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## Synthesis and Spectral characterization of some novel (2, 5-dimethoxyphenyl) (2, 4-disubstituted-thiazol-5-yl) methanone as possible antibacterial agents

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### ABSTRACT

Thiazole derivatives are known to have wide spectrum of antibacterial activity. So, *N*-(substituted benzoyl) morpholine/piperidine/*N*-methyl piperazine carbothioamide (3) were prepared by condensing substituted benzoyl isothiocyanate (2) with different secondary heterocyclic amines, like morpholine/piperidine/*N*-methyl piperazine. *N*-substituted Carbothioamide (3) on treatment with 2, 5-dimethoxyphenacyl bromide (4) affords 2, 4, 5-trisubstituted thiazoles (5a-h). The newly synthesized compounds were characterized by IR, <sup>1</sup>H NMR and Mass spectral studies. The newly synthesized thiazole derivatives were screened for *in vitro* anti bacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa* bacterial strains by paper disc diffusion method. All the compounds show moderate to good anti bacterial activity. Among the tested compounds (5f) thiazole carrying 2-piperidino, 4-phenyl, 4-nitrobenzoyl is showing good activity against all the tested species.

**Key Words:** Substituted Thiazole; 2,5-dimethoxy phenacyl bromide; Antibacterial.

### INTRODUCTION

Heterocyclic ring containing nitrogen and sulphur have been under investigation for a long time because of their important medicinal properties. Thiazole and their derivative are found to be associated with various biological activities, such as antibacterial, antifungal and anti inflammatory activities [1-3]. They have attracted continuing interest over the years because of their varied biological activities[4,5] recently found in many applications in drug

development for the treatment of allergies[6], hypertension [7], schizophrenia[8], HIV infections[9], and more recently for the treatment of pain[10], as fibrinogen receptor antagonists with antithrombotic activity. Prompted by these report and in continuation of our search for biological active molecule to synthesize of some new 2, 4, 5-trisubstituted thiazole derivatives in order to investigate their antibacterial activity.

### MATERIALS AND METHODS

#### Chemistry

All reagents and solvents used were of analytical grade obtained from the supplier or recrystallized/redistilled as necessary. Thin layer chromatography was performed on microscopic slides (2x7.5cm) coated with silica gel G and spots were visualized by normal TLC and exposure to iodine vapor. Melting points were recorded on open capillary melting point apparatus and are uncorrected. Mass spectra were recorded on Micromass Q-T, TOF MS ES+4.73e3. Nuclear Magnetic Resonance spectra ( $^1\text{H}$  NMR) were recorded in  $\text{CDCl}_3/\text{DMSO-d}_6$  on Bruker advance at 400 MHz using Tetra methyl silane (TMS) as internal standard and the chemical shift ( $\delta$ ) are reported in parts per million.

#### Scheme: 1 Synthesis of targeted compounds

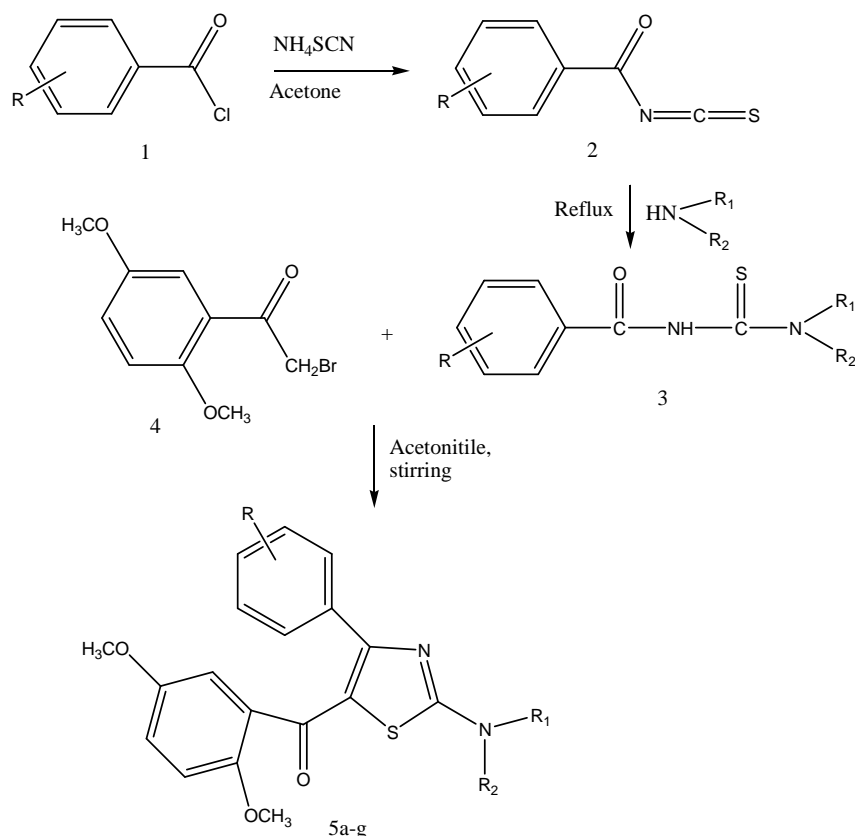


Table: 1 Substitution at R, R<sub>1</sub>, R<sub>2</sub> in targeted compounds

Compound No.	R	R <sub>1</sub>	R <sub>2</sub>
5a	2-Cl	-(CH <sub>2</sub> ) <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -	
5b	3-Cl	-(CH <sub>2</sub> ) <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -	
5c	4-Cl	-(CH <sub>2</sub> ) <sub>2</sub> -O-(CH <sub>2</sub> ) <sub>2</sub> -	
5d	H	-(CH <sub>2</sub> ) <sub>5</sub> -	
5e	2-Cl	-(CH <sub>2</sub> ) <sub>5</sub> -	
5f	H	-(CH <sub>2</sub> ) <sub>2</sub> -N(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> -	
5g	4-Cl	-(CH <sub>2</sub> ) <sub>2</sub> -N(CH <sub>3</sub> )-(CH <sub>2</sub> ) <sub>2</sub> -	

Table: 2 Physical data of synthesized compounds (5a-g)

Compound No.	Molecular Formula	Molecular weight	Yield (%)	M.P.( °C)	R <sub>f</sub> value
5a	C <sub>22</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>4</sub> S	444.93	46.06	148-150	0.58
5b	C <sub>22</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>4</sub> S	444.93	71.66	132-134	0.70
5c	C <sub>22</sub> H <sub>21</sub> ClN <sub>2</sub> O <sub>4</sub> S	444.93	59.62	124-126	0.62
5d	C <sub>23</sub> H <sub>24</sub> N <sub>2</sub> O <sub>3</sub> S	408.51	64.47	116-118	0.72
5e	C <sub>23</sub> H <sub>23</sub> ClN <sub>2</sub> O <sub>3</sub> S	442.96	49.35	174-176	0.76
5f	C <sub>23</sub> H <sub>25</sub> N <sub>2</sub> O <sub>3</sub> S	423.53	69.51	128-130	0.82
5g	C <sub>23</sub> H <sub>24</sub> ClN <sub>2</sub> O <sub>3</sub> S	457.97	73.83	195-197	0.76

R<sub>f</sub>-Value: (4.8:0.2, Toluene: Methanol)

## Spectral Characterization of targeted compounds:

Table 3: Spectral Characteristic of (2, 5-dimethoxyphenyl) (2, 4-disubstituted-thiazol-5-yl) methanone (5a-g)

Sr No	IR (cm <sup>-1</sup> ) (KBr)	<sup>1</sup> HNMR (DMSO-d <sub>6</sub> ) (ppm)	Mass (m/z)
5a	1620 (C=O) 1230(C-O-C) 870-720 (Ar-H) 640 (C-S)	δ 3.52 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 3.62-3.67 (t, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.81-3.84 (t, 4H, -H <sub>2</sub> C-O-CH <sub>2</sub> -) δ 6.43-6.75 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 7.01-7.26 (m, 4H, C <sub>6</sub> H <sub>4</sub> -Cl)	444 (M <sup>+</sup> ), 446 (M <sup>+2</sup> )
5b	1630 (C=O) 1230(C-O-C) 870-720 (Ar-H) 640 (C-S)	δ 3.59 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 3.63-3.65 (t, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.81-3.85 (t, 4H, -H <sub>2</sub> C-O-CH <sub>2</sub> -) δ 6.46-6.97 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 6.99-7.19 (m, 4H, C <sub>6</sub> H <sub>4</sub> -Cl)	444 (M <sup>+</sup> ), 446 (M <sup>+2</sup> )
5c	1620 (C=O) 1210(C-O-C) 910-740 (Ar-H) 640 (C-S)	δ 3.54 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 3.64-3.68 (t, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.81-3.84 (t, 4H, -H <sub>2</sub> C-O-CH <sub>2</sub> -) δ 6.43-6.75 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 7.01-7.26 (m, 4H, C <sub>6</sub> H <sub>4</sub> -Cl)	444 (M <sup>+</sup> ), 446 (M <sup>+2</sup> )
5d	1620 (C=O) 1230(C-O-C) 890-720 (Ar-H) 640 (C-S)	δ 1.70 (s, 6H, -H <sub>2</sub> C-CH <sub>2</sub> -CH <sub>2</sub> -) δ 3.54 (s, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.62 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 6.38-6.67 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 7.00-7.26 (m, 4H, C <sub>6</sub> H <sub>5</sub> -)	408 (M <sup>+</sup> ), 410 (M <sup>+2</sup> )
5e	1610 (C=O) 1220(C-O-C) 880-720 (Ar-H) 630 (C-S)	δ 1.70 (s, 6H, -H <sub>2</sub> C-CH <sub>2</sub> -CH <sub>2</sub> -) δ 3.57 (s, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.62-3.71 (m,6H,2,5-di-OCH <sub>3</sub> ) δ 6.31-6.75 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 6.88-7.08 (m, 4H, C <sub>6</sub> H <sub>4</sub> -Cl)	442 (M <sup>+</sup> ), 444 (M <sup>+2</sup> )
5f	1680 (C=O) 1250(C-O-C) 870-720 (Ar-H) 650 (C-S)	δ 2.36 (s, 3H,N-CH <sub>3</sub> ) δ 2.55-2.61 (t, 4H, -H <sub>2</sub> C-NCH <sub>3</sub> -CH <sub>2</sub> -) δ 3.63-3.73 (t, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.85 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 6.41-7.49 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 7.51-7.83 (m, 5H, C <sub>6</sub> H <sub>5</sub> -)	424 (M <sup>+</sup> ), 426 (M <sup>+2</sup> )
5g	1620 (C=O) 1230(C-O-C) 900-720 (Ar-H) 650 (C-S)	δ 2.35 (s, 3H,N-CH <sub>3</sub> ) δ 2.51-2.55 (m, 4H, -H <sub>2</sub> C-NCH <sub>3</sub> -CH <sub>2</sub> -) δ 3.67 (s, 4H, -H <sub>2</sub> C-N-CH <sub>2</sub> -) δ 3.78 (s,6H,2,5-di-OCH <sub>3</sub> ) δ 6.32-6.86 (m,3H,2,5-di-OCH <sub>3</sub> -C <sub>6</sub> H <sub>3</sub> -) δ 6.96-7.83 (m, 4H, C <sub>6</sub> H <sub>4</sub> -Cl)	457 (M <sup>+</sup> ), 459 (M <sup>+2</sup> )

## General Procedure for Synthesis of (2, 5-dimethoxyphenyl) (2, 4-disubstituted-thiazol-5-yl) methanone:

As shown in Scheme 1, substituted benzoyl isothiocyanate (2) was obtained by reacting ammonium thiocyanate (0.1379 mole) in 100 ml acetone at room temperature, with benzoyl chloride/substituted benzoyl chloride (1) (0.1263 mole) in 5 minutes. The reaction mixture was refluxed for 15 minutes. N-(Substituted benzoyl) morpholine/piperidine/ N-methyl piperazine carbothioamide (3) was synthesized by nucleophilic addition of

substituted benzoyl isothiocyanate and morpholine/piperidine/N-methyl piperazine (0.1149 mole) at reflux temperature [11]. The target compounds, 2, 4, 5-trisubstituted thiazoles(5a-g) were synthesized by adding substituted phenacyl bromide (4) (0.002 mmol) to a solution of the N-(Substituted benzoyl) morpholine/piperidine/N-methyl piperazine carbothioamide (3) (0.002 mmol) in acetonitrile (15 ml). The reaction mixture was stirred on magnetic stirrer until the solid separated. The yellow solid that separated was filtrated and washed with acetonitrile.

#### Experimental procedure of antibacterial testing:

The newly synthesized thiazole derivatives were screened for anti bacterial activity against *Escherichia coli*, *Staphylococcus aureus*, *Micrococcus luteus*, *Bacillus subtilis*, *Bacillus cereus*, *Pseudomonas aeruginosa* bacterial strains by paper disc diffusion method. The disc measuring 6.25mm diameter was cut from whatman No. 1 filter paper. Discs were dispensed to screw cap bottles and sterilized by dry heat at 150<sup>0</sup>C for 1 an hour. The test compounds were prepared in different concentration using dimethyl sulfoxide as a solvent. The discs for each concentration were prepared in triplicate. Nutrient agar plates seeded with fresh bacteria were exposed to discs of different concentration and the plates were incubated for 24hrs at 37<sup>0</sup>C. Similar treatments were used for the standard drug ciprofloxacin and solvent and growth controls were also kept. The zone of inhibitions was noted [12].

**Table 4: Antibacterial activity data of synthesized compounds (5a-g)**

Compound No.	Zone of inhibition in mm					
	<i>Escherichia coli</i>	<i>Staphylococcus aureus</i>	<i>Micrococcus luteus</i>	<i>Bacillus subtilis</i>	<i>Bacillus cereus</i>	<i>Pseudomonas aeruginosa</i>
5a	3.00	3.00	2.25	2.75	3.25	3.00
5b	1.25	1.5	1.75	1.5	2.75	2.5
5c	2.25	2.5	3.75	3.5	3.25	2.5
5d	2.25	1.25	2.25	2.5	3.25	2.5
5e	1.5	1.5	1.25	1.5	1.5	2.00
5f	3.25	2.75	2.5	2.75	2.00	3.25
5g	2.25	3.0	2.75	1.25	2.00	1.25
Ciprofloxacin	<b>7.25</b>	<b>7.25</b>	<b>8.25</b>	<b>7.25</b>	<b>7.25</b>	<b>7.25</b>

## RESULTS AND DISCUSSION

The target compounds, 2, 4, 5-trisubstituted thiazoles [5a-g] were synthesized in good yield by reaction of 2, 5-dimethoxy phenacyl bromide (4) to a solution of the N-(Substituted benzoyl) morpholine/piperidine/N- methyl piperazine carbothioamide (3) in stirring with acetonitrile (15 ml). Compound, 5g, containing p-chloro phenyl group was revealed higher melting point than other compounds, 5a-f, containing o/m-chloro phenyl group/unsubstituted phenyl group at 4<sup>th</sup> position of thiazole moiety that data listed in Table 2. <sup>1</sup>H NMR spectrum of 2, 4, 5-trisubstituted thiazoles series showed singlate at  $\delta$  3.52-3.78 of 2,5-di-OCH<sub>3</sub> and  $\delta$  3.81-3.86 of -CH<sub>2</sub>-O-CH<sub>2</sub>- of morpholine in similar range. Aromatic protons of phenyl ring showed multiplate at  $\delta$  6.38-7.83. Mass spectral studies of compounds 5a-h showed intense molecular ion peak at m/z 444,444,444, 408,442, 424 and 457, respectively, with their respective molecular formulae. The result of above studies is given in Table 4, it is clear that all the compounds showing moderate to good anti bacterial activity. Among the tested compounds 5f thiazole carrying 2-methyl piperazino, 4-chlorophenyl is showing good activity against all the tested species.

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