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Research Article

SYNTHESIS, ANTIFUNGAL AND ANTI BACTERIAL ACTIVITY OF N-(4-CHLORO-2-TRIFLUOROACTYL PHENYL) - AMINOTHIAZOLE DERIVATIVES

Sujatha.K [1]*, Shilpa [2], Ramesh S.Gani [2]
[1]Department of Chemistry, Karnatak Universty, Pavate Nagara Dharwad-580003 India
[2]Department of Chemistry, JSS, Dharwad-580003, India
[3]Department of Industrial Chemistry, Mangalore University, Mangalagangothri-575199, India
*Corresponding Author Email: sujathak4@rediffmail.com

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ABSTRACT

In this study,1-(2-amino-5-chlorophenyl)-2,2,2-trifluoroethanone was synthesized by reacting p-chloroaniline with ethyl trifluroacetate in presence of n-butyl lithium, further reacting with ammonium thiocyanate with hydrochloric acid leads to 1-(4-chloro-2-(2,2,2-trifluoroacetyl)phenyl)urea. Then reacted with $ArCOCH_2Br$ and sodium acetate gave 1-{5-chloro-2[(4-substituted-1, 3-thiazol-2-yl) amino] phenyl}-2,2,2-trifluroethanone derivatives. The chemical structure of newly synthesized compounds has been confirmed on the basis of elemental analysis, IR, ^1H NMR and Mass spectral data. The newly synthesized compounds were screened for their antibacterial activity invitro against Gram-positive bacteria namely Escherichia coli, Staphylococcus aureus, and Gram-negative bacteria namely Pseudomonas aeruginosa, Bacillus subtilis and the fungus namely Candida albicans by disc diffusion method. Among the synthesized compounds 5b, 5f, 5g, 5h, 5j were found to have a very good antibacterial and antifungal activity.

Key words: Aminothiazole, trifluroetahnone, thiosemicarbazone, antibacterial, antifungal.

INTRODUCTION

Now days due to increase in no of multi-disease, consumption of antibiotic drugs quantity is increasing because of this reason abnormal side effects have become predominant, therefore, pathogenic bacteria[1] has developed resistance to beta lactam antibiotics. The thiazole and its derivatives are playing a very important role in medicinal chemistry. Its intermediates are used as synthetic drugs, dyes and fungicides[2]. Due to the Therapeutic importance of heterocyclic compounds, chemists are showing more interest in the preparation of new heterocyclic compounds in order to explore their biodynamic properties[3-4]. Nitrogen and sulfur containing organic compounds show wide range of biological activity[5]. According to the literature survey 2-amino thiazole nucleus have been incorporated into a wide variety of therapeutically interesting candidates. Thiazoles Particularly are showing effective antimicrobial activity[6-10]. Fungal infections are caused by microscopic organism that can invade the epithelial cells in immune compromised[11] patients. Simple 2-aminothiazole is known as thyroid inhibitor[12]. In market many 2-aminothiazole derivatives drugs such as sulfathiazole and ceftibuten encouraging us to synthesize aminothiazole derivatives [13-14]. Ritonavir is an anti-HIV agent, Nizatidine is an antacid used for the treatment of gastroesophageal reflux disease, dasatinib is an antineoplastic agent and ravuconazole is an antifungal agent[15]. Thiazole derivatives not only show potent FabI and FabK inhibitory activity, but also have an antibacterial effect. Abafungin is the low toxic thiazole containing antimicrobial[16] present in market, which unlike imidazole and triazole antifungals directly impairs the fungal cell membrane and in addition inhibits stero-2,4-methyl transformation modifying the composition of cell membrane, it also acts as antibiotic against Gram +ve bacteria. 5-fluorocytosine is an antifungal used along with amphotericin –B specifically for serious candida infection. Cefdinir is broad spectrum cephalosporin antibiotic used for treatment of pneumonia, chronic bronchitis, sinusitis, pharyngitis, tonsillitis[17]. 4-Chloro-2-(trifluoroacetyl)aniline is one of the important pharmacophore found in the anti HIV Effavirenz, the fluorine containing moiety are most widely found in active pharma ingredients due its high biological activity. Due to the demand of the trend for more safe and effective antifungal agents made us to bring two different biologically active scaffolds like 2-aminothiazole and 4-Chloro-2-(trifluoroacetyl)aniline in one frame to synthesis new and novel thiazole derivative having very good antimicrobial activity.

MATERIALS AND METHODS

The general method to prepare the title compounds is outlined in **scheme 1**. The synthesis of 2-mercaptothiazoles was first attempted in a stepwise manner *via* the isolation of intermediate, Phenacyl bromides (**1a-k**) employed in the preparation of 2,4-disubstituted-1,3-thiazoles (**5**) are prepared by the reaction of various substituted acetophenones with bromine in chloroform at 0°C. However in few cases readily available phenacyl chlorides were used instead of phenacyl bromides. Further reaction of 4-Chloro-2-(trifluoroacetyl)aniline hydrochloride with ammonium thiocyanate was carried out by heating the mixture of 4-Chloro-2-(trifluoroacetyl)aniline hydrochloride with ammonium thiocyanate in presence of Hydrochloric acid and water yielded 1-[4-Chloro-2-(trifluoroacetyl) substituted phenyl] thiourea **(4)**. 4-Chloro-2-(trifluoroacetyl)aniline **(3)** was in turn obtained by the reaction of *p*-chloroaniline with ethyl trifluoroacetate in presence of n-butyl lithium at -70°C. The Hantz reaction of 1-[4-Chloro-2-(trifluoroacetyl)phenyl] thiourea **(4)** with appropriate phenacyl bromides (**1a-k**) in aqueous alcoholic medium employing sodium

acetate as catalyst gave the desired 2,4-disubstituted-1,3-thiazoles (**5**).

EXPERIMENTAL

Phenacyl bromides (1)

To a cold solution of substituted acetophenone (0.1mol) in chloroform (30mL), bromine (0.12mol) in chloroform (10mL) was gradually added (30 minutes) with continuous stirring and maintaining the temperature of the reaction mixture at 0^0C. Then the reaction mixture was slowly brought to room temperature and stirring was continued for another 60 minutes until the evolution of hydrogen bromide gas ceased. Solvent was removed under reduced pressure. The solid that formed was washed with petroleum ether and collected by filtration, which is then recrystallized from minimum quantity of ethanol. Compounds prepared by this procedure are

a. Phenacyl bromide, m.p. 50^0C (Lit[50]. 50^0C).
b. 4-Nitro phenacyl bromide, m.p. 97^0C (Lit[51]. 98-99^0C).
c. 4-Chloro phenacyl bromide, m.p. 96^0C (Lit[50]. 96-96.5^0C).
d. 2, 4-Dichloro phenacyl bromide, m.p. 103^0C (Lit[52]. 105-107^0C).
e. 4-Methyl phenacyl bromide, m.p. 61^0C (Lit[53]. 61^0C).
f. 4-Methoxy phenacyl bromide, m.p. 75^0C (Lit[53]. 75-76^0C).
g. 4-Hydroxy phenacyl bromide, m.p. 125^0C (Lit[52]. 125-126^0C).
h. 3-Bromo-6-bromocoumarin, m.p. 176^0C (Lit[54]. 176^0C)

1-[4-Chloro-2-(trifluoroacetyl) substituted phenyl] thiourea (4):

A mixture of substituted aniline (0.01mol), concentrated hydrochloric acid (0.01mol), ammonium thiocyanate (0.015mol) and water (20ml) were mixed well with constant stirring for one hour at room temperature, and then refluxed for about four hours for completion of reaction. The reaction mixture was then poured on to crushed ice. The precipitate formed was collected by filtration, washed with water and recrystallized from ethanol.

1-{5-Chloro-2[(4-substituted-1, 3-thiazol-2-yl) amino] phenyl}-2, 2, 2-trifluroethanone (5a-k):

A mixture of 1-[4-Chloro-2-(trifluoroacetyl) substituted phenyl] thiourea (0.01mol), a pinch of sodium acetate in ethanol (10ml) and suitable bromoacetyl derivatives (0.01mol) was refluxed for 1-3 hours. The reaction mixture was then cooled to RT and the solid separated was collected by filtration, dried and recrystallized from ethanol. The yield, melting point and other characterization data of compounds prepared by this procedure are given in **Table-1**

Compound 5k. IR ((νmax, cm^{-1}): 3047(N-H), 2913 (C-H), 1564 (C=N);The ^{1}H–NMR(300 Hz DMSO-d_6)**:** δ, 4.97 (s,1H, -NH), 7.57-7.72 (m, 5H, ArH), 7.73 (s, 1H, thiazole), 8.027-8.039 (m, 2H protons of p-fluoro phenyl), 7.72 (s, 1H)

Compound 5g. IR ((νmax, cm^{-1}): 3199(N-H), 2953 (C-H), 1584 (C=N), 1724 cm^{-1} (c=o); The ^{1}H–NMR(300 Hz DMSO-d_6)**:**δ, 8.027-8.039 (m, 2H, ArH), 7.827, (s, 1H, ArH), 7.796 (s, 1H, thiazole), 7.605-7.640 (2d, 1H ArH), 8.0810-8.118 (2d, 1H ArH), 7.54 (s, 1H ArH), 4.807 (s, 1H, NH) Mass: m/z, 382 (molecular formula $C_{17}H_{10}ClF_3N_2OS$)

Compound 5b.:^{1}H NMR (DMSO-d_6): δ, 7.15 (s, 1H,), 7.158 (s, 1H, Ar-H), 4.0 (s, 1H, NH-), 7.35 (m, 2H, Ar-H), 7.558 (d, 2H, ortho protons of p-fluoro phenyl), 7.580 (d, 2H- meta protons p-fluoro phenyl).

Compound 5f:^{1}H-NMR (DMSO-d_6): δ, 5.03 (s, 1H, -NH), 7.708 (s, 1H, -5H), 7.731 (s, 1H, Ar-H), 8.07 (m, 2H, Ar-H), 8.3 (d, 2H-o-protons of p-nitro phenyl) 8.42 (d, 2H, m-protons of p-nitro phenyl)

RESULTS AND DISCUSSION

Antimicrobial studies

The newly synthesized compounds were screened for their antibacterial activity *in vitro* against Gram-positive bacteria namely *Escherichia coli, Staphylococcus aureus*, and Gram-negative bacteria namely *Pseudomonas aeruginosa, Bacillus subtilis* and the fungus namely *Candida albicans* by disc diffusion method[18]. The test compounds were dissolved in N, N-Dimethylformamide (DMF) to obtain a solution of 10mg/ml concentration. The inhibition zones of microbial growth produced by different compounds were measured at the end of an incubation period of 48 hours at 37ºC. DMF alone showed no inhibition. Penicillin and Fluconazole were used as reference standards to evaluate the potency of the tested compounds. The results are presented in the **Table 2.**

This study reports the successful synthesis of the title compounds. The antimicrobial activity study revealed that some of the thiazoles possess significant antifungal activity.

The compounds **5a-k** synthesized as per the outlined **scheme (1)** were purified by recrystallization and the purity was ascertained by TLC using Silica Gel Gas stationary phase. The instrumental data suggested the formation of the compounds as desired. Antimicrobial screening of the compounds was performed using four different strains of bacteria and one strain of fungi. Compounds **5b, 5c, 5f, 5g, 5h, 5j** showed good activity against three different Microbial strains (bacteria). The structural make up of the compounds were thought of to be responsible of their antimicrobial activities.

The compounds **5b, 5f, 5g, 5h, 5j,** showed very good activity against microbial fungal strains even better than the standard, the structural makeup of the compounds were thought of to be responsible for their antimicrobial activities. Compounds **5b, 5f, 5h, 5j** are having a 4-Chloro-2-(trifluoroacetyl)aniline at 2nd position and 4-fluorophenyl, 4-chorophenyl, 2,4-dichlorophenyl, 4-nitrophenyl, 2-chloro-2-sulphanmide thiophene and 2,4-dibromocoumrin group as aromatic substituent.

Due to the presence of 4-Chloro-2-(trifluoroacetyl)aniline at 2nd position of 1, 3-thiazole nucleus. The aryl group gives the compound extra stability while entering the bacterial cell membrane and the thiol group enhances penetration into fungal cell wall. Introduction of chloro (Cl) moiety at 4-position into the aromatic ring attached to the thiazole nucleus resulted in poor antimicrobial activity with less antifungal activity, i.e. compound **5d** showed poor activity. Further substituted aniline attached to the thiazole nucleus leads very good antimicrobial activity. Compound containing a 5-Chlorothiophene-2-sulfonamide moiety attached to the thiazole nucleus further enhances the lipophilicity of the molecule enabling it to penetrate the microbial cell more Easily, thus showing good activity.

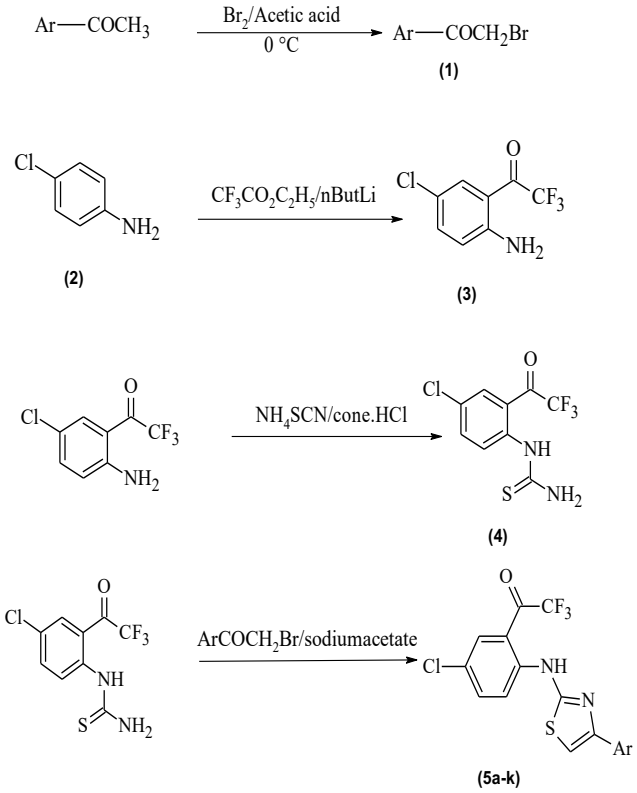
Table 1: Characterization data of compound 5a-k

Compd No	Ar	M.P (◦C)	Yield %	Color	Molecular Formula (M. W)
5a	Methyl phenyl	225-28	68	Cream	$C_{18}H_{12}ClF_3N_2OS$ (396)
5b	4-Fluorophenyl	230-231	55	Light yellow	$C_{17}H_9ClF_4N_2OS$ (400.77)
5c	4-Chlorophenyl	196-198	60	Yellowish brown	$C_{17}H_9Cl_2F_3N_2OS$ (417.23)
5d	4-Amino-2-hyroxyphenyl	198-200	72	Yellow	$C_{17}H_{11}ClF_3N_3O_2S$ (413.80)
5e	5-Aminophenyl	140-42	67	Yellow	$C_{17}H_{11}ClF_3N_3OS$ (397.80)
5f	4-Nitrophenyl	150-52	76	Yellow crystalline	$C_{17}H_9ClF_3N_3O_3S$ (427.78)
5g	2.4-Dichlorophenyl	104-06	78	Pale yellow	$C_{17}H_8Cl_3F_3N_2OS$ (451.67)
5h	5-Chloro-2-sulphanamide thiophene	184-86	64	Yellowish orange	$C_{16}H_8Cl_2F_3N_3O_2S_2$ (466.28)
5i	9h-Carbazole	168-70	65	Yellow	$C_{23}H_{13}ClF_3N_3OS$ (471.88)
5j	2,4-Dibromocoumarine	194-96	56	Deep yellow	$C_{20}H_9BrClF_3N_2O_3S$ (529.71)
5k	Phenyl	169-70	65	White	$C_{17}H_{10}ClF_3N_2OS$ (382.78)

Solvent for recrystallization: ethanol.

Table 2: Antibacterial and antifungal data of compounds (5a-k)

Compd No	Antibacterial activity (MIC in µg/mL)				Antifungal activity (MIC in µg/mL)
	E.coli	***Aureus***	***P.aeruginosa***	***B.subtitis***	***C.albicans***
5a	12.5	25	6.25	12.5	12.5
5b	6.25	6,25	6.25	6.25	3.12
5c	6.25	3.12	6.25	12.5	6.25
5d	6.25	12.5	6.25	6.25	12.5
5e	12.5	12.5	6.25	12.5	12.5
5f	6.25	6.25	3.12	6.25	3.12
5g	6.25	6.25	12.5	6.25	3.12
5h	3.12	6.25	3.12	3.12	3.12
5i	6.25	6.25	6.25	6.25	6.25
5j	6.25	12.5	3.12	12.5	3.12
5k	6.25	6.25	6.25	6.25	6.25
Standard: Penicillin	0.12	0.12	0.12	0.12	---
Standard: Fluconazole	-	-	-	-	8.0
Control: DMF	-	-	----	---	---



Reaction scheme 1

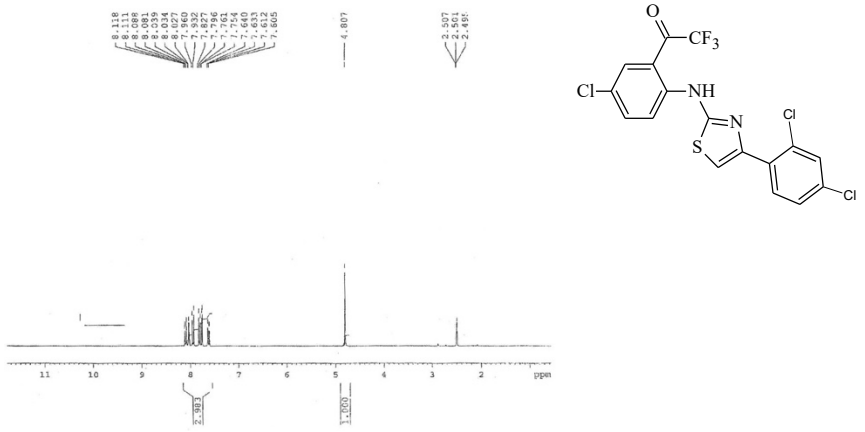


Figure: 01. 5g-2-4 chlorophenyl

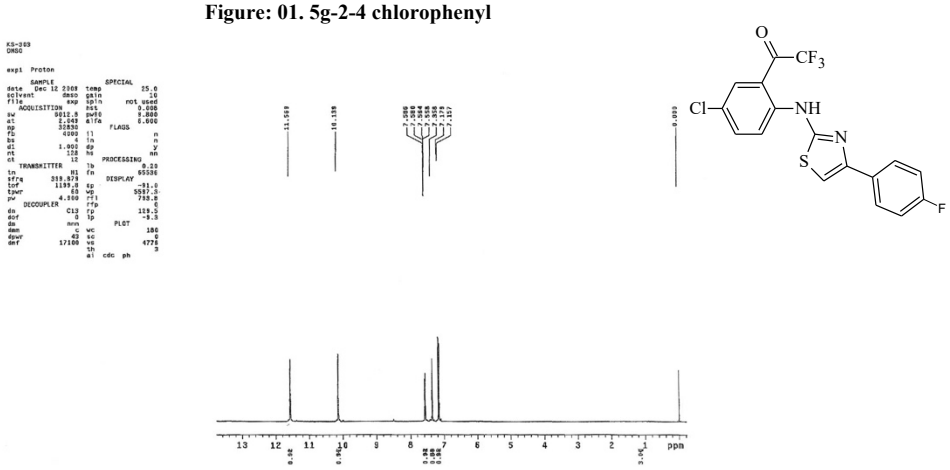


Figure: 02.5b-4-Flurophenyl

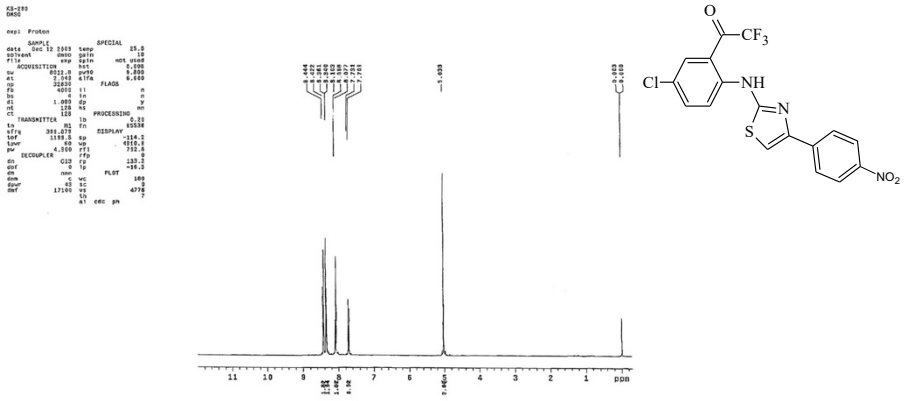


Figure: 03. 5f-4 Nitro phenyl

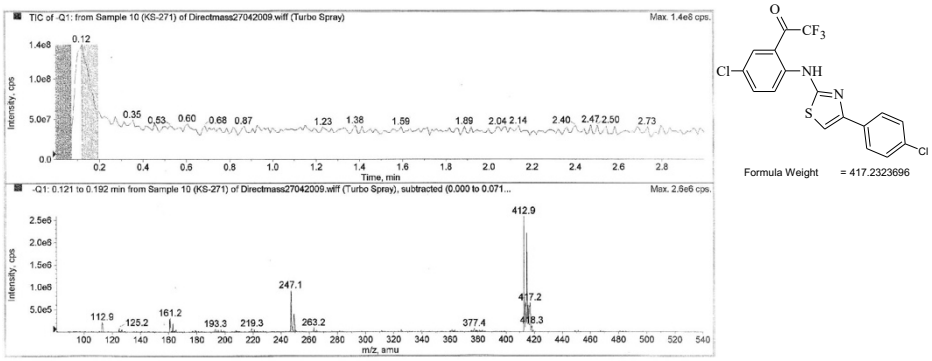


Figure:04. 5c-4-chlorophenyl

CONCLUSION

This work describe the synthesis of 2-aminothiazole derivatives, The synthesized compounds were characterized by IR,^{1}HNMR and mass spectral studies, all compounds were screened for antibacterial and antifungal activity, Out of the sixteen compounds hereby reported that compound **5b,5f, 5h, 5j** showed the best activity against microbial strains *Candida albicans* with an MIC of 3.12 mg/ml. The activity is found to be better than standard.

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