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DESIGN, SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITIES OF SOME NOVEL THIAZOLE AND THIADIAZOLE DERIVATIVES CLUBBED WITH 1*H*-BENZIMIDAZOLE

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ABSTRACT

A series of *N*-(4-(substituted phenyl)thiazol-2-yl)-2-(1-(substituted benzyl or pyridinyl methyl)-1*H*-benzo[*d*]imidazol-2-ylthio)acetamide **4(A-I)** & 2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(substituted phenyl, benzyl)-1,3,4-thiadiazol-2-yl)acetamide **7(A-H)** have been prepared. Synthesis of thiazol compounds **4(A-I)** was carried out in four different steps, which included synthesis of 2-amino-4-substituted thiazoles **1(A-C)**, chloroacetylated-2-amino-4-substitutedthiazoles **2(A-C)** and reaction of these chloroacetylated-2-amino-4-substitutedthiazoles with 2-mercaptobenzimidazole to produce 2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-substituted phenylthiazol-2-yl)acetamide **3(A-C)**. Finally desired compounds **4(A-I)** were prepared by the reaction of substituted benzyl or pyridinyl methyl halide with compounds **3(A-C)**. On the other hand synthesis of thiadiazole compounds **7(A-H)** included three steps which comprised of synthesis of 2-amino-5-substituted thiadiazoles **5(A-H)** and chloroacetylated 2-amino-5-substituted thiadiazoles **6(A-H)**. Finally reaction of these chloroacetylated thiadiazole compounds with 2-mercaptobenzimidazole produced compounds **7(A-H).** All the synthesized compounds were characterized by IR, ^{1}H NMR and mass spectral techniques and evaluated for their antimicrobial activity.

Keywords: Thiazole, Thiadiazole, Benzimidazole, 2-Mercaptobenzimidazole, Antimicrobial activities

INTRODUCTION

Heterocycles are an essential class of compounds, making up more than half of all known organic compounds. A wide variety of drugs, most of the vitamins, many natural products, biomolecules and biologically active compounds, including antitumor, antibiotic, anti-inflammatory, antimalarial, antidepressant, anti-HIV, antimicrobial, antifungal, antiviral, antidiabetic herbicidal, fungicidal, and insecticidal agents consist of heterocyclic compounds. Also, they have been often found as a key structural unit in synthetic pharmaceuticals and agrochemicals.

Thiazoles are one of the most intensively studied classes of aromatic five-membered heterocycles. It was first described by Hantzsch and Weber in 1887.This five membered ring system containing sulfur and nitrogen hetero atoms at positions-1 and -3, respectively and it is involved in many of the natural products. For example, the thiazolium ring present in vitamin B_1 functions as an electron sink, and its coenzyme form is important for the decarboxylation of α-ketoacids[1]. The properties of thiazole are analogous to those of oxazole and the basic nature of ring is attributed to the nitrogen atom with unshared pair of electron. Among the various aromatic heterocycles, thiazoles occupy a prominent position in the drug discovery process[2] and this ring structure is present in several marketed drugs which are given below with their pharmaceutical activity. It can also be utilized in a scaffold hopping[3] or as an amide isostere[4] during the analysis of structure activity relationships for lead optimization. As a result, thiazoles are frequently included in the design or are used as a fundamental structure for the synthesis of chemical libraries[5].Thus the thiazole nucleus has been much investigated in the field of organic and medicinal

chemistry. The thiazole system has found broad therapeutic application as a antimicrobial & antifungal[6], anti-inflammatory[7], anticancer[8], antihypertensive[9], anti-HIV[10], anticonvulsant[11], antidiabetic[12].

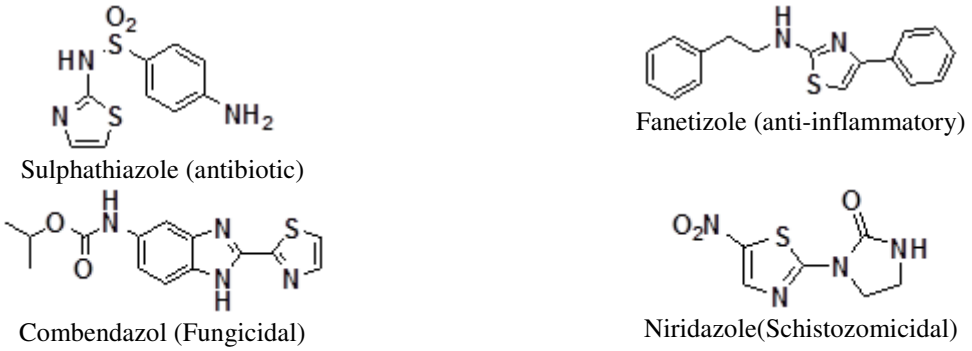


Fig.-1: Clinically used thiazole

The structure of thiazole can be considered as the resonance hybrid of the following resonating structures. Moreover, some additional resonating structures are also possible with the involvement of d-orbitals of sulfur.

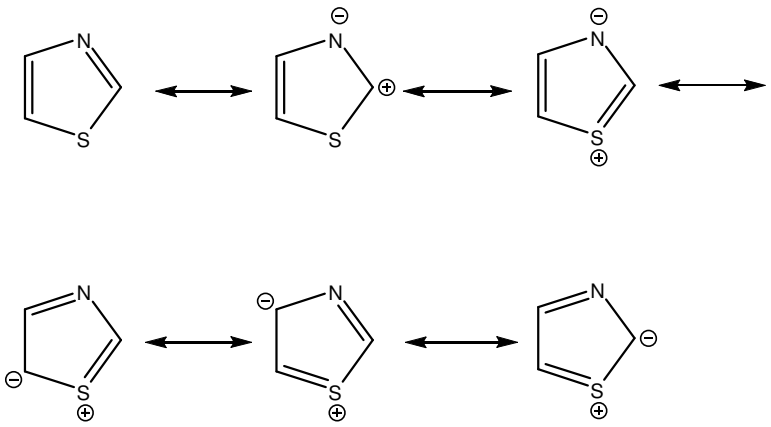


Fig.-2: Resonating structure of Thiazole

Five membered heterocyclic compounds exhibit several types of biological activity among them 2,5-disubstituted 1,3,4-thiadiazoles are responsible for diverse biological activity probably due to –N=C-S- grouping. Therapeutic importance of these rings encouraged us to develop selective molecules in which substituent could be arranged in a pharmacophoric pattern to exhibit higher pharmacological activities. Thiadiazoles have occupied an important place in drug industry, 1,3,4-thiadiazoles have extensive applications in many fields. Initial uses were in the pharmaceutical area as an antibacterial with known sulphonamides drugs. Some of other uses are antitumor, anti-inflammatory, pesticides, herbicides, dyes, lubricants, and analytical reagents[13].

1, 3, 4-thiadiazole derivatives possess remarkable biological activity probably due to strong aromaticity of the ring system which results into great *in vivo* stability and generally, a lack of toxicity for higher vertebrates, including humans when various functional groups those interact with biological receptors are attached to aromatic ring[14]. It is well-known fact that minor alteration in the structure of certain compounds are able to bring drastic changes to yield better drug with less toxicity to the host and it has been observed that chemical modification not only alters physiochemical properties but also

pharmacological properties[15]. The biological importance of 1,3,4-thiadiazole can be described in following different categories which are antimicrobial[16],anti-inflammatory[17],anticancer[18], antidepressant[19] anticonvulsant[20]according to their therapeutic evaluation carried out by different researchers. Thiadiazole moiety acts as a "hydrogen binding domain" and "two-electron donor system". Thiadiazole act as a bioisosteric replacement of thiazole moiety. So, it serves as third and fourth generation cephalosporin. Thiadiazole is a five membered ring system containing sulphur and nitrogen atom. They occur in four isomeric form *viz.*, 1,2,3-thiadiazole , 1,2,4-thiadiazole, 1,2,5-thiadiazole , 1,3,4-thiadiazole.

1, 2, 3-Thiadiazole 1, 2, 4-thiadiazole 1, 2, 5-thidiazole 1, 3, 4-thiadiazole

Fig.-3

EXPERIMENTAL

Materials and Method

All chemicals and solvents were supplied by Merck, S.D. Fine Chem limited. All the solvents were distilled and dried before use. The reactions were monitored with the help of thin-layer chromatography using pre-coated aluminum sheets with GF254 silica gel, 0.2 mm layer thickness (E. Merck). Various solvent systems used for developing the chromatograms were (a) chloroform/methanol (9:1), (b) chloroform/ methanol (9.5:0.5), (c) ethyl acetate/hexane (5:5). Melting points of the synthesized compounds were recorded on the Veego (VMP-MP) melting point apparatus and not corrected. IR spectrum was acquired on a Shimadzu Infrared Spectrometer, (model FTIR-8400S). 1H NMR spectra of the synthesized compounds were performed in DMSO with IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using direct inlet probe technique.^{1}H NMR and ^{13}C NMR was determined in DMSO-d6 solvent on a Bruker AC 400 MHz spectrometer. 2-amino-4substituted phenyl thiazoles **1(A-C)** were prepared according to method described in literature[21].

General procedure for the synthesis of compounds 2 (A-C)

To a three neck 50ml round bottom flask containing a solution of 4-(substituted phenyl)thiazol-2-amine **1(A-C)** (0.004mole) in tetrahydrofuran (20ml) were added triethylamine (0.008mole) and chloroacetylchloride (0.008mole).The reaction mixture was refluxed for 3h and cooled to room temperature. The precipitated triethylamine hydrochloride salt was filtered and filtrate was concentrated under vacuum to get crude 2-chloro-*N*-(4-(substituted phenyl) thiazol-2-yl) acetamide **2(A-C)** which were further purified by diethyl ether (70% yield)

General procedure for the synthesis of compounds 3(A-C)

A mixture of 2-mercaptobenzimidazole (2-MBI) (0.0030mole), 2-chloro-*N*-(4-(substituted phenyl) thiazol-2-yl) acetamide **2(A-C)** (0.0030mole) and piperidine (0.0060mole) in acetonitrile was heated at 60^{o}C for 3h. The reaction mixture was cooled and poured into crushed ice and resulting solid was filtered, washed with water, dried well. The dry solid was purified in methanol to get desired 2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-(substituted phenyl) thiazol-2-yl) acetamide in **3(A-C)** 70% yield.

General procedure for the synthesis of compounds 4 (A-I)

Benzyl or substituted benzyl bromide and 2-(chloromethyl)-3, 4-dimethoxypyridin hydrochloride (0.002mole) and potassium carbonate (0.004mole) were added to a solution of 2-(1*H*-benzo[d]imidazol-2-ylthio)-*N*-(4-(substitutedphenyl) thiazol-2-yl) acetamide **3(A-C)** (0.002 mole) in acetonitrile (20ml) and refluxed for 2h. The reaction mixture was cooled and poured into crushed ice. The resulting solid was collected via filtration, washed with water and dried well. The purification of crude compounds was

carried out in methanol to obtained pure *N*-(4-(substituted phenyl) thiazol-2-yl)-2-(1-(substituted benzyl or pyridinyl methyl)-1*H*-benzo[*d*]imidazol-2-ylthio) acetamide **4 (A-I)**

General procedure for the synthesis of compounds 5 (A-H)
Synthesis of 2-amino-5-substituted thiadiazoles was carried out as per procedure given in literature.[13] which included cyclisation of thiosemicarbezides in con.H_2SO_4 and these thiosemicarbezides, in turns were synthesized by the reaction of corresponding acid hydrazides and potassium thiocynate in acidic medium.

General procedure for the synthesis of compounds 6 (A-H)
Chloro acetyl chloride (0.01mole) was added drop wise at 0ºC to a solution of 2-amino-5-subsituted phenyl or benzyl thiadiazoles **5 (A-H)** (0.005mole) and triethyl amine (0.0125mole) in THF. The reaction mixture was stirred for 2hr at room temperature. THF was evaporated and residue was taken into ice cold water, the resulting solid was collected via filtration, washed with water and dried well to get 2-Chloro-*N*-(5-(substituted phenyl, benzyl)-1,3,4-thiadiazol-2-yl)acetamide **6(A-H)** 75% yield.

General procedure for the synthesis of compounds 7(A-H)
A mixture of 2-mercaptobenzimidazole (2MBI, 0.005mole), piperidine (0.010mole) and 2-Chloro-*N*-(5-(substituted phenyl, benzyl)-1, 3, 4-thiadiazol-2-yl) acetamide **6(A-H)** (0.005mole) in acetonitrile was heated at 60ºC for 3h .The reaction mixture was cooled and poured into crushed ice. The resulting solid was collected via filtration, washed with water and dried well and purified with methanol to get 2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(substituted phenyl, benzyl)-1,3,4-thiadiazol-2-yl)acetamide**7(A-H).**

2-(1-benzyl-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-phenylthiazol-2-yl) acetamide (4A)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1687(–C=O stretching amide), 3058 (C–H stretching, aromatic ring), 2932, 2809 (C–H stretching, –CH2–), 1604, 1434 (C=C, thiazole ring stretching)1549, 1452(C=C stretching, aromatic ring), 1492(–C=N–, thiazole ring), 1452 (C–H bending, –CH2–),1242(–C–S–C–,thiazole ring),^{1}H NMR (400 MHz, DMSO-d6)**:** 4.48(s, 2H), 5.46(s, 2H), 7.16-7.40(m,7H), 7.43-7. 56 (m, 5H), 7.66(s, 1H), 7.86-7.93(m, 2H) MS: m/z 457.2(M+H) +; m.p.138-141 ºC, Yield: 65%.

2-(1-(4-nitrobenzyl)-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-phenylthiazol-2-yl) acetamide (4B)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1687(–C=O stretching amide), 3055 (C–H stretching, aromatic ring), 2936, 2850 (C–H stretching, –CH2–), 1606, 1432(C=C, thiazole ring stretching) 1555, 1456(C=C stretching, aromatic ring), 1494(–C=N–, thiazole ring), 1454 (C–H bending, –CH2–), 1240(–C–S–C–,thiazole ring), 1510,1325 (–NO_2),^{1}H NMR (400 MHz, DMSO-d6): 4.48(s, 2H), 5.46(s, 2H), 7.22-7.28(m, 2H), 7.43-7.47(m, 1H), 7.51-7.68(m, 7H), 7.82-7.89(m, 2H), 8.20-8.24(m,2H), MS: m/z 502.10 (M+H)+; m.p.205-209 ºC, Yield: 70%.

(3, 4-dimethoxypyridin-2-yl) methyl)-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-phenylthiazol-2 yl) acetamide (4C)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1685(–C=O stretching amide), 3037 (C–H stretching, aromatic ring), 2978, 2941 (C–H stretching, –CH2–), 1716, 1541(C=C, thiazole ring stretching),1533, 1419(C=C, stretching, aromatic ring), 1491(–C=N–, thiazole ring),1446 (C–H bending, –CH2–),1249(–C–S–C–,thiazole ring), 1239,1072 (C–O, stretching),^{1}H NMR (400 MHz, DMSO-d6): 3.99(s,6H), 4.41(s, 2H), 5.4(s, 2H), 7.07-7.28(m,4H), 7.30-7.67 (m,5H), 7.80-7.92(m,2H), 8.03-8.099(m,1H), MS**:** m/z 518.13 $(M+H)^+$; m.p.180-184 ºC, Yield: 52%.

2-(1-benzyl-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-(3-bromophenyl) thiazol-2-yl) acetamide (4D)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1680(–C=O stretching amide), 3054 (C–H stretching, aromatic ring), 2976 ,2931 (C–H stretching, –CH2–),

1610, 1440 (C=C, thiazole ring stretching)1547, 1456(C=C stretching, aromatic ring), 1496(–C=N–, thiazole ring), 1458 (C–H bending, –CH2–),1243(–C–S–C–,thiazole ring), 1070 (C–Br),^{1}H NMR (400 MHz, DMSO-d6): 4.48(s, 2H), 5.46(s, 2H), 7.20-7.44(m,7H), 7.47-7.53(m,2H),7.58-7.63(m,4H),7.76-7.80(m,1H) ,MS: m/z 536.2 $(M+H)^+$; m.p.170-173 ºC Yield**:** 58%.

***N*-(4-(3-bromophenyl) thiazol-2-yl)-2-(1-(4-nitrobenzyl)-1*H*-benzo[*d*]imidazole-2-ylthioac –etamide (4E)**

This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm-1): 1660(–C=O stretching amide), 3045 (C–H stretching, aromatic ring), 2930 ,3051 (C–H stretching, $–CH_2–$), 1605, 1425 (C=C, thiazole ring stretching)1537, 1446(C=C stretching, aromatic ring), 1490(–C=N–, thiazole ring), 1438 (C–H bending, $–CH_2–$),1235(–C–S–C–,thiazole ring), 1060 (C–Br), 1507,1315 ($–NO_2$),^{1}H NMR (400 MHz, DMSO-d6): 4.48(s, 2H), 5.46(s, 2H), 7.23-7.28(m, 2H), 7.41-7.44(m, 1H), 7.48-7.51(m, 3H), 7.58-7.63(m, 5H), 7.75-7.77(m,1H), 8.22-8.26(m,2H), MS**:** m/z 581.1 $(M+H)^+$; m.p.175-178 ºC Yield: 75%.

***N*-(4-(3-bromophenyl) thiazol-2-yl)-2-(1-((3, 4-dimethoxypyridin-2-yl) methyl)-1*H*-benzo [d]imidazol-2-ylthio) acetamide (4F)**

This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm-1):1670(–C=O stretching amide), 3039 (C–H stretching, aromatic ring), 2980, 2947 (C–H stretching, $–CH_2–$), 1725, 1551(C=C, thiazole ring stretching),1541, 1425(C=C stretching, aromatic ring), 1498(–C=N–, thiazole ring),1449 (C–H bending, $–CH_2–$), 1249(–C–S–C–,thiazole ring), 1240,1072 (C–O, stretching),^{1}H NMR (400 MHz, DMSO-d6): 3.99(s,6H), 4.41(s, 2H), 5.4(s, 2H), 7.10-7.22(m,2H), 7.30-7.46 (m,2H), 7.50-7.72(m,6H), 8.05-8.11(m,1H), MS**:** m/z 597.03 $(M+H)^+$; m.p.135-139 ºC Yield: 55%.

2-(1-benzyl-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-(4-methoxyphenyl) thiazol-2-yl) acetami -de (4G)

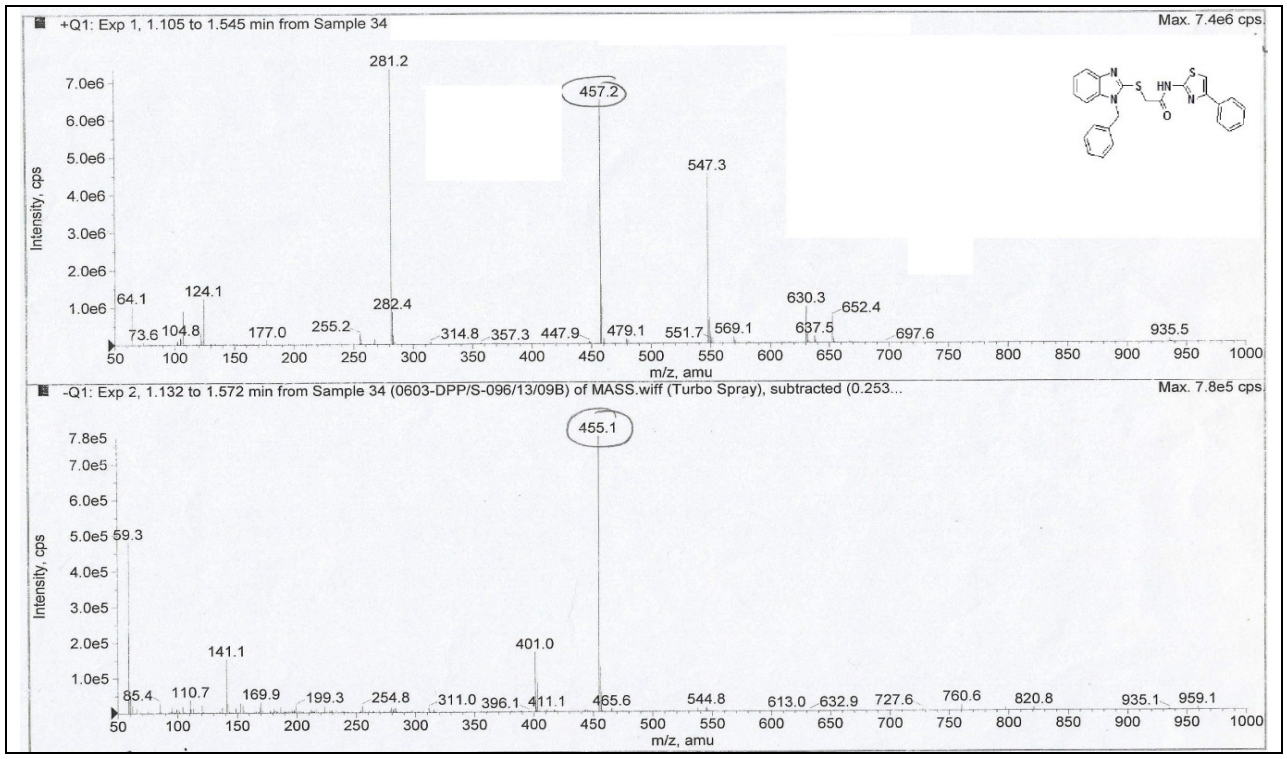
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm-1): 1664(–C=O stretching amide), 3053, 3036 (C–H stretching, aromatic ring), 2929 (C–H stretching, $–CH_2–$), 1619, 1420(C=C, thiazole ring stretching),1533, 1437(C=C, aromatic ring stretching), 1494(–C=N–, thiazole ring), 1452 (C–H bending, $–CH_2–$), 1251(–C–S–C–,thiazole ring), 1209,1033 (C–O, stretching),^{1}H NMR (400 MHz, DMSO-d6): 3.85(s,3H), 4.48(s, 2H), 5.46(s, 2H), 7.10-7.14(m,2H),7.24-7.40(m,7H),7.59-7.65(m,5H), MS**:** m/z 487.1 $(M+H)^+$; m.p.165-167 ºC Yield: 54%.

***N*-(4-(4-methoxyphenyl) thiazol-2-yl)-2-(1-(4-nitrobenzyl)-1*H*-benzo[*d*]imidazol-2-ylthio) Acetamide. (4H)**

This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm-1): 1668(–C=O stretching amide), 3034 (C–H stretching, aromatic ring), 2952, 3040 (C–H stretching, $–CH_2–$), 1609, 1435 (C=C, thiazole ring stretching),1540, 1417(C=C stretching, aromatic ring), 1494(–C=N–, thiazole ring), 1440 (C–H bending, $–CH_2–$),1240(–C–S–C–,thiazole ring), 1247,1068 (C–O, stretching), 1515,1305 ($–NO_2$) ,^{1}H NMR (400 MHz, DMSO-d6): 3.85(s,3H), 4.48(s, 2H), 5.46(s, 2H), 7.10-7.14(m,2H), 7.22-7.28(m,2H), 7.53-7.65(m, 7H),8.21-8.25(m,2H), MS: m/z 532.1 $(M+H)^+$; m.p.207-210ºC; Yield: 78%

2-(1-((3, 4-dimethoxypyridin-2-yl) methyl)-1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(4-(4-methoxyphenyl) thiazol-2-yl) acetamide (4I)

This compound was prepared and purified as per the above mentioned procedure. 1689(–C=O stretching amide), 3034 (C–H stretching, aromatic ring), 2981, 2951 (C–H stretching, $–CH_2–$), 1715, 1540(C=C, thiazole ring stretching),1537, 1429(C=C stretching, aromatic ring), 1490(–C=N–, thiazole ring),1449 (C–H bending, $–CH_2–$),1249(–C–S–C–,thiazole ring), 1238,1076 (C–O, stretching),^{1}H NMR (400 MHz, DMSO-d6): 3.85(s,9H), 4.41(s, 2H), 5.4(s, 2H), 7.08-7.11(m,2H),7.24-7.30(m,2H), 7.58-7.65 (m,6H), 8.27(d,1H), MS: m/z 548.13 $(M+H)^+$; M.P 130-133ºC, Yield: 58%.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547.3
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Max. 7.8e5 cps.
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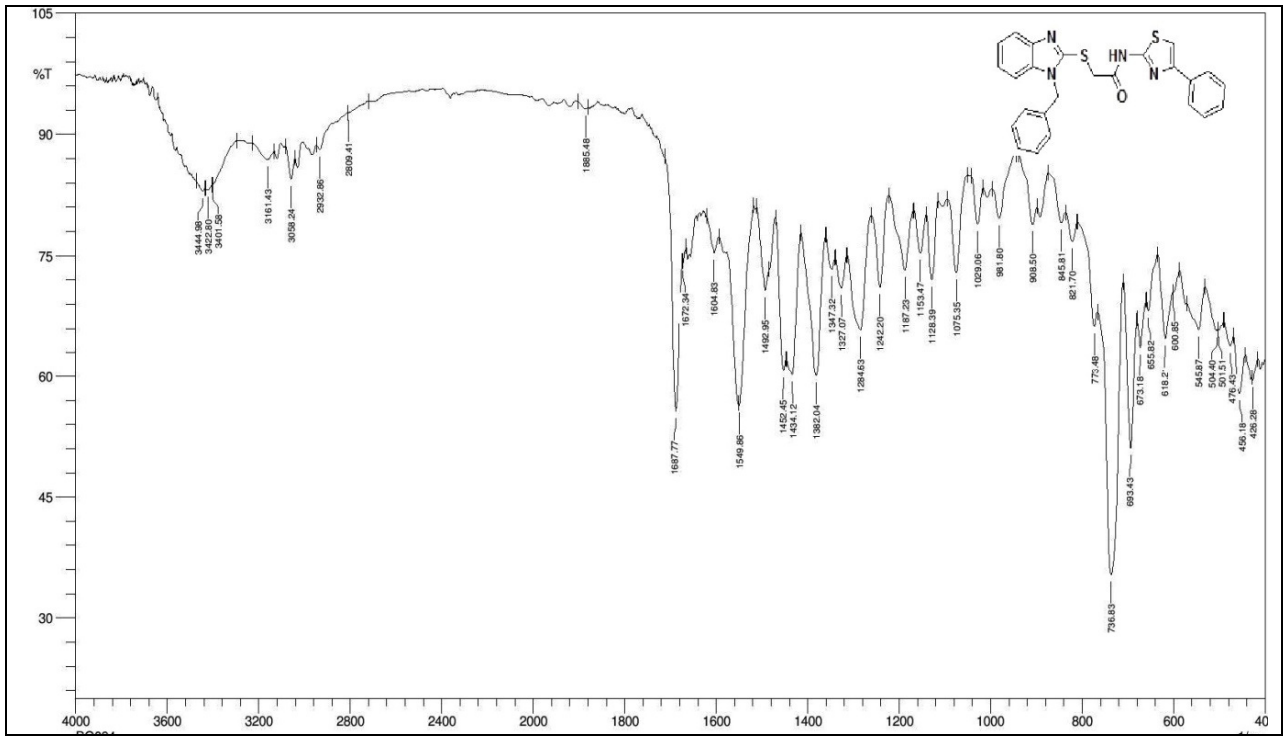
401.0
141.1
59.3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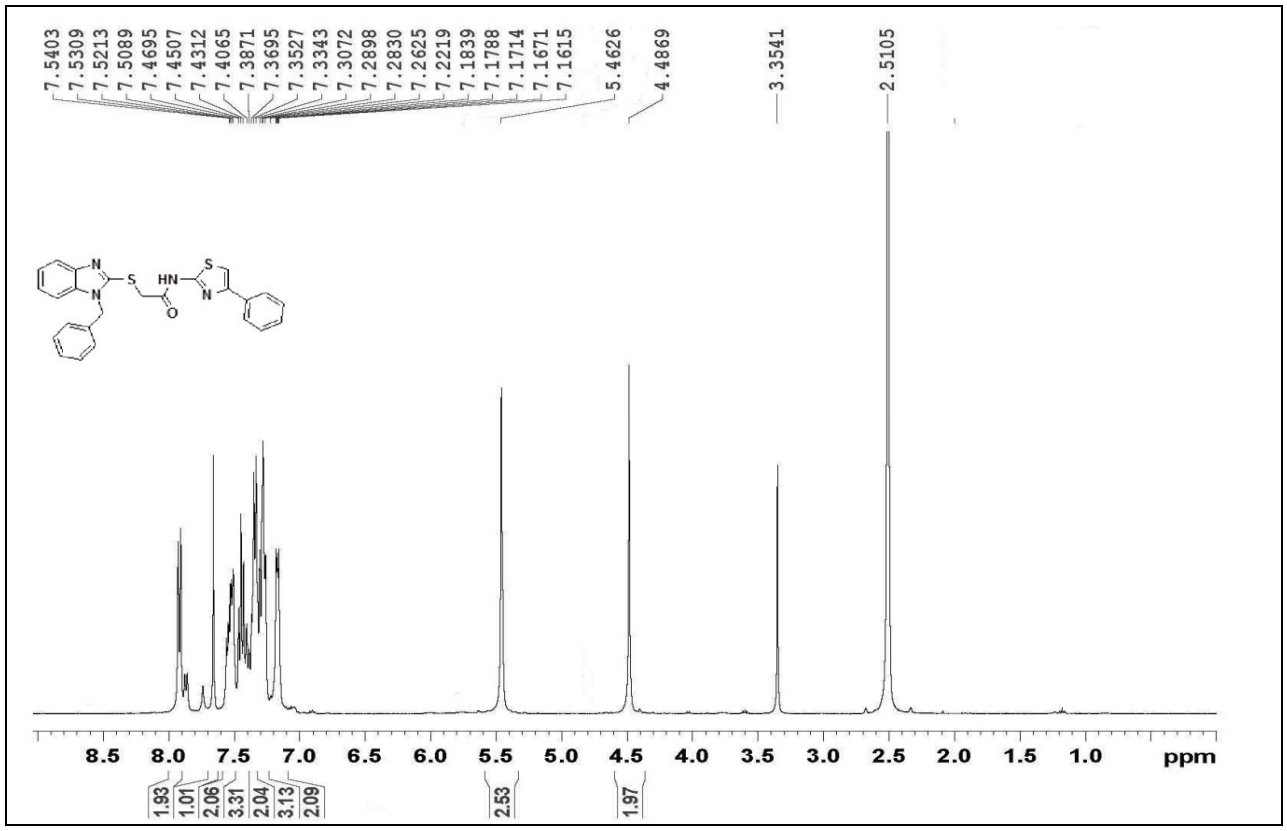


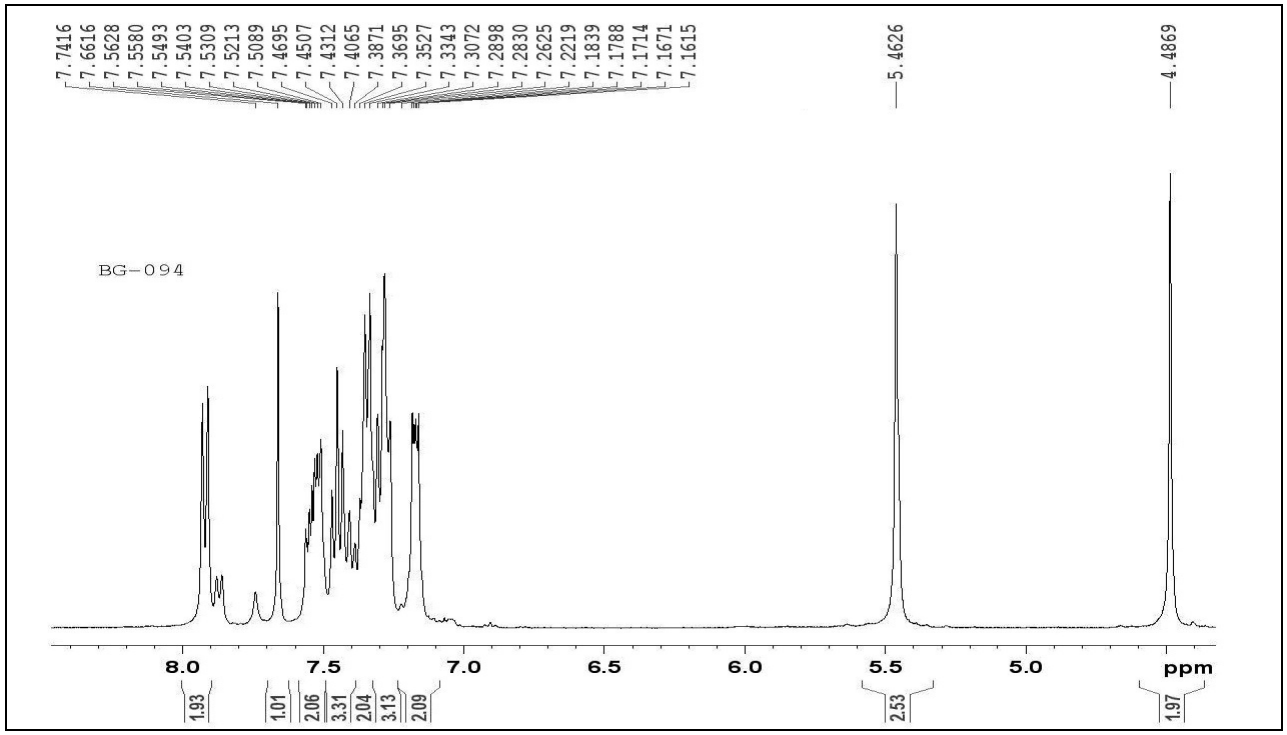
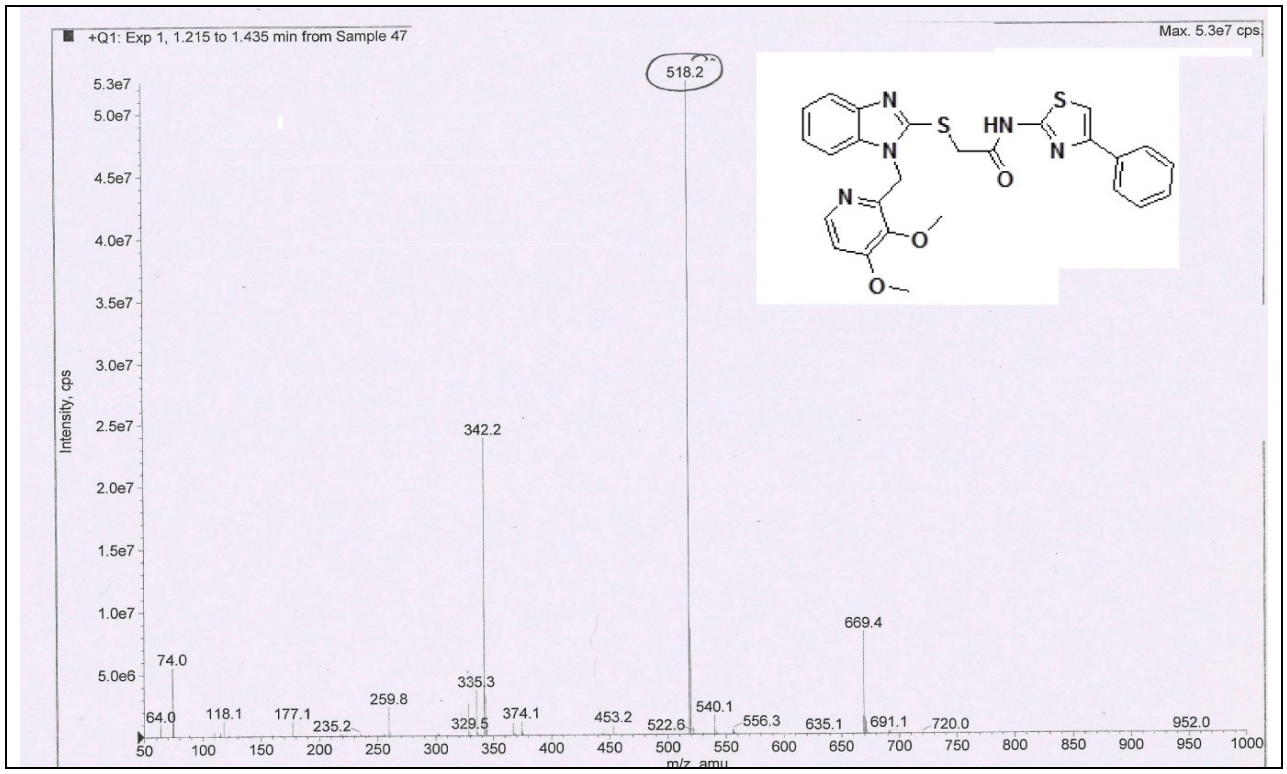


Fig.-4: Mass,IR and NMR spectrum of 4(A)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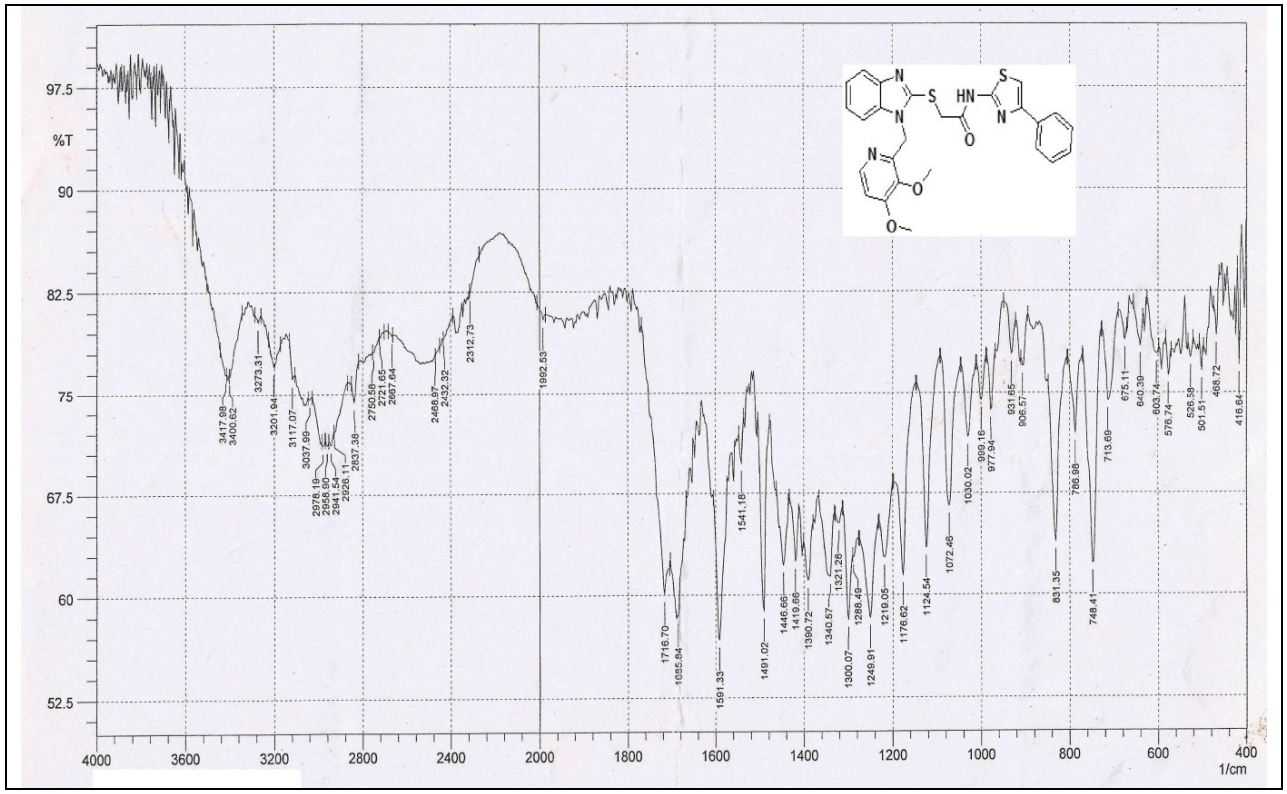
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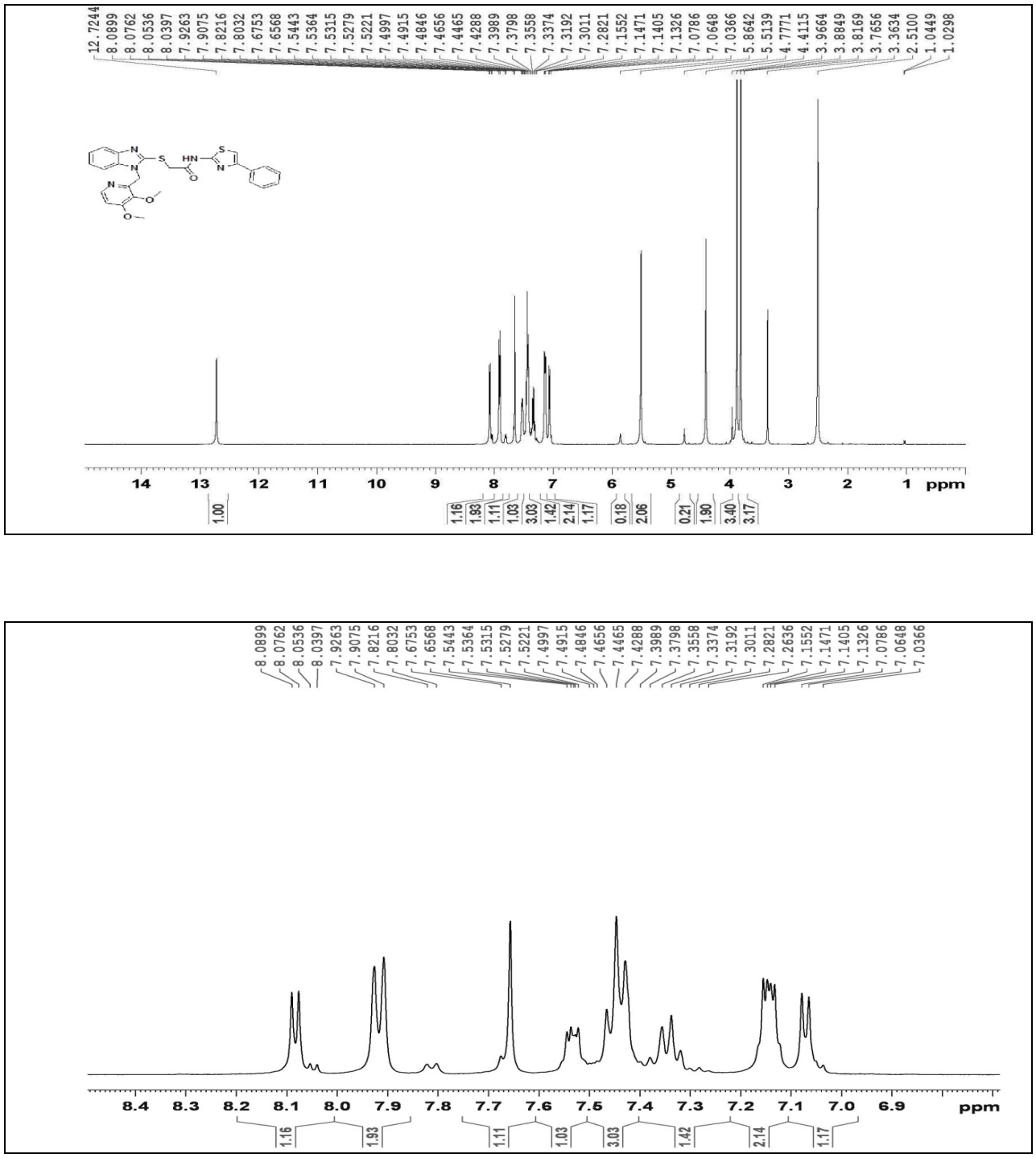


Fig.- 5: Mass,IR and NMR spectrum of 4(I)

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-phenyl-1, 3, 4-thiadiazol-2-yl) acetamide (7A)

This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}):1677(–C=O stretching amide), 3045, 3010 (C–H stretching, aromatic ring), 2920, 2887, (C–H stretching, $–CH_2–$), 1557, 1400(C=C, stretching, aromatic ring), 1443 (C–H bending, $–CH_2–$),^{1}H NMR (400 MHz, DMSO-

d6): 4.42(s, 2H), 7.13-7.19(m,2H), 7.46-7.61(m,5H),7.80-7.95(m,2H), MS: m/z 368.02 $(M+H)^+$; M.P 183-186°C, Yield: 58%.

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(4-chlorophenyl)-1, 3, 4-thiadiazol-2-yl) acetamide (7B)
This compound was prepared and purified as per the above mentioned procedure IR (KBr, cm^{-1}): 1679(–C=O stretching amide),3054, 3022 (C–H stretching, aromatic ring), 2916,2893 (C–H stretching, $–CH_2–$), 1559, 1400(C=C, stretching, aromatic ring) 1439 (C–H bending, $–CH_2–$), 743 (C–Cl),^{1}H NMR (400 MHz, DMSO-d6): 4.44(s,2H), 7.11-7.13(m,2H), 7.43-7.58 (m,4H),7.93-7.98(d,2H), MS: m/z 402.1 $(M+H)^+$; M.P 195-199+°C , Yield: 60%.

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-p-tolyl-1, 3, 4-thiadiazol-2-yl) acetamide (7C)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1674(–C=O stretching amide), 3044, 3012 (C–H stretching, aromatic ring), 2910,2891 (C–H stretching, $–CH_2–$), 1554, 1402(C=C, aromatic ring stretching), 1438 (C–H bending, $–CH_2–$), ^{1}H NMR (400 MHz, DMSO-d6): 2.24(s,3H), 4.44(s,2H), 7.14-7.27(m,4H), 7.45-7.59 (m,4H), MS: m/z 382.1 $(M+H)^+$; M.P 188-192°C, Yield: 65%.

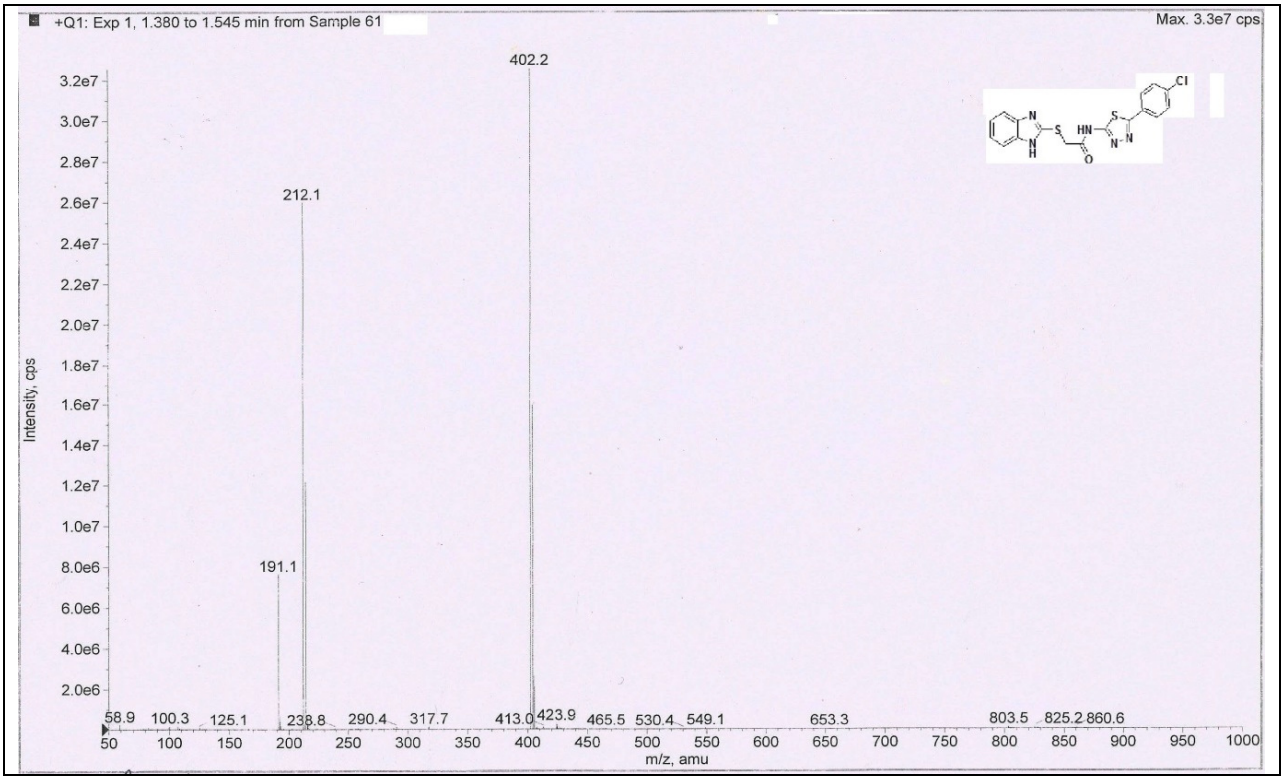
2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(4-methoxyphenyl)-1, 3, 4-thiadiazol-2-yl) ac -etamide (7D)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1680(–C=O stretching amide), 3038, 3018 (C–H stretching, aromatic ring), 2917,2889 (C–H stretching, $–CH_2–$), 1550, 1406(C=C stretching, aromatic ring), 1434 (C–H bending, $–CH_2–$), 1207,1036 (C–O, stretching),^{1}H NMR (400 MHz, DMSO-d6): 3.84(s,3H), 4.44(s,2H), 6.96-7.05(m,2H), 7.13-7.26(m,2H), 7.42-7.56 (m,4H), MS: m/z 398.2 $(M+H)^+$; M.P 193-195°C, Yield: 55%

2-(1*H*-benzo[*d*]imidazol-2-ylthio) - *N*-(5-benzyl-1, 3, 4-thiadiazol-2-yl) acetamide (7E)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1676(–C=O stretching amide), 3058, 3031 (C–H stretching, aromatic ring), 2967,2884 (C–H stretching, $–CH_2–$), 1490, 1590(C=C stretching, aromatic ring), 1437 (C–H bending, $–CH_2–$),^{1}H NMR (400 MHz, DMSO-d6): 4.34(s, H),4.6(s, 2H),7.24-7.42(m,7H), 7.60 (dd,2H),7.79(d,2H),7.89(d,2H),10.39(s,1H), MS: m/z 382.1 $(M+H)^+$; M.P 165-168°C Yield: 59%

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(4-methylbenzyl)-1, 3, 4-thiadiazol-2-yl) acetamide (7F)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1673(–C=O stretching amide), 3056, 3037 (C–H stretching, aromatic ring), 2964 (C–H stretching, $–CH_2–$), 1487, 1581(C=C stretching, aromatic ring), 1440 (C–H bending, $–CH_2–$),^{1}H NMR (400 MHz, DMSO-d6): 4.09(s, 2H),4.6(s, 2H),7.24-7.42(m,7H), 7.60 (dd,2H),7.79(d,2H),7.89(d,2H),10.39(s,1H), MS: m/z 396.3 $(M+H)^+$. M.P 185-187°C Yield: 53%.

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(4-fluorobenzyl)-1, 3, 4-thiadiazol-2-yl) acetamide (7G)
This compound was prepared and purified as per the above mentioned procedure., IR(KBr, cm^{-1}): 1668(–C=O stretching amide), 3054, 3027 (C–H stretching, aromatic ring), 2970 (C–H stretching, $–CH_2–$), 1491, 1570(C=C stretching, aromatic ring), 1442 (C–H bending, $–CH_2–$), 1130(C–F),**^{1}H NMR (400 MHz, DMSO-d6):** 4.09(s, 2H),4.6(s, 2H),7.24-7.42(m,7H), 7.60(dd,2H), 7.79(d,2H), 7.89(d,2H), 10.39(s,1H),MS: m/z 400.1 $(M+H)^+$. M.P 222-226°C, Yield: 55%.

2-(1*H*-benzo[*d*]imidazol-2-ylthio)-*N*-(5-(4-chlorobenzyl)-1, 3, 4-thiadiazol-2-yl) acetamide (7H)
This compound was prepared and purified as per the above mentioned procedure. IR (KBr, cm^{-1}): 1673(–C=O stretching amide), 3050, 3023 (C–H stretching, aromatic ring), 2973 (C–H stretching, $–CH_2–$), 1483, 1566(C=C stretching, aromatic ring), 1443 (C–H bending, $–CH_2–$), 740(C–Cl), ^{1}H NMR (400 MHz, DMSO-d6): 4.09(s, 2H),4.6(s, 2H),7.24-7.42(m,7H), 7.60 (dd,2H),7.79(d,2H),7.89(d,2H),10.39(s,1H)MS: m/z 416.3 $(M+H)^+$. M.P 210-214°C, Yield: 62%.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Intensity, cps
m/z, amu
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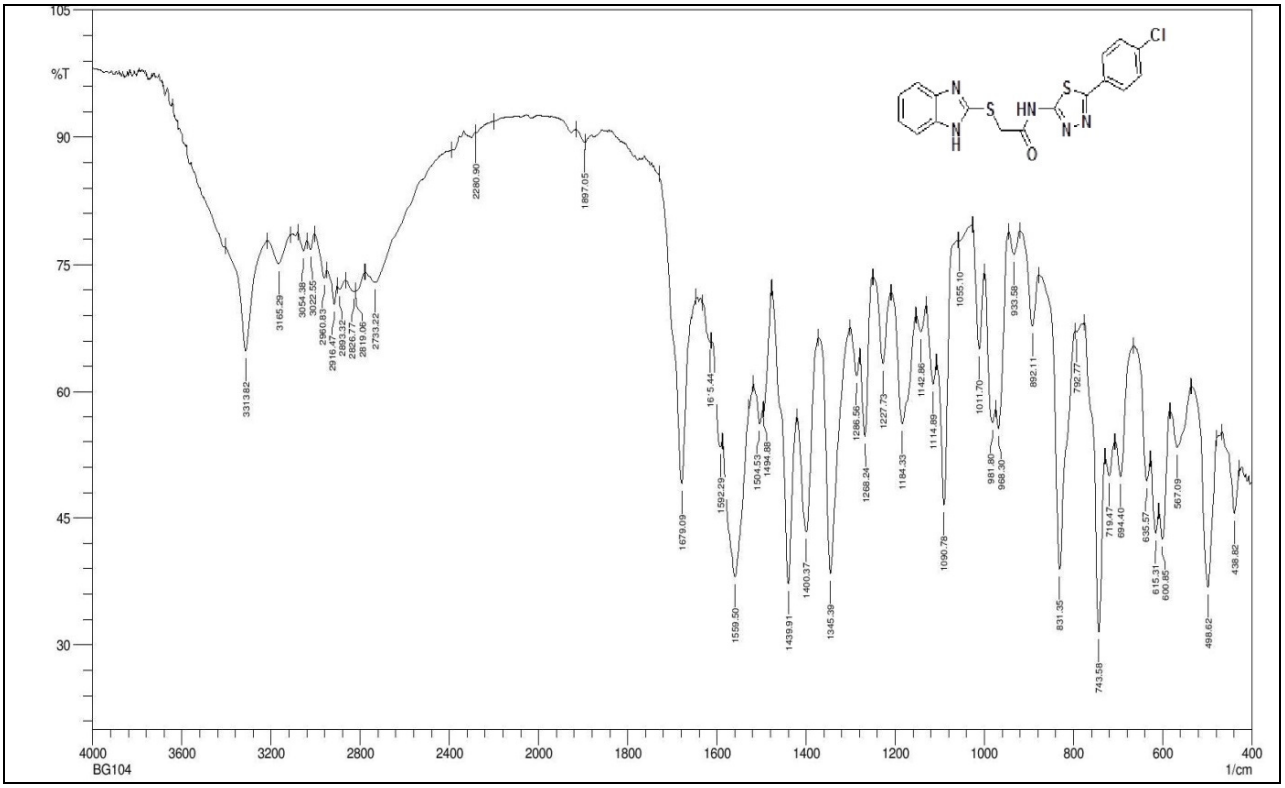
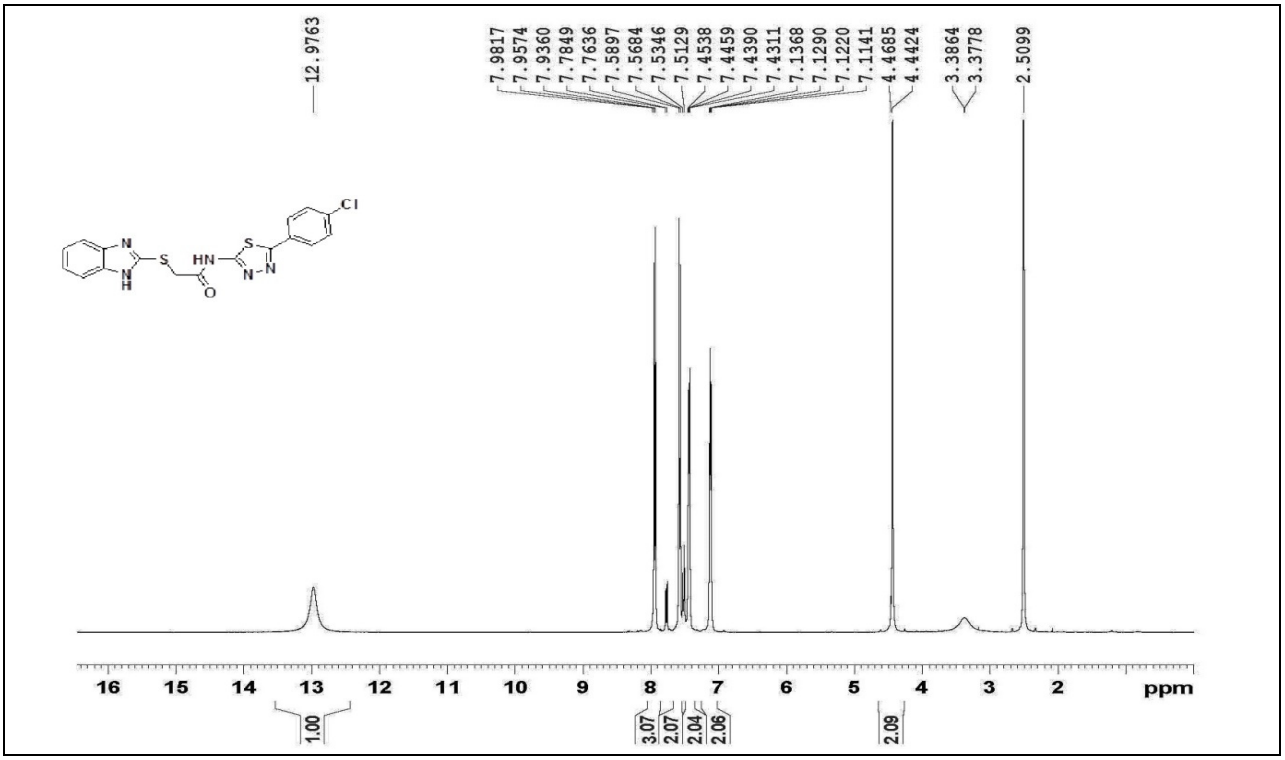
212.1
191.1


%T
1/cm
BG104



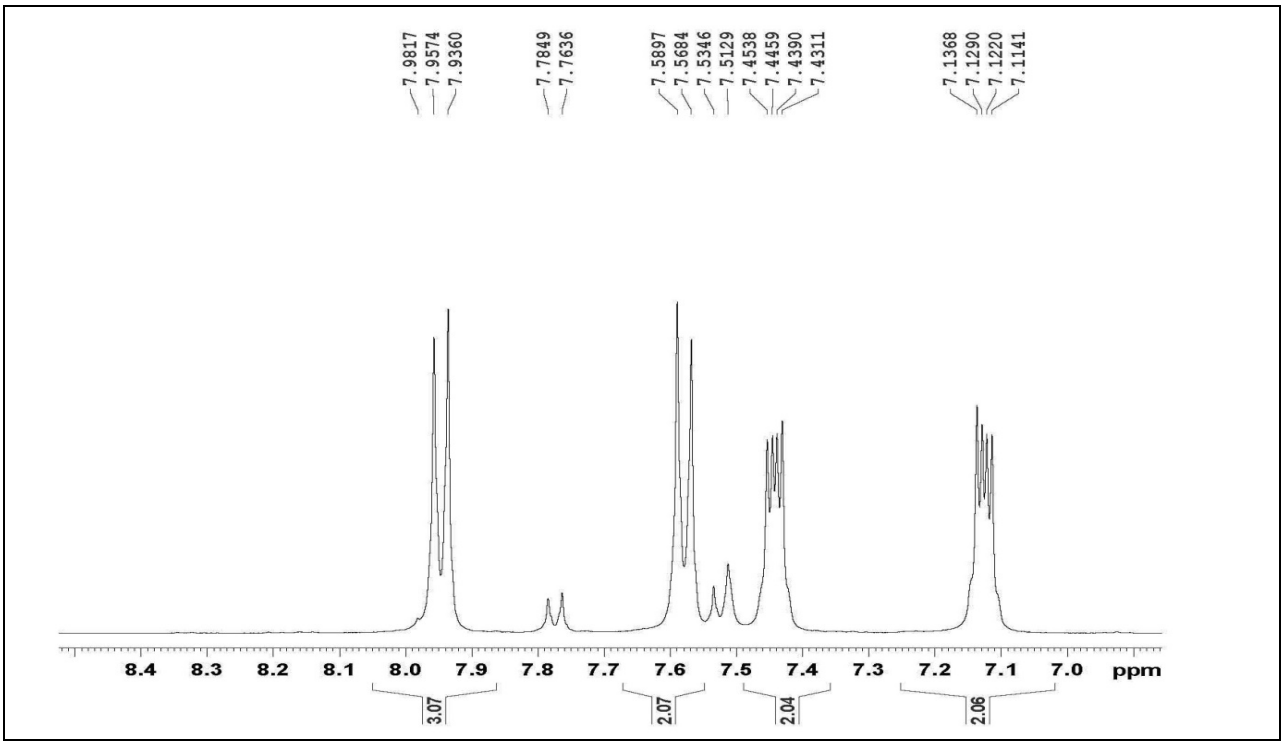
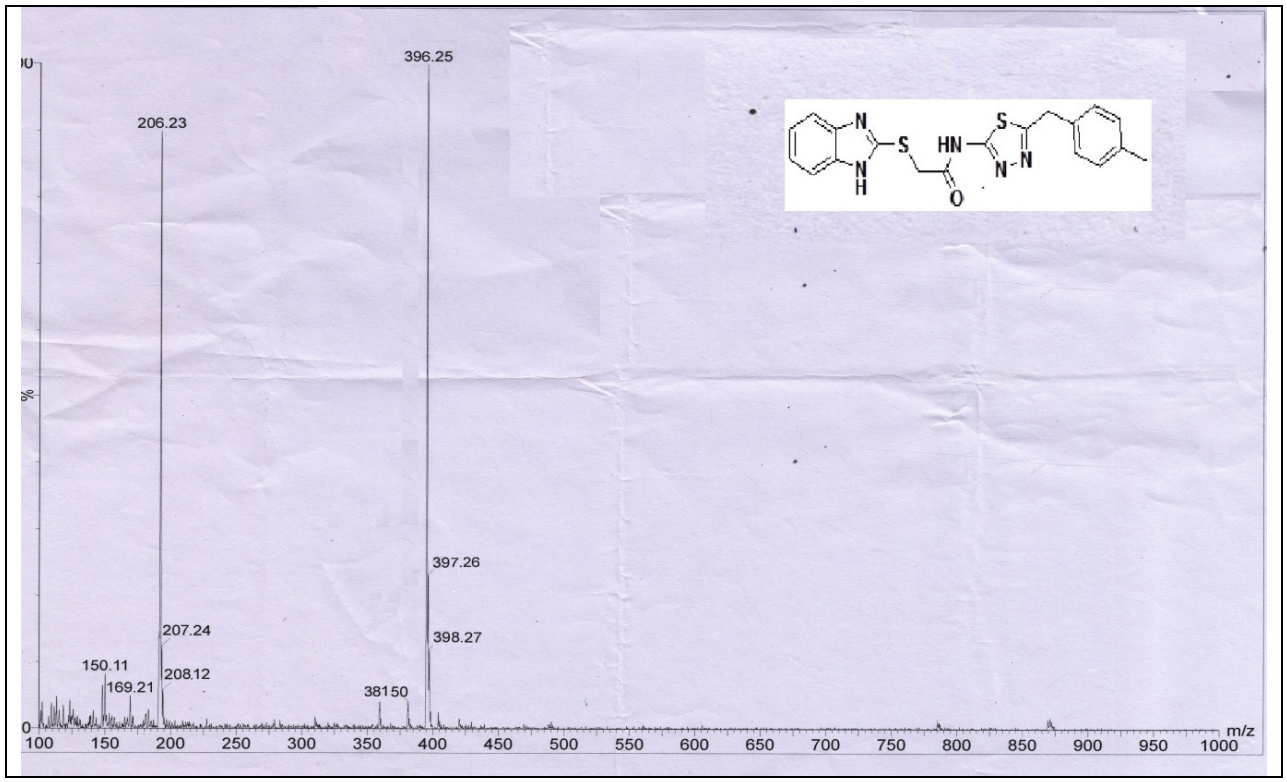
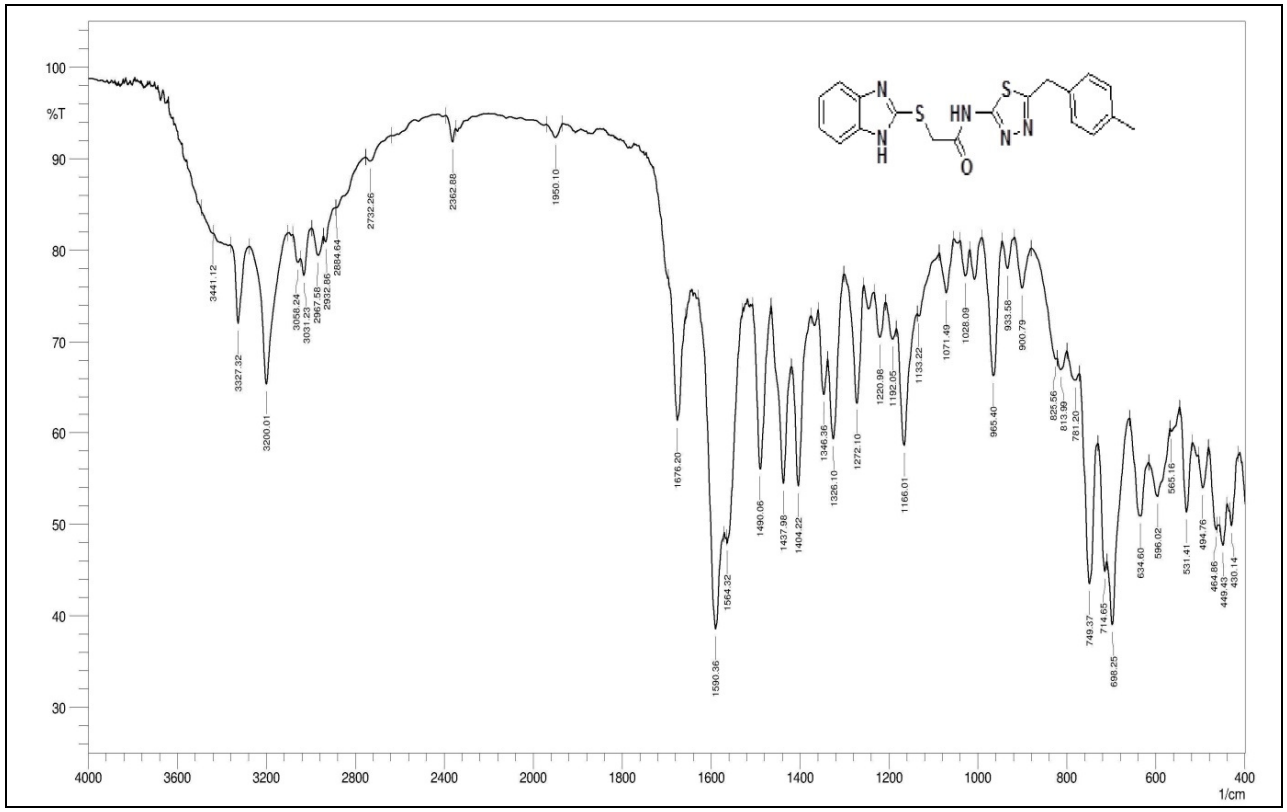


Fig.- 6: Mass,IR and NMR spectrum of 7(B)


396.25
206.23
397.26
207.24
398.27
150.11
208.12
169.21
381.50
%
m/z
100 150 200 250 300 350 400 450 500 550 600 650 700 750 800 850 900 950 1000


%T
100 90 80 70 60 50 40 30
3441.12
3327.32
3200.01
3058.24
3031.23
2967.58
2932.86
2884.64
2732.26
2362.88
1950.10
1676.20
1590.36
1564.32
1490.06
1437.98
1404.22
1346.36
1326.10
1272.10
1220.98
1192.05
1166.01
1133.22
1071.49
1028.09
965.40
933.58
900.79
825.56
813.99
781.20
749.37
714.65
698.25
634.60
596.02
565.16
531.41
494.76
464.86
449.43
430.14
4000 3600 3200 2800 2400 2000 1800 1600 1400 1200 1000 800 600 400
1/cm

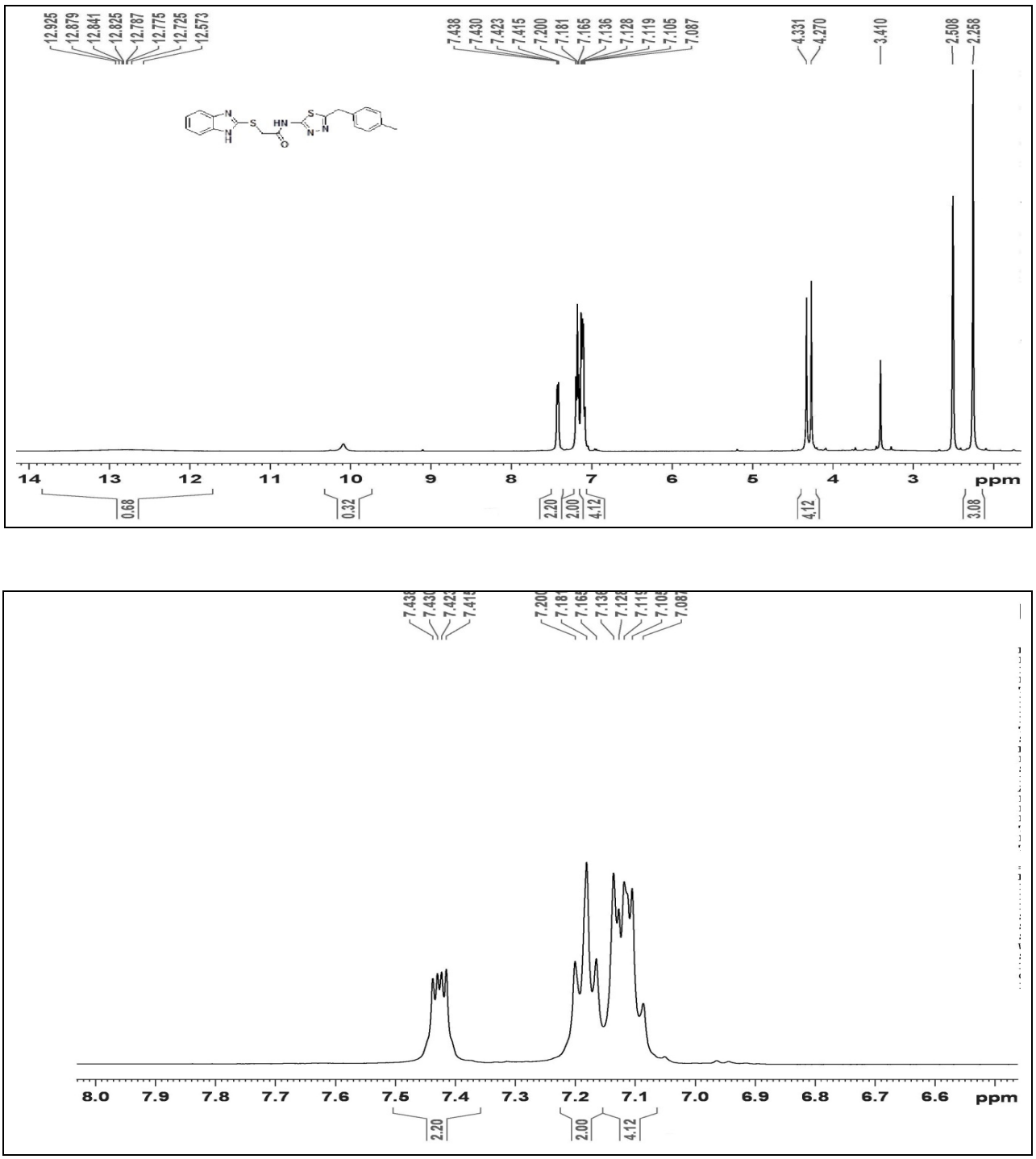
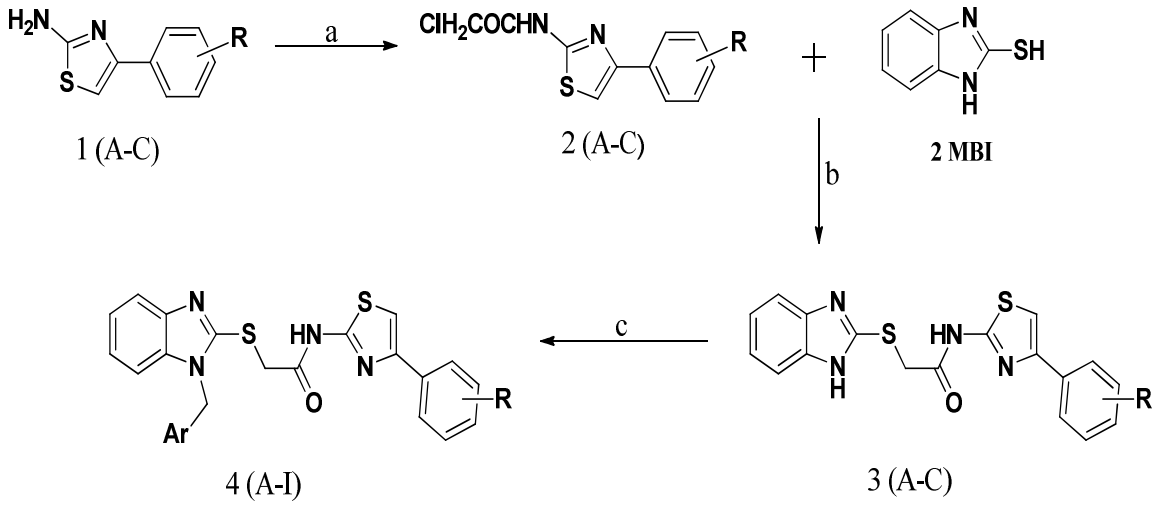


Fig.- 7: Mass,IR and NMR spectrum of 7(F)

Antimicrobial activity

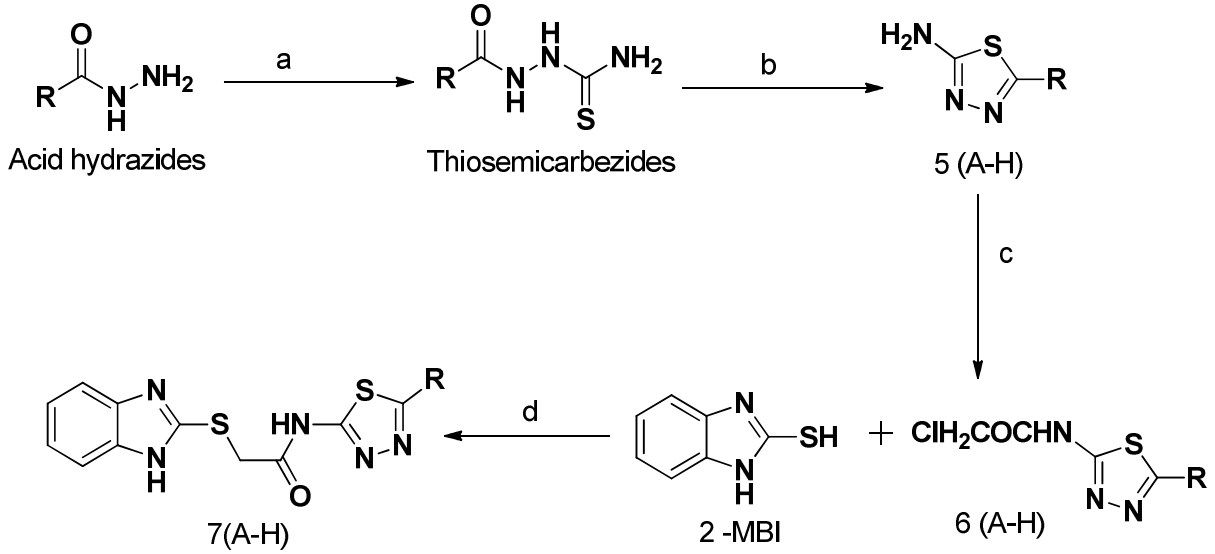
All the synthesized compounds 4(A-I) and 7(A-H) were tested in vitro for their antibacterial and antifungal activity. All the glass apparatus used were sterilized before use. The broth dilution technique was used to determine the minimum inhibitory concentration (MIC) of the synthesized compounds. Bacterial strain of *Staphylococcus aureus* (MTCC737) ,*Bacillus megaterium* (MTCC2444) as a gram

positive, *Escherichia coli* (MTCC1687) *Pseudomonas aeruginosa* (MTCC3541) as a gram negative used in a present study. Fungal strains of *Aspergillus niger* (MTCC282) and *Aspergillus flavus* (MTCC418) were taken. DMSO was used as the solvent for the compounds. A blank test was carried out to check the antimicrobial activity of DMSO. Ampicillin, streptomycin were used as the standard drugs for antibacterial activity and nystatin was used as the standard drug for antifungal activity. Activity results are depicted in Tables- 1 and 2.



Where, R = -H, Br, -OMe, Ar = -C_6H_5, -4-$NO_2C_6H_5$, -3, 4-di $OMeC_5H_2N$;
(a) $ClCH_2COCl$, triethylamine THF, 60°C (b) Piperidine, CH_3CN, 60°C (c) K_2CO_3, CH_3CN, reflux

Scheme-1



Where, R= -H, -Cl,-Me, -OMe, -$CH_2C_6H_5$, -$CH_2C_6H_4F$, -$CH_2C_6H_4Cl$, -$CH_2C_6H_4CH_3$
(a) KSCN, Con.HCl, Water (b) Con.H_2SO_4, NH_4OH, (c) $ClCH_2COCl$, triethylamine THF (d) Piperidine, CH_3CN, 60°C

Scheme-2

Table-1: Antimicrobial activity (Minimum inhibition concentration, µg/ml) 4 A-I

Compounds	*Bacillus megaterium*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Aspergillus flavus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
4A	1000	500	1000	250	1000	1000
4B	500	500	500	500	500	500
4C	250	500	500	500	500	1000
4D	250	500	500	500	500	1000
4E	1000	500	125	500	500	250
4F	250	250	250	250	250	500
4G	500	500	500	500	250	500
4H	500	1000	1000	1000	250	500
4I	500	500	500	500	500	500

Table-2: Antimicrobial activity (Minimum inhibition concentration, µg/ml) 7 A-H

Compounds	*Bacillus megaterium*	*Staphylococcus aureus*	*Escherichia coli*	*Pseudomonas aeruginosa*	*Aspergillus niger*	*Aspergillus flavus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
7A	250	500	500	250	250	500
7B	500	500	500	500	500	500
7C	500	500	500	500	500	500
7D	500	500	1000	500	500	500
7E	500	500	500	250	250	250
7F	500	500	1000	500	500	500
7G	1000	1000	1000	500	500	1000
7H	125	500	500	500	500	500

RESULTS AND DISCUSSION

In the present work, first three different 2-amino-4-substituted thiazoles **1(A-C)** were synthesized using known methodology, which were then chloroacetylated to obtain chloroacetylated thiazoles **2(A-C).**Reaction of these chloroacetylated thiazoles **2(A-C)** with 2-mercapto benzimidazole **(2-MBI)** to produced 2-(1H-benzo[d]imidazol-2-ylthio)-N-(4-substituted phenylthiazol-2-yl)acetamide **3(A-C)**. Finally A series of N-(4-(substituted phenyl) thiazol-2-yl)-2-(1-(substituted benzyl or pyridinyl methyl)-1H-benzo[d]imidazol-2-ylthio) acetamide **4 (A-I)** has been synthesized from **3(A-C)** via substitution reaction at N-1 position of Benzimidazole nucleus present in **3(A-C)** with various benzyl and pyridinylmethyl halides.

The present work also described the synthesis of 2-amino-5-substituted phenyl, benzyl1, 3, 4-thiadiazoles **5(A-H)** from their respective thiocarbezides and chloroacetylation of these thiadiazoles to chloroacetylated 2-amino-5-substituted phenyl, benzyl or phenoxy methyl 1, 3, 4-thiadiazoles **6(A-H).**

Finally synthesis of A series of 2-(1H-benzo[d]imidazol-2-ylthio)-N-(5-(substituted phenyl , benzyl)-1,3,4-thiadiazol-2-yl)acetamide **7(A-H)** from **6(A-H)** and 2-mercaptobenzimidazole **(2-MBI).**

The spectral data of the title compounds **4(A-I)** shown IR band at 1660-1689 cm^{-1},which confirmed the presence of $–CONH_2$ group and bands at 1490-1498 cm^{-1} and 1235-1251 cm^{-1} confirmed the presence of –C=N– and –C–S–C– and thereby confirmed the presence of thiazol nucleus in the title compounds of 1, 3, 4-oxadiazol-2-yl-ring. In ^1H NMR two singlet between 4.0-4.46 ppm confirmed the presence of $–S-CH_2–$ & $–N-CH_2–$respectively. The formation of the title compounds further confirmed by the mass spectral data.

Whereas the spectral data of the title compounds 7(A-H) shown indicative IR band for $–CONH_2$ group at 1668-1679 cm^{-1} and bands at 1062 cm^{-1} and 667 cm^{-1} attributed to the presence of –N–N– and –C–S–C– confirmed the presence of thiadiazole nucleus. In ^1H NMR one singlet between 4.42-4.6 ppm confirmed the presence of $–S-CH_2–$. Finally structure elucidation was completed by mass spectral analysis.

The MIC values (µg/ML) of 4 A-I and 7 A-H along with standard drugs against selected microbes are presented in Table 1 and 2. Microbial activity data showed that compound 4C and 4D showed mild antibacterial activity (250µg/ML) against Bacillus megaterium as compared to standard drug Ampicilin (100µg/ML). Compound 4E exhibited mild antibacterial (125µg/ML) and antifungal activity (250µg/ML) against Escherichia coli and Aspergillus flavus as compared to standard drug Streptomycin (50µg/ML) and Nystatin (100µg/ML).Compound 4F showed both mild antibacterial and antifungal activity (250µg/ML) against Bacillus megaterium, Staphylococcus aureus and Aspergillus niger. On the other hand Compound 4G and 4H showed mild antifungal activity against both Aspergillus niger and Aspergillus flavus as compared to standard drug Nystatin (100µg/ML). Remaining compounds of this series were not active towards bacteria and fungi.

On the other hand Microbial activity data also showed that compound 7A exhibited mild antibacterial antifungal activity (250µg/ML) against Bacillus megaterium and Aspergillus niger as compared to standard drug Ampicilin (100µg/ML) and Nystatin(100 µg/ML). Compound 7E exhibited mild antifungal activity (250µg/ML) against Aspergillus flavus and Aspergillus niger as compared to standard drug Nystatin (100µg/ML). Compound 7H showed moderate antibacterial activity (125µg/ML) against Bacillus megaterium only. Remaining compounds of this series were not active towards bacteria and fungi.

CONCLUSION

Due to easy preparation and ability to undergo countless modification by numerous reaction modes in various position and biological activities, thiazole nucleus has gained much attention of many researchers. Hence the synthesis of a series of N-(4-(substituted phenyl) thiazol-2-yl)-2-(1-(substituted benzyl or pyridinyl methyl)-1H-benzo[d]imidazol-2-ylthio) acetamide **(4A-I)** was the part of the quest to explore many more modifications on Thiazole moiety. When these synthesized compounds were subjected for microbial activities, some of them showed mild antibacterial and antifungal activities.

Scientist from all over world are doing extensive research work, in order to discover a more effective and safer antibacterial agent. Literature survey revealed that various group of scientists have also drawn their attention towards thiadiazoles nucleus as a result of usefulness of this moiety in medicinal chemistry. Hence it was decided to prepare a series of A series of 2-(1H-benzo[d]imidazol-2-ylthio)-N-(5-(substituted phenyl, benzyl)-1, 3, 4-thiadiazol-2-yl) acetamide **(7A-H).** When these compounds were subjected for their microbial activities, it was noticed that they were not active against microbes as we expected.

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