International Journal of Pharma and Bio Sciences

SYNTHESIS, CHARACTERIZATION AND ANTI-MICROBIAL ACTIVITIES OF NOVEL THIAZOLE DERIVATIVES

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ABSTRACT

In the present study, a novel thiazoles were synthesized by incorporation of pyrazole moiety at 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide **(5)** by treating with chalcones **(7a-7j)**. The chemical structures of the synthesized compounds were confirmed by means of IR, ^{1}H-NMR, Mass spectral and Elemental analysis. These compounds were screened for anti-bacterial (*Staphylococcus aureus* ATCC 9144*, Staphylococcus epidermidis* ATCC 155*, Micrococcus luteus* ATCC 4698, *Bacillus cereus* ATCC 11778*, Escherichia coli* ATCC 25922*, Pseudomonas aeruginosa* ATCC 2853*,* and *Klebsiella pneumoniae* ATCC 11298*))* and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique. Most of the synthesized compounds exhibited significant anti-bacterial and anti-fungal activities. Among the synthesized compounds, 2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide **(8f)** was found to exhibit the highest anti-bacterial activity and 2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide**(8j)** exhibited highest anti-fungal activity.

KEY WORDS

Thiazole, Pyrazole, Chalcone, Anti-bacterial and Anti-fungal.

INTRODUCTION

Thiazoles and pyrazoles are highly versatile ring systems displaying a large number of mild to potential pharmacological activities. Some of them are utilized as medicines[1]. According to literature survey, Thiazoles were reported to possess anti-microbial[2], analgesic[3], anti-inflammatory[4], anti-cancer[5], anti-tubercular[6], anthelmintic[7] & diuretic[8] activities. Anti-microbial activities of some substituted thiazoles are well established because it posses (S-C=N) toxophoric unit. Thiazoles have enhanced lipid solubility with hydrophilicity. Thiazoles are easily metabolized by routine biochemical reactions and are non-carcinogenic in nature[9]. In addition, pyrazoles are reported as anti-microbial[10], analgesic[11], anti-inflammatory[12], anti-

hypertensive[13], anti-depressant[14] and anti-cancer[15] agents. Above observation prompted us to synthesize the title compounds **(8a – 8j)** with presumption that incorporation of pyrazole moiety at 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide **(5)** by treating with chalcones **(7a-7j)** would produce novel thiazole derivatives with potent biological activities. Their chemical structure was confirmed by IR, ^{1}H-NMR, Mass spectral and Elemental analysis. These compounds were screened for their anti-bacterial activity against four gram + ve bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698 and *Bacillus cereus* ATCC 11778), three gram - ve bacteria (*Escherichia coli* ATCC 25922, *Pseudomonas aeruginosa* ATCC 2853, *and Klebsiella pneumoniae* ATCC 11298) and anti-fungal (*Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC 46645) activities by paper disc diffusion technique.

MATERIALS AND METHODS

The melting points were taken in open capillary tube and are uncorrected. The IR spectra of the compounds were recorded on ABB Bomem FT-IR spectrometer MB 104 with KBr pellets. The ^{1}H-NMR (300 MHz) spectra were recorded on a Bruker 300 NMR spectrometer (with TMS as internal references). Mass spectra were recorded on Shimadzu GC MS QP 5000. Microanalyses were obtained with an elemental Analyses system GmbH VarioEL V300 element analyzer. The purity of the compounds was checked by TLC on pre-coated SiO_2 gel (HF_{254}, 200 mesh) aluminium plates (E Merk) using ethanol and benzene visualized in iodine chamber. The reagent grade chemicals were purchased from the commercial sources and purified by either distillation or recrystallisation before use.

***CHEMISTRY*:**Title compounds **(8a – 8j)** were synthesized by incorporation of pyrazole moiety at 2nd position of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide **(5)** by treating with chalcones **(7a-7j)**. The 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide **(5)** was synthesized from 2-amino-4-phenyl thiazole **(3)** through 2-chloro-N-(4-phenyl thiazol-2-yl) acetamide **(4)**

2-Amino-4-phenyl thiazole (3):To a mixture[16] consisting of acetophenone (0.1 mol) and thiourea (0.2 mol), bromine (0.2 mol) were added drop wise very slowly. After the addition of bromine the reaction mixture was heated on water bath for overnight, and water was added to it and again heated until most of the solid has gone into solution. The reaction mixture was filtered when it is hot and the filtrate was cooled. It was made alkaline with concentrated ammonium hydroxide to separate 2-amino-4-phenyl thiazole. The product was filtered, washed with alcohol and dried over P_2O_5. It was recrystallised from ethanol, as colorless needles Yield 84 % ; m.p. 120-122^{0}C .

***2-Chloro-N-(4-phenyl thiazol-2-yl) acetamide (4)*:**0.05 mole of 2-amino 4-phenyl thiazole[16] **(3)** was dissolved in 25ml of glacial acetic acid containing a saturated solution of sodium acetate (25ml). To the above mixture 0.06 mole of chloro acetyl chloride was added with stirring. Then the mixture was heated on water bath for 6 hrs, and then the reaction mixture was poured on crushed ice .The product is then filtered, dried and recrystallised from alcohol.

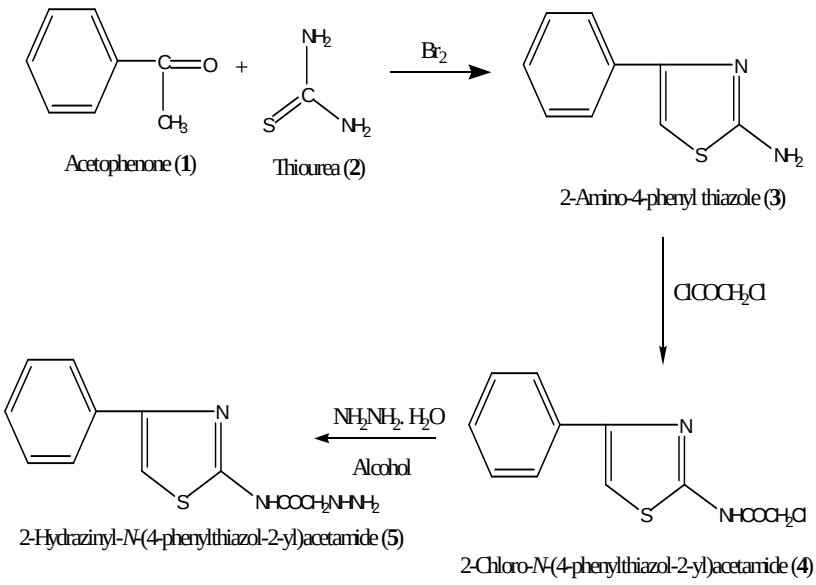
***2-Hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide (5)*:**0.01 moles of 2-chloro-N-(4-phenylthiazole -2-yl)-acetamide[16] **(4)** was dissolved in 25ml of alcohol. To the above mixture 0.01 mole of hydrazine hydrate was added and the resultant mixture was refluxed for 8 hrs. After 8 hrs the reaction mixture was poured on the crushed ice to separate the product. (m.p. 143-145ºC)

Chalcones (7a-7j):0.01 mole of substituted aromatic aldehyde[17] and 0.01 mole of acetophenone were taken in beaker. This mixture was dissolved in minimum quantity of ethanol and 3 to 4 drops of concentrated sodium hydroxide is added to the above mixture. The resultant mixture was stirred using magnetic stirrer for a period of 2 hrs. After 2 hrs, the reaction mixture was poured over crushed ice

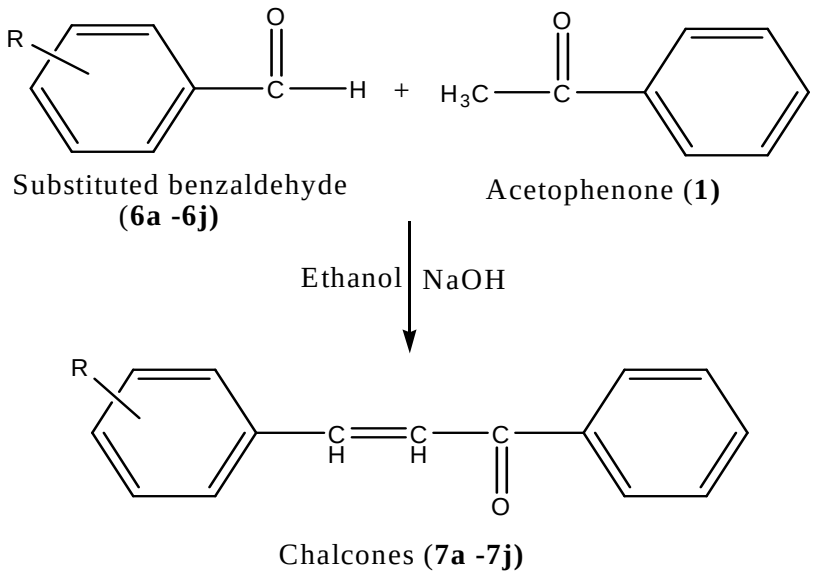
and was placed on ice chest over night. The precipitated product was filtered and dried.

***Title compounds (8a-8j)*:**0.05 mole of chalcone **(7a-7j)** was added to the 0.1 mole of 2-hydrazinyl –N-(4-phenylthiazole -2-yl) acetamide **(5)** in 100 ml round bottom flask containing 30 ml 0f N, N-dimethyl formamide. The above mixture was refluxed at 120-140ºC for a period of 10 hrs. Then the reaction mixture was cooled and poured in to a beaker containing ice cold water. The obtained product was separated by filtration, dried over the filter paper and recrystallised using butanol.

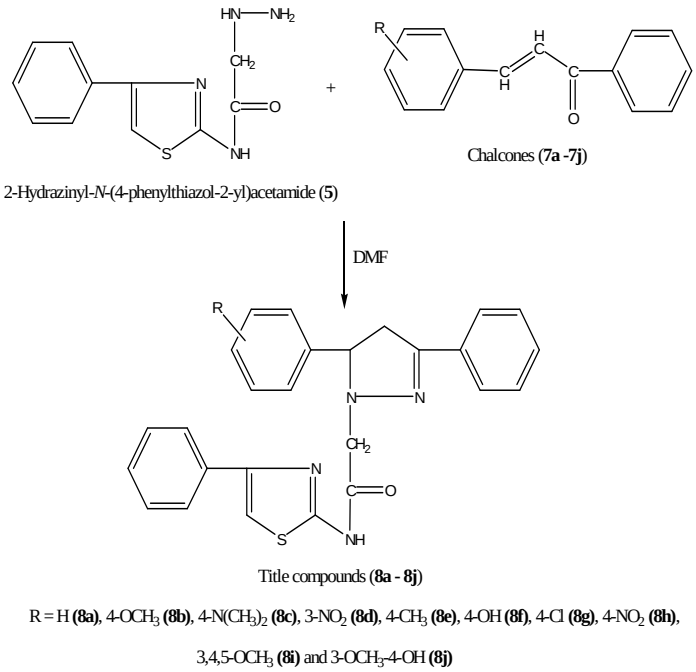
Scheme - 1: Synthesis of 2-hydrazinyl-N-(4-phenylthiazol-2-yl) acetamide **(5)**



Scheme - 2: Synthesis of chalcones **(7a-7j)**



Scheme - 3: Synthesis of title compounds **(8a-8j)**



R = H **(8a)**, 4-OCH_3 **(8b)**, 4-$N(CH_3)_2$ **(8c)**, 3-NO_2 **(8d)**, 4-CH_3 **(8e)**, 4-OH **(8f)**, 4-Cl **(8g)**, 4-NO_2 **(8h)**, 3,4,5-OCH_3 **(8i)** and 3-OCH_3-4-OH **(8j)**

ANTI-MICROBIAL SCREENING

The anti-bacterial activity of the synthesized compounds was tested against four gram + ve bacteria (*Staphylococcus aureus* ATCC 9144, *Staphylococcus epidermidis* ATCC 155, *Micrococcus luteus* ATCC 4698 and *Bacillus cereus* ATCC 11778) and three gram – ve bacteria (*Escherichia coli* ATCC 25922 *Pseudomonas aeruginosa* ATCC and *Klebsiella pneumoniae* ATCC 11298) using nutrient agar medium (Hi-Media Laboratories, India). The anti-fungal activities of the compounds were tested against two fungi namely *Aspergillus niger* ATCC 9029 and *Aspergillus fumigatus* ATCC using sabouraud dextrose agar medium (Hi-Media Laboratories, India).

***Paper disc diffusion technique*:** The sterilized[78] (autoclaved at 120℃ for 30min) medium (40-50℃) was inoculated (1mL/100mL of medium) with the suspension (10^5 cfu mL^{-1}) of the micro-organism (matched to McFarland barium sulphate standard) and poured into a petridish to give a depth of 3-4 mm. The paper impregnated with the test compounds (100 µg/disc) was placed on the solidified medium. The plates were pre-incubated for 1 hr at room temperature and incubated at 37℃ for 24 and 48 hrs for anti-bacterial and anti-fungal activities, respectively. Ciprofloxacin (100 µg/disc) and Fluconazole (100 µg/disc) were used as standard for anti-bacterial and anti-fungal activities, respectively. The observed zone of inhibition is presented in Table-1.

Table 1.
Anti-microbial activity of the synthesized compounds (100 µg/disc)

Compounds	Invitro activity - zone of inhibition (in mm)								
	Gram + ve bacteria				Gram - ve bacteria			Fungi	
	S.aureus	*S.epidermidis*	*M.luteus*	*B.cereus*	*E.coli*	*P.aeuriginosa*	*K.pneumoniae*	*A.niger*	*A.fumigatus*
8a	5	7	6	5	3	4	3	8	7
8b	9	11	8	7	6	4	5	10	12
8c	8	9	9	6	5	6	5	12	8
8d	10	12	10	8	5	4	7	13	10
8e	7	10	9	7	6	7	8	11	9
8f	15	18	16	15	12	10	13	19	15
8g	12	10	13	11	9	8	10	15	13
8h	10	12	11	9	8	9	8	14	12
8i	8	11	10	8	7	6	6	12	10
8j	13	16	14	12	10	11	9	20	17
Ciprofloxacin	25	29	27	23	29	25	27	-	-
Fluconazole	-	-	-	-	-	-	-	29	26
Control (DMF)	-	-	-	-	-	-	-	-	-

RESULTS AND DISCUSSION

CHEMISTRY

IR, ^{1}H-NMR, Mass spectra and Elemental analysis were consistent with the assigned structures.

2-(3,5-diphenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8a)

Yield: 76%; m.p. 88-90 ℃; IR (KBr, cm $^{-1}$): 3155 (N-H), 3017 (Ar-CH), 1698 (C=O), 1580 (C=N), 1565 (C=C), 683 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.20 (s, 1H, -NH-), 7.03-7.54 (m, 15H, Ar-H), 6.54 (s, 1H, -S-CH=), 3.88 (t, 1H, -N-CH-), 3.48 (s, 2H, -CH_2-), 1.57-1.85 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 438 (Calcd. for $C_{26}H_{22}N_4OS$; 438.54). Anal. Calcd. for $C_{26}H_{22}N_4OS$; C, 71.21; H, 5.06; N, 12.78. Found: C, 71.15; H, 5.10; N, 12.76.

2-(5-(4-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8b)

Yield: 67%; m.p. 59-60 ℃; IR (KBr, cm $^{-1}$): 3159 (N-H), 3024 (Ar-CH), 1694 (C=O), 1586 (C=N), 1563 (C=C), 677 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.06 (s, 1H, -NH-), 6.75-7.63 (m, 14H, Ar-H), 6.57 (s, 1H, -S-CH=), 3.90 (t, 1H, -N-CH-), 3.77 (s, 3H, -O-CH_3), 3.45 (s, 2H, -CH_2-), 1.59-1.88 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 468 (Calcd. for $C_{27}H_{24}N_4O_2S$; 468.57). Anal. Calcd. for $C_{27}H_{24}N_4O_2S$; C, 69.21; H, 5.16; N, 11.96. Found: C, 69.25; H, 5.14; N, 11.91.

2-(5-(4-(dimethylamino)phenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8c)

Yield: 73%; m.p. 72-75 ℃; IR (KBr, cm^{-1}): 3150 (N-H), 3013 (Ar-CH), 1691 (C=O), 1579 (C=N), 1560 (C=C), 685 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.12 (s, 1H, -NH-), 6.53-7.58 (m, 14H, Ar-H), 6.55 (s, 1H, -S-CH=), 3.86 (t, 1H, -N-CH-), 3.47 (s, 2H, -CH_2-), 2.88 (s, 6H, -N(CH_3)$_2$), 1.60-1.84 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 481 (Calcd. for $C_{28}H_{27}N_5OS$; 481.61). Anal. Calcd. for $C_{28}H_{27}N_5OS$; C, 69.83; H, 5.65; N, 14.54. Found: C, 69.87; H, 5.69; N, 14.50.

2-(5-(3-nitrophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8d)

Yield: 65%; m.p. 104-105 ℃; IR (KBr, cm^{-1}): 3153 (N-H), 3018 (Ar-CH), 1687 (C=O), 1585 (C=N), 1567 (C=C), 681 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.17 (s, 1H, -NH-), 7.21-8.09 (m, 14H, Ar-H), 6.59 (s, 1H, -S-CH=), 3.93 (t, 1H, -N-CH-), 3.51 (s, 2H, -CH_2-), 1.55-1.87 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 483 (Calcd. for $C_{26}H_{21}N_5O_3S$; 483.54). Anal. Calcd. for $C_{26}H_{21}N_5O_3S$; C, 64.58; H, 4.38; N, 14.48. Found: C, 64.61; H, 4.36; N, 14.44.

2-(5-(4-methylphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8e)

Yield: 68%; m.p. 69-72 ℃; IR (KBr, cm^{-1}): 3157 (N-H), 3015 (Ar-CH), 1702 (C=O), 1577 (C=N), 1561 (C=C), 689 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.03 (s, 1H, -NH-), 7.15-8.00 (m, 14H, Ar-H), 6.51 (s, 1H, -S-CH=), 3.96 (t, 1H, -N-CH-), 3.40 (s, 2H, -CH_2-), 2.39 (s, 3H, -CH_3), 1.60-1.87 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 452 (Calcd. for $C_{27}H_{24}N_4OS$; 452.57). Anal. Calcd. for $C_{27}H_{24}N_4OS$; C, 71.65; H, 5.35; N, 12.38. Found: C, 71.70; H, 5.32; N, 12.36.

2-(5-(4-hydroxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8f)

Yield: 70%; m.p. 78-81 ℃; IR (KBr, cm^{-1}): 3154 (N-H), 3011 (Ar-CH), 1693 (C=O), 1581 (C=N), 1564 (C=C), 682 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.09 (s, 1H, -NH-), 6.67-7.63 (m, 14H, Ar-H), 6.63 (s, 1H, -S-CH=), 4.95 (s, 1H, -OH), 3.82 (t, 1H, -N-CH-), 3.47 (s, 2H, -CH_2-), 1.53-1.92 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 454 (Calcd. for $C_{26}H_{22}N_4O_2S$; 454.54). Anal. Calcd. for $C_{26}H_{22}N_4O_2S$; C, 68.70; H, 4.88; N, 12.33. Found: C, 68.74; H, 4.85; N, 12.29.

2-(5-(4-chlorophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8g)

Yield: 61%; m.p. 92-94 ℃; IR (KBr, cm^{-1}): 3160 (N-H), 3019 (Ar-CH), 1689 (C=O), 1586 (C=N), 1567 (C=C), 688 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.16 (s, 1H, -NH-), 7.09-7.67 (m, 14H, Ar-H), 6.60 (s, 1H, -S-CH=), 3.87 (t, 1H, -N-CH-), 3.51 (s, 2H, -CH_2-), 1.56-1.84 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 472 (Calcd. for $C_{26}H_{21}ClN_4OS$; 472.99). Anal. Calcd. for $C_{26}H_{21}ClN_4OS$; C, 66.02; H, 4.48; N, 7.50. Found: C, 66.08; H, 4.49; N, 7.54.

2-(5-(4-nitrophenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8h)

Yield: 69%; m.p. 100-102 ℃; IR (KBr, cm^{-1}): 3152 (N-H), 3016 (Ar-CH), 1695 (C=O), 1587 (C=N), 1562 (C=C), 686 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.11 (s, 1H, -NH-), 7.14-8.07 (m, 14H, Ar-H), 6.58 (s, 1H, -S-CH=), 3.91 (t, 1H, -N-CH-), 3.49 (s, 2H, -CH_2-), 1.51-1.86 (d, 2H, pyrazole –CH_2-). EI-MS m/z (M^+): 483 (Calcd. for $C_{26}H_{21}N_5O_3S$; 483.54). Anal. Calcd. for $C_{26}H_{21}N_5O_3S$; C, 64.58; H, 4.38; N, 14.48. Found: C, 64.55; H, 4.41; N, 14.42.

2-(3-phenyl-5-(3,4,5-trimethoxyphenyl)-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8i)

Yield: 73%; m.p. 62-65 ℃; IR (KBr, cm^{-1}): 3156 (N-H), 3012 (Ar-CH), 1689 (C=O), 1574 (C=N), 1563 (C=C), 673 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.01 (s, 1H, -NH-), 6.05-7.59 (m, 12H, Ar-H), 6.53 (s, 1H, -S-CH=), 3.85 (t, 1H, -N-CH-), 3.70 (s, 9H, -(OCH_3)$_3$), 3.46 (s, 2H, -CH_2-), 1.59-1.92 (d, 2H,

pyrazole –C<u>H</u>$_2$-). EI-MS m/z (M^+): 528 (Calcd. for $C_{29}H_{28}N_4O_4S$; 528.62). Anal. Calcd. for $C_{29}H_{28}N_4O_4S$; C, 65.89; H, 5.34; N, 10.60. Found: C, 65.94; H, 5.33; N, 10.56.

2-(5-(4-hydroxy-3-methoxyphenyl)-3-phenyl-4,5-dihydropyrazol-1-yl)-N-(4-phenylthiazol-2-yl)acetamide (8j)

Yield: 62%; m.p. 83-85 ℃; IR (KBr, cm $^{-1}$): 3163 (N-H), 3024 (Ar-CH), 1692 (C=O), 1588 (C=N), 1560 (C=C), 679 (C-S). ^{1}H-NMR ($CDCl_3$) δ: 8.15 (s, 1H, -N<u>H</u>-), 6.41-7.68 (m, 13H, Ar-<u>H</u>), 6.57 (s, 1H, -S-C<u>H</u>=), 5.06 (s, 1H, -O<u>H</u>), 3.89 (t, 1H, -N-C<u>H</u>-), 3.76 (s, 3H, -OC<u>H</u>$_3$), 3.43 (s, 2H, -C<u>H</u>$_2$-), 1.63-1.94 (d, 2H, pyrazole –C<u>H</u>$_2$-). EI-MS m/z (M^+): 484 (Calcd. for $C_{27}H_{24}N_4O_3S$; 484.57). Anal. Calcd. for $C_{27}H_{24}N_4O_3S$; C, 66.92; H, 4.99; N, 11.56. Found: C, 66.96; H, 5.03; N, 11.52.

ANTI-MICROBIAL SCREENING

Most of the synthesized compounds exhibited mild to moderate anti-microbial activity against the tested microorganisms. Compounds **8f** and **8j** were found to possess significant anti-bacterial and anti-fungal activity when compared to standard drug (Ciprofloxacin and Fluconazole for anti-bacterial and anti-fungal respectively). Compounds **8g, 8h and 8d** displayed moderate anti-microbial activity where as the remaining compounds shown lesser activity. The entire synthesized compound exhibited better anti-fungal activity than anti-bacterial activity. In addition to that, many compounds are most active against gram '+' ve bacteria than the gram '–' ve one. The potent anti-microbial activity exhibited by **8f** and **8j** may be due to the incorporation of electron donating groups like phenolic OH and –OCH_3. The interesting results we observed that both electrons donating as well as electron withdrawing groups was found to increase the anti-microbial properties, where as unsubstituted derivatives exhibited lesser degree of activity. In conclusion, the present study highlights the importance of pyrazole and thiazole ring features responsible for the anti-microbial activities and therefore may serve as a lead molecule for further modification to obtain clinically useful novel entities.

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