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DESIGNED SYNTHESIS OF A NOVEL ANALOGOUS OF QUINAZOLIN-6-ONE FROM BENZIMIDAZOLE VIA DITHIAZOLE MOIETY PROMOTED TRANSITION METAL CATALYST

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ABSTRACT

The present study describes the novel synthesis of quinazolin-6-one derivatives from benzimidazole's starting material via dithiazole molecule. These derivatives can be obtained from the compound (5) treated with aryl aldehyde, dimedone promoted by copper halide as a catalystin a polar solvent at reflux. Compound (5) was prepared by the mixture of thiosemicarbazide and compound (4) in the presence of 50% H_2SO_4 in acetonitrile solvent and subsequently, compound (4) can be synthesized from compound (3) with chloroacetic acid in the presence strong base in a non-polar solvent, Finally, the starting compound (3) can be obtained by the mixture of 6-bromophenyl 1, 2-diamine and 4-methoxy benzaldehyde subjected by the $ZrOCl_2$ in ethanol as solvent. The novel analogous can be predicted by advanced spectral analysis such as ^{1}HNMR, ^{13}C NMR, and LCMS. The derivatives were also evaluated by anti-microbial properties against bacterial as well as fungal strains.

Keywords: 6-Bromodiphenylamine, 4-Methoxybenzaldehyde, Dithiazoleamine, Quinazolin-6-One Analogous, Zirconyl Chloride, Copper Iodide.

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INTRODUCTION

In recent days, thechemistry of heterocycleshas occupied over half of the research part worldwide and isplaying asignificant rolein the enhancement of modern organic synthesis. Among them, the azole family plays a unique role and also occupies a majority part in the field of organic synthesis. In the present work, the titled compounds comprise three important azole familiescalled “benzimidazoles”, “thiazoles” and “quinazalones”.The heterocyclic compounds containing thiazoles and their analogous exhibita variety of therapeutic properties and are also well-known in medicinal,and synthetic organic chemistry.The N, S atom fused heterocyclic compounds play an important role in the pharmaceutical field due to their active physiological properties[1-3]. Interestingly,benzimidazole,thiazole, and quinazalonederivatives are involved in biological applicationand pharmacological properties such as Antimicrobial Activity[4-8], antitumor activity[9],anticancer activity[10,11], antitubercular[12], antioxidant, anticonvulsant[13,14], α-amylase and α-glycosidase[15], Anti-Hepatic Cancer Agents[16],Anti-HIV Activity[17]etc.In the previously reported survey, we observed that Lewis acids are applied fordifferent organicconversionsdue to their non-metallic, non-toxic character and also easy availability in nature. Here, molecular iodine can be considered the most important catalyst in the execution of multiple-componentreactions. As mentioned by earlier reports, thiadiazolo [2,3-b] quinazolin-6-(7H) one was prepared by usingtetrabutylammonium hydrogensulfate (Bu_4NHSO_4)[18] as a phase transfer catalyst by p-toluene sulfonic acidmediated[19] three-component reaction in water media.To synthesize newthiadiazolo-[2,3-b] quinazolin-6-(7H)-one,CuI_2[20],diphenhydraminehydrochloride-$CoCl_2\cdot6H_2O$[21]etc are used.The total effort and main focus of the present work are on the synthesis of novel derivatives of thiadiazolo[2,3-b]quinazolin-6-ones by using transition metal halide catalytic systems via straight and multi-stagesynthetic paths. We report biologically effectivethiadiazolo [2,3-b] quinazolin-6-one derivatives via the reaction of 5-((5-bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-thia diazol-2-amine(5), substituted arylaldehyde(6) and dimedone (7) promoted by CuI_2 in polar solvent refluxed at 70^{0}C (Scheme-1).

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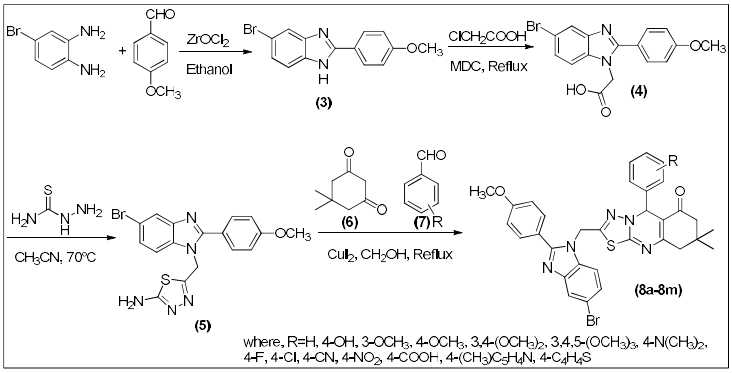
According to the literature survey,we developed a few molecules containing N and S fused Heterocycles which is more feasible in antimicrobial activity.



Scheme-1: Preparation of Compounds 8a-8m

EXPERIMENTAL

Materials and Methods

Commercial grade suppliers like Merck, and Sigma Aldrich supplied all the required raw materials and used them as such. Themelting pointsof thecompounds are recorded byFluke 51 II thermo scientificmelting point instrument with model number IA 9100 and reported uncorrected. The structures of moleculesare estimated by advancedtechniques such as ^{1}HNMR of 400 MHz and ^{13}CNMR of 100 MHz and that were measured at constant temperature on Bruker NMR instrument with reference toTMS internal standard and in deuterated chloroform ($CDCl_3$) solvent. The molecular weights of the compounds werecalculated by Shimadzu GC-MS 2010 spectrometer, of 70 eV in positive mode.

General Procedures

Synthesis of 5-Bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (3)

6-bromodiphenylamine (1.0 mol),and 4-methoxy benzaldehyde (1.15mol) were dissolved in 25 of ethanol andzirconyl chloride (catalytical amount)was added. The contents are stirred for about 5 hours and monitored by TLC (mobile phase: 30% Ethyl acetate in hexanes). After completion of the reaction, the reaction masswaspoured into crushed ice (50gm),saturated solution of a base was used to neutralize the reaction massfollowed by ethyl acetate extraction.The organic layer was separated, washed with water twice (2x100mL), and concentrated under a vacuum to get the crude compound. The crude compound is then purified by using column chromatography to obtain a pure product.Brown solid; M.P-214-216^{0}C; Yield-91%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.246(s, 1H), 8.034(2H,d,J=6.4Hz), 7.763(1H,s),7.422(1H,d,J= 8.0Hz),7.284(1H, J=5.6Hz,d), 6.947(2H,d,J=7.6Hz,), 3.584(3H,-OCH_3,s);^{13}CNMR (125MHz, $CDCl_3$)ppm: 153.46, 148.05, 138.71, 137.36, 128.67, 128.42, 128.04, 124.37, 119.06, 116.17, 114.38, 51.02;Molecular weight:304.29(M+2);Formulae of the compound: $C_{14}H_{11}BrN_2O$.

Synthesis of 2-(5-bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) AceticAcid (4)

To a solution of 5-Bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazole (1.12mol) in dichloromethane,acetyl chloride (1.15mol) isadded and fitted on the magnetic stirrer. Triethyl amine is poured into the reaction mass and the content is refluxed for about 3 hours till the starting material is completed as shown by TLC (mobile phase: 50% ethyl acetate in hexanes) The reaction massis thenadded into crushed ice and neutralized with a saturated base solution followed by ethyl acetate extraction. The Ethylacetate layer is washed with water thrice (3X100). The required layer is separated and distilled off under vacuum. The desired product wasthen purified by using column chromatography and get the required product.Pale brown solid; M.P-232-234^{0}C; Yield-88%; ^{1}HNMR (400MHz, CDCl3) ppm: 11.923(1H,s), 7.932(2H,J=7.6Hz,d), 7.789(1H,s), 7.425(1H,d,J=8.0Hz), 7.342(1H,d, J=9.6Hz), 6.879(d, J=5.4Hz, 2H), 3.921(s,3H,-OCH_3), 3.617(s,3H,-OCH_3);^{13}CNMR (125MHz, $CDCl_3$)ppm: 181.37, 156.59, 151.18, 139.77, 165.08, 128.93, 127.26, 125.63, 122.05, 118.88, 115.07, 113.33, 54.08, 50.45; Molecular weight: 362.55(M+2); Formulae of the compound: $C_{16}H_{13}BrN_2O_3$.

Synthesis of 5-((5-bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-thiadiazol-2-amine (5)

To a solution of compound (4) (1.0 mol) in 25 mL of acetonitrile, another was added other reactant such as thiosemicarbazide (1.125mol) followed by mineral acid, conc H_2SO_4 (2.5mL) dropwise,and the mixture is maintained at 70^0C for 5 hours.Thedevelopment of the reaction was identified by TLC and poured into 100gm crushed ice after completion of the reaction and also neutralized with a suitable base ($NaHCO_3$). The reaction crude was extracted with Ethyl acetate and washed with water (2X100). After the separation of Ethyl acetate, distilled under a vacuum and finally getsthe required compound.Pale brown solid; M.P-237-239^{0}C; Yield-90%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 7.874(d, J=7.2Hz, 2H), 7.816(s, 1H),7.442-7.392 (2H,m), 6.745(d, J=5.4Hz, 2H), 5.248(s,2H), 4.214(s,2H), 3.715 (s, 3H, -OCH_3);^{13}CNMR (125MHz, $CDCl_3$)ppm: 169.72, 158.33, 155.24, 150.05, 140.25, 138.39, 128.74, 127.32, 124.58, 123.02, 118.45, 115.26, 113.05, 53.82, 50.62; Molecular weight: 417.46(M+2); Formulae of the compound: $C_{17}H_{14}BrN_5O_3$.

Synthesis of 2-((5-bromo-2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-8,8-dimethyl-5-phenyl-5,7,8,9-tetrahydro-6H-[1,3,4]thiadiazolo[2,3-b]quina zolin-6-one derivatives (8a-8m)

Compound 5 (1.015mol),substituted aromatic aldehyde (1.125mol), and dimedone (1.0mol) are added to a 50mL RB flask containing a freshly generated catalytic amount of CuI_2 in ethanol. The reactions wererefluxed for about 6 hours and monitored by TLC using 40% ethyl acetate in hexane as the mobile phase. After completion of the reaction, the content waspoured into crushed ice followed by ethyl acetate extraction. The organic phase was washed with aqueous hydrochloric acid, dried over anhydrous sodium sulfate, and concentrated to obtain the desired product as a solid. It was then recrystallized from ethanol.

RESULTS AND DISCUSSION

The structures of the disclosed compounds (8a-8m) were characterized by ^{1}H and^{13}CNMR, mass analysis. ^{1}H NMR spectrum of the desired derivatives exhibited signals at various regions like aromatic protons at δ 8.324 to 6.445 ppm and aromatic protons of benzimidazole at δ 7.617. The methoxy protons showed at 3.804 to 3.558 and the methyl protons appeared at 1.089-0.897ppm. N-H protons appeared at 11.247 of imidazole and hydroxyl protons at 9.523 and 9.246 ppm. The carboxylic acid protons appear at 11.573ppm. The mass spectrum of all the derivatives exhibited molecular ion peaks at (m/z)(M+2).

Derivative (8a)

Brown solid; M.P-258-260^{0}C; Yield-82%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 7.957(2H,d, J=5.6Hz), 7.717(s,1H), 7.446(1H,d, J= 8.8Hz), 7.388(1H,d, J=12.4Hz), 7.327-7.208(5H,m), 4.523(s,2H),3.892(s,3H),3.714(s,3H), 2.094(s,2H), 1.642(s,2H),0.950(s,6H);13CNMR: (125MHz, $CDCl_3$)ppm:196.26, 161.44, 158.35, 152.71, 151.38, 150.55, 140.38, 138.38, 136.66, 130.86, 128.78, 128.12, 127.64, 125.57, 123.09, 119.04, 117.21, 116.36, 113.38, 63.62, 53.86, 50.39, 48.77, 39.11, 30.04, 27.92, 26.64; Molecular weight: 627.43(M+2); Formulae of the compound: $C_{32}H_{28}BrN_5O_2S$.

Derivative (8b)

Pale brownsolid; M.P-248-250^{0}C; Yield-90%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 9.246(s, 1H), 8.042(2H,d, J=8.0Hz), 7.645(1H,s), 7.453(1H,d, J=4.4Hz), 7.392(1H,d, J=4.4Hz), 7.114(2H,d,J=6.8Hz),7.028-6.841(m,4H),4.114(s.1H,-CH-), 3.940 (s,2H,-CH_2-), 3.679(s,3H), 2.049(s,2H),1.7140 (s,2H),1.012(s,6H);^{13}CNMR (100MHz,$CDCl_3$): 196.11, 160.05, 158.04, 150.72, 148.14, 145.80, 140.92, 136.65, 130.23, 129.19, 128.46, 127.59, 125.66, 121.84, 118.35, 116.57, 114.06, 60.42, 54.37, 48.86, 39.02, 30.41, 28.05, 26.42; Molecular weight:643.94(M+2), Formulae of the compound: $C_{32}H_{28}BrN_5O_3S$.

Derivative (8c)

Pale brown compound; M.P-256-258^{0}C; Yield-87%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 9.523(1H,s), 7.927(1H,d, J=8.8Hz), 7.683(s, 1H), 7.440(1H,d, J= 7.2Hz), 7.374(1H,d, J=6.0Hz),7.115-6.794(m,5H),4.337(s.1H,-CH-),4.024(s,2H,-CH2-),3.726(s,3H),3.590(s,3H),
2.104(s,2H),1.776(s,2H),1.076(s,6H);^{13}CNMR (100MHz, $CDCl_3$):196.92, 161.04, 156.62, 153.33, 150.72, 148.48, 145.66, 144.76, 140.45, 135.11, 131.55, 129.64, 128.47, 127.06, 126.56, 121.17, 119.07,

65.08, 55.61, 53.24, 50.06, 48.44, 38.25, 30.02, 28.31, 26.96; Molecular weight: 673.68(M+2), Formulae of the compound: $C_{33}H_{30}BrN_5O_4S$.

Derivative (8d)

Brown compound; M.P-250-252^{0}C; Yield-85%; ^{1}HNMR (400MHz, CDCl3) ppm: 7.968(1H,d,J=7.2Hz),7.692(1H,s),7.452(1H,d,J=5.6Hz),7.287(1H,d,J=4.2Hz),6.976-6.734(5H,m),4.381(s.1H,-CH-),4.052(s,2H,-CH_2-)3.804(s,3H),3.723(s,3H),3.640(s,3H),2.081(s,2H),1.690(s,2H),0.964(s,6H); ^{13}CNMR (100MHz, $CDCl_3$): 194.26, 161.04, 157.24, 155.91, 152.02, 150.08, 146.42, 145.08, 140.19, 135.75, 131.07, 129.83, 128.75, 128.26, 125.67, 123.05, 120.94, 118.66, 116.48, 114.75, 112.33, 110.62, 65.73, 56.44, 54.02, 50.62, 48.74, 37.39, 30.80, 27.96, 26.05; Molecular weight: 687.24 (M+2), Formulae of the compound: $C_{34}H_{32}BrN_5O_4S$.

Derivative(8e)

Pale brown compound; M.P-268-270^{0}C; Yield-83%;^{1}HNMR(400MHz,$CDCl_3$) ppm: 8.024-7.912(m,2H),7.774(s,1H),7.484(1H,d,J=9.6Hz),7.365(1H,d,J=8.0Hz),6.924(2H,d,J=6.8Hz), 4.447(s.1H,-CH-),3.942(s,2H,-CH_2-),3.796(s,6H),3.774(s,3H),3.558(s,3H),1.857(s,2H), 1.552(s,2H),0.957(s,6H); ^{13}CNMR (100MHz, $CDCl_3$)ppm: 193.08, 159.73, 157.64, 155.07, 153.75, 150.37, 148.07, 141.45, 138.62, 135.72, 132.92, 130.54, 128.85, 127.08, 126.77, 125.78, 123.09, 119.21, 117.05, 115.24, 113.24, 110.06, 63.56, 59.71, 55.24, 52.08, 48.69, 39.07, 32.25, 28.92, 26.15; Molecular weight: 717.49 (M+2), Formulae of the compound: $C_{35}H_{34}BrN_5O_5S$.

Derivatives (8h)

Pale brown compound; M.P-268-2700C; Yield-83%;^{1}HNMR(400MHz,$CDCl_3$) ppm: 7.926(2H,d,J=3.6Hz),7.8.8(s,1H),7.437(1H,d,J=8.8Hz),7.416(1H,d,J=13.2Hz),7.214-6.845 (m,6H),4.319(s.1H,-CH-),4.045(s,2H,-CH_2-),3.668(s,3H), 2.045(s,2H), 1.831 (s,2H), 1.544 (s,6H), 0.974(s,6H);^{13}CNMR(100MHz, $CDCl_3$)ppm: 196.77, 160.23, 157.44, 153.11, 150.47, 140.05, 138.94, 136.07, 132.45, 130.22, 128.46, 127.56, 126.05, 123.91, 120.02, 119.41, 117.33, 115.81, 114.62, 114.03, 65.26, 53.29, 48.24, 38.36, 28.02, 26.24, 20.35.Molecular weight: 656.29 (M+2), Formulae of the compound: $C_{34}H_{35}BrN_6O_2S$.

Derivative (8g)

Yellowsolid;M.P-241-243^{0}C;Yield-85%;^{1}HNMR(400MHz,$CDCl_3$)ppm:8.021(d,J= 4.8Hz,2H),7.862(1H,d,J=9.6Hz),7.720(s,1H),7.551(1H,d,J=8.8Hz),7.430(1H,d,J=7.2Hz),7.323(1H,d,J=8.0Hz),4.412(s.1H,-CH-),4..32(s,2H,-CH_2-),3.770(s,3H),2.092(s,2H),1.776(s,2H),0.944(s,6H); ^{13}CNMR(100MHz, $CDCl_3$)ppm: 198.11, 161.04, 158.36, 152.92, 150.08, 142.72, 138.95, 135.64, 133.47, 129.88, 128.65, 128.21, 127.35, 125.74, 123.68, 121.05, 118.94, 116.60, 114.74, 112.35, 110.65, 65.24, 51.26, 39.45, 31.46, 27.86, 26.82; Molecular weight: 645.73(M+2), Formulae of the compound: $C_{32}H_{27}BrFN_5O_2S$**.**

Derivative (8h)

Pale yellow compound;M.P-250-252^{0}C; Yield-85%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 8.026(1H,d, J= 5.5Hz), 7.917(d, 1H,J=8.8Hz), 7.765(s, 1H), 7.480(d,1H, J= 8.0Hz), 7.424(d,J=10.4Hz,1H),7.098-6.6842(m,2H),4.428(s.1H),4.116(s,2H),3.572(s,3H),2.059 (s,2H),1.771(s,2H),955(s,6H);^{13}CNMR(100MHz, $CDCl_3$)ppm: 196.39, 161.27, 158.74, 153.04, 150.04, 148.02, 145.44, 141.05, 137.77, 132.56, 129.28, 127.41, 125.24, 123.35, 123.35, 120.07, 118.16, 115.24, 113.65, 110.74, 66.06, 55.38, 51.11, 48.36, 38.47, 31.06, 28.21, 25.05; Molecular weight: 661.07(M+2), Formulae of the compound: $C_{32}H_{27}BrClN_5O_2S$.

Derivative (8i)

Brown solid; M.P-252-254^{0}C; Yield-86%; 1HNMR(400MHz,$CDCl_3$)ppm: 8.0247.894(m,2H),7.846(s,1H),7.812-7.564(m,4H,), 7.456-7.224(m,4H), 4.330(s.1H,-CH-),4.162(s,2H,-CH2-),3.740(s,3H),2.143(s,2H), 1.891 (s,2H),1.024(s,6H); ^{13}CNMR(100MHz, $CDCl_3$)ppm: 197.37, 160.09, 157.33, 154.71, 151.06, 151.76, 147.58, 143.44, 140.07, 136.74, 132.69, 130.82, 129.37, 128.51, 128.02, 127.49, 125.71, 123.45, 120.62, 118.798, 117.62, 115.38, 112.62, 109.74, 66.74,55.08, 50.38, 38.15, 32.02, 28.49, 26.66;Molecular weight: 652.28(M+2), Formulae of the compound: $C_{33}H_{27}BrN_6O_2S$.

Derivative (8j)
Darkbrowncompound; M.P-261-263^{0}C; Yield-82%; ^{1}HNMR(400MHz, $CDCl_3$)ppm: 8.296(2H, d,J=7.6Hz), 8.145(d,J=12.8Hz,2H), 8.055(d,J=8.8Hz,2H), 7.474=7.039(m,4H,Ar), 4.247(s.1H,-CH-), 4.198(s,2H,-CH_2-), 3.771(s,3H), 2.049(s,2H), 1.884(s,2H),1.064(s,3H),0.960(s,3H);^{13}CNMR (100MHz, $CDCl_3$) ppm: 196.47, 161.24, 158.33, 154.69, 150.74, 148.56, 147.71, 142.74, 136.03, 132.66, 129.11, 128.38,127.52, 125.09, 124.74, 120.62, 118.39,116.46, 115.35, 113.67, 66.16, 58.88, 55.39, 51.08, 38.67,32.38, 28.04, 27.51;Molecular weight: 672.38(M+2), Formulae of the compound: $C_{32}H_{27}BrN_6O_4S$**.**

Derivatives (8k)
Brown solid; M.P-245-247^{0}C; Yield-85%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 11.573(1H,s,), 8.324(1H,J=12.4Hz,d),8.226(1H,d,J=11.2Hz),8.086(1H,d,J=8.0Hz),7.805(s,1H),7.456-7.116(m,4H), 7.392(1H,d,J=4.4Hz), 4.448(s.1H,-CH-), 4.208(s,2H,-CH_2-), 3.784s,1H), 2.068(s,2H),1.723 (s,2H), 0.944(s,6H);^{13}CNMR (100MHz, CDCl3) ppm: 197.38, 184.62, 161.49, 159.33,156.33 156.04, 152.68, 149.11, 146.44, 143.33, 140.05, 131.65, 129.84, 128.71, 128.04, 126.06, 12.13, 120.22,118.07, 116.62, 113.36, 65.08,56.34,52.22, 48.94, 41.02, 30.62, 27.92, 25.06;Molecular weight: 672.38(M+2), Formulae of the compound: $C_{32}H_{27}BrN_6O_4S$.

Derivative (8l)
Brown solid; M.P-238-240^{0}C; Yield-88%; ^{1}HNMR (400MHz, $CDCl_3$) ppm: 8.416(1H,s),8.315(1H,d,J=9.6Hz),8.021(2H,d,J=8.8Hz),7.886(1H,d,J=6.8HzH),7.774(s,1H,R),7.450(1H,d ,J=3.2Hz),7.384(d,1H,J=5.6Hz),6.940(d,J=8.0Hz,2H),4.412(s.1H,-CH-),4.168(s,2H,-CH_2-),3.614(s,1H),2.156(s,2H),1.904(s,2H),1.625(s,2H),0.983(s,6H);^{13}CNMR(100MHz,$CDCl_3$)ppm:194.28, 159.36, 158.45, 156.07, 152.36, 150.05, 144.72, 140.66, 137.42, 131.73, 130.64, 129.75, 128.46, 125.57, 122.79, 120.08, 117.25,114.62, 113.38, 65.68, 54.38, 50.47, 48.45, 41.72, 32.03,28.84, 25.62, 20.48;Molecular weight: 642.24(M+2), Formulae of the compound: $C_{32}H_{29}BrN_6O_2S$.

Derivative (8m)
Yellowsolid;M.P-235-237^{0}C;Yield-86%;^{1}HNMR(400MHz,$CDCl_3$)ppm:8.142(2H,J=7.6Hz,d),7.705(s,1H),7.496(1H,d,J=4.8Hz),7.415(1H,d,J =8.8Hz),7.126(2H,d,J=13.6Hz), 6.742-6.445(m,2H,thiophene), 4.267(s.1H,-CH-), 4.088(s,2H,-CH_2-), 3.749(s,3H),2.148(s,2H),1.550 (s,2H),1.042(s,3H),0.918(s,3H);^{13}CNMR(100MHz,$CDCl_3$)ppm:192.75, 159.34, 155.06, 153.78, 149.44, 148.02, 145.63, 141.25, 1321.72, 129.66, 128.73, 125.47, 124.05, 123.47, 121.02, 120.34, 118.11, 117.36, 115.67, 114.75, 112.62, 110.39, 62.64, 56.04, 51.44, 48.55, 41.02, 30.68, 28.38, 25.62; Molecular weight: 633.68(M+2), Formulae of the compound: $C_{30}H_{26}BrN_5O_2S_2$.

RESULTS AND DISCUSSION

The syntheses of desired derivatives (8a-8m) are carried out as outlined by Scheme-1.Initially, the intermediate moiety (3) is prepared from 6-bromodiphenylamine and 4-methoxy benzaldehyde by using zirconium oxychloride ($ZrOCl_2$) as a catalyst. Various Lewis acid catalysts like ferric chloride ($FeCl_3$), Titanium dioxide (TiO_2), and Aluminium chloride ($AlCl_3$)were employed for the job but proved to be inferior to $ZrOCl_2$ at selected reaction conditions. The corresponding results are shown in Table-1.

Table-1: The Catalyst's Effect on the Preparation of Derivatives (3)[a]

Entry	catalyst	NO of moles catalyst	Solvent	Time(hrs)	Yield (%)[b]
1	$FeCl_3$	1mol	C_2H_5OH	6	54
2	$SnCl_2$	1mol	C_2H_5OH	6	49
3	TiO_2	1mol	C_2H_5OH	6	67
4	$ZrOCl_2$	1mol	C_2H_5OH	6	91

[a].6-bromodiphenylamine (1.0mol) and 4-methoxy benzaldehyde (1mol) promoted by the $ZrOCl_2$ in ethanol;[b] Isolated yields.

This compound-3 prepared from optimized conditions is reacted with chloroacetic acid in the presence oftriethylamine as base and dichloromethane as a solvent to give compound (4). Further, compound (4) is reacted with thiosemicarbazide in a protic acid medium to achieve compound 5. Finally, the desired derivatives (8a-8m) can be obtained by reacting compound-5 with aryl aldehyde and dimedone promoted

by copper halide as a catalyst.The universality of the reaction was examined by using various aryl aldehydes and dimedones where the reactions are catalyzed by copper halide at reflux temperature and noticed much improvement in the isolated yield. The role of different copper halides like copper bromide ($CuBr_2$), copper chloride ($CuCl_2$), and copper iodide (CuI_2)along with copper acetate is studied while performing the reactions. Even though copper acetate seems to be comparable with other copper halides, copper iodide emerged as a more effective catalyst when the isolated yields of the desired products were compared. Also, the time of reaction is decreased drastically by using copper iodide. The reaction time vs isolated yield by using different copper catalysts is illustrated in Table-2.

Table-2: The Effect of DifferentCopper Catalysts on the Preparation of Compounds (8b)[a]

Entry	catalyst	Time (hrs)	Yield (%)[b]
1	$CuCl_2$	10	71
2	$CuBr_2$	8	80
3	CuI_2	5	90
4	$Cu(OAc)_2$	14	57

[a].Reaction conditions: compound(5) (1 m mol), dime done (1 m mol) with aryl aldehyde (1 m mol) in and CuI_2 in C_2H_5OH (10 mL) were refluxed at 70°C.[b] Isolated yields.

As discussed above, the catalyst plays a vital role in the progress of the reaction. However, the quantity of catalyst that has been loaded in the reaction also affects the reaction time and isolated yields in the preparation of desired derivatives (8a-8m) as shown in Table-3.

Table-3: The Effect of Catalyst-Loaded Quantity for the Preparation of Derivatives (8b)[a]

Entry	Amount of catalyst	Time (hrs.)	Yield (%)[b]
1	1.0 mole	5	20
2	1.5 mole	5	52
3	2.0 mole	5	75
4	2.5 mole	5	90
5	3.0 mole	5	92

[a]Reaction conditions: compound (5) 1 mmol), dimedone (1 mmol) with aryl aldehydes (1 mmol), and CuI_2 in ethanol (10mL) were refluxed at 70°C.[b] Isolated yields.

Moreover, the solvent role has also proved to play having significant role in the progress of the reaction. By fixing the reaction time, different solvents were employed for the preparation of 8a-8m, and noticed that there was a huge variation in the isolated yields. The yields increased with the increase in solvent polarity and the results of same are shown inTable-4.

Table-4: The Effect of Solvent for the Preparation of Derivatives (3b)[a]

S.No.	Solvent	Time (hrs.)	Yield (%)[b]
1	MDC	5	32
2	Toluene	5	64
3	CH_3CN	5	71
4	C_2H_5OH	5	90
5	H_2O	5	56

[a].Reaction conditions: compound (5) (1mol), dimedone (1mol) with aryl aldehydes (1 mol), and CuI_2 in ethanol (10mL) were refluxed at 70°C.[b] Isolated yields.

Another important observation while synthesizing the target compounds is that the analogs bearing electron releasing group have yielded a maximum (8b-8f) than the products(8i-8k) of the derivatives having electron attracting group. Further, the compounds bearing the halogen-containing group (8g and 8h) also got excellent yields. In this hetero aromatic aldehydeare also used for desired compounds (8l and 8m). The advantages of these catalysts, it was commercially available, easy to handle when it was applied during the reaction, have short reaction times, have easy work-up and excellent product yields, easy to simple work-up procedure, and the desired products were purified by recrystallization process.

Antibacterial Activity

The titled derivatives (8a-8m) have been evaluated for in vitro antibacterial activity against bacterial strains like S. aureus, E. coli, S. typhi, and B. substill. Agar plates containing bacterial nutrition broth

were used to assess the test analogous's in vitro activity. Every microbiological species was tested against the titledderivatives with references to Streptomycin and a common medication has been compared to the test compounds strong antibacterial action.Table-5 was indicates the derivatives' antimicrobial inhibitions, which are assessed as the area of the zone of inhibition.

Antifungal Activity

As test strains, A. Niger and Candida Albicans were utilized to determine the antifungal activity in vitro. Dimethyl sulfoxide (DMSO) was used to dissolve the tested moietiesat a concentration of 10 mg/mL. These compounds' antifungal activity was assessed using the broth microdilution method. The growth medium was Sabouraud maltose broth, and the modified antimicrobial susceptibility test was based on a reference medication. Finally, 100 µL of functional fungal culture was added to each well. In the antifungal test, fluconazole was utilized as a reference medication. As control testing, wells with broth and DMSO serially diluted were made. For 24 to 30 hours, the plate was covered and incubated at 37°C. The studied derivatives' minimum inhibitory concentration (MIC) values were ascertained in Table-5.

Antimicrobial Activity

The antibacterial activity of derivatives (8a–8m) was assessed, and the results are disclosed inTable-5. The tested analogous's greater variants of the MIC findings show that it may have had a positive impact against bacterial and fungal strains. Excellent action against bacterial strains was demonstrated by the compound "8h and 8l" (Table-5).The results show that the activity of analogous compounds with halogens at the 4-position of substituents in aromatic rings is also lower than that of donor substituents like OH and OMe in 4c or substituted phenyl ring compounds like "8b, 8c, 8d, and 8e." Better activity against Mycobacterium was obtained by derivatives with substitution at the 4-position in the benzene ring.Additionally, these antifungal compounds' antimicrobial potency was assessed against A. niger, and C. Albicans was introduced as a good to outstanding antifungal activity test. The compounds 8g, 8k, and 8l demonstrated exceptional antifungal activity, while the majority of the treated compounds demonstrated poor activity against C. Albicans.

Table-5: Antimicrobial Activity Screening Activity Synthesized Scaffold

Entry	*Zone of Inhibition in (mm)					
	Bacteria				Fungi	
	S.Aureus	*E.Coli*	*S. Typhi*	*B.Substill*	*A. Niger*	*C. Albicans*
8a	07	09	08	10	07	08
8b	18	19	19	18	12	14
8c	20	20	19	21	15	13
8d	22	22	21	20	15	14
8e	22	20	22	21	16	15
8f	19	19	18	20	10	08
8g	22	23	23	23	18	18
8h	23	21	21	22	16	17
8i	12	15	09	10	11	12
8j	07	09	12	13	08	05
8k	16	16	17	12	18	18
8l	23	24	22	22	18	17
8m	22	22	20	21	10	15
Streptomycin	27	27	25	25	NA	NA
fluconazole	NA	NA	NA	NA	22	22
DMSO	---	----	---	---	---	---

CONCLUSION

Using Streptomycin and fluconazole as standards, we have successfully synthesized an equivalent (8a-8m) starting material from 4-bromobenzene-1,2-diamine with 4-methoxybenzalde aldehyde in a simple technique with good yield and assessed its antibacterial efficacy in vitro. The bulk of the compounds that showed the strongest antibacterial activity in this investigation will undergo additional structural modifications to find a new molecule. Additionally, these findings might offer some important recommendations for the creation of a new class of antimicrobials.

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CONFLICT OF INTERESTS

The authors confidently dismiss the conflict of interest.

AUTHOR CONTRIBUTIONS

All the authors contributed significantly to this manuscript, participated in reviewing/editing and approved the final draft for publication. The research profile of the authors can be verified from their ORCID ids, given below:

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