropeptide antagonist [9]. Several alkaloids containing 3,4-dihydropyrimidine have been isolated from marine sources and among them the batzelladine alkaloids are found to be potent HIV-gp-120- CD4 inhibitors [10, 11]. Along with the varied biological activities of pyrimidine, other heterocycles fused with pyrimidines play an essential role in several biological processes and have a considerable chemical and pharmacological importance like hypoglycemic action [12], analgesic, anti-inflammatory and ulcerogenic activities [13].

They are shown to produce their action through the inhibition of the enzyme Dihydrofolate Reductase (DHFR). DHFR is essential for the folate metabolism in the organism or any cell. The inhibition of this enzyme has shown to be one of the most promising ways to control the bacterial and parasitic diseases [13]. In the view of the facts mentioned above and as part of our initial efforts to discover potentially active new agents. Hence, we have synthesized some new Heterocyclic Compounds Containing Pyrimidine rings. The novel derivatives were characterized by spectral data and elemental analysis and these compounds were used for their antibacterial and antifungal activity.

MATERIALS AND METHODS

Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting point was determined by Micro control based melting point instrument and is uncorrected. All reactions were monitored by thin-layer chromatography on 0.25 mm silica gel (60GF-254) plates, by using ethyl acetate: butanol: chloroform in the ratio of [1:2:1] as mobile phase and visualized with UV light. Column chromatography was performed on silica gel (200–300 mesh). Infra red (IR) spectra was recorded by using KBr disk on a Thermo Nicolate IR-400 FTIR spectrophotometer, 1H NMR spectra was recorded on Bruker Avance-300F spectrometer (300 MHz) using tetramethylsilane as internal standard (chemical shift in δ ppm).. Mass spectra were recorded on a Triple Quadrupole LC–MS–MS (Sciex with ESI source) spectrometer.

Spectra facilities and elemental analysis were carried out by Department of University scientific instrument centre, Karnataka University, Dharwad, India and Suven Life Sciences, Hyderabad India.

EXPERIMENTAL

General procedure for the preparation of chalcone derivatives (1a-l) [14]

To a solution of 5.5 gm of NaOH in 50 mL of distilled water, 30 mL of ethanol was added in the flask .The flask was immersed in a bath of crushed ice. After adding 0.1 mole of acetophenone (substituted), then the mixure was stirred. Then 0.1 mole of aromatic aldehyde was added. This mixture was vigorously stirred for 2-3 h maintained at 25^{o}C. The reaction mixture kept in the ice chest for 24 h and the solid obtained were filtered and washed using cold water until neutral to the litmus. Crude product recryastllized using rectified spirit.

General procedure for the preparation of pyrimidine derivatives (2a-l) [14]

A mixture of appropriate chalcones (1a-l) and guanidine hydrochloride in absolute ethanol (10 mL) were refluxed on a water bath for 6 h. The solvent was completely evaporated and the residue was poured into ice cold water. The precipitated solid was collected by filtration.

General Procedure for the synthesis of schiff's base of N-(4-methoxy benzylidine)-4,6-diphenyl pyrimidine 2-amine [15]

A mixture of 0.01 mole of 6-diphenyl pyrimidine 2-amine, aldehyde (0.01mol) and 2–3 drops of glacial acetic acid in ethanol was refluxed for about 2 h. The solvent was removed under

reduced pressure to afford product Schiff base. Obtained products are recrystllized from rectified spirit.

General Procedure for the synthesis of n-(4, 6-disubstituted phenyl) pyrimidin-2yl-2-(4-methoxyphenyl) thiazolidine-4-one [16]

A mixture of appropriate (0.01 mol) **N**-(4-methoxy benzylidine)-4, 6-diphenyl pyrimidine 2-amine, thioglycolic acid (0.015 mol) and a pinch of anhydrous $ZnCl_2$ in dry 1,4-dioxane was refluxed for 12–14 h. The reaction mixture was cooled and neutralized with 10% sodium bicarbonate solution. The separated solid was filtered, washed with water and recryastllized from ethanol.

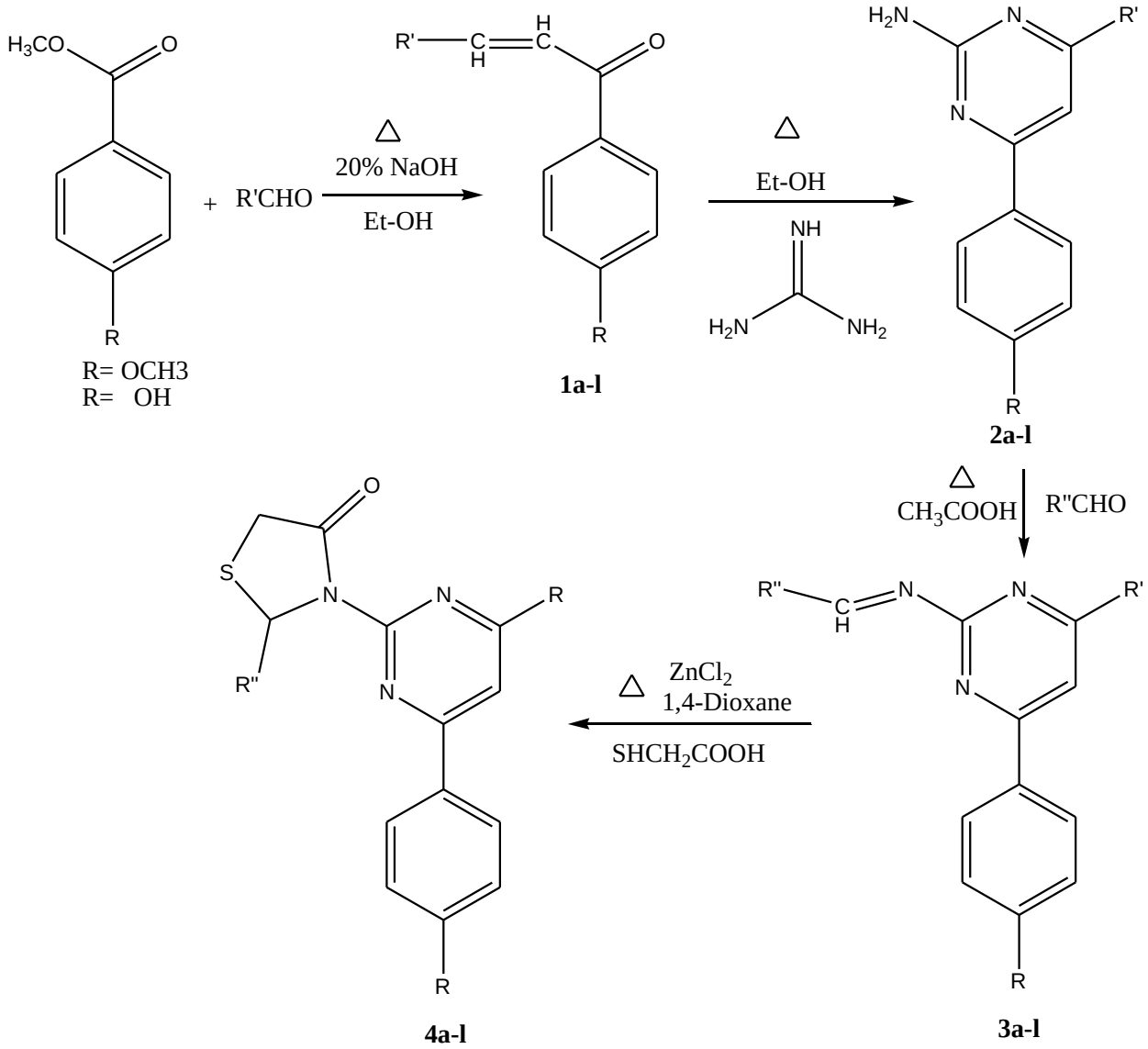


Figure 1 Scheme 1. Synthetic route of compounds (1a-l)-(4a-l)

Antimicrobial Activity [17,18]

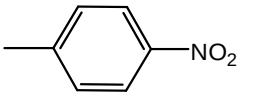
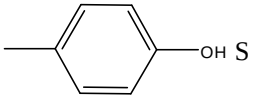
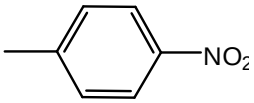
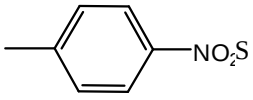
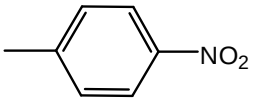
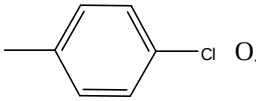
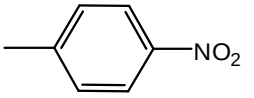
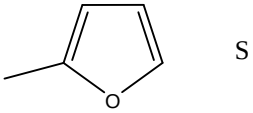
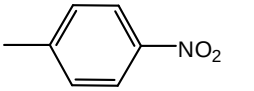
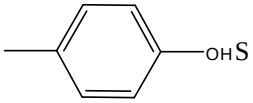
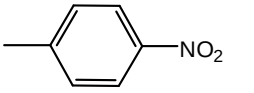
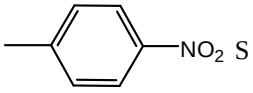
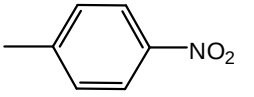
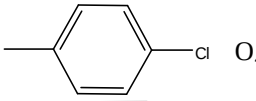
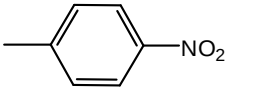
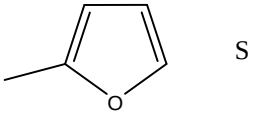
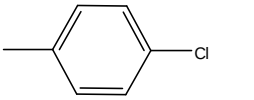
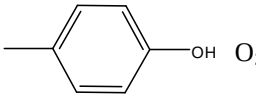
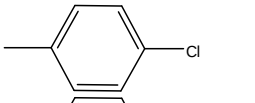
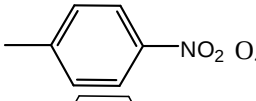
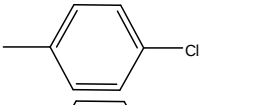
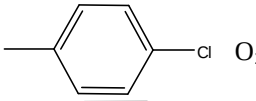
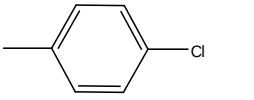
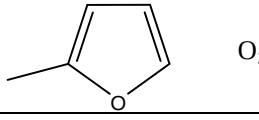
Applying the agar plate diffusion technique all of the newly synthesized compounds were screened *in-vitro* for antibacterial activity against Escherichia coli (Gram-negative), staphylococcus aureus (Gram-positive) at 100 µg/ml concentrations, respectively. Under identical conditions, the antibiotics Ciprofloxacin at 100 µg/ml showed zone of inhibition 28 mm for Gram negative organism and showed zone of inhibition 30 mm for gram positive organism respectively.

Similarly, the antifungal screening of the compounds was carried out *in-vitro* by paper disc method against two fungi A. niger and c. albicans by using Griseofulvin at 100 µg/ml showed zone of inhibition 28 mm and 25 mm respectively, as the zone of inhibition.

RESULTS AND DISCUSSION

From the literature survey it reveals that the substituted pyrimidine and thiazolidinone moieties are already known for different biological activities. Here we have synthesized some novel analogues with different substituted aromatic aldehydes ring system in view to be good antimicrobial and antifungal agents with more resistance. Physiochemical properties of the synthesized derivatives are presented in **Table-1.**

Table-1: Physicochemical data of compounds (4a-4l)

Com. Code	R	R'	R'	Mol.formula	Mol.Wt	M.P	Rf Value
4a	-OCH_3			$C_{25}H_{18}N_4O_5S$	501	101-103	0.56
4b	-OCH_3			$C_{26}H_{19}N_5O_6S$	530	102-105	0.47
4c	-OCH_3			$C_{26}H_{19}ClN_4O_4S$	519	108-110	0.53
4d	-OCH_3			$C_{24}H_{18}N_4O_5S$	475	109-111	0.50
4e	-OH			$C_{25}H_{18}N_4O_5S$	486	115-117	0.58
4f	-OH			$C_{25}H_{17}N_5O_6S$	515	119-121	0.54
4g	-OH			$C_{25}H_{17}ClN_4O_4S$	504	120-122	0.60
4h	-OH			$C_{23}H_{16}N_4O_5S$	460	125-127	0.53
4i	-OCH_3			$C_{26}H_{20}ClN_3O_3S$	489	124-126	0.51
4j	-OCH_3			$C_{26}H_{19}ClN_4O_4S$	518	129-131	0.52
4k	-OCH_3			$C_{26}H_{19}Cl_2N_3O_2S$	507	135-137	0.55
4l	-OCH_3			$C_{24}H_{18}ClN_3O_3S$	463	134-136	0.49

Spectral data of thiazolidinone derivatives

2-(4-hydroxyphenyl)-3-(4-(4-methoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one(4a):

IR (ATR, cm-1): 3300 (OH), 3018 (Ar C-H), 2896 (Aliphatic C-H), 1716 (C=O), 1625 (C=N), 1589 (C=C), 1511 (Ar-NO_2), 1354 (C-N), 1214 (C-O-C), 720 (C-S); 1H NMR (CDCl3, δppm): 7.20-7.93 (m, 13H,Ar-H), 5.80 (s, 1H, –NCHS), 4.94 (s, 1H, OH), 3.87 (s, 3H, O-CH_3), 3.46 (s, 2H, S-CH2); MS: m/z 501.12 (M+1).

3-(4-(4-methoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (4b):

IR (ATR, cm-1): 3039 (Ar C-H), 2932 (Aliphatic C-H), 1720 (C=O), 1623 (C=N), 1527 (C=C), 1520 (Ar-NO_2), 1340 (C-N), 1210 (C-O-C), 722 (C-S); 1H NMR (CDCl3, δppm): 6.92-7.73 (m, 13H,Ar-H), 5.72 (s, 1H, –NCHS), 3.71 (s, 3H, O-CH_3), 3.42 (s, 2H, S-CH2); MS: m/z 530.11 (M+1).

2-(4-chlorophenyl)-3-(4-(4-methoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one (4c):

IR (ATR, cm-1): 3032 (Ar C-H), 2911 (Aliphatic C-H), 1700 (C=O), 1624 (C=N), 1593 (C=C), 1516 (Ar-NO_2), 1356 (C-N), 1224 (C-O-C), 726 (C-S), 714 (C-Cl); ^{1}H NMR (CDCl3, δppm): 7.10-7.90 (m, 13H,Ar-H), 5.75 (s, 1H, –NCHS), 3.81 (s, 3H, O-CH_3), 3.41 (s, 2H, S-CH2); MS: m/z 518.12 (M+1).

2-(furan-2-yl)-3-(4-(4-methoxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one (4d):

IR (ATR, cm-1): 3040 (Ar C-H), 2920 (Aliphatic C-H), 1691 (C=O), 1621 (C=N), 1596 (C=C), 1524 (Ar-NO_2), 1360 (C-N), 1221 (C-O-C), 723 (C-S); ^{1}H NMR (CDCl3, δppm): 6.50-7.95 (m, 13H,Ar-H), 5.75 (s, 1H, –NCHS), 3.81 (s, 3H, O-CH_3), 3.41 (s, 2H, S-CH2); MS: m/z 474.10 (M+1).

2-(4-hydroxyphenyl)-3-(4-(4-hydroxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one (4e):

IR (ATR, cm-1): 3349 (OH), 3034 (Ar C-H), 2937 (Aliphatic C-H), 1698 (C=O), 1625 (C=N), 1590 (C=C), 1520 (Ar-NO_2), 1355 (C-N), 1225 (C-O-C), 724 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 6.90-7.80 (m, 13H, Ar-H), 5.65 (s, 1H, –NCHS), 4.97 (s, 2H, 2.OH), 3.38 (s, 2H, S-CH2); MS: m/z 486.10 (M+1).

3-(4-(4-hydroxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (4f):

IR (ATR, cm-1): 3360 (OH), 3025 (Ar C-H), 2931 (Aliphatic C-H), 1710 (C=O), 1622 (C=N), 1587 (C=C), 1527 (Ar-NO_2), 1355 (C-N), 1221 (C-O-C), 728 (C-S); ^{1}H NMR ($CDCl_3$, δ ppm): 6.95-7.90 (m, 13H, Ar-H), 5.50 (s, 1H, –NCHS), 4.96 (s, H, OH), 3.40 (s, 2H, S-CH2); MS: m/z 515.09 (M+1)

2-(4-chlorophenyl)-3-(4-(4-hydroxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one (4g):

IR (ATR, cm-1): 3342 (OH), 3045 (Ar C-H), 2927 (Aliphatic C-H), 1705 (C=O), 1630 (C=N), 1580 (C=C), 1523 (Ar-NO_2), 1351 (C-N), 1223 (C-O-C), 719 (C-S) 710 (C-Cl); ^{1}H NMR ($CDCl_3$, δ ppm): 7.00-7.90 (m, 13H, Ar-H), 5.61 (s, 1H, –NCHS), 4.92 (s, H, OH), 3.39 (s, 2H, S-CH2); MS: m/z 504.07 (M+1).

2-(furan-2-yl)-3-(4-(4-hydroxyphenyl)-6-(4-nitrophenyl)pyrimidin-2-yl)thiazolidin-4-one (4h):

IR (ATR, cm-1): 3367 (OH), 3042 (Ar C-H), 2922 (Aliphatic C-H), 1688 (C=O), 1624 (C=N), 1595 (C=C), 1520 (Ar-NO_2), 1361 (C-N), 1223 (C-O-C), 723 (C-S); ^{1}H NMR (CDCl3, δppm): 6.60-7.92 (m, 12H,Ar-H), 5.77 (s, 1H, –NCHS), 4.98(s, 1H, OH), 3.40 (s, 2H, S-CH2); MS: m/z 460.08 (M+1).

3-(4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)-2-(4-hydroxyphenyl)thiazolidin-4-one(4i):

IR (ATR, cm-1): 3340 (OH), 3010 (Ar C-H), 2921 (Aliphatic C-H), 1709 (C=O), 1648 (C=N), 1583 (C=C), 1353 (C-N), 1225 (C-O-C), 722 (C-S) 713 (C-Cl); ^{1}H NMR ($CDCl_3$, δ ppm): 6.60-7.80 (m, 13H, Ar-H), 5.80 (s, 1H, –NCHS), 4.98 (s, H, OH), 3.70 (s, 3H, O-CH_3), 3.40 (s, 2H, S-CH2); MS: m/z 489.09 (M+1).

3-(4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)-2-(4-nitrophenyl)thiazolidin-4-one (4j):

IR (ATR, cm-1): 3031 (Ar C-H), 2919 (Aliphatic C-H), 1719 (C=O), 1641 (C=N), 1580 (C=C), 1521 (Ar-NO_2) 1352 (C-N), 1239 (C-O-C), 719 (C-S) 705 (C-Cl); ^{1}H NMR ($CDCl_3$, δ ppm): 7.00-8.10 (m, 13H, Ar-H), 5.82 (s, 1H, –NCHS), 3.64 (s, 3H, O-CH_3), 3.35 (s, 2H, S-CH2); MS: m/z 518.08 (M+1).

2-(4-chlorophenyl)-3-(4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)thiazolidin-4-one (4k):

IR (ATR, cm-1): 3025 (Ar C-H), 2914 (Aliphatic C-H), 1709 (C=O), 1640 (C=N), 1583 (C=C), 1524 (Ar-NO_2) 1350 (C-N), 1235 (C-O-C), 715 (C-S) 704 (C-Cl); ^{1}H NMR ($CDCl_3$, δ ppm): 6.90-7.50 (m, 13H, Ar-H), 5.90 (s, 1H, –NCHS), 3.70 (s, 3H, O-CH_3), 3.45 (s, 2H, S-CH2); MS: m/z 507.06 (M+1).

3-(4-(4-chlorophenyl)-6-(4-methoxyphenyl)pyrimidin-2-yl)-2-(furan-2-yl)thiazolidin-4-one (4l):

IR (ATR, cm-1): 3021 (Ar C-H), 2923 (Aliphatic C-H), 1690 (C=O), 1623 (C=N), 1598 (C=C), 1525 (Ar-NO_2), 1362 (C-N), 1224 (C-O-C), 720 (C-S), 708 (C-Cl); ^{1}H NMR (CDCl3, δppm): 6.50-7.60 (m, 12H,Ar-H), 5.90 (s, 1H, –NCHS), 3.75 (s, 3H, O-CH_3), 3.40 (s, 2H, S-CH2); MS: m/z 463.08 (M+1).

ANTIMICROBIAL ACTIVITY

The antimicrobial activities of compounds (4a-4l) are reported in **(Table No. 2)**.

Compounds with para nitro, para methoxy, para chloro substitution in the compounds, such as **4a, 4b, 4e, 4f, 4i and 4k** revealed good antibacterial activity as compared to compounds **4c, 4d, 4g, 4h, 4j** and **4l**. While the compounds with para nitro, para methoxy, para chloro substitution in the compounds, such as **4a, 4c, 4e, 4f, 4j** and **4k** revealed good antifungal activity as compared to compounds **4b, 4d, 4g, 4h** and **4i.**

Under identical conditions the standard antibiotic ciprofloxacin (100 µg/ml) exhibited a zone of inhibition of 28 and 30 mm against *E. coli* and *S. aureus* respectively and standard antifungal Griseofulvin (100 µg/ml) exhibited a zone of inhibition of 28 and 25 against *A. niger* and *C. albicans.* The antibacterial activity of compound **4b** is almost identical to that of ciprofloxacin against E. coli and S. aureus and antifungal activity of **4e** is almost identical to that of A. niger and C. albicans.

Table 2: Antimicrobial activity of compounds (4a-4l)

Compd. Code	Zone of inhibition at 100 µg/ml (in mm)			
	Anti-bacterial		Anti-fungal	
	E. coli	*S.aureus*	*A. niger*	*C. albicans*
4a	**24**	**23**	**22**	**20**
4b	**26**	**27**	14	12
4c	19	17	**23**	**23**
4d	18	20	18	17
4e	**23**	**24**	**26**	**23**
4f	**22**	**25**	**23**	**21**
4g	13	17	12	15
4h	17	15	14	16
4i	**22**	**24**	17	18
4j	13	18	**20**	**21**
4k	**22**	**20**	**24**	**23**
4l	18	16	17	18
Ciprofloxacin	**28**	**30**	-	-
Griseofulvin	-	-	**28**	**25**

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