CHAPTER II

SYNTHESIS, CHARACTERIZATION AND BIOLOGICAL ACTIVITY STUDIES OF SOME NOVEL 1,3-THIAZOLE DERIVATIVES
Section 2.1

Synthesis, characterization and antimicrobial studies of some novel 1,3-thiazole derivatives

Abstract

A series of novel N-[4-(substituted)-1,3-thiazol-2-yl]-2-(substituted)acetamide (107a-m) and methyl 2-(2-(2-(substituted)acetamido)thiazol-4-yl)acetate (107n-p) derivatives have been synthesised and compounds were characterised by spectral and analytical studies. All compounds were screened for their *invitro* antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumonia* by disc diffusion method and for antifungal activity against *Pencillium marneffei*, *Trichophyton mentagrophytes*, *Aspergillus flavus*, *Aspergillus fumigatus* by serial plate dilution method. Compounds N-(4-methylthiazol-2-yl)-2-m-tolylacetamide (107b), 2-(3,4-dimethylphenoxy)-N-(4-methylthiazol-2-yl)acetamide (107e), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m), methyl 2-(2-(2-m-tolylacetamido)thiazol-4-yl)acetate (107o) exhibited growth inhibition against all the tested bacterial strains, with MIC values varying from 12.5µg/mL to 6.25µg/mL. Among the compounds tested for antifungal activity, N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a), N-(4-methylthiazol-2-yl)-2-m-tolylacetamide (107b), N-(4-methylthiazol-2-yl)-2-phenylacetamide (107d), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k), methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p), methyl 2-(2-(2-p-tolylacetamido)thiazol-4-yl)acetate (107n) showed wide range of activity against all the tested strains. Most of newly synthesized compounds were effective against fungal strains rather than bacterial strains. However some of the compounds like N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a), 2-(3,4-dimethylphenoxy)-N-(4-methylthiazol-2-yl)acetamide (107e), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k), 2-(3,4-dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide (107i) showed selective sensitivity against some of the bacterial strains where as they were unable to sustain the growth of other strains.
Introduction

Thiazole and its derivatives are very useful compounds in various fields of chemistry including medicine and agriculture. Heterocycles containing a thiazole ring system are found to exhibit a wide spectrum of biological activities. Antimicrobial activity of thiazole derivatives has been extensively studied by many researchers (Sarojini et al., 2010; Liaras et al., 2011; Parameshwar et al., 2013). Organic compounds bearing thiazoles of different pharmacodynamic moieties found to possess antimalarial activity (Parameshwar et al., 2014), and antiinflammatory activity (Holla et al., 2003). Compounds containing thiazole ring system were also used as antiviral agents (Osama et al., 2009). Antitumor activities of thiazole derivatives were well known in the literature (Shahenda et al., 2012). Many thiazole-containing compounds were reported as herbicides (Aldo et al., 1996; Tingting et al., 2010), and fungicides (Narayana et al., 2004). Few thiazole derivatives were identified as a TRPV1 antagonists (Ning et al., 2005). Thiazole and thiadiazole analogues have been recently proposed as a novel promising class of adenosine A1 and A3 receptor antagonists. (Alice et al., 2005). Thiazole derivatives were described as inhibitors of vascular endothelial growth factor receptor I and II (Alexander et al., 2006). Replacement of carboxyl group of ethacrynic acid (EA) by a heterocyclic thiazole exhibited improvement over EA to inhibit GSTpi activity (Ting et al., 2012). Triazolyl thiazole series were reported as cdk5/p25 inhibitors, potentially useful for the treatment of Alzheimer’s disease, (Mahendra et al., 2007). The thiazole-diamides have been identified as highly potent γ-secretase inhibitors (Yuhpyng et al., 2007). In view of the importance of thiazoles and their derivatives, several methods for the preparation of thiazole derivatives have been reported.

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\begin{align*}
\text{Scheme – 2.1 : Mechanism of Hantzsch thiazole synthesis.}
\end{align*}
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Hantzsch first describes the synthesis of thiazole in 1887 (Hantzsch et al., 1887). Hantzsch’s synthesis of thiazole involves cyclization of α-halocarbonyl compounds by a great variety of reactants bearing the N-C-S fragment includes thioamide, thiourea, ammonium thiocarbamate or dithiocarbamate and their derivatives. This is the most widely used method of thiazole synthesis. The mechanism of formation of 2,4-dimethyl thiazole (58) from thioacetamide (55) and α-haloketone (54) in presence of base is represented in the reaction **Scheme 2.1**.

Tcherniac (1892) describes the synthesis of 2-hydroxy thiazoles (60) from thiocyanatoketones (59) by cyclization in aqueous acid or alkaline solution.

![Scheme 2.2: synthesis of 2-hydroxy substituted thiazole.](image)

Synthesis of thiazoles from acylaminocarbonyl compounds and phosphorus pentasulfide and related condensation was described by Gabriel (Gabriel, 1910 a & b). This reaction involves reaction of acylaminoketone (61) with an equimolecular amount of phosphorus pentasulfide to yield 2-phenyl-5-alkyl-thiazole (62).

![Scheme 2.3: synthesis 2-phenyl-5-alkyl-thiazole.](image)

Watt (1939) describes the synthesis of 2-aminothiazoles or their N-substituted derivatives (64), by the reaction of thiocyanatoketones (63) with ammonium chloride or alkyl amine.
The Cook–Heilbron thiazole synthesis is the chemical reaction of α-aminonitrile (65) with carbon disulfide to form 5-amino-2-mercapto-thiazoles (66; Cook et al., 1949).

Bernd et al. (2003) describe the synthesis of substituted 2-acyloxymethyl thiazoles (70) by a new multicomponent reaction (MCR) of thiocarboxylic acid (67), aldehydes (68) and methyl 3-(N,N-dimethylamino)-2-isocyanoacrylate (69), under Lewis acid catalysis.

Kazmaier et al. (2005) describe the microwave assisted synthesis of 2-substitued thiazole (72) from endothiopeptide (71) using TMSCl-NaI in acetonitrile.
Sheldrake et al. (2006) describe the synthesis of 5-arylthiazoles (74) by the treatment of \(N,N\)-diformylaminomethyl aryl ketones (73) with triethylamine and phosphorus pentasulfide in chloroform at 60 °C.

Biswanath and co-worker (2006) developed a convenient method for the synthesis of thiazoles and aminothiazoles (77) by treatment of phenacyl bromides (75) with thioamides/thiourea (76) in the presence of ammonium-12-molybdophosphate at room temperature. The products are formed rapidly (within 20 min) and in excellent yields. 

A highly efficient and rapid synthesis of 2-amino-4-arylthiazoles and 2-methyl-4-arylthiazole (80) from \(\alpha\)-bromoketone (78) and thiourea/thioamide (79) is described using ionic liquid at ambient conditions. The method is simple, rapid and practical, generating thiazole derivatives in excellent yields (Taterao et al., 2007).
Scheme – 2.10: Synthesis of 2-amino-4-arylthiazoles and 2-methyl-4-arylthiazole.

A variety of 2,4-disubstituted-5-acetoxythiazoles (84) were prepared from the substituted methyl benzoates in good yields using a three-step sequence (Qiao et al., 2008). This method involves ester (81) to thionoester (82) conversion, coupling with an amino acid (83), and acetic anhydride mediated cyclization.

Scheme – 2.11: Synthesis of 2,4-disubstituted-5-acetoxythiazoles.

Castagnolo et al. (2009) performed a cyclization reaction of propargyl bromides (85) with thioureas (86) allows the synthesis of 2-aminothiazoles (87) under microwave irradiation at 135 °C leading to desired compounds in high yields within few minutes.

Scheme – 2.12: Synthesis of 4-sustituted-2-aminothiazoles.

Double acylation of a protected glycine affords intermediate α-amido-β-ketoesters (88), which was reacted with Lawesson’s reagent to furnish 2,4-disubstituted 1,3-thiazoles (89) was reported by Sanz-Cervera et al. (2009).
Scheme 2.13: Synthesis of 2,4-disubstituted 1,3-thiazoles.

Madhav et al. (2012) reported one-pot synthetic procedure for the synthesis of 4-aryl-2-(substituted)amino 1,3-thiazoles (92) from monosubstituted thiourea (91) and alkynes (90) via intermediate 2,2-dibromo-1-phenylethanone. The reaction is catalyzed by β-cyclodextrin in aqueous medium.

Scheme 2.14: Synthesis of 4-aryl, 2-(substituted)amino 1,3-thiazoles.

Janardhan et al. (2014) described sodium fluoride as a simple, mild and efficient catalyst for the synthesis of 2,4-disubstituted 1,3-thiazoles (95) utilizing phenacyl bromides (93) and thiourea/phenylthiourea (94) in aqueous methanol at ambient temperature. Analytically pure products are formed within 1–3 min in excellent yields.

Scheme 2.15: Synthesis of 2,4-disubstituted 1,3-thiazoles.
Laichun *et al.* (2014) reported NBS-mediated sequential one-pot synthesis of multifunctionalized thiazoles (98) from 1,3-dicarbonyl compounds (96) (β-diketone, β-ketoester or β-ketoamide) and mercaptonitrile salts (97) have been developed under mild conditions. This transformation involves sequential bromination, SN2 alkylation, Thorpe–Ziegler cyclization and regio-selective elimination of α–COR group, affording the desired products in good yields.

![Scheme 2.16: Synthesis of multifunctionalized thiazoles.](image)

The present chapter describes the synthesis of \(N\)-[4-(substituted)-1,3-thiazol-2-yl]-2-(substituted)acetamide, methyl-2-(2-(2-(substituted)acetamido)thiazol-4-yl) acetate derivatives and characterization by \(^1\)H & \(^{13}\)C NMR, IR, LCMS, elemental analysis. Antibacterial activity against *Staphylococcus aureus*, *Escherichia coli*, *Pseudomonos aeruginosa*, *Klebsiella pneumonia* and antifungal activity against *Pencillium marneffei*, *Trichophyton mentagrophytes*, *Aspergillus flavus*, *Aspergillus fumigatus* are evaluated.

**Experimental**

All reagents were used as received. All chemistry was performed under a nitrogen atmosphere using standard techniques. Completion of the reaction was monitored by TLC. TLC was run on a Merck silica gel 60 F254 coated aluminum plates. Melting points were determined by Buchi B-545 apparatus. All the NMR spectra were measured using Bruker AMX 400 instrument with 5 mm PABBO BB-\(^1\)H tubes. \(^1\)H NMR spectra were measured for approximately 0.03 M solutions in d6-DMSO at 400 MHz with TMS as internal reference. \(^{13}\)C NMR spectra were measured for approximately 0.05 M solutions in d6-DMSO at 100 MHz with TMS as internal reference. LCMS were obtained using Agilent 1200 series LC and Micromass zQ spectrometer. Column chromatography was performed using a Silica gel (230–400 mesh) pet ether and ethyl acetate or pet ether and diethyl ether as eluent.
General procedure for the synthesis of 2-bromo-1-(3-substituted phenyl)ethanone (100 a-b)

To a stirred solution of substituted acetophenone (0.01 mol) in acetic acid (10 v), bromine (0.011 mol) was added at 0-5 °C. Reaction mixture was stirred at room temperature for 3-5 h. After the completion of the reaction, the reaction mass was quenched with ice and extracted to methyl tert-butyl ether (50 ml). Organic layer was washed with aq.10% NaHCO₃ solution, water (50 ml x 1), brine (50 ml x 1), dried over Na₂SO₄, filtered and concentrated under vacuum to afford the crude product which was purified by column chromatography using a silica gel (230–400 mesh) pet ether and diethyl ether as eluent.

General procedure for the synthesis of 4-(3-substituted phenyl)-1,3-thiazol-2-amine (101)

To a solution of 2-bromo-1-(3-substituted phenyl)ethanone (100) in ethanol thiourea and sodium acetate was added and stirred at room temperature for 2-3 h. After the completion of the reaction, reaction mass was poured to ice, precipitated
solid was filtered to afford the crude product which was purified either by washing with cold ethanol or by column chromatography using a silica gel (230–400 mesh)) pet ether and ethyl acetate as eluent to obtain the pure product.

**4-(3-Chlorophenyl)-1,3-thiazol-2-amine (101a)**

Purified by column chromatography (petether : ethyl acetate, 4:1), isolated yield 88%, (pale yellow solid). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 7.13 (s, 2H), 7.17 (s, 1H), 7.29-7.32 (m, 1H), 7.39 (t, J = 7.80 Hz, 1H), 7.75 (d, J = 7.76 Hz, 1H), 7.84 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 103.58(C-5), 124.44(C-12), 125.65(C-8), 127.30(C-10), 130.81(C-11), 133.77(C-7), 137.30(C-9), 148.55(C-4), 168.78(C-2). MS calcld. for C$_9$H$_7$ClN$_2$S: 210.6; found: 211.2 (M$^+$). Anal. calcld. for C$_9$H$_7$ClN$_2$S, C, 51.31; H, 3.35; Cl, 16.83; N, 13.30; S, 15.22. found C, 51.30; H, 3.32; S, 15.22.

**4-(3-Fluorophenyl)thiazol-2-amine (101b)**

Purified by column chromatography (petether : ethyl acetate, 4:1), isolated yield 82%, (yellow solid). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 7.05-7.10 (m, 1H), 7.12 (br s, 2H), 7.14 (s, 1H), 7.37-7.42 (m, 1H), 7.55-7.59 (m, 1H), 7.64 (d, J = 7.88 Hz, 1H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 103.06(C-5), 112.15(C-10), 113.92(C-8), 121.53(C-12), 130.50(C-11), 137.28(C-7), 148.50(C-4), 161.30(C-9), 168.32(C-2). MS calcld. for C$_9$H$_7$FN$_2$S: 194.2; found, 195.2 (M$^+$). Anal. calcld. for C$_9$H$_7$FN$_2$S, C, 55.65; H, 3.63; F, 9.78; N, 14.42; S, 16.51; found: C, 55.62; H, 3.62; S, 16.50.

**General procedure for the synthesis of 4-methylthiazol-2-amine (104)**

To a suspension of thiourea (0.01 mol) in water (10 vol), chloroacetone was added under stirring. Resulting solution was refluxed for 4h. Reaction mass was cooled basified with NaOH (pH~14) and extracted to ethyl acetate. Organic layer was washed with water (100 ml x 1), brine (100 ml x 1), dried over Na$_2$SO$_4$, filtered and concentrated under vacuum to afford the crude product which was purified by column chromatography using a silica gel (230–400 mesh)) pet ether and ethyl acetate as eluent to obtain the pure product (104).

**4-Methylthiazol-2-amine (104)**

Purified by column chromatography (petether : ethyl acetate, 1:1), isolated yield 66%, (pale brown solid). $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.06 (s, 3H), 6.07 (s, 1H), 6.80 (br s, 2H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 17.53(C-6), 36
100.80(C-5), 148.00(C-4), 168.45(C-2). MS calcd. for C₄H₆N₂S, 114.1; found: 115.2 (M⁺). Anal. calc. for C₄H₆N₂S, C, 42.08; H, 5.30; N, 24.54; S, 28.09; found, C, 42.06; H, 5.28 S, 28.07.

**General procedure for the synthesis of methyl (2-amino-1,3-thiazol-4-yl)acetate (106)**

(2-Amino-1,3-thiazol-4-yl)acetic acid was refluxed in methanol in presence of catalytic amount of conc. H₂SO₄ for 3 h. Excess of methanol was removed under vacuum. Residue was dissolved in ethyl acetate and washed with aq.10% NaHCO₃ solution, water (50 ml x 1), brine (50 ml x 1), dried over Na₂SO₄, filtered and concentrated under vacuum to afford the title compound (106).

**General procedure for the synthesis of N-(4-methyl-1,3-thiazol-2-yl)-2-phenoxy or phenyl acetamide or acetate (107)**

To a solution of ethyl (2-amino-1,3-thiazol-4-yl)acetate (106) or 4-(substituted)-1,3-thiazol-2-amine (101 or 104) (0.01 mol) in dichloromethane (10 vol), substituted phenyl acetic acid (0.011 mol) triethylamine (0.015 mol) and propylphosphonic Anhydride (T₃P) (0.01 mol) was added at 0°C. Reaction mixture was stirred at room temperature for 1 h. After the completion of the reaction, water was added and the layers were separated. Organic layer was washed with aq.10% NaHCO₃ solution, aq.10% citric acid solution (10 ml), water (10 ml x 1), brine (10 ml x 1), dried over Na₂SO₄, filtered and concentrated under vacuum to afford the crude solid which was washed with cold ethanol to obtain the pure product (107) in good yield.

**N-(4-Methylthiazol-2-yl)-2-p-tolylacetamide (107a)**

Isolated yield 87 %, (pale yellow solid), m.p. 98-100°C. ¹H-NMR (400 MHz, DMSO-d₆) δ (ppm): 2.25 (s, 3H), 2.27 (s, 3H), 3.68 (s, 2H), 6.72 (s, 1H), 7.12 (d, J = 7.56 Hz, 2H), 7.20 (d, J = 7.32 Hz, 2H), 12.25 (br s, 1H). ¹³C-NMR (400 MHz, DMSO-d₆) δ (ppm): 17.31(C-9), 21.09(C-17), 41.82(C-10), 108.09(C-5), 129.41(C12,C-13, C-15, C16), 132.43(C-11), 136.30(C-14), 147.07(C-4), 157.73(C-2), 169.62(C-7). IR (KBr, cm⁻¹): 3230 (N-H),1689 (C=O), 1307 (C-N). MS calcd. for C₁₃H₁₄N₂OS, 246.3; found:247.0 (M⁺). Anal. calc. for C₁₃H₁₄N₂OS, C, 63.39; H, 5.73; N, 11.37; O, 6.50; S, 13.02; found: C, 63.38; H, 5.71; S, 13.01.
N-(4-Methylthiazol-2-yl)-2-m-tolylacetamide (107b)

Isolated yield 85 %, (off white solid), m.p. 130-132°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): $\delta$ 2254.00 (s, 3H), 2.29 (s, 3H), 3.69 (s, 2H), 6.73 (s, 1H), 7.06 (d, $J = 7.44$ Hz, 1H), 7.11 (d, $J = 7.68$ Hz, 1H), 7.13 (s, 1H), 7.21 (t, $J = 7.48$ Hz, 1H), 12.26 (br s, 1H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 17.31(C-9), 21.42(C-17), 42.16(C-10), 108.12(C-5), 126.71(C-16), 127.87(C-14), 128.75(C-15), 130.25(C-12), 135.37(C11), 137.93(C13), 147.07(C-4), 157.70(C-2), 169.50(C-7). IR (KBr, cm$^{-1}$): 3227(N-H), 1653 (C=O), 1317 (C-N). MS calcd. for C$_{13}$H$_{14}$N$_2$OS: 246.3; found: 247.0 (M$^+$). Anal. calc. for C$_{13}$H$_{14}$N$_2$OS; C, 63.39; H, 5.73; N, 11.37; O, 6.50; S, 13.02; found, C, 63.37; H, 5.72; S, 13.00.

2-(3-Methoxyphenyl)-N-(4-methylthiazol-2-yl)acetamide (107c)

Isolated yield 79 %, (pale yellow solid), m.p. 104-106°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.25 (s, 3H), 3.70 (s, 2H), 3.74 (s, 3H), 6.73 (s, 1H), 6.82 (d, $J = 2.16$ Hz, 1H), 6.86 (d, $J = 14.96$ Hz, 1H), 6.91 (s, 1H), 7.23 (t, $J = 8.12$ Hz, 1H), 12.26 (br s, 1H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 17.31(C-9), 42.26(C-10), 55.45(C-18), 108.14(C-5), 112.62(C-16), 115.48(C-12), 121.84(C-14), 129.87(C-15), 136.89(C-11), 147.10(C-14), 157.69(C-13), 159.72(C-2), 169.32(C-7). IR (KBr, cm$^{-1}$): 3232 (N-H), 1655 (C=O), 1315 (C-N). MS calcd. for C$_{13}$H$_{14}$N$_2$O$_2$S, 262.33; found: 263.0 (M$^+$). Anal. calc. for C$_{13}$H$_{14}$N$_2$O$_2$S: C, 59.52; H, 5.38; N, 10.68; O, 12.20; S, 12.22; found, C, 59.50; H, 5.36; S, 12.20.

N-(4-Methylthiazol-2-yl)-2-phenylacetamide (107d)

Isolated yield 75 %, (pale yellow solid), m.p. 103-105°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.26 (s, 3H), 3.74 (s, 2H), 6.73 (s, 1H), 7.32-7.37 (m, 5H), 12.29 (br s, 1H). $^{13}$C-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 17.32(C-9), 42.21(C-10), 108.13(C-5), 127.24(C-14), 129.01(C-13,C-15), 129.65(C-12, C-16), 135.50(C-11), 147.10(C-4), 157.70(C-2), 169.47(C-7). IR (KBr, cm$^{-1}$): 3238(N-H), 1653 (C=O), 1319 (C-N). MS calcd. for C$_{12}$H$_{12}$N$_2$OS: 232.3; found: 233.0 (M$^+$). Anal. calc. for C$_{12}$H$_{12}$N$_2$OS, C, 62.04; H, 5.21; N, 12.06; O, 6.89; S, 13.80; found C, 62.01; H, 5.20; S, 13.80.
2-(3,4-Dimethylphenoxy)-N-(4-methylthiazol-2-yl)acetamide (107e)

Isolated yield 73 %, (off white solid), m.p. 106-108°C.  
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.13 (s, 3H), 2.17 (s, 3H), 2.26 (s, 3H), 4.76 (s, 2H), 6.65 (d, J = 2.64 Hz, 1H), 6.68 (d, J = 14.80 Hz, 1H), 6.78 (s, 1H), 7.02 (t, J = 8.28 Hz, 1H).  
$^{13}$C-NMR (400 MHz, DMSO-$d_6$) δ (ppm ): 16.88(C-9), 18.46(C-19), 19.68(C-18), 66.10(C-10), 108.05(C-5), 111.35(C13), 116.02(C-17), 128.77(C-15), 130.19(C-14), 137.36(C-16), 146.71(C-4), 155.91(C-12), 166.91(C-12), 170.47(C-7). IR (KBr, cm$^{-1}$): 3398 (N-H), 1689 (C=O), 1309 (C-N). MS calcd. for C$_{14}$H$_{16}$N$_2$O$_2$S, 276.35; found: 277.2 (m+).  
Anal. calc. for C$_{14}$H$_{16}$N$_2$O$_2$S, C, 60.85; H, 5.84; N, 10.14; O, 11.58; S, 11.58.

N-(4-Methylthiazol-2-yl)-2-(2-nitrophenyl)acetamide (107f)

Isolated yield 76 %, (brown solid), m.p. 160-162°C.  
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.26 (s, 3H), 4.20 (s, 2H), 6.73 (s, 1H), 7.57-7.60 (m, 2H), 7.71-7.75 (m, 1H), 8.08-8.09 (m, 1H), 12.31 (s, 1H). 
$^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm ): 17.32(C-9), 39.32(C-10), 108.10(C-5), 125.19(C-13), 129.17(C-11), 130.34(C-16), 134.25(C-15), 147.12(C-4), 149.11(C-12), 157.63(C-2), 168.30(C-7).  
IR (KBr, cm$^{-1}$): 3404 (N-H), 1656 (C=O), 1595 (N-O), 1327 (C-NO$_2$), 1259 (C-N). MS calcd. for C$_{12}$H$_{11}$N$_3$O$_3$S, 277.3; found: 278.2 (m$^2$).  
Anal. calc. for C$_{12}$H$_{11}$N$_3$O$_3$S, C, 51.98; H, 4.00; N, 15.15; O, 17.31; S, 11.56; found, C, 51.95; H, 3.097; S, 11.53.

N-(4-(3-Fluorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107g)

Isolated yield 83 %, (yellow solid), m.p. 173-175°C.  
$^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.28 (s, 3H), 3.75 (s, 2H), 7.07 (d, J = 7.40 Hz, 1H), 7.12-7.17 (m, 3H), 7.21 (t, J = 7.44 Hz, 1H), 7.44-7.49 (m, 1H), 7.67-7.70 (m, 1H), 7.74 (s, 1H), 7.76 (s, 1H), 12.51 (bs, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm ): 21.00(C-23), 41.68(C-15), 109.55(C-5), 114.39(C-10), 121.71(C-4), 126.36(C-21), 127.52(C-19), 128.37(C-20), 129.90(C-13), 130.78(C-17), 134.80(C-9), 136.66(C-16), 137.55(C-18), 147.45(C-4), 161.42(C-11), 163.83(C-2), 169.65(C-7). IR (KBr, cm$^{-1}$): 1552 (C=O), 1325 (C-N). MS calcd. for C$_{18}$H$_{15}$FN$_2$OS, 326.3; found: 327.0 (M$^+$).  
Anal. calc. for C$_{18}$H$_{15}$FN$_2$OS, C, 66.24; H, 4.63; F, 5.82; N, 8.58; O, 4.90; S, 9.82; found: C, 66.22; H, 4.61; S, 9.81.
N-(4-(3-Fluorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107h)

Isolated yield 80 %, (off white solid), m.p. 160-162°C.  $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.27 (s, 3H), 3.73 (s, 2H), 7.12-7.23 (m, 5H), 7.46-7.49 (m, 1H), 7.68 (d, $J = 10.40$ Hz, 1H), 7.73 (s, 1H), 7.75 (s, 1H), 12.50 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm): 21.11(C-23), 41.76(C-15), 109.96(C-5), 114.81(C-12), 115.01(C-10), 122.13(C-14), 129.44(C-17, C-18, C-20, C-21), 131.20(C-13), 132.28(C-16), 136.38(C-9), 137.10(C-19), 147.95(C-4), 161.84(C-11), 164.25(C-2), 170.20(C-7). IR (KBr, cm$^{-1}$): 3228 (N-H) 1649 (C=O), 1257 (C-N). MS calcd. for C$_{18}$H$_{15}$FN$_2$OS, 326.3; found: 327.0 (M$^+$). Anal. calc. for C$_{18}$H$_{15}$FN$_2$OS, C, 66.24; H, 4.63; F, 5.28; N, 8.58; O, 4.90; S, 9.80.

2-(3,4-Dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide (107i)

Isolated yield 79 %, (yellow solid), m.p. 158-159°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.12 (s, 3H), 2.17 (s, 3H), 4.81 (s, 2H), 6.66-0.00 (m, 1H), 7.13 (d, $J = 8.32$ Hz, 1H), 7.45-7.50 (m, 1H), 7.69-7.72 (m, 1H), 7.76 (d, $J = 7.84$ Hz, 1H), 7.79 (s, 1H), 12.50 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm):18.87(C-25), 20.09(C-24), 66.54(C-15), 110.22(C-5), 111.81(C-18), 112.59(C-12), 112.82(C-22) 115.08(C-10), 122.18(C-14), 129.25(C-20), 130.64(C-19), 131.22(C-13), 137.01(C-9), 137.09(C-21), 148.08(C-4), 157.92(C-17), 161.84(C-11), 164.26(C-2), 167.83(C-7). IR (KBr, cm$^{-1}$): 3469 (N-H) 1697 (C=O), 1352 (C-O-C), 1249 (C-N). MS calcd. for C$_{19}$H$_{17}$FN$_2$O$_2$S, 356.41; found: 357.0 (M$^+$). Anal. calc. for C$_{19}$H$_{17}$FN$_2$O$_2$S, C, 64.03; H, 4.81; F, 5.33; N, 7.86; O, 8.98; S, 9.00.

N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j)

Isolated yield 76 %, (white solid), m.p. 194-196°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) $\delta$ (ppm): 2.26 (s, 3H), 3.73 (s, 2H), 7.13 (d, $J = 7.84$ Hz, 2H), 7.22 (d, $J = 7.88$ Hz, 2H), 7.37 (d, $J = 7.96$ Hz, 1H), 7.45 (t, $J = 7.84$ Hz, 1H), 7.76 (s, 1H), 7.85 (d, $J = 7.72$ Hz, 1H), 7.95 (s, 1H), 12.50 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) $\delta$ (ppm):21.11(C-23), 41.78(C-15), 110.04(C-5), 124.63(C-14), 125.84(C-10), 127.96(C-12), 129.44(C-18, C-20), 129.57(C-17, C-21), 131.13(C-13), 132.27(C-16), 134.05(C-9), 136.38(C-11), 136.76(C-19), 147.66(C-4), 158.57(C-2), 170.19(C-7). IR (KBr, cm$^{-1}$): 3448 (N-H) 1649 (C=O), 1325 (C-O-C), 1249 (C-N). MS calcd. for C$_{18}$H$_{15}$ClN$_2$OS, 342.84; found: 343.2. Anal. calc. for C$_{18}$H$_{15}$ClN$_2$OS, C, 63.06; H, 4.41; Cl, 10.34; N, 8.17; O, 4.67; S, 9.35; found: C, 63.04; H, 4.40; S, 9.32.
N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k)

Isolated yield 74 %, (white solid), m.p. 186-188°C. \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.30 (s, 3H), 3.75 (s, 2H), 7.08 (d, \(J = 7.48\) Hz, 1H), 7.14 (d, \(J = 7.72\) Hz, 1H), 7.16 (s, 1H), 7.22 (t, \(J = 7.44\) Hz, 1H), 7.37-7.40 (m, 1H), 7.47 (t, \(J = 7.84\) Hz, 1H), 7.78 (s, 1H), 7.86-7.88 (m, 1H), 7.96 (t, \(J = 1.80\) Hz, 1H). \(^13\)C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 21.43 (C-23), 42.12 (C-15), 110.06 (C-5), 124.64 (C-14), 125.84 (C-21), 126.78 (C-10), 127.94 (C-19), 127.97 (C-12), 128.79 (C-20), 130.31 (C-13), 131.14 (C-17), 134.05 (C-9), 135.21 (C-11), 136.75 (C-16), 137.97 (C-18), 147.67 (C-4), 158.55 (C-2), 170.06 (C-7). IR (KBr, \(cm^{-1}\)): 3404 (N-H), 1647 (C=O), 1321 (C-N). MS calcd. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\), 342.84; found: 343.0. Anal. calc. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\)S, C, 63.06; H, 4.41; Cl, 8.17; O, 4.67; S, 9.34; found: C, 63.03; H, 4.39; S, 9.34.

N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)acetamide (107l)

Isolated yield 81 %, (white solid), m.p. 166-168°C. \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 3.75 (s, 3H), 3.77 (s, 2H), 6.83-6.86 (m, 1H), 6.91 (s, 1H), 6.92-6.93 (m, 1H), 7.25 (t, \(J = 7.96\) Hz, 1H), 7.37-7.39 (m, 1H), 7.47 (t, \(J = 7.80\) Hz, 1H), 7.78 (s, 1H), 7.85-7.88 (m, 1H), 7.96 (t, \(J = 1.76\) Hz, 1H). \(^13\)C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 42.20 (C-15), 55.48 (C-24), 110.08 (C-5), 112.70 (C-17), C-19), 115.56 (C-21), 121.91 (C-14), 124.64 (C-10), 125.84 (C-12), 127.97 (C-20), 129.91 (C-13), 131.14 (C-9), 134.05 (C-11), 136.74 (C-16), 147.68 (C-4), 158.53 (C-17), 158.73 (C-2), 169.91 (C-7). IR (KBr, \(cm^{-1}\)): 3406 (N-H), 1651 (C=O), 1321 (C-N). MS calcd. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\), 358.84; found: 359.0 (M\(^+\)). Anal. calc. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\)S, C, 60.25; H, 4.21; Cl, 8.88; N, 7.81; O, 8.92; S, 8.94 Found: C, 60.23; H, 4.20; S, 8.91.

N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m)

Isolated yield 85 %, (pale yellow solid), m.p. 156-157°C. \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.13 (s, 3H), 2.18 (s, 3H), 4.82 (s, 2H), 6.68 (d, \(J = 5.96\) Hz, 1H), 6.79 (s, 1H), 7.03 (d, \(J = 8.00\) Hz, 1H), 7.38 (d, \(J = 7.32\) Hz, 1H), 7.46 (t, \(J = 7.68\) Hz, 1H), 7.81 (s, 1H), 7.87 (d, \(J = 7.36\) Hz, 1H), 7.96 (s, 1H), 12.49 (s, 1H). \(^13\)C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 18.47 (C-25), 19.68 (C-24), 66.08 (C-15), 109.89 (C-5), 111.35 (C-18), 116.06 (C-22), 124.25 (C-14), 125.44 (C-10), 127.61 (C-12), 128.82 (C-20), 130.21 (C-19), 130.74 (C-13), 133.64 (C-9), 136.24 (C-11), 137.40 (C-21), 147.33 (C-4), 155.87 (C-17), 157.55 (C-2), 167.42 (C-7). IR (KBr, \(cm^{-1}\)): 3404 (N-H), 1650 (C=O), 1321 (C-N). MS calcd. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\), 358.84; found: 359.0 (M\(^+\)). Anal. calc. for C\(_{18}\)H\(_{15}\)ClN\(_2\)O\(_2\), C, 63.06; H, 4.41; Cl, 8.17; O, 4.67; S, 9.34; found: C, 63.03; H, 4.39; S, 9.34.

N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m)

Isolated yield 85 %, (pale yellow solid), m.p. 156-157°C. \(^1\)H-NMR (400 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 2.13 (s, 3H), 2.18 (s, 3H), 4.82 (s, 2H), 6.68 (d, \(J = 5.96\) Hz, 1H), 6.79 (s, 1H), 7.03 (d, \(J = 8.00\) Hz, 1H), 7.38 (d, \(J = 7.32\) Hz, 1H), 7.46 (t, \(J = 7.68\) Hz, 1H), 7.81 (s, 1H), 7.87 (d, \(J = 7.36\) Hz, 1H), 7.96 (s, 1H), 12.49 (s, 1H). \(^13\)C-NMR (100 MHz, DMSO-\(d_6\)) \(\delta\) (ppm): 18.47 (C-25), 19.68 (C-24), 66.08 (C-15), 109.89 (C-5), 111.35 (C-18), 116.06 (C-22), 124.25 (C-14), 125.44 (C-10), 127.61 (C-12), 128.82 (C-20), 130.21 (C-19), 130.74 (C-13), 133.64 (C-9), 136.24 (C-11), 137.40 (C-21), 147.33 (C-4), 155.87 (C-17), 157.55 (C-2), 167.42 (C-7). IR (KBr, \(cm^{-1}\)):
3155 (N-H), 1627 (C=O), 1381 (C-N). MS calcd. for C_{19}H_{17}ClN_{2}O_{2}S, 372.87; found, 373.2. Anal. calc. for C_{19}H_{17}ClN_{2}O_{2}S, C, 61.20; H, 4.60; Cl, 9.51; N, 7.51; O, 8.58; S, 8.60; found: C, 61.19; H, 4.58; S, 8.59.

Methyl 2-(2-(2-p-tolylacetamido)thiazol-4-yl)acetate (107n)

Isolated yield 73 %, (pale yellow solid), m.p. 128-130°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.27 (s, 3H), 3.61 (s, 3H), 3.68 (s, 2H), 3.70 (s, 2H), 6.97 (s, 1H), 7.13 (d, J = 7.88 Hz, 2H), 7.20 (d, J = 8.00 Hz, 2H), 12.38 (bs, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 20.68(C-21), 36.52(C-9), 41.36(C-13), 51.76(C-12), 110.49(C-5), 129.00(C-15, C19) 131.92(C-C16, C-18), 135.92(C-14), 143.57(C-4), 157.73(C-2), 169.40(C-10), 170.52(C-7). MS calcd. for C_{15}H_{16}N_{2}O_{3}S, 304.36; found, 303.2 (M -), 305.2 (M +). Anal. calc. for C_{15}H_{16}N_{2}O_{3}S, C, 59.19; H, 5.30; N, 9.20; O, 15.77; S, 10.54; found: C, 59.16; H, 5.28; S, 10.52.

Methyl 2-(2-(2-m-tolylacetamido)thiazol-4-yl)acetate (107o)

Isolated yield 71 %, (pale yellow solid), m.p. 116-118°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 2.28 (s, 3H), 3.61 (s, 3H), 3.69 (s, 2H), 3.71 (s, 2H), 6.97 (s, 1H), 7.06 (d, J = 7.48 Hz, 1H), 7.12 (d, J = 7.72 Hz, 1H), 7.14 (s, 1H), 7.21 (t, J = 7.48 Hz, 1H), 12.40 (bs, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 21.41(C-21), 36.39(C-9), 42.14(C-13), 52.17(C-12), 110.93(C-5), 126.72(C-19), 127.90(C-17), 128.77(C-18), 130.26(C-15), 135.29(C-14), 137.96(C-16), 144.01(C-4), 158.14(C-2), 169.71(C-10), 170.95(C-7). MS calcd. for C_{15}H_{16}N_{2}O_{3}S, 304.36; found: 303.2 (M'), 305.2 (M'). Anal. calc. for C_{15}H_{16}N_{2}O_{3}S, C, 59.19; H, 5.30; N, 9.20; O, 15.77; S, 10.54; found: C, 59.17; H, 5.29; S, 10.51.

Methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p)

Isolated yield 68 %, (pale yellow solid), m.p. 128-129°C. $^1$H-NMR (400 MHz, DMSO-$d_6$) δ (ppm): 3.61 (s, 3H), 3.69 (s, 2H), 3.70 (s, 2H), 3.74 (s, 3H), 6.82-6.84 (m, 1H), 6.88 (s, 1H), 6.89-6.90 (m, 1H), 24200.49 (t, J = 7.84 Hz, 1H), 12.40 (s, 1H). $^{13}$C-NMR (100 MHz, DMSO-$d_6$) δ (ppm): 36.94(C-9), 42.23(C-13), 52.18(C-12), 55.45(C-22), 110.96(C-5), 112.66(C-17), 115.49(C-15), 121.84(C-19), 129.90(C-18), 136.80(C-14), 144.02(C-4), 158.11(C-16), 159.71(C-2), 169.52(C-10), 170.95(C-7). MS calcd. for C_{15}H_{16}N_{2}O_{4}S, 320.36; found, 319.2 (M'), 321.0 (M'). Anal. calc. for C_{15}H_{16}N_{2}O_{4}S, C, 56.24; H, 5.03; N, 8.74; O, 19.98; S, 10.01; found: C, 56.22; H, 5.01; S, 10.01.
BIOLOGY

The evaluation of newly synthesized thiazole derivatives for their antibacterial activity against *Staphylococcus aureus* (ATTC-25923), *Escherichia coli* (ATTC-25922), *Pseudomonas aeruginosa* (ATTC 27853), *Klebsiella pneumonia* (Recultered) bacteria and antifungal activity against *Pencillium marneffei* (Recultered), *Trichophyton mentagrophytes* (Recultered), *Aspergillus flavus* (NCIM No.524), *Aspergillus fumigatus* (NCIM No.902) was carried out.

**Antibacterial activity**

The newly synthesized thiazoles were screened for their antibacterial activity against bacterial strains by disc diffusion method. The discs measuring 6.25 mm in diameter were punched from Whatman No.1 filter paper. Batches of 100 discs were dispensed to each screw capped bottle and sterilized by dry heat at 140°C for an hour. The test compounds were prepared with different concentrations using dimethylformamide. One millilitre containing 100 times the amount of chemical required in each disc was added to each bottle which contains 100 discs. The discs of each concentration were placed in triplicate in nutrient agar medium seeded with fresh bacteria separately. The incubation was carried out at 37.8°C for 24h. Ampicillin was used as a standard drug. Solvent and growth controls were kept. The zone of inhibition and minimum inhibitory concentrations [MIC] was noted. The MIC values of tested compounds are given in Table 2.1

**Antifungal activity**

Antifungal activity for newly prepared compounds was screened by serial plate dilution method. Sabourand's agar media was prepared by dissolving peptone (1g), D-glucose (4g) and agar (2g) in distilled water (100ml) and adjusting the pH to 5.7. Normal saline was used to make a suspension of spores of fungal strain for lawning. A loop full of particular fungal strain was transferred to 3 ml saline to get a suspension of corresponding species. A 20 ml of agar media was poured into each of the petridishes. Excess of suspension was decanted and the plates were dried by placing in an incubator at 37°C for 1 h. Using an agar punch wells were made on these seeded agar plates and 10 mg/ml of the test compounds in DMSO were added into each well labeled. A control was also prepared for the plates in the same way using solvent DMSO. The petridish were prepared in triplicate and maintained at 37°C for
3-4 days. Antifungal activity was determined by measuring the diameter of the inhibition zone. Activity of each compound was compared with Itraconazole as standard. The minimum inhibitory concentration (MIC) for the Itraconazole in DMSO was more than 1mg/ml against the tested species. The MIC values of tested compounds are given in Table 2.2.

**Table 2.1**: Antibacterial activity of the compounds 107a-p (MIC in µg/ml).

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<th>Compound</th>
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<th>Staphylococcus aurus (ATTC-25923)</th>
<th>Escherichia coli (ATTC-25922)</th>
<th>Pseudomonas Aeruginosa (ATTC 27853)</th>
<th>Klebsiella pneumonia (recultured)</th>
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### Table – 2.2: Antifungal activity of the compounds 107a-p (MIC in µg/mL).

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<th>Trichophyton mentagrophytes (Recultered)</th>
<th>Aspergillus Flovus (NCIM No.524)</th>
<th>Aspergillus Fumigatus (NCIM No.902)</th>
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Result and discussion

The reaction sequences employed for synthesis of title compound \(N\)-[4-(substituted)-1,3-thiazol-2-yl]-2-(substituted)acetamide and methyl 2-(2-(substituted)acetamido)thiazol-4-yl)acetate derivatives (107a-p) is shown in Scheme 2.17. The intermediate, \(\alpha\)-haloketones (100a-b) were synthesized from substituted acetopheone (99a-b) by bromination with bromine in acetic acid. 4-(Substituted phenyl)thiazol-2-amine (101a-b) were synthesised by Hantzsch’s thiaazole synthesis from \(\alpha\)-heloketone (100a-b) and thiourea in presence of sodium acetate in ethanol at room temperature for 2-3 h in 82-88% yield.

The structure of newly synthesized compounds were established on the basis of elemental analysis and spectral (\(^1\)H & \(^{13}\)C NMR and LCMS) data. \(^1\)H NMR spectrum of 4-(3-chlorophenyl)thiazol-2-amine (101a) showed a broad singlet at \(\delta 7.13\) integrating for two proton were due to NH\(_2\) group. The C\(_5\)-H proton of thiazole and C\(_5\)-H proton of phenyl ring appeared as singlet at \(\delta 7.17\) and \(\delta 7.84\) respectively. Proton of phenyl ring positioned at C\(_{10}\) appeared as multiplet at \(\delta 7.29\)\(-7.32\), C\(_{11}\)-H and C\(_{11}\)-H proton of phenyl ring appeared as triplet at \(\delta 7.39\) and doublet at \(\delta 7.75\) with coupling constant \(J = 7.80\) Hz and \(J = 7.76\) Hz respectively. The \(^{13}\)C NMR spectrum showed signal corresponding to C-NH\(_2\) carbon (C\(_2\)) of thiazole appeared at \(\delta 168.78\), C\(_4\) carbon which linked to phenyl ring appeared at \(\delta 148.55\) and C\(_5\) carbon of thiazole came into resonance at \(\delta 103.58\). The carbon of phenyl ring (C\(_7\)) which linked to thiazole showed peak at \(\delta 133.77\) and C\(_9\) carbon of phenyl ring which bonded to chlorine appeared at 137.30. C\(_8\), C\(_{10}\), C\(_{11}\) and C\(_{12}\) carbon peak of phenyl ring resonance at 125.65, 127.30, 130.81 and 124.44 respectively. The mass spectrum of this compound showed molecular ion peak at 211.2 (M\(^+\)).

Further Hantzsch reaction of chloroacetone (102) with thiourea (103), refluxed in water gave 4-methylthiazol-2-amine (104). Fischer esterification of 2-amino-1,3-thiazol-4-yl)acetic acid (105) in methanol to gave methyl (2-amino-1,3-thiazol-4-yl)acetate (106). \(N\)-[4-(substituted)-1,3-thiazol-2-yl]-2-(substituted)acetamide and methyl-2-(2-(substituted)acetamido)thiazol-4-yl)acetate derivatives (107a-p) were prepared by coupling substituted phenyl acetic acid with 4-(substituted phenyl)thiazol-2-amine (101a-b), 4-methylthiazol-2-amine (104) and methyl (2-amino-1,3-thiazol-4-yl)acetate (106), by using propylphosphonic Anhydride (T3P) as a coupling reagent.
The structure of newly synthesized compounds were established on the basis of elemental analysis and spectral (IR, \(^1\text{H NMR}\), \(^{13}\text{C NMR}\) and LCMS) data. The \(^1\text{H NMR}\) spectrum of N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a) showed two singlet at \(\delta\) 2.25 and \(\delta\) 2.27 integrating for three protons each were due to methyl group of thiazole and phenyl ring respectively. The Ph-CH\(_2\)- proton came into resonance at \(\delta\) 3.68 as singlet. The C\(_5\)-H proton of thiazole appeared as singlet at \(\delta\) 6.72. The C\(_{13}\), C\(_{15}\) and C\(_{12}\), C\(_{16}\) protons of phenyl ring resonated as doublet at \(\delta\) 7.12 and \(\delta\) 7.20 respectively with coupling constant \(J=7.5\) Hz each integrating for two protons. The \(^{13}\text{C NMR}\) spectrum showed signal corresponding to methyl group of thiazole (C\(_9\)) and phenyl ring (C\(_{17}\)) resonance at 17.31 and 21.09 respectively. –CH\(_2\)-Ph carbon C\(_{10}\) appears at 41.82. C\(_5\) carbon of thiazole came into resonance at \(\delta\) 108.09. C\(_{12}\), C\(_{13}\), C\(_{15}\) and C\(_{16}\) carbon peak of phenyl ring resonance at 129.41. C\(_{11}\) and C\(_{14}\) carbon of phenyl ring resonance at 132.43 and 136.30 respectively. C\(_4\) carbon of thiazole came into resonance at \(\delta\) 147.07. C-NH (C\(_2\)) and CO (C\(_7\)) resonance at 157.73 and 169.62 respectively. IR spectrum showed absorption band in the region of 3230 cm\(^{-1}\), characteristic of NH group. The \(\text{C=O}\) and \(\text{C-NH}\) stretching was observed at 1689 cm\(^{-1}\) and 1307 cm\(^{-1}\) respectively. The mass spectrum of this compound showed molecular ion peak at 247.0 (M\(^+\)).

The structure of the obtained compounds was elucidated by spectral data. In the \(^1\text{H-NMR}\) spectra of compounds 107a–p, NHCO proton was observed at 12.38–12.90 ppm as a singlet or broad singlet. The signal due to -(C=O)-CH\(_2\) methylene protons, of all the compounds, appeared in the region 4.05– 4.30 ppm, as singlet. The signal due to -(C=O)CH\(_2\)-OPh was observed at 4.81 ppm. The signals for other aromatic and aliphatic protons were observed at expected regions (aliphatic-1.95ppm to 4.81ppm, aromatic-6.06ppm to 8.10ppm). In \(^{13}\text{C-NMR}\), the –NHCO- carbon peak was observed at 167.42-170.95 ppm. All the other signals in the spectra were accounted for the all equivalent and non-equivalent carbons present in the molecule. According to the IR spectroscopic data of the compounds 107 a–p, exhibited characteristic C=O (amide) stretching bands in the region 1690–1645 cm\(^{-1}\). Mass spectra (LCMS) of compounds showed either M\(^+\) peaks in positive mode or M\(^-\) peak in negative mode, in agreement with mass calculated for their molecular formula. The elemental analysis gave satisfactory percentage of C, H and N present in new compounds. All compound showed antibacterial and antifungal activity.
**Antibacterial activity**

Among the tested compounds, N-(4-methylthiazol-2-yl)-2-p-tolylacetamide \(107a\), N-(4-methylthiazol-2-yl)-2-m-tolylacetamide \(107b\), 2-(3-methoxyphenyl)-N-(4-methylthiazol-2-yl)acetamide \(107c\), 2-(3,4-dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide \(107i\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide \(107j\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide \(107k\) and N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide \(107m\), were found to be active and the minimum inhibitory concentration (MIC) were 6.25 µg/ml. These compounds were active against all the tested microorganisms. It is noteworthy that all the active compounds contain either m-tolyl or p-tolyl groups at the amide end as one of the substituent.

**Antifungal activity**

In the antifungal assay the compounds N-(4-methylthiazol-2-yl)-2-phenylacetamide \(107d\), N-(4-(3-fluorophenyl)thiazol-2-yl)-2-m-tolylacetamide \(107g\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide \(107j\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide \(107k\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)acetamide \(107l\), N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide \(107m\), methyl 2-(2-(2-p-tolylacetamido)thiazol-4-yl)acetate \(107n\), and methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate \(107p\), were found to be more active against all the tested strains with MIC values ranging from 6.25 µg/ml. Compounds N-(4-methylthiazol-2-yl)-2-p-tolylacetamide \(107a\), N-(4-methylthiazol-2-yl)-2-m-tolylacetamide \(107b\), 2-(3,4-dimethylphenoxy)-N-(4-methylthiazol-2-yl)acetamide \(107c\), N-(4-methylthiazol-2-yl)-2-(2-nitrophenyl)acetamide \(107f\) and methyl 2-(2-(2-m-tolylacetamido)thiazol-4-yl)acetate \(107o\) were moderately active with MIC 12.5 µg/ml for all the tested strains. Other compounds were active against some of the tested strains and inactive against some of them. The active compounds possessed either m-tolyl or p-tolyl groups at the amide end as one of the substituent.

However, for the standard compounds, MIC was below 6.25 µg/ml. But this is a promising preliminary result. In the preliminary evaluation for the antimicrobial activity, compounds N-(4-methylthiazol-2-yl)-2-m-tolylacetamide \(107b\), 2-(3,4-dimethyl phenoxy)-N-(4-methylthiazol-2-yl)acetamide \(107e\), N-(4-(3-chlorophenyl) thiazol-2-
yl)-2-(3,4-dimethylphenoxy)acetamide (107m), were found to be active against both *Escherichia coli* and *Klebsiella pneumonia* with minimum inhibitory concentration (MIC) 6.25 µg/ml. Antifungal activity showed that N-(4-methylthiazol-2-yl)-2-phenylacetamide (107d) active against *Trichophyton mentagrophytes* and *Aspergillus flavus*, N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j) against *Pencillium marneffei* and *Aspergillus flavus*, N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k) against *Aspergillus flavus* and *Aspergillus fumigates*, methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p) against *Pencillium marneffei* and *Aspergillus fumigates* with minimum inhibitory concentration (MIC) 6.25 µg/ml. It is difficult to arrive at the structure activity relationship with respect to their antimicrobial activities. However, the compounds with either p-tolyl or m-tolyl substitution at the amide end exhibited better activity than the rest.
Figure – 2.1: $^1$H NMR spectrum of 4-(3-chlorophenyl)thiazol-2-amine (101a)

Figure – 2.2: $^{13}$C NMR spectrum of 4-(3-chlorophenyl)thiazol-2-amine (101a)
Figure – 2.3: LCMS spectrum of 4-(3-chlorophenyl)thiazol-2-amine (101a)
Figure – 2.4: $^1$H NMR spectrum of N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a)

Figure – 2.5: $^{13}$C NMR spectrum of N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a)
Figure – 2.6 : Mass spectrum of N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a)

Figure – 2.7 : IR spectrum of N-(4-methylthiazol-2-yl)-2-p-tolylacetamide (107a)
Figure – 2.8: $^1$H NMR spectrum of N-(4-methylthiazol-2-yl)-2-m-tolylacetamide (107b)

Figure – 2.9: $^{13}$C NMR spectrum of N-(4-methylthiazol-2-yl)-2-m-tolylacetamide (107b)
Figure – 2.10: LCMS spectrum of N-(4-methylthiazol-2-yl)-2-m-tolylacetamide (107b)

Figure – 2.11: $^1$H NMR spectrum of 2-(3-methoxyphenyl)-N-(4-methylthiazol-2-yl) acetamide (107c)
Figure – 2.12: $^{13}$C NMR spectrum of 2-(3-methoxyphenyl)-N-(4-methylthiazol-2-yl) acetamide (107c)

Figure – 2.13: LCMS spectrum of 2-(3-Methoxyphenyl)-N-(4-methylthiazol-2-yl) acetamide (107c)
Figure – 2.14 : $^1$H NMR spectrum of N-(4-methylthiazol-2-yl)-2-(2-nitrophenyl)acetamide (107f)

Figure – 2.15 : $^{13}$C NMR spectrum of N-(4-Methylthiazol-2-yl)-2-(2-nitrophenyl)acetamide (107f)
Figure – 2.16: $^1$H NMR spectrum of N-(4-(3-fluorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107g)

Figure – 2.17: $^{13}$C NMR spectrum of N-(4-(3-fluorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107g)
Figure – 2.18 : LCMS spectrum of N-(4-(3-fluorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107g)

Figure – 2.19 : $^1$H NMR spectrum of N-(4-(3-fluorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107h)
Figure – 2.20 : $^{13}$C NMR spectrum of N-(4-(3-fluorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107h)

Figure – 2.21 : LCMS spectrum of N-(4-(3-Fluorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107h)
Figure – 2.22 : $^1$H NMR spectrum of 2-(3,4-dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide (107i)

Figure – 2.23 : $^{13}$C NMR spectrum of 2-(3,4-dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide (107i)
Figure – 2.24 : LCMS spectrum of 2-(3,4-dimethylphenoxy)-N-(4-(3-fluorophenyl)thiazol-2-yl)acetamide (107i)

Figure – 2.25 : $^1$H NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j)
Figure – 2.26: $^{13}$C NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j)

Figure – 2.27: LCMS spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-p-tolylacetamide (107j)
Figure – 2.28 : $^1$H NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k)

Figure – 2.29 : $^{13}$C NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k)
Figure – 2.30 : LCMS spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-m-tolylacetamide (107k)

Figure – 2.31 : $^1$H NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)acetamide (107l)
Figure – 2.32 : $^{13}$C NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)acetamide (1071)

Figure – 2.33 : LCMS spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3-methoxyphenyl)acetamide (1071)
Figure – 2.33 : $^1$H NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m)

Figure – 2.34 : $^{13}$C NMR spectrum of N-(4-(3-chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m)
Figure – 2.35 : LCMS spectrum of N-(4-(3-Chlorophenyl)thiazol-2-yl)-2-(3,4-dimethylphenoxy)acetamide (107m)

Figure – 2.36 : $^1$H NMR spectrum of methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p)
Figure – 2.37 : $^{13}$C NMR spectrum of methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p)

Figure – 2.38 : LCMS spectrum of Methyl 2-(2-(2-(3-methoxyphenyl)acetamido)thiazol-4-yl)acetate (107p)
References


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