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Microwave-Assisted Synthesis and Molecular Docking Studies of New Azole Derivatives as Potential Anticancer Activity

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In this work, the synthesis and characterization of novel azole derivatives by microwave assisted method were carried out. The azole nuclei condensed with imidazole, indole-2-one and sulphonyl moieties in the novel azole hybrids-MNSR (**3a-d**, **4a-h**) to produce effective anticancer agents. All structures were confirmed by spectral analysis and yield was found to be in the range from 75-90%. Their anticancer activity was determined by MTT based assay with MCF-7 cell lines. Anthelmintic activity was performed by Indian earthworms and molecular docking studies were performed with EGFR enzyme by Schrödinger suite. Compound MNSR-**3b** at 12.36 ± 0.32 µg/mL, MNSR-**4d** at 19.12 ± 0.23 µg/mL showed to be more potent anticancer activity, whereas compound MNSR-**3c**, MNSR-**4a**, **4d**, **4h** showed excellent anthelmintic activity when comparing with the standard albendazole. Compounds MNSR-**3b**, MNSR-**4d** showed good binding affinity to EGFR with respective binding energies -8.833 and -8.483 kcal/mol.

Keywords: Isatin, 4-Methyl imidazole, Anticancer, Anthelmintic, MCF 7 cell line, EGFR enzyme.

INTRODUCTION

Azole derivatives is a principal structural concept establish in numerous of natural and therapeutically active molecules. Azole ring with different heterocyclic rings itself is a needful pharmacophore in present-days and has been used as privileged platform to synthesize particular drugs of engrossment in pharmaceutical industry [1,2]. The applications of medicinal chemistry is devoted to the discovery and development of new compounds for treating diseases [3]. Azole and its derivatives have always been a unique heterocyclic moiety for the medicinal chemist; thus, an exhaustive research has been done on the azole that resulted in the discovery and introduction of several drugs in market [4].

Schiff bases have a comprehensive of biological properties [5-7] along with antibacterial, antifungal, analgesic, anticancer, antiviral, anthelmintic, anti-inflammatory, antioxidant, cardiovascular, anti-tubercular and also used as a local anesthetic drugs. As well as Schiff bases have extensive applications in organometallic chemistry, catalyst, removal of dyes, foodstuff industrial, diagnostic chemistry, an agricultural chemicals such as an insecticide and herbicidal drugs [8-10]. Microwave technique offers significant benefits like reduced reaction times, increased product yields, the ability to transport product isolation to remote locations, precise temperature control and improved product purity [11,12].

The current work aim to design, microwave assisted synthesis, characterization and evaluate the therapeutic effects of novel azole derivatives. In continuation of our interest with regard to development of useful green synthetic methodologies, herein, we report the successful use of microwave irradiation for the selective Schiff bases of various substituted isatin, substituted benzaldehydes with amines.

EXPERIMENTAL

All the chemicals and solvents were purchased from different commercial suppliers and used as such. Melting was performed by Thieles method using liquid paraffin as solvent and after without any pre-correction, the melting point were determined. Thin-layer chromatography was utilized to check their progress during the synthesis. The TLC plate, aluminum-backed silica

gel 60 F_{254} sheet and mobile phase (*n*-hexane, ethyl acetate, 8:2) were applied. In column chromatography, 100-200 mesh silica gel was used and performed. For visualization, UV absorption or iodine vapours was used on TLC plates. The IR spectrum were obtained from a Thermo-Nicolet Nexus 670 spectrophotometer using KBr disc. ^{1}H NMR was recorded on a Bruker/Top-Spin 3.2 spectrometer at 500 MHz, in DMSO solvent. Mass spectrometry was performed using a Shimadzu LCMS-8030 with electron spray ionization.

Synthesis of 4-(4-methyl-1*H*-imidazole-1-sulfonyl)-aniline (I): The open vessel containing Teflon coated stir jar was taken and added a solution of 4-amino benzene sulphonyl chloride (1.96 g, 0.1 M) in 10 mL ethanol and 4-methyl imidazole (0.82 g, 0.1 M). Then, the microwave irradiation reaction composition at the power of 160 watts for 3 min, was performed. The reaction mixture was allowed to stand overnight in refrigerator, the precipitated solid was filtered and recrystallized from ethanol to obtain pure compound [13].

Synthesis of 5-methyl-3-{[4-(4-methyl-1*H*-imidazole-1-sulfonyl)phenyl]imino}-1,3-dihydro-2*H*-indol-2-one (3a-d): To equimolar quantity of 4-(4-methyl-*1H*-imidazole-1-sulfonyl)-aniline (I) (0.28 g, 0.01 mol), 5-substituted isatin (0.14 g, 0.01 mol) in 20 mL of ethanol and 5 mL of glacial acetic acid were taken in an open vessel containing a Teflon coated stir jar. The reaction mixture was then heated under microwave irradiation at 160 W for 2-3 min. The progress of the reaction was monitored by TLC (*n*-hexane:ethyl acetate, 8:2). Then the reaction mixture was cooled to room temperature after 3 min and the solvent was distilled. The obtained product was recrystallized using ethanol [14].

(*E*)-N-{4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-imino}-1,3-dihydro-2*H*-indole-2-one (MNSR-III-3a): Yield: 81%, m.p.: 161-163 ºC; m.f./m.w.: $C_{18}H_{14}N_4O_3S$/366.08. IR (KBr, ν_{max}, cm^{-1}): 3016 (-CH *str.* in aromatic-H); 2991, 2839, 2790 (-CH *str.* in aliphatic-H); 1706 (-C=O *str.* in indole-CO); 1602 (-C=N *str.* in imine-C=N); 1494 (-C=CH *str.* in aromatic-H); 1047 (-C-N *str.*); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.703 (1H, s imine proton); 8.01-8.02 (2H, d aromatic proton); 7.98-7.93 (2H, d proton in aromatic); 7.86-8.86 (2H, d proton in aromatic-H); 7.79-7.73 (2H, t proton in aromatic); 7.60-7.50 (3H, t proton in aromatic-H); 4.68 (2H, s proton in -N-CH_2 proton); 2.20 (3H, s protons aromatic-CH_3 proton). Mass (LC-MS): *m/z* 366.08 (M); 367.21 (M+1, 100%).

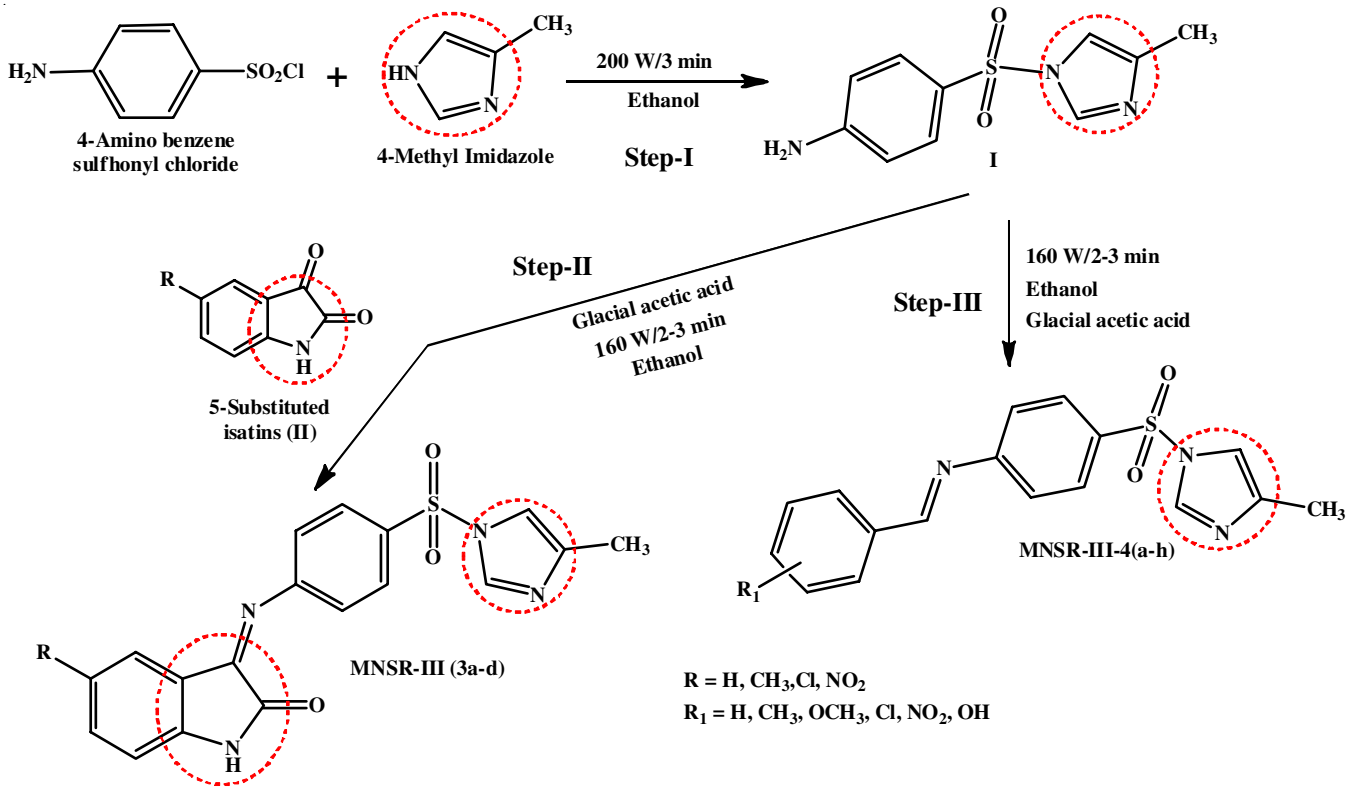
(3*Z*)-5-Methyl-3-{[4-(4-methyl-1*H*-imidazole-1-sulfonyl)-phenyl]imino}-1,3-dihydro-2*H*-indole-2-one (MNSR-3b): Yield: 85%, m.p.: 147-149 ºC; m.f./m.w.: $C_{19}H_{16}N_4O_3S$/380.09. IR (KBr, ν_{max}, cm^{-1}): 1217 (-C=N *str.* in imine); 1495 (-C=CH *str.* in Ar-H); 1061 (-C-N *str.*); 2980, 2832, 2739 (CH *str.* in aliphatic); 1712 (-CO *str.* in indole).^{1}H NMR (400 MHz, DMSO) δ ppm: 4.59 (2H, s proton in -N-CH_2 proton); 2.30 (3H, s in aromatic-methyl on imidazole ring); 8.19 (s, 1H, Ar-H); 7.89-7.88 (d, 2H, Ar-H); 7.65-7.64 (d, 2H, Ar-H); 7.61 (d, 2H, Ar-H); 7.56-7.55 (t, 3H, Ar-H); 1.98 (s, 2H, Ar-CH_3 proton); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 173.43, 162.05, 156.04, 149.45, 143.7, 142.67, 138.90, 136.43, 133.02, 130.23, 129.21, 127.82, 125.03, 123.43, 120.03, 118.25, 116.02, 28.82. Mass (LC-MS): *m/z* 380.09 (M); 381.21 (M+1, 100%).

(3*Z*)-3-{[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl] imino}-5-nitro-1,3-dihydro-2*H*-indol-2-one (MNSR-III-3c): Yield: 79%, m.p.: 177-179 ºC; m.f./m.w.: $C_{18}H_{13}N_5O_5S$/411.06. IR (KBr, ν_{max}, cm^{-1}): 1221 (C=N *str.*); 1468 (-C=CH *str.* in Ar-H); 1098 (-C-N *str.*); 2956, 2898, 2778 (-CH *str.* in aliphatic); 1709 (-CO *str.* in indole);^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.65 (s, 1H, -N=CH proton); 8.21 (s, 1H, A-H); 7.97-7.80 (d, 2H, Ar-H); 7.60-7.50 (d, 2H, Ar-H); 7.39-7.30 (d, 2H, Ar-H); 7.19-7.04 (t, 2H, Ar-H); 4.60 (s, 2H, -N-CH_2 proton); 2.30 (s, 3H, -CH_3 on imidazole ring); 1.89 (s, 3H, CH_3 proton on aromatic ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 170.09, 162.98, 162.04, 154.89, 152.09, 146.03, 143.56, 140.23, 138.92, 136.05, 133.23, 130.21, 127.04, 125.56, 123.22, 120.98, 117.43, 115.23, 110.32, 28.56, 24.43. Mass (LC-MS): *m/z* 411.13 (M); 412.32 (M+1, 100%).

(3*Z*)-5-Chloro-3-{[4-(4-methyl-1*H*-imidazole-1-sulfonyl)phenyl]imino}-1,3-dihydro-2*H*-indol-2-one (MNSR-III-3d): Yield: 81%, m.p.: 161-163 ºC; m.f./m.w.: $C_{18}H_{14}N_4O_3S$/366.08. IR (KBr, ν_{max}, cm^{-1}): 3084 (-CH *str.* in Ar-H); 2930,2930, 2873, 2724 (-CH *str.* in aliphatic); 1715 (-CO *str.* in indole-CO); 1680 (-C=N *str.*); 1476 (-C=CH *str.* in aromatic-H); 1086 (-C-N *str.*); 798 (-CCl *str.*, Ar-Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 7.7943-7.7863 (2H, d protons aromatic-H); 7.7462-7.7342 (2H, d protons in aromatic-H); 7.698-7.6903 (2H, d protons in aromatic); 7.6273-7.6032 (3H, t proton in aromatic-H); 4.5543 (2H, s protons in -N-H_2 proton); 2.2032 (3H, s protons in imidazole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 173.23, 164.23, 158.43, 148.03, 143.78, 138.33, 137.21, 135.21, 133.04, 127.03, 125.43, 124.34, 120.65, 118.04, 116.33, 24.45. Mass (LC-MS): *m/z* 400.04 (M), 402.32 (M+2, 30%); 401 (M+1, 100%).

Synthesis of *N*-[4-(4-methyl-1*H*-imidazole-1-sulfonyl)-phenyl]-1-(3-nitro phenyl)methanimine (4a-h): To a mixture of compound **3a-d** (0.45g, 0.01 mol) and substituted benzaldehyde (1.47 g, 0.01 mol) were taken in an open vessel containing a Teflon coated stir jar. Added 20 mL of absolute alcohol and 10 mL of glacial acetic acid. The reaction mixture was carried out under microwave irradiation at 160 watts for 2-3 min. After the completion of the reaction, the mixture was cooled to room temperature and the solvent was distilled off. The obtained product was recrystallized by using ethanol (**Scheme-I**). The progress of the reaction was monitored by TLC (*n*-hexane and ethyl acetate, 7:3).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(phenyl)methanimine (MNSR-III-4a): Yield: 94%, m.p.: 179-181 ºC; m.f./m.w.: $C_{17}H_{15}N_3O_2S$/325.09. IR (KBr, ν_{max}, cm^{-1}): 3102 (-CH *str.* in Ar-H); 2984, 2866, 2793 (-CH *str.* in aliphatic); 1712 (CO *str.* in indole); and); 1518 (-C=N *str.*); 1492 (-C=CH *str.* in Ar-H); 1102 (-C-N *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 9.46 (1H, s protons in imine =CH proton); 8.30 (1H, s proton in aromatic-H); 8.14-8.02 (2H, d protons in aromatic-H); 7.87-7.80 (2H, d protons in aromatic-H); 7.47-7.39 (2H, d protons in aromatic-H); 7.21-7.19 (2H, d protons in aromatic-H); 4.8023 (2H, s protons in N-CH_2); 2.38 (3H, s protons of -CH_3 on imidazole ring); 2.09 (6H, s methyl protons on aromatic ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 175.32, 163.23, 157.09, 146.32, 142.04, 138.56, 135.21,



Scheme-I: Schematic representation of novel azole derivatives [(Scheme-III-**3a-d**, **4a-h**]

132.12, 128.98, 127.43, 124.54, 120.43, 115.34, 29.03. Mass (LC-MS): *m/z* 32 6.23 (M+1, 100%); 325.09 (M).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(4-methylphenyl)methanimine (MNSR-III-4b): Yield: 78%, m.p.: 151-153 ºC; m.f./m.w.: $C_{18}H_{17}N_3O_2S$/339.10. IR (KBr, ν_{max}, cm^{-1}): 1518 (-C=N *str.*); 1492 (-C=CH *str.* in Ar-H); 1102 (-C-N *str.*); 2984, 2866, 2793 (-CH *str.* in aliphatic); 1712 (-CO *str.* in indole); and 3102 (-CH *str.* in Ar-H); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.46 (1H, s proton in N=CH); 8.30 (1H, s proton in aromatic-H); 8.14-8.02 (2H, d proton in aromatic-H); 7.87-7.80 (2H, d proton in aromatic-H); 7.47-7.40 (2H, d proton in aromatic-H); 7.21-7.19 (2H, d protons in aromatic-H); 4.80 (2H, s protons in N-CH_2); 2.37 (s, 3H, -CH_3 on Imidazole ring); 2.09-2.00 (s, 3H, -CH_3 proton on aromatic ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.34, 161.23, 158.34, 152.34, 150.65, 148.04, 143.23, 142.22, 138.04, 136.23, 130.23, 128.56, 126.34, 123.09, 120.18, 115.23, 30.23, 25.12. Mass (LC-MS): *m/z* 339.10 (M); 340.21 (M+1, 100%).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(4-methoxy phenyl)methanimine (MNSR-III-4c): Yield: 86%, m.p.: 185-187 ºC; m.f./m.w.: $C_{18}H_{17}N_3O_3S$/355.10. IR (KBr, ν_{max}, cm^{-1}): 3095 (-CH *str.* in Ar-H); 2976, 2854, 2787 (-CH *str.* in aliphatic); 1715 (-CO *str.* in indole); 1604 (-C=N *str.)*; 1488 (-C=CH *str.* in Ar-H); 1093 (-C-N *str.*); 801 (-C-Cl *str.* in Ar-Cl) are recorded. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.70 (1H, s proton in -N=CH); 8.21 (1H, s proton in aromatic-H); 8.20-8.12 (2H, d protons in aromatic-H); 7.90-7.82 (2H, d protons in aromatic-H); 7.67-7.60 (2H, d protons in aromatic-H); 7.31-7.23 (2H, d protons in aromatic-H); 4.68 (2H, s proton in -N-CH_2 proton); 2.29 (3H, s protons of -CH_3 on aromatic ring), 1.99 (3H, s potons, -CH_3 proton on indole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 170.87, 160.34, 154.21, 150.65, 148.98, 143.78, 138.90, 132.34, 130.21, 129.04, 127.43, 125.89, 124.23, 120.32, 118.03, 26.43, 20.32. Mass (LC-MS): *m/z* 355.10 (M); 356.23 (M+1, 100%).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(4-chlorophenyl)methanimine (MNSR-III-4d): Yield: 83%, m.p.: 213-215 ºC; m.f./m.w.: $C_{17}H_{14}N_3O_2SCl$/359.05. IR (KBr, ν_{max}, cm^{-1}): 3079 (-CH *str.* in Ar-H); 2973, 2867 and 2792 (-CH *str.* in aliphatic), 1709 (-CO *str.* in indole); 1612 (-C=N *str.*); 1495 (-C=CH *str.* in Ar-H); 1087 (-C-N *str.*); 798 (-C-Cl *str.* in Ar-Cl). ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.41 (1H, s protons in -N=CH); 8.31 (1H, s proton in aromatic ring); 8.21-8.10 (2H, d protons in aromatic-H), 7.89-7.78 (2H, d, aromatic-H); 7.59-7.43 (2H, d protons in aromatic ring); 7.23-7.21 (2H, d protons on aromatic ring); 4.76 (2H, s protons in-N-CH_2); 2.20 (3H, s protons of CH_3 on imidazole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 71.23, 166.34, 154.34, 149.04, 143.34, 142.12, 138.05, 135.23, 133.76, 130.91, 127.45, 124.23, 122.21, 118.33, 25.93. Mass (LC-MS): *m/z* 359.05 (M); 370.32 (M+1, 100%).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(4-nitrophenyl)methanimine (MNSR-III-4e): Yield: 90%, m.p.: 205-207 ºC; m.f./m.w.: $C_{17}H_{14}N_4O_4S$/370.07. IR (KBr, ν_{max}, cm^{-1}): 3102 (-CH *str.* in Ar-H); 2998, 2849, 2798 (-CH *str.* in aliphatic); 1710 (-CO *str.* in indole), 1619 (C=N *str.*); 1480 (-C=CH *str.* in Ar-H); 1068 (-C-N *str.*); 804 (-C-Cl *str.* in Ar-Cl); ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.6732 (1H, s protons in -N=CH); 8.2902-8.2313 (2H, d protons on aromatic-

H); 8.20-8.09 (2H, d protons on aromatic-H); 7.77-7.67 (2H, d protons aromatic-H); 7.39-7.28 (2H, d protons on aromatic-H); 7.10-7.00 (2H, t protons on aromatic-H); 4.36 (2H, s protons, -N-CH_2 proton); 2.20 (3H, s -CH_3 on imidazole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.23, 160.32, 154.21, 148.43, 138.04, 135.23, 133.87, 132.12, 128.43, 125.23, 123.12, 120.65, 116.32. Mass (LC-MS): *m/z* 370.07 (M); 371.21 (M+1, 100%).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(4-hydroxy phenyl)methanimine (MNSR-III-4f): Yield: 81%, m.p.: 195-197 ºC; m.f./m.w.: $C_{17}H_{15}N_3O_3S$/341.08. IR (KBr, ν_{max}, cm^{-1}): 3023 (-CH *str.* in aromatic ring); 2934, 2874, 2745 (-CH *str.* in aliphatic group); 1712 (-CO *str.* in indole-CO); 16 09 (-C=N *str.*); 1434 (-C=CH *str.* in aromatic ring); 1102 (-C-N *str.*); ^{1}H NMR (400 MHz, DMSO-d_6): δ ppm: 9.34 (1H, s proton-N=CH); 8.10-8.09 (2H, d proton on aromatic-H); 7.84-7.82 (2H, d protons on aromatic-H); 7.67-7.52 (2H, d protons on aromatic-H); 7.29-7.20 (2H, d protons on aromatic-H); 7.09-7.02 (2H, t protons on aromatic-H); 4.71 (2H, s protons -N-CH_2 proton); 3.81 (3H, s protons on -OCH_3); 2.40 (3H, s proton-CH_3 on imidazole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 172.34, 160.87, 155.34, 152.32, 148.04, 145.32, 142.67, 140.21, 138.54, 136.34, 132.43, 130.54, 128.55, 125.10, 120.33, 117.34, 28.09. Mass (LC-MS): *m/z* 342.43 (M+1, 100%); 341.21 (M).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(3,4-dimethoxyphenyl)methanimine(MNSR-III-4g): Yield: 78%, m.p.: 173-175 ºC; m.f./m.w.: $C_{19}H_{19}N_3O_4S$/387.17. IR (KBr, ν_{max}, cm^{-1}): 3087 (-CH *str.* in Ar-H); 2987, 2882, 2761 (CH *str.* in aliphatic); 1709 (CO *str.* inindole); 1602 (C=N*str.);* 1422 (-C=CH *str.* in Ar-H); 1109 (-C-N *str.*) are the IR values. ^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.20 (1H, s protons -N=CH); 8.32 (1H, s potons aromatic-H), 8.10-8.09 (2H, d protons aromatic-H); 7.89-7.80 (2H, d protons aromatic-H); 7.57-7.51 (2H, d protons aromatic-H); 7.39-7.27 (2H, d protons on aromatic-H); 4.59 (2H, d protons -N-CH_2 proton); 3.67 (3H, s protons -OCH_3); 2.30 (3H, s protons -CH_3 on imida-zole ring); 2.02 (3H, s protons -CH_3 proton on indole ring);^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 171.32, 159.03, 158.23, 153.21, 149.02, 143.24, 140.23, 138.23, 131.06, 129.54, 127.43, 126.05, 124.23, 123.93, 120.87, 115.34, 58.03, 38.32, 28.5, 24.09. Mass (LC-MS): *m/z* 386.34 (M+1, 100%); *m/z* 385.11 (M).

(*E*)-*N*-[4-(4-Methyl-1*H*-imidazole-1-sulfonyl)phenyl]-1-(3-nitrophenyl)methanimine (MNSR-III-4h): Yield: 80%, m.p.: 211-213 ºC; m.f./m.w.: $C_{17}H_{14}N_4O_4S$/370.07. IR (KBr, ν_{max}, cm^{-1}): 3067 (-CH *str.* in Ar-); 2990, 2871, 2775 (-CH *str.* in aliphatic); 1710 (-CO *str.* in indole).1510 (-CO *str.* in indole); 1612 (-C=N *str.*); 1418 (-C=CH *str.* in Ar-H); 1092 (-C-N *str.*); 801 (-C-Cl *str.,* Ar-Cl);^{1}H NMR (400 MHz, DMSO-d_6) δ ppm: 9.41 (s, 1H, N=CH proton); 8.28 (s, 1H, Ar-H), 8.02-8.00 (d, 2H, Ar-H); 7.98-7.87 (d, 2H, Ar-H); 7.78-7.68 (d, 2H, Ar-H), 7.59-7.47 (d, 2H, Ar-H); 4.82 (s, 2H, NCH_2 proton); 3.59 (3H, s protons -OCH_3); 2.20 (3H, s protons -CH_3 on imidazole ring); ^{13}C NMR (400 MHz, DMSO-d_6) δ ppm: 174.23, 160.23, 158.21, 153.21, 148.09, 144.21, 140.27, 138.92, 135.23, 134.12, 130.01, 128.09, 127.23, 125.78, 123.23, 120.29, 117.25, 52.34, 38.09, 24.21, 22.04. Mass (LC-MS): *m/z* 370.07 (M); 371.34 (M+1, 100%).

Pharmacological activity

Anticancer activity: Using an MTT-based cell viability assay, novel azoles derivatives were evaluated for their anticancer potential on the MCF-7 cell line. In the mitochondria of living cells, the yellow MTT is spectrophotometrically converted to purple formazan, which was utilized to assess the solubility of the insoluble formazan following the addition of a DMSO solution to a coloured solution. To enable adhesion, cells were placed in a 96 well plate at 1×10^4 cells/well for 24 h at 37 ºC in an incubator with 5% CO_2. Following that, the cells were cultured for 48 h at 37 ºC with varying doses of test chemicals (5, 10, 25, 50 and 100 µg/mL) in an incubator with 5% CO_2. Following incubation, 20 µg/mL of 5 mg/mL MTT solution was added and the mixture was incubated for an additional 4 h. Following the suctioning of the medium, PBS was used to wash the well. To dissolve the formazan crystals, 200 µL of DMSO was given to each well after 2 h of drying and all plates were placed on a shaker. The absorbance was then measured at 570 nm. Three duplicates of each experiment condition were tested [15,16]. The following formula was used to determine the percentage of cell viability:

$$\text{Cell viability (\%)} = \frac{\text{Mean absorbance of control}}{\text{Mean absorbance of sample}} \times 100$$

Anthelmintic activity: Earthworms were used to test all of the newly synthesized azole derivatives for the anthelmintic activity. At room temperature, six roughly equalized earthworms were submerged in standard and test solutions. Albendazole was utilized as a standard and regular saline solution serves as a control. To get concentrations of 0.1% w/v, 0.2% w/v and 0.5% w/v, all of the compounds were dissolved in a minimum amount of DMSO and the volume was adjusted up to 10 mL with regular saline solution. Six earthworms were released into each of the test suspensions (0.1% w/v, 0.2% w/v and 0.5% w/v) and 15 mL of control solution [17].

In each petri dish, six worms were placed, and the duration till paralysis and death was recorded. After confirming that the worms did not move in response to external stimuli or shaking, the death time (min) of each worm was noted. The decline in the worms' movement and the gradual loss of their vibrant coloration signified the expiration.

Molecular docking studies: The binding mode of target compounds *via* specific EGFR proteins with PDB ID 1M17 for MCF-7 cancer cell lines was examined using molecular docking models during the drug design and development process [18]. Hydrogen atoms were added in place of all the water molecules that surrounded the protein. In order to rationalize the observed biological data, the synthesized ligands were docked into the EGFR protein's active site using the Schrödinger suite's Ligprep tool. Using structurally refined protein shapes and the Glide Xp docking methodology, the protein-ligand interactions of the dataset ligands were predicted. Initially, a 3D grid was established. First, all of the dataset ligands were docked into a 3D grid that was used to set up the binding active packets (site) of the EGFR protein. The Glide score was used to compute the binding interactions, which included polar interactions, van der Waals energy, metal binding groups, hydrophobic and hydro-

philic interactions and others. For each ligand, the maximum docked pose with the lowest glide score was noted and the Schrödinger suite software was used for additional precision.

RESULTS AND DISCUSSION

The microwave assisted synthesis was used to synthesize novel azole derivatives-MNSR-III-**3a-d**,**4a-h** using Schiff bases (**Scheme-I**). In this reaction between 4-(4-methyl-1*H*-imidazole-1-sulfonyl)aniline (I) with substituted benzaldehyde and substituted benzene sulphonyl chloride.

The spectral characterization of novel azole derivatives contains imidazole, indole-2-one and sulphonyl moieties was performed by IR spectroscopy. In all the synthesized compounds, the aromatic and aliphatic –CH stretching frequency, as expected is observed at around 3100-3000 cm^{-1} and 2998-2733 cm^{-1}, respectively. All the compounds have also shown strong absorption in the 1720-1698 cm^{-1} region, which confirmed the presence of C=O stretching frequency. Most of the compounds also exhibit the C=C stretching of the aromatic rings at 1534-1465 cm^{-1} respectively. The Ar-Cl stretching exhibits a strong absorption in the range of 825-792 cm^{-1}, while several compounds containing the $–NO_2$ group display peaks attributed to stretching observed at 1648-1620 cm^{-1}, respectively. Similarly, the ^1H NMR spectra of azole derivatives showed a singlet at δ 10.03-12.54 ppm indicates the presence of –NH proton in indole ring. The chemical shift values between δ 9.02-9.78 ppm in imine (-N=CH) proton. All compounds have aromatic protons were found between δ 8.27-6.87 ppm as a singlet, doublet and triplet protons. Compounds exhibit a singlet at δ 3.54-3.98 ppm confirmed the $–OCH_3$ protons. Few compounds show a singlet at δ 1.89-2.376 ppm for $–CH_3$ protons. The mass spectrum of the all **MNSR-III-3a-d, 4a-h** derivatives were also conformed by their molecular ion peak and molecular weight.

Anticancer activity: The MTT cell proliferation assay calculates the rate of cell division and, on the other hand, the decrease in cell viability that occurs when metabolic processes result in necrosis or apoptosis. The MTT assay was used to test the new azole derivatives' *in vitro* anticancer efficacy against the human breast cancer cell line MCF-7. The evaluation of the anticancer effects on MCF-7 cell lines, alongside doxorubicin as a positive control, was conducted through an MTT assay, utilizing a tetrazolium salt. All findings are shown in Table-1. In the culture system, the compounds grew normally and DMSO did not appear to have any discernible impact on cellular growth.

TABLE-1
NOVEL AZOLE DERIVATIVES TREATED WITH MCF-7 CELLS SHOWING THE IC_{50} VALUES

Sample	IC_{50} (μg)	Sample	IC_{50} (μg)
MNSR-III-**3a**	42.21 ± 0.542	MNSR-III-**4c**	58.32 ± 0.393
MNSR-III-**3b**	12.36 ± 0.32	MNSR-III-**4d**	19.12 ± 0.231
MNSR-III-**3c**	38.21 ± 1.044	MNSR-III-**4e**	56.43 ± 0.123
MNSR-III-**3d**	46.64 ± 0.312	MNSR-III-**4f**	35.51 ± 0.203
MNSR-III-**4a**	23.64 ± 0.312	MNSR-III-**4g**	44.29 ± 0.298
MNSR-III-**4b**	38.23 ± 0.283	MNSR-III-**4h**	58.23 ± 0.872
		Doxorubicin	12.54 ± 0.104

Anthelmintic activity: *In vitro* anthelmintic activity of new azole derivatives was studied by using Indian earthworms with standard albendazole. From the results (Table-2), compounds **MNSR-III-3c**,**4a**,**4d** and **4h** showed excellent anthelmintic activity when compared with albendazole standard in dose dependent manner giving shortest time paralysis and death with distinctive concentration of the derivatives.

Molecular docking studies: The molecular docking simulation and ligand binding energy calculation had been carried out using the Schrödinger suit software was used to analyzed compounds binding mode against breast cancer cell lines. Molecular docking lookup carried out by means of the use of the Ligprep tool of Schrödinger suite and Glide score of the dataset ligand with the interplay of amino acid. From the effects with EGFR protein, the docking score of the all target molecules have been ranged between -8.833-5.72 (compound **MNSR-III-3b** and **MNSR-III-3c**) (Fig. 1). The synthesized compound **MNSR-III-3b** mentioned the highest significant docking score of -8.833 with glide binding energy of -42.338 Kcal/mol (Table-3). MET 768 and THR 830 are the most common amino acids with H-bonds. Compound **MNSR-III-4f** is having only one H-bond interaction with GLU 738 and pi-pi stacking are identified between PHE 699 (Fig. 2).

TABLE-2
ANTHELMINTIC ACTIVITY OF COMPOUNDS MNSR-III-**3(a-d)**, **4(a-h)**.

Compound	For paralysis time (min)			For death time (min)		
	0.1%	0.2%	0.5%	0.1%	0.2%	0.5%
Control	–	–	–	–	–	–
Albendazole	17 ± 0.002	12 ± 0.001	8 ± 0.021	41 ± 0.010	30 ± 0.001	26 ± 0.003
MNSR-III-**3a**	28 ± 0.312	34 ± 0.512	28 ± 0.398	54 ± 2.041	49 ± 2.056	38 ± 1.045
MNSR-III-**3b**	31 ± 1.084	26 ± 2.003	23 ± 1.045	58 ± 0.943	50 ± 0.374	38 ± 1.054
MNSR-III-**3c**	20 ± 0.012	18 ± 0.002	14 ± 0.012	43 ± 0.001	34 ± 0.024	29 ± 0.014
MNSR-III-**3d**	28 ± 2.041	23 ± 0.874	21 ± 0.583	61 ± 0.1762	50 ± 0.253	32 ± 1.087
MNSR-III-**4a**	21 ± 0.021	19 ± 0.031	16 ± 0.021	43 ± 0.001	40 ± 0.002	30 ± 0.001
MNSR-III-**4b**	29 ± 1.902	24 ± 0.783	21 ± 1.093	58 ± 2.013	46 ± 2.046	33 ± 1.056
MNSR-III-**4c**	30 ± 2.001	35 ± 1.002	23 ± 1.043	62 ± 2.001	58 ± 2.109	40 ± 0.967
MNSR-III-**4d**	20 ± 0.001	15 ± 0.012	12 ± 0.003	42 ± 0.022	33 ± 0.001	28 ± 0.014
MNSR-III-**4e**	31 ± 0.921	29 ± 2.003	29 ± 1.043	59 ± 1.032	49 ± 1.003	36 ± 0.132
MNSR-III-**4f**	27 ± 0.167	23 ± 1.054	20 ± 2.043	48 ± 0.0372	44 ± 0.521	38 ± 0.412
MNSR-III-**4g**	33 ± 1.902	26 ± 0.782	24 ± 0.043	59 ± 0.652	48 ± 0.291	37 ± 0.522
MNSR-III-**4h**	19 ± 0.001	16 ± 0.011	11 ± 0.004	44 ± 0.002	32 ± 0.001	28 ± 0.013

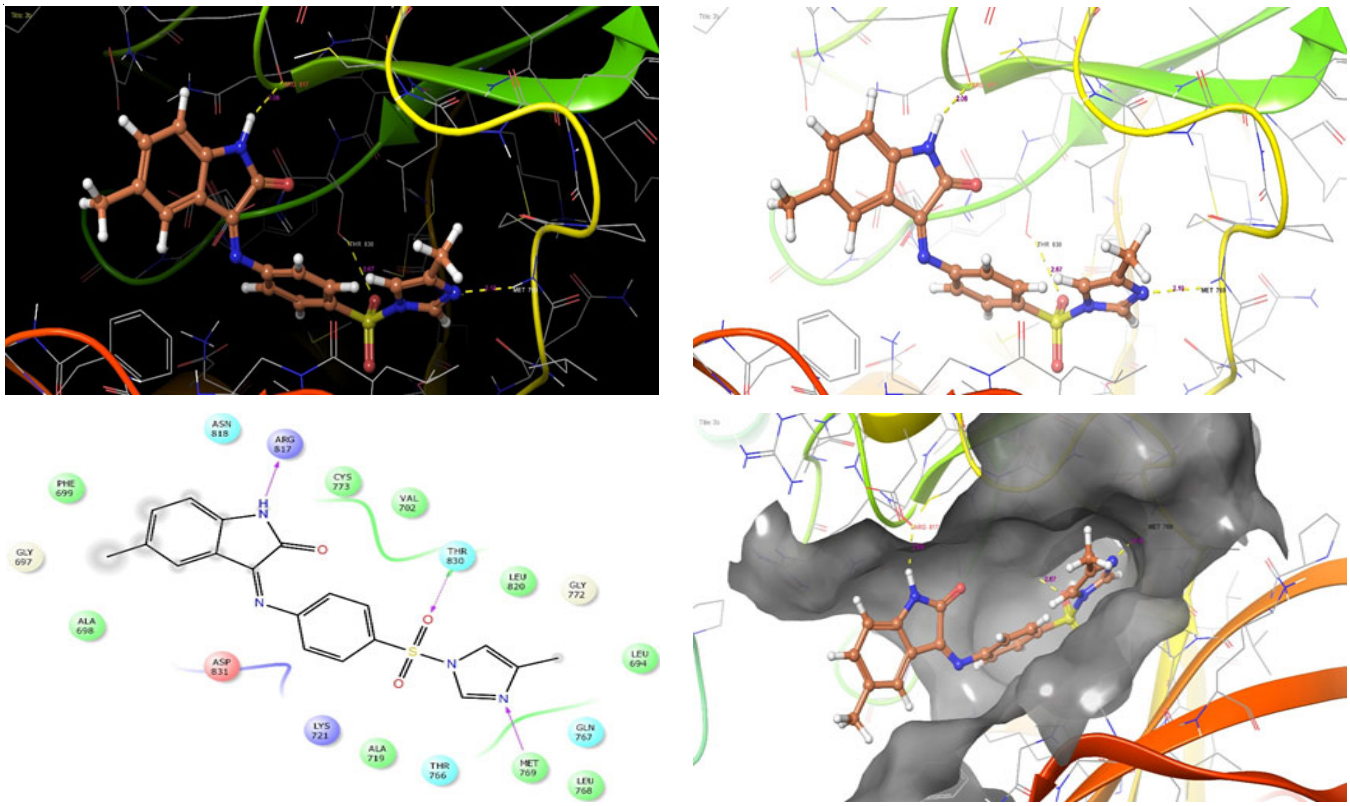


Fig. 1. Docking pose between the ligand and the protein (Dock 1, Dock 2 and 2d, 3d)- Compound-III-**3b**

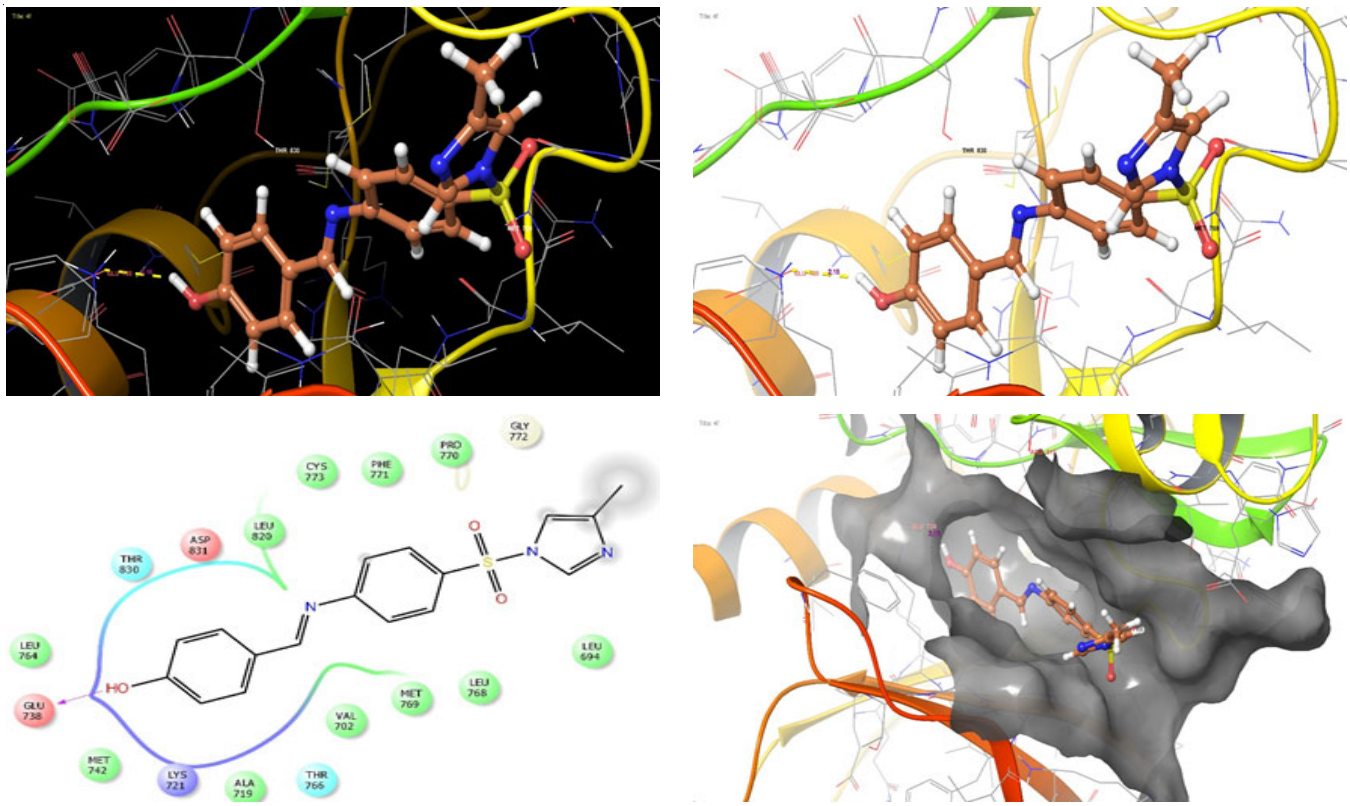


Fig. 8. Docking pose between the ligand and the protein (Dock 1, Dock 2 and 2d, 3d)- Compound-III-**4f**

Conclusion

The microwave assisted synthesis of newer azole derivatives (MNSR-III **3a-d**,**4a-h**) using Schiff base compounds were successfully conducted. Novel synthesized compounds were characterized by physical, spectral analysis and *in vitro* screening of the anthelmintic and anticancer activities of novel

TABLE-3
In silico EGFR INHIBITION OF NOVEL AZOLE DERIVATIVES
(**Scheme-III**, MNSR-III(**3a-d**, **4a-h**)-DOCK SCORE OF THE DATASET LIGANDS

Compound	Dock score XP GScore	No of H-bonds	Interacting amino acids	H-bond lengths (Å)	Emodel energy	Glide energy
MNSR-III-**3b**	-8.833	3	ARG 817, THR 830, MET 769	2.06, 2.67, 2.19	-58.482	-42.338
MNSR-III-**4d**	-8.483	2	THR 830, MET 769	2.70, 2.08	-49.291	-35.753
MNSR-III-**4f**	-7.417	1	GLU 738	2.16	-46.056	-31.855
MNSR-III-**4a**	-7.222	2	THR 830, MET 769	2.68, 2.12	-42.75	-37.512
MNSR-III-**3a**	-6.190	1	ARG 817	1.23	-42.132	-34.893
MNSR-III-**4b**	-6.103	1	THR 830	2.09	-36.109	-30.290
MNSR-III-**4c**	-6.001	2	ARG 817, THR 830	1.56, 2.91	-36.54	-38.283
MNSR-III-**3d**	-5.95	1	MET 769	2.02	-41.322	-39.503
MNSR-III-**4h**	-5.832	1	THR 830	2.02	-45.12	-40.243
MNSR-III-**4g**	-5.82	1	LYS 721	1.23	-54.222	-40.723
MNSR-III-**4e**	-5.80	2	GLU 738, MET 769	2.32, 1.25	-61.221	-34.182
MNSR-III-**3c**	-5.72	2	MET 769, LYS 721	1.99, 2.13	-63.278	-44.357

derivatives were also evaluated. The most of the compounds showed good inhibitory activity against the epidermal growth factor receptor (EGFR) in molecular docking studies.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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