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Synthesis and antimicrobial activity of novel substituted thaizole-2-semicarbazides and its derivatives

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ABSTRACT

Substituted-thiazole-2-semicarbazides **(3a-b)** on reaction with ethyl acetoacetate/ethylcyanoacetate/ acetylacetone/carbon disulphide-potassium hydroxide and different substituted aromatic acids in presence of phosphorous oxychloride yielded the corresponding 3-methyl-N-(4-substituted-1'3'-thiazol-2'-yl)-5-oxo-4,5-dihydro-1H-pyrazole -1-carboxamides **(4a-b)**/3-amino-N-(4-substituted-1'3'-thiazol-2'-yl)-5-oxo-4,5dihydro-1H-pyrazole-1-carboxamide **(5a-b)**/3,5-dimethyl-N-(4-substituted-1'3'-thiazol-2'-yl)-1H-pyrozole-1-carboxamide **(6a-b)**/5-[(4-substituted-1',3'-thiazol-2'-yl)amino]-1,3,4-oxadiazole-2(3H)-thione **(7a-b)**/2-(substituted)-5-[(4-substituted-1,3-thiazol-2-yl)amino]-1,3,4-oxadiazole **(8a-h)** respectively. Structures of the all the newly synthesized compounds were confirmed by spectral data. All these compounds have been screened for their antimicrobial activity.

KEYWORDS

Thiazoles;
Pyrrazoles;
Oxadiazoles;
Biological activity.

INTRODUCTION

Heterocycles containing thiazole rings are associated with a wide range of biological properties such as antiprotozoal[1], anticonvulsant[2], depressant effect on the central nervous system[3], anti-helimintic[4], antidiabetics[5], inhibitors of dihydrofolate[6], inflammation inhibitors[7-8], antitumor[9-11], herbicides[12], antimicrobial[13-18], antiviral[19] and antianaphylactic[20] activities due to toxophoric -N=C-S- group. Pyrrazoles represent one of the most active classes of compounds prossessing a wide spectrum of biological activities, such as anti-inflammatory[21], antipyretic, analgesic and smooth muscle relaxant action[22] activities. Many pyrazole derivatives associated with antifungal, antidia betics[23], bactericidal[24] and hypotensive[25] activities. Large number of oxadiazole derivatives reported in the literature possess broad spectrum of pharmacological activities such as antimicrobial, antimalarial, anticonvulsant, anticancer, cyclooxygenase, anti HIV property[26] and anti-inflammatory[27] activities. Substituted-1, 3, 4-oxadiazole-2-thiones and their derivatives possess CNS depressant[28], Pesticidal[29,30] and antitubercular[31] activities. In view of all these findings and in continuation of our research work on 4-substituted thiazole-2-semicarbazides and their derivatives[13,14], we here by report for the first time the synthesis and antimicrobial activity of some thiazole derivatives, wherein 3-methyl pyrazole-5-one, 3-amino pyrazole-5-one and 3, 5 dimethyl pyrazole systems are linked at their 1 position to 2-position of 4-substituted thiazole system via carboxyl amino function. We are also reporting here for the first

time the synthesis of systems wherein 1, 3, 4-oxadiazolin-5-thione moiety linked to 2 position of 4-substituted thiazole system at their 2 position via amino bridge and 5-substituted-1, 3, 4-oxadiazole moiety linked to 2 position of 4-substituted thiazole system at their 2 position via amino bridge.

All the newly synthesized compounds have been evaluated for their antimicrobial activity.

EXPERIMENTAL

Melting points were determined in open capillary tubes and are uncorrected. IR spectra were recorded in KBr discs(ν_{max} in cm^{-1}) on Perkin- Elmer FT-IR (Spectrum ONE) spectrophotometer, ^{1}H-NMR spectra on a Bruker AMX (400 MHz) spectrophotometer using DMSO as solvent using TMS as an internal standard (chemical shifts in δ) and mass spectra on a mass spectrophotometer JOEL sx-102(FAB) instrument. Compounds were checked for their purity by TLC on silica gel G plates and spots were located by iodine vapours.

The starting compounds substituted thiazole-2-semicarbazides[13,14] **(3a-b)** were prepared according to the reported method. Synthesis of 3-methyl-*N*-(substituted-1′3′-thiazol-2′-yl)-5-oxo-4,5-dihydro-1H-pyrazole -1-carboxamides **(4a-b)**/3-amino-N-(substituted-1′3′-thiazol-2′-yl)-5-oxo-4,5dihydro-1H-pyrazole-1-carboxamide **(5a-b)**/3,5-dimethyl-N-(substituted-1′3′-thiazol-2′-yl)-1H-pyrozole-1-carboxamide **(6a-b)**.

To a solution of **(3a-b)** (0.001 mole) in ethanol (10 ml), appropriate diketone like ethylacetoacetate/ethylcynoacetate/acetylacetone (0.001 mole) were added and the mixture was refluxed for 12 hr in presence of catalytic amount of glacial acetic acid. Excess of ethanol was removed by distillation and the crystalline residue obtained was filtered, washed with ethanol, dried and recrystallized from ethanol to yield compounds (4a-b, 5a-b, 6a-b) in good yield.

3-Methyl-N-(4-phenyl-1′3′-thiazol-2′-yl)-5-oxo-4,5-dihydro-1H-pyrazole-1-carboxamides (4a)

708 (C-S-C), 1605, 1625 (C=N/C=N), 1682, 1719 (C=O/C=O), 3333 (NH).1H NMR (TMS) δ ppm: 2.07 (s, 3H, CH_3), 3.42 (s, 1H, CH_2), 6.25 (s, 1H, CH of thiazole), 6.80-7.40 (m, 5H, ArH), 9.09 (s, 1H, NH).MS; m/z (in %), 300 (58%), 203 (100%), 175 (28%), 134 (37%), 89 (9%).

3-methyl-N-(4-methyl-1′3′-thiazol-2′-yl)-5-oxo-4,5-dihydro-1H-pyrazole -1-carboxamides (4b)

IR (KBr) ν cm^{-1} : 694 (C-S-C), 1578, 1601 (C=N/C=N), 1674, 1718 (C=O/C=O), 3348 (NH).

3-amino-N-(4-phenyl-1′3′-thiazol-2′-yl)-5-oxo-4,5dihydro-1H-pyrazole-1-carboxamide (5a)

IR (KBr) ν cm^{-1} : 694 (C-S-C), 1601, 1618 (C=N/C=N), 1680, 1721 (C=O/C=O), 3188 (NH), 3431 (NH_2).1H NMR (TMS) δppm; 3.51 (s, 2H, CH_2), 4.14 (s, 2H, NH_2), 6.21 (s, 1H, CH of thiazole), 6.54-7.20 (m, 5H, ArH), 9.19 (s, 1H, NH).

3-amino-N-(4-methyl-1′3′-thiazol-2′-yl)-5-oxo-4,5dihydro-1H-pyrazole-1-carboxamide (5b)

IR (KBr) νcm^{-1}: 698 (C-S-C), 1606, 1621 (C=N/C=N), 1698, 1741 (C=O/C=O), 3264 (NH), 3411 (NH_2).

3, 5-dimethyl-N-(4-phenyl-1′3′-thiazol-2′-yl)-1H-pyrozole-1-carboxamide (6a)

IR (KBr) ν cm^{-1}: 717 (C-S-C), 1577, 1605 (C=N/C=N), 1681 (C=O), 3362 (NH).1H NMR (TMS) δ ppm; 1.81 (s, 3H, CH_3), 1.98 (s, 3H, CH_3), 6.39 (s, 1H, CH of thiazole), 6.41 (s, 1H, CH of pyrrazole), 7.12-7.91 (m, 5H, ArH), 9.14 (s, 1H, NH).

3, 5-dimethyl-N-(4-methyl-1′3′-thiazol-2′-yl)-1H-pyrozole-1-carboxamide 6b:

(KBr) ν cm^{-1}: 704 (C-S-C), 1564, 1602 (C=N/C=N), 1677 (C=O), 3312 (NH).

Synthesis of 5-[(substituted-1′, 3′-thiazol-2′-yl)amino]-1,3,4-oxadiazole-2(3*H*)-thione (7a-b)

A mixture of **(3a-b)** (0.001 mole), potassium hydroxide (0.002 mole) and carbon disulphide (0.002 mole) in methanol (20 ml) was refluxed on a steam bath until the evolution of hydrogen sulphide ceases (42 hr). The solvent was evaporated and the residue dissolved in ice-cold water. The resulting clear solution was filtered and the filtrate acidified with dilute hydrochloric acid. The separated solid was filtered, washed with water, dried and crystallized from dioxane to furnish compounds **(7a-b)** in good yield.

5-[(4-phenyl-1′, 3′-thiazol-2′-yl)amino]-1,3,4-oxadiazole-2(3H)-thione (7a)

IR (KBr) ν cm^{-1}: 715 (C-S-C), 1156 (C-O-C), 1281 (C=S), 1585, 1598 (C=N/C=N), 3255, 3435 (NH/NH).^{1}HNMR (TMS) δppm; 6.22 (s, 1H, CH of thiazole), 6.71-7.51 (m, 5H, ArH), 9.19 (s, 1H, NH), 9.48 (s, 1H, NH). MS;m/z (in %), 276 (44%), 203 (100%), 175 (15%), 147 (42%).

5-[(4-methyl-1′, 3′-thiazol-2′-yl)amino]-1,3,4-oxadiazole-2(3H)-thione (7b)

IR (KBr) ν cm^{-1}: 708 (C-S-C), 1158 (C-O-C), 1274 (C=S), 1601, 1605 (C=N/C=N), 3245, 3385 (NH/NH).

Synthesis of 2-(substituted)-5-[(4-substituted-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8a-h)

A Mixture of 3a-b (0.001 mole), substituted aromatic acids (0.001) and phosphorous oxychloride (15 ml) were refluxed at 100-110^0 c for 6 hr. The excess phosphorous oxychloride was distilled off, the residue was poured in to ice-cold water, neutralized with ammonia, solid separated was filtered, dried and recrystallised from 1, 4-dioxane to get 8a-h in good yield.

2-(benzyl)-5-[(4-phenyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8a)

IR (KBr) ν cm^{-1}: 701 (C-S-C), 1149 (C-O-C), 1576, 1613, 1634 (C=N/C=N/C=N), 3281 (NH); 1H NMR δppm: 3.24 (s, 2H, CH_2), 6.27 (s, H, CH of thiazole), 6.88-7.71 (m, 10H, ArH), 9.31 (s, 1H, NH).MS; m/z (in %), 335 (100%), 334 (41%), 243 (5%), 203 (48%), 175 (2%), 147 (4%).

2-(phenyl)-5-[(4-phenyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8b)

IR (KBr) ν cm^{-1}: 701 (C-S-C), 1153 (C-O-C), 1599, 1622, 1646 (C=N/C=N/C=N), 3149 (NH). ^{1}H NMR δppm: 6.21 (s, 1H, CH of thiazole), 6.81-7.41 (m, 10H, ArH), 9.24 (s, 1H, NH).

2-(p-chloro phenyl)-5-[(4-phenyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8c)

IR (KBr) ν cm^{-1}: 700 (C-S-C), 1149 (C-O-C), 1614, 1621, 1651 (C=N/C=N/C=N), 3268 (NH); ^{1}H NMR δppm: 6.32 (s, 1H, CH of thiazole), 6.71-7.68 (m, 9H, ArH), 9.20 (s, 1H, NH).

2-(p-nitro phenyl)-5-[(4-phenyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8d)

IR (KBr) ν cm^{-1}: 700 (C-S-C), 1149 (C-O-C), 1616, 1631, 1654 (C=N/C=N/C=N), 3265 (NH). ^{1}H NMR δppm: 6.38 (s, 1H, CH of thiazole), 6.82-7.80 (m, 9H, ArH), 9.18 (s, 1H, NH).

2-(benzyl)-5-[(4-methyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8e)

IR (KBr) ν cm^{-1}: 700 (C-S-C), 1125 (C-O-C), 1585, 1601, 1634 (C=N/C=N/C=N), 3326 (NH).

2-(phenyl)-5-[(4-methyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8f)

IR (KBr) ν cm^{-1}: 701 (C-S-C), 1148 (C-O-C), 1608, 1631, 1652 (C=N/C=N/C=N), 3181 (NH).

2-(p-chloro phenyl)-5-[(4-methyl-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8g)

IR (KBr) ν cm^{-1}: 713 (C-S-C), 1174 (C-O-C), 1601, 1631, 1653 (C=N C=N/C=N), 3248 (NH).

2-(p-nitro phenyl)-5-[(4-substituted-1, 3-thiazol-2-yl)amino]-1,3,4-oxadiazole (8h)

IR (KBr) ν cm^{-1}: 703 (C-S-C), 1147 (C-O-C), 1576, 1621, 1659 (C=N C=N/C=N), 3251 (NH).

RESULTS AND DISCUSSION

Compound **(3a-b)** when allowed to reacted with diketones like ethylacetoacetate/ ethylcynoacetate/ acetylacetone in ethanol in presence of catalytic amount of glacial acetic acid under reflux conditions offered 3-methyl-N-(4-substituted-1′3′-thiazol-2′-yl)-5-oxo-4,5-dihydro-1H-pyrazole -1-carboxamides **(4a-b)**/3-amino-N-(4-substituted-1'3'-thiazol-2'-yl)-5-oxo-4,5dihydro-1H-pyrazole-1-carboxamide **5a-b**/3,5-dimethyl-N-(4-substituted-1'3'-thiazol-2'-yl)-1H-pyrozole-1-carboxamide **(6a-b)** in good yield. The structures of these compounds were conformed by spectral data. The IR spectrum of compound **(4a)** displayed absorption bands at 708, 1605, 1625, 1682, 1719 and 3333 cm^{-1} due to C-S-C, C=N/ C=N, C=O/ C=O and NH functions respectively. Its ^{1}HNMR spectrum displayed four singlets and a multiplet at 2.07, 3.42,

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TABLE 1: Physical data and elemental data of synthesized compounds

Comp. no.	R	R^1	Colour (Solvent*)	MP ^{0}C (Yield %)	Mol. formula	Analysis % found (calcud)		
						C	H	N
(4a)	C_6H_5	-	Colourless(Ethanol)	185(68)	$C_{14}H_{12}N_4O_2S$	55.78(5.99)	3.98(4.03)	18.54(18.65)
(4b)	CH_3	-	Colourless(Ethanol)	169(72)	$C_9H_{10}N_4O_2S$	45.14(45.37)	4.19(4.23)	23.40(23.51)
(5a)	C_6H_5	-	Colourless(Ethanol)	155(75)	$C_{13}H_{11}N_5O_2S$	51.74(51.82)	3.49(3.68)	23.12(23.24)
(5b)	CH_3	-	Colourless(Ethanol)	194(74)	$C_8H_9N_5O_2S$	39.91(40.16)	3.72(3.79)	29.16(29.27)
(6a)	C_6H_5	-	Colourless(Ethanol)	204(68)	$C_{15}H_{14}N_4OS$	60.21(60.38)	4.64(4.73)	18.58(18.78)
(6b)	CH_3	-	Colourless(Ethanol)	265(65)	$C_{10}H_{12}N_4OS$	50.61(50.83)	5.06(5.12)	23.60(23.71)
(7a)	C_6H_5	-	Brown(Dioxane)	241(80)	$C_{11}H_8N_4OS_2$	47.68(47.81)	2.81(2.92)	20.21(20.27)
(7b)	CH_3	-	Brown(Dioxane)	235(75)	$C_6H_6N_4OS_2$	33.48(33.63)	2.76(2.82)	25.98(26.15)
(8a)	C_6H_5	$-CH_2C_6H_4$	Pale yellow(Dioxane)	284(72)	$C_{18}H_{14}N_4OS$	64.48(64.65)	4.04(4.22)	16.68(16.75)
(8b)	C_6H_5	C_6H_5	Paleyellow(Dioxane)	251(65)	$C_{17}H_{12}N_4OS$	63.41(63.73)	3.69(3.78)	17.31(17.49)
(8c)	C_6H_5	p-Cl,C_6H_4-	Pale yellow(Dioxane)	249(68)	$C_{17}H_{11}N_4OSCl$	57.41(57.55)	3.08(3.12)	15.68(15.79)
(8d)	C_6H_5	p-$NO_2C_6H_4$ -	Pale yellow(Dioxane)	251(74)	$C_{17}H_{11}N_5O_3S$	55.76(55.88)	2.81(3.03)	19.01(19.17)
(8e)	CH_3	$-CH_2C_6H_5$	Pale yellow(Dioxane)	261(78)	$C_{13}H_{12}N_4OS$	57.18(57.34)	4.39(4.44)	20.46(20.57)
(8f)	CH_3	C_6H_5-	Red(Dioxane)	244(69)	$C_{12}H_{10}N_4OS$	55.61(55.80)	3.82(3.90)	21.58(21.69)
(8g)	CH_3	p-Cl,C_6H_4-	Paleyellow(Dioxane)	286(69)	$C_{12}H_9N_4OSCl$	49.10(49.23)	3.01(3.10)	19.09(19.14)
(8h)	CH_3	p-$NO_2C_6H_{4+}$	Red(Dioxane)	191(71)	$C_{12}H_{11}N_5O_3S$	47.28(47.52)	2.84(2.99)	22.99(23.09)

***Solvent for recrystallisation**

6.25, 9.09 and 6.80-7.40 δ due to three protons of the methyl group of pyrrazole moiety, two protons of methylene group of pyrrazole moiety, a proton at 5-position of the thiazole moiety, a proton of NH function and five aromatic protons at 4-position of thiazole moiety respectively. Mass spectrum of compound **(4a)** displayed molecular ion peak M^+ at 300 (58%), which is equivalent to its molecular weight. Further fragment ions recorded at m/z 203 (100%), 175 (28%), 134 (37%) and 89 (9%) due to sequential loss of NCO radical and C_3H_5N, CO molecule, CHN_2 molecule and CS and hydrogen radical respectively. All these data are in conformity with the structure **(4a)**.

Compound **(3a-b)** when reacted with potassium hydroxide and carbondisuplide in ethanol under reflux conditions for 42 hr yielded 5-[(4-substituted-1′,3′-thiazol-2′-yl)amino]-1,3,4-oxadiazole-2(3H)-thione **(7a-b)** in a good yield. The IR spectrum compound 7a showed absorption bands at 715, 1156, 1281, 1585, 1598, 3255 and 3435 cm^{-1} due to C-S-C, C-O-C, C=S, C=N/C=N, NH and NH functions respectively. In the ^{1}HNMR spectrum of compound **(7a)** a proton at 5-position of the thiazole moiety, one proton of NH function of oxadiazole moiety, a proton of bridged NH function at 2-position of thiazole and five aromatic protons at 4-position of thiazole moiety have resonated as three distinct singlets and a multiplet at 6.22, 9.19, 9.48 and 6.71-7.51δ respectively. Mass spectrum of compound **(7a)** displayed molecular ion peak M^+ at 276 (44%). Due to simultaneous loss of hydrogen radical, N_2 molecule and CS molecule sequential loss of CO and a N_2 molecule from the molecular ion of compound **(7a)** gave fragment ions at m/z 203 (100%, base peak), 175 (15%) and 147 (42%) respectively.

Compound **(3a-b)** on reaction with substituted aromatic acids in presence of $POCl_3$ under reflux conditions offereded 2-(substituted)-5-[(4-substituted-1,3-thiazol-2-yl)amino]-1,3,4-oxadiazole **8a-h** in a good yield. The structures of these compounds were conformed by spectral data. The IR spectrum of compound 8a displayed absorption bands at 701, 1149, 1576, 1613, 1634 and 3281 cm^{-1} due to C-S-C, C-O-C, C=N/C=N/C=N and NH functions respectively. The ^{1}HNMR spectrum of compound **(8a)** displayed peaks at 3.24, 6.27, 6.88-7.71 and 9.31s δ were due to a singlet for two protons of bridged methylene at 2-positon of oxadiazole moiety, a proton at 5-position of the thiazole moiety, a multiplet of ten aromatic protons of two benzene rings and a singlet due to proton of bridged amine functions respectively. Mass spectrum **(8a)** displayed molecular ion peak M^+ at 334 (41%), which is equivalent to its molecular weight and M+1 peak at 335 (100%) which is also base peak. Further fragment ions recorded at m/z 243 (5%), 203 (48%), 175 (2%) and 147 (4%) were due to sequential loss of $C_6H_5CH_2$, CN_2 molecule, CO molecule and N_2 from the molecular ion fragment of compound **(8a)**. All these data are in conformity with the structure of **(8a)**.

The physical data and elemental analysis data of the all the newly synthesized compounds were tabu-

TABLE 2: Anti-microbial activity of the synthesized compounds

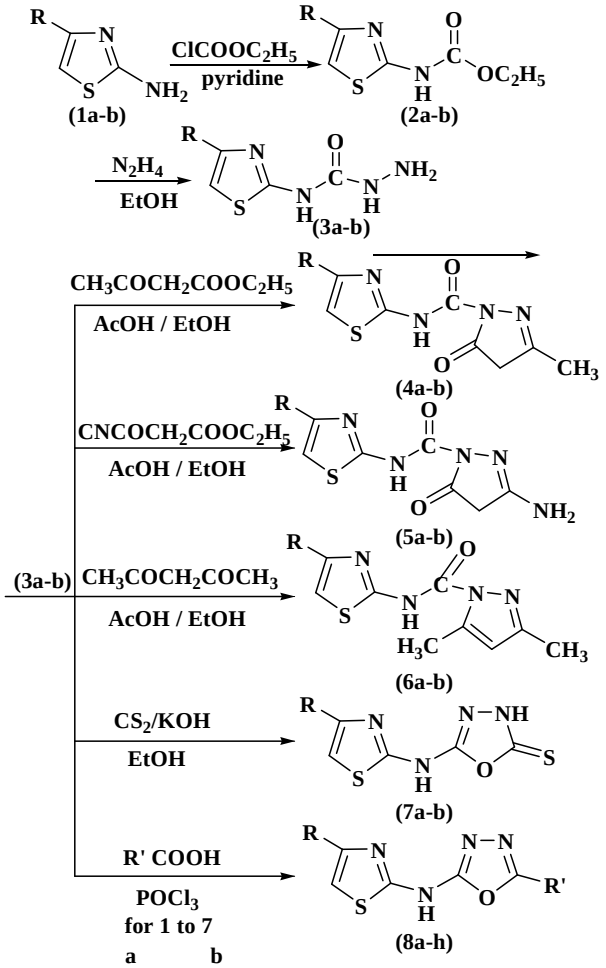
Comp. no.	Concc (µg/ml) in DMF	Zone of inhibition in mm				
		Antibacterial activity			Antifungal activity	
		S.aureus	*E.coli*	*B.subtilus*	*A.niger*	*C.albicans*
(4a)	1000	11	09	10	09	10
(4b)	1000	09	10	09	10	09
(5a)	1000	15	14	16	19	20
(5b)	1000	16	15	15	18	19
(6a)	1000	11	14	14	12	11
(6b)	1000	09	11	09	11	12
(7a)	1000	17	18	17	19	21
(7b)	1000	16	15	16	18	19
(8a)	1000	13	12	10	11	13
(8b)	1000	14	14	14	19	17
(8c)	1000	19	18	17	21	19
(8d)	1000	15	14	14	15	16
(8e)	1000	09	09	09	12	13
(8f)	1000	12	14	10	17	15
(8g)	1000	17	17	18	21	20
(8h)	1000	14	12	13	15	14
Gentamycin	1000	20	19	19	-	-
Nystatin	1000	-	-	-	22	21
Control (DMF)	-	-	-	-	-	-

lated in the TABLE 1.

Antimicrobial activity

The *in-vitro* biological screening of the compounds was undertaken against the bacteria *Staphylococcus aureus*, *E.Coli* and *Bacillus subtilus*, fungi *Aspergillus niger* and *Candida albicans* by cup-plate method[13-14] using nutrient agar as medium. Then holes of 6mm diameter were punched carefully using a sterile cork borer and these were filled with test solutions (1000µg/ml in DMF) and DMF used as control. The plates were incubated at 37^{0}C for 24 h in case of antibacterial activity and 72 h in case of antifungal activity. The diameter of the zone of inhibition for all the test compounds was measured and the results were compared with the standard drug Gentamycin for antibacterial activity and Nystatin for antifungal activity is tabulated in TABLE 2.

The results were showed that the compounds **(5a**, **5b**, **7a**, **7b**, **8c)** and **(8g)** showed good activity, compounds **(8a**, **8b**, **8d)** and **(8h)** exhibited moderate activity with Gentamycin against *S.aureus*. Compounds **(5b**, **7a**, **7b**, **8c)** and **(8g)** showed good activity, compounds **(5a**, **6a**, **8b**, **8d)** and **(8f)** exhibited comparable activity with Gentamycin against *E.coli*. Compounds **(5a**, **5b**, 7a, **7b**, **8c)** and **(8g)** showed good activity, compounds **(6a**, **8b)** and **(8d)** exhibited comparable activity with Gentamycin against *B.substilus*. Compounds **(5a**, 5b, **7a**, **7b**, **8b**, **8c)** and **(8g)** showed



	a	b		
R	C_6H_5	$-CH_3$		

for 8

	a	b	c	d
R	C_6H_5	C_6H_5	C_6H_5	C_6H_5
R'	$-CH_2C_6H_5$	C_6H_5	$-C_6H_4Cl$	$-C_6H_5NO_2$

	e	f	g	h
R	$\cdot CH_3$	$\cdot CH_3$	$\cdot CH_3$	$^-CH_3$
R'	$-CH_2C_6H_5$	$-C_6H_5$	$-C_6H_4Cl$	$-C_6H_5NO_2$

SCHEME 1

good activity, compounds **(8d**, **8f)** and **(8h)** exhibited comparable activity with Nystatin against *A.niger*. Compounds **(5a**, **5b**, **7a**, **7b**, **8c)** and **(8g)** showed good activity, compounds **(8b**, **8d)** and **(8f)** exhibited comparable activity with Nystatin against *C.albicans*.

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