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Research Article

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Synthesis of some novel 2, 4, 5 –trisubstituted thiazoles 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/pyrrolidine carbothioamide (3) were prepared by condensing substituted benzoyl isothiocyanate (2) with different secondary heterocyclic amines, like morpholine/piperidine/pyrrolidine. N-substituted Carbothioamide (3) on treatment with substituted phenacyl bromide (4) affords 2, 4, 5-trisubstituted thiazoles (5a-h).The newly synthesized compounds were characterized by ^{1}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; Substituted phenacyl bromide; Antibacterial.

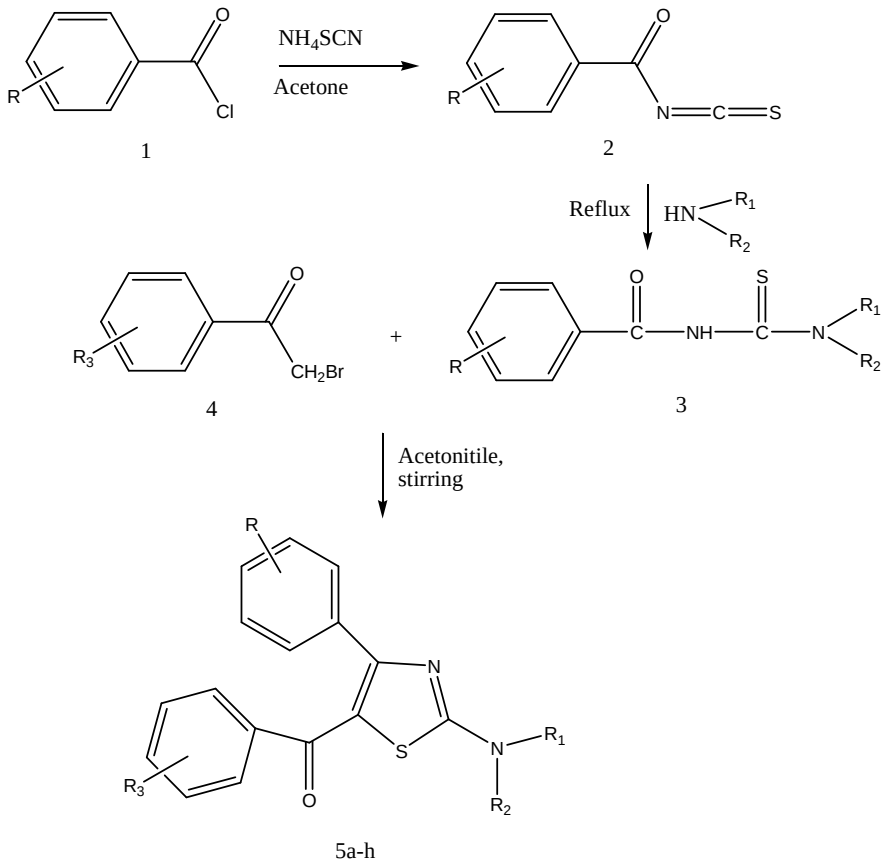
INTRODUCTION

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.

EXPERIMENTAL SECTION

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}H NMR) were recorded in $CDCl_3$/DMSO-d6 on Bruker advance at 400 MHz using Tetra methyl silane (TMS) as internal standard and the chemical shift (δ) are reported in parts per million.



Scheme: 1 Synthesis of targeted compounds

Table: 1 Substitution at R R_1, R2 and R_3

Compound No.	R	R_1=R_2	R_3
5a	C_6H_5-	-$(CH_2)_2$-O-$(CH_2)_2$-	4-NO_2
5b	3-Cl-C_6H_5-	-$(CH_2)_2$-O-$(CH_2)_2$-	4-NO_2
5c	4-Cl-C_6H_5-	-$(CH_2)_2$-O-$(CH_2)_2$-	4-NO_2
5d	4-Cl-C_6H_5-	-$(CH_2)_2$-O-$(CH_2)_2$-	3-NO_2
5e	C_6H_5-	-$(CH_2)_4$-	4-NO_2
5f	C_6H_5-	-$(CH_2)_5$-	4-NO_2
5g	3-Cl-C_6H_5-	-$(CH_2)_5$-	4-NO_2
5h	C_6H_5-	-$(CH_2)_2$-O-$(CH_2)_2$-	2,5-di-OCH_3

General Procedure for Synthesis of (2-morpholino/piperidine/pyrrolidine-4-substitutedphenyl thiazol-5-yl) (substituted phenyl)methanone :

As shown in Scheme 1, substituted benzoyl isothiocynate (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/pyrrolidine carbothioamide (3) was synthesized by nucleophilic addition of substituted benzoyl isothiocyanate and morpholine/piperidine/pyrrolidine (0.1149 mole) at reflux temperature[11]. The target compounds, 2,4,5-trisubstituted thiazoles(5a-h) were synthesized by adding substituted phenacyl bromide (4) (0.002 mmol) to a solution of the N-(Substituted benzoyl) morpholine/piperidine/pyrrolidine 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.

Table: 2 Characterization data of synthesized compounds (5a-h)

Compound No.	Molecular Formula	Yield (%)	M.P.(°C)	Rf value
5a	$C_{20}H_{17}N_3O_4S$	80	161-163	0.83
5b	$C_{20}H_{16}N_3O_4SCl$	76	126-128	0.83
5c	$C_{20}H_{16}N_3O_4SCl$	78	221-223	0.78
5d	$C_{20}H_{16}N_3O_4SCl$	72	195-197	0.68
5e	$C_{20}H_{17}N_3O_3S$	54	140-142	0.78
5f	$C_{20}H_{19}N_3O_3S$	64	178-180	0.80
5g	$C_{20}H_{18}N_3O_3SCl$	72	148-150	0.84
5h	$C_{22}H_{22}N_2O_4S$	51	135-137	0.48

Rf-Value: *(9.6:0.4, Toluene: Methanol)*

(2-morpholino-4-phenylthiazol-5-yl)(4-nitrophenyl)methanone (5a)
^{1}H NMR: *($CDCl_3$,* δ, *ppm)* 3.68-3.70 (t, 4H, 3rd and 5th CH_2 morpholine at 2nd position of thiazole ring), 3.84- 3.86 (t, 4H, 2nd and 6th CH_2 morpholine at 2nd position of thiazole ring), 7.86-7.90 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.02-7.22 (m, 5H, aromatic proton of phenyl ring); MASS m/z: 396 ($M^{+\cdot}$), 397(M^{+1}), 398(M^{+2}).

(4-(3-chlorophenyl)-2-morpholinothiazol-5-yl)(4-nitrophenyl) methanone (5b)
^{1}HNMR : (*$CDCl_3$,* δ, *ppm*) 3.68-3.70 (t, 4H, 3rd and 5th CH_2 of morpholine at 2nd position of thiazole ring), 3.82-3.84 (t, 4H, 2nd and 6th CH_2 of morpholine at 2nd position of thiazole ring), 7.54-7.98 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.06-7.21(m, 4H, aromatic protons of 3-chlorophenyl ring). MASS m/z: 429 ($M^{+\cdot}$)

(4-(4-chlorophenyl)-2-morpholinothiazol-5-yl)(4-nitrophenyl) methanone (5c)
^{1}HNMR : (*DMSO*, δ, *ppm*) 3.64-3.69 (t, 4H, 3rd and 5th CH_2 of morpholine at 2nd position of thiazole ring), 3.83-3.86 (t, 4H, 2ndand 6th CH_2 of morpholine at 2nd position of thiazole ring), 7.53-7.99 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.05-7.26 (m, 4H, aromatic protons of 4-chlorophenyl ring); MASS m/z: 430 ($M^{+\cdot}$), 432(M^{+2}).

(4-(4-chlorophenyl)-2-morpholinothiazol-5-yl)(3-nitrophenyl) methanone (5d)
^{1}H NMR (*DMSO*, *δ*, *ppm*) 3.61-3.63(t, 4H, 3rd and 5th CH_2 of morpholine at 2nd position of thiazole ring), 3.77-3.79 (t, 4H, 2nd and 6th CH_2 of morpholine at 2nd position of thiazole ring), 7.33-8.08 (m, 4H, aromatic protons of 3-nitrophenyl ring), 6.95-7.16(m, 4H, aromatic protons of 4-chloro phenyl ring); MASS m/z: 430 ($M^{+\cdot}$), 432(M^{+2}), 433(M^{+3})..

(4-nitrophenyl)(4-phenyl-2-(pyrrolidin-1-yl) thiazol-5-yl)methanone (5e)
^{1}H NMR (*DMSO*, *δ*, *ppm*) 2.04-2.09 (m, 4H, 3rd and 4th CH_2 of pyrrolidine at 2nd position of thiazole ring), 3.51 (s, 4H, 2nd and 5th CH_2 of pyrrolidine at 2nd position of thiazole ring), 7.45-7.87 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.06- 7.38 (m, 5H, aromatic protons of phenyl ring); MASS m/z: 380 ($M^{+\cdot}$), 381(M^{+1}), 382(M^{+2}).

(4-nitrophenyl)(4-phenyl-2-(piperidin-1-yl) thiazol-5-yl) methanone (5f)
^{1}H NMR (*CDCl3*, *δ*, *ppm*), 1.73(s, 6H, 3rd ,4th and 5th CH_2 of piperidine at 2nd position of thiazole ring), 3.67 (s, 4H, 2nd and 6th CH_2 of piperidine at 2nd position of thiazole ring), 7.46-7.88 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.00-7.26 (m, 5H, aromatic protons of phenyl ring); MASS m/z: 394 ($M^{+\cdot}$), 395(M^{+1}), 396(M^{+2}).

(4-(3-chlorophenyl)-2-(piperidin-1-yl) thiazol-5-yl) (4-nitrophenyl) methanone (5g)
^{1}H NMR (*DMSO*, *δ*, *ppm*), 1.74(s, 6H, 3rd ,4th and 5th CH_2 of piperidine at 2nd position of thiazole ring), 3.67 (s, 4H, 2nd and 6th CH_2 of piperidine at 2nd position of thiazole ring), 7.50-7.97 (m, 4H, aromatic protons of 4-nitrophenyl ring), 7.02-7.20 (m, 4H, aromatic protons of 3-chloro phenyl ring) ; MASS m/z: 428 ($M^{+\cdot}$), 430(M^{+2}), 431(M^{+3}).

(2, 5-dimethoxyphenyl) (2-morpholino-4-phenyl thiazol-5-yl) methanone (5h)
^{1}H NMR: *(DMSO, δ, ppm)* 3.62-3.64 (t, 4H, 3rd and 5th CH_2 of morpholine at 2nd position of thiazole ring), 3.79-3.81(t, 4H, 2nd and 6th CH_2 of morpholine at 2nd position of thiazole ring), 3.35 (s, 3H, 2-OCH_3), 3.52(s, 3H, 5-OCH_3),6.44-6.68 (m, 3H, aromatic protons of 2,5-di methoxy phenyl ring), 7.02-7.22 (m, 5H, aromatic proton of phenyl ring); MASS m/z: 411 ($M^{+\cdot}$), 412(M^{+1}), 413(M^{+2}).

Experimental procedure of antibacterial testing:
The newly synthesized thiazole derivatives were screened for anti bacterial activity against E*scherichia 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^{0}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^{0}C. Similar treatments were used for the standard drug tetracycline and solvent and growth controls were also kept. The zone of inhibitions was noted [12].

Table: 3: Antibacterial activity data of synthesized compounds (5a-h)

	Zone of inhibition in mm					
Compound No.	***Escherichia coli***	***Staphylococcus aureus***	***Micrococcus luteus***	***Bacillus subtilis***	***Bacillus cereus***	***Pseudomonas aeruginosa***
5a	5.25	6.25	6.25	6.25	6.25	6.25
5b	7.25	5.25	5.25	5.25	5.25	5.25
5c	6.25	5.25	5.25	5.25	5.25	5.25
5d	1.25	1.25	1.00	1.25	1.25	1.25
5e	6.25	6.25	5.00	6.25	6.25	6.25
5f	7.25	7.25	7.25	7.25	7.25	6.25
5g	3.25	5.25	3.25	6.25	6.25	3.25
5h	3.25	5.25	3.25	6.25	6.25	3.25
Ciprofloxacin	**7.25**	**7.25**	**8.25**	**7.25**	**7.25**	**7.25**

RESULTS AND DISCUSSION

The target compounds, 2, 4, 5-trisubstituted thiazoles [5a-h] were synthesized in good yield by reaction of substituted phenacyl bromide (4) to a solution of the N-(Substituted benzoyl) morpholine/piperidine/pyrrolidine carbothioamide (3) in stirring with acetonitrile (15 ml). Compounds, 5c and 5d, containing p-chloro phenyl group were revealed higher melting point than other compounds, 5a-b and 5e-h, containing m-chloro phenyl group/unsubstituted phenyl group at 4th position of thiazole moiety that data listed in Table 2. ^{1}H NMR spectrum of 2, 4, 5-trisubstituted thiazoles series showed triplate at δ 3.61-3.70 of -CH_2-N-CH_2- and δ 3.82-3.86 of -CH_2-O-CH_2- of morpholine in similar range. Aromatic protons of phenyl ring showed multiplate at δ 7.02-7.26. Aromatic protons of m-nitro phenyl ring showed multiplate at δ 7.45-7.90. Mass spectral studies of compounds 5a-h showed intense molecular ion peak at m/z 396,429,430, 430,380, 394 428 and 411, respectively, with their respective molecular formulae.

The result of above studies is given in Table 3 from the result it is clear that all the compounds showing 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 and is having zone of inhibition very similar to the standard drug used. Compound 5b is also showing good anti bacterial activity against all the species but it is more potent against *Escherichia coli.*

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