Synthesis and Antimicrobial Activities of Some Novel Benzimidazole and Benzotriazole Derivatives containing β-Lactam Moiety

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Abstract: A new series of benzimidazole and benzotriazole derivatives bearing β-lactam moiety has been synthesized. The reaction was achieved through N-and S-alkylation of 1H-benzo[d][1,2,3]triazole, 2-(4-methoxyphenyl)-1H-benzo[d]imidazole and 1H-benzo[d]imidazole-2-thiol with ethyl-2-chloroacetate to give the corresponding ethyl esters which upon refluxing with hydrazine hydrate afforded the desired hydrazides. Condensation of these hydrazides with a variety of aromatic aldehydes yielded the corresponding substituted benzylideneacetohydrazides. Cyclization of the later hydrazides with 2-chloroacetyl chloride gave the corresponding β-lactam derivatives. In addition, cyclization of 1H-benzo[d]imidazole-2-thiol with chloro acetic acid and carbon disulphide gave thiazolo and thiazeto –thione derivatives respectively.While the cyclization of (1H-benzo[d]imidazol-2-yl) methanethiol with chloroacetic acid gave thiazino derivatives. On the other hand cyclocondensation of 1H-benzo[d]imidazole-2-thiol and(1H-benzo[d]imidazol-2-yl)methanethiol with substituted aromatic aldehyde in the presence of p-TsOH gave thiazeto and thiazolo derivatives respectively.The reaction of benzimidazole hydrazide with carbon disulphide in alkaline medium afforded, after acidic treatment, oxadiazole -2-thiol which was subsequently reacted with 2-chloro acetyl chloride in the presence of triethyl amine to produce the corresponding S- alkyl oxadiazole which upon refluxing with urea and thiourea gave thiazolo and oxazolo compounds respectively. The newly synthesized compounds were characterized by both analytical and spectral data (IR,[1]H-NMR and MS). Selected compounds were screened in vitro for their antimicrobial activities by disc diffusion method against different strains of Gram-positive bacteria *staphylococcus aureus* (ATCC 25923), *streptococcus aglactiae* (ATCC 29212) and *Bacillus subttilus* Gram-negative bacteria *Escherichia coli* (ATCC 25922) and *Pseudomonas aureginosa* (ATCC 9027) and strain of fungus *Candida albicans* (ATCC 125022) The results showed that most of the synthesized compounds have a good antibacterial activity. However, all the synthesized compounds have no anticandida activity.
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1.Introduction

Benzimidazole nucleus can be termed "Master Key" as it is an important core in many compounds acting at different targets to elicit varied pharmacological properties [(1)] like anti cancer [(2)], anti-viral [(3)], anti-bacterial [(4)], anti-fungal [(5)], anti-inflammatory [(6)], anti-histaminic [(7)], anti-oxidant [(8)], anti-hypertensive [(9)] and anti-coagulant [(10)]. Optimization of substituent around the benzimidazole nucleus has resulted in many drugs like albendazole, mebendazole, thiabendazole as antihelmintics; omeprazole, lansoprazole, pantoprazole as proton pump inhibitors and many lead compounds in a wide range of other therapeutic areas [(11)]. Though all seven positions in the benzimidazole nucleus can be substituted with a variety of chemical entities, but most of the biologically active benzimidazole based compounds bear functional groups at 1, 2 and/or 5(or 6) positions.

On the other hand, benzotriazole derivatives are synthetically important analogues and are associated with several biological and pharmacological properties [(12)]. Benzotriazole derivatives exhibit analgesic [(13)] anti inflammatory [(14)], anticonvulsant [(15)], antifungal [(16)], and antitumor agents [(17)] resulting from the potent bioactivity of benzotriazole. In addition, β-lactam ring system is the common structural feature of a number of broad spectrum β-lactam antibiotics [(18)], including penicillins, cephalosporins, carbapenems, nocardicins and monobactams, which have been widely used as chemotherapeutic agents to treat bacterial infections and microbial diseases [(19)] .The efficacy of β-lactam antibiotics has been over shadowed in the last 20 years by the emergence of drug-resistant bacterial strains resulting from evolutionary responses to the widespread overuse and abuse of antibiotics in clinical traits. Based on these findings, the aim of this study was to synthesize compounds containing benzimidazoles, benztriazoles and related heterocycles derivatives containing β-lactam moiety and to screen them for their antimicrobial Activity.

2. Materials and Methods

Apparatus

Melting points were measured in open capillary tubes using Stuart melting point apparatus SMP10 **(**UK**).** Infrared (IR) spectra were recorded using KBr discs on a Shimadzu Spectrophotometer (υ_{max} in cm^{-1}) (Kyoto, Japan). Proton Magnetic Resonance (^{1}H-NMR) spectra were recorded on Mercury–300 BB (NMR 300) spectrometer (300 MHz). Chemical shifts are reported in δ values (parts per million, ppm) relative to tetramethylsilane (TMS) as internal standard. Abbreviations used in NMR analysis are as follows: d=doublet, m=multiplet, q=quartet, s=singlet, t= triplet. Electron impact mass spectra (EI-MS) were recorded on DI Analysis Shimadzu QP-2010 Plus mass spectrometer. Elemental analyses were recorded on Vario EL-CHNS Elemental Analyzer (GmbH, Germany). The results of elemental analyses (C, H, N) were found to be in good agreement (±0.5%) with the calculated values. IR, ^{1}H -NMR, EI-MS and Elemental analyses were performed in the Microanalytical center, Cairo University, Egypt. Reactions were monitored by thin layer chromatography (TLC) on Merck silica gel 60 $_{F254}$ and visualized with UV light.

Chemicals and Reagents:

Carbon disulphide, 2-chloroacetic acid, o-pheneylene diamine, sodium acetate. DMF, 2-chloro acetyl chloride, anisaldehyde, m-nitrobenzaldehyde, salicyaldehyde, hydrazine hydrate and thioglycolic acid were obtained from Sigma, St. Louis, MO, USA and Merck, Darmstadt, Germany

Experimental

1- Chemistry

1H-benzo[d]imidazole-2-thiol 1:

A mixture of o-phenylene diamine (15.2 g, 0.14 mol), ethanol (240 ml), carbon disulfide (31 ml, 0.42 mol), and potassium hydroxide (15.6 ml, 0.28 mol) was heated under reflux for 4h. Then the solvent was distilled off and the residue was poured into 240 ml of cold water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. [20]

Mp: > 300˚C, (yield 90%). IR (cm^{-1}): 707(C-S), 2566(S-H), 3154(NH). Mass spectrum: m/z (%): 150(M^+, 100%), 118(14.9%), 106(14.5%), 65(23.2%).

1H-benzo[d][1,2,3]triazole 2:

A solution of o-phenylenodiamine (0.22 g, 0.02 mol), in acetic acid (10 mL), sodium nitrite (0.3 g, 0.04 mol) was added at 5° C and irradiated in a water bath of the ultrasonic cleaner at 5-10 °C for 30 min. After completion of the reaction the solvent was removed and the organic phase extracted with methylene dichloride (20 mL), washed with water (3 X 10 mL) and dried with $MgSO_4$. The solvent was removed under reduced pressure and the products were isolated with satisfactory purity [21]

Mp: 100˚C, (yield 80%).

2-(4-Methoxyphenyl)-1H-benzo[d]imidazole 3:

A mixture of o-phenylene diamine (0.1 g , 1 mol), sodium metabisulfite adduct of 4-methoxy benzaldehyde (0.2 g, 0.012 mol) in N,N-dimethyl formamide (DMF, 5ml) was heated at 110 °C for 5 h. Water was added to the reaction mixture and the solid product was collected by filtration and washed with water. The crude product was recrystallized from EtOH. [22]

Mp 223-225˚C (yield 85%). IR (cm^{-1}): 1456(C=N), 3228(NH). Mass spectrum: m/z(%): 224(M^+, 18.37%), 206(12.39%), 194(13.98%), 180(4.07%), 167(3.02%), 140(1.58%), 119(53.82%), 103(7.23%), 93(100%), 77(33.91%), 66(20.71%).

General procedure for preparation of ethyl 2-(1H-benzo[d]imidazol-2-ylthio) acetate(4), ethyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)acetate(5) and Ethyl 2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetate(6):

A mixture of ethyl chloro acetate (1.2 ml , 0.01 mol) ,1H-benzo[d]imidazole-2-thiol **(1)** or 1H-benzo[d][1,2,3]triazole **(2)** or 2-(4-Methoxyphenyl)-1H-benzo[d]imidazole **(3)** (0.01 mol) ,acetone (20 ml) and anhydrous K_2CO_3 (1 g) was refluxed for 10 h. Acetone was removed after completion of reaction and the residue crystallized from ethanol. [23]

Ethyl 2-(1H-benzo[d]imidazol-2-ylthio) acetate 4:

Mp: 117˚C, (yield 75%). IR (cm^{-1}): 738(C-S), 1730(C=O), 3449(N-H). Mass spectrum: m/z(%): 236(M^+,69.73%), 217(3.82%),191(13.18%),163(100%),149(21.85%).

Ethyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)acetate 5:

Mp: 68-70˚C, (yield 70%). IR (cm^{-1}): 1620(N=N), 1745(C=O). Mass spectrum: m/z (%): 205(M^+,6.70%),191(0.18%),177(0.47%),132(51.43 %),104(41.53%),77(100%).

Ethyl 2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) acetate 6:

Mp: 151-153˚C. IR (cm^{-1}): 1205(C-O-C), 1746(C=O ester). Mass spectrum: m/z(%): 310(M^+, 68%), 296(75.03%), 281(0.65%), 265(12.29%), 237(100%), 222(34.23%), 206(11.25%), 194(23.76%), 167(0.05%), 140(1.47%), 129(7.79%), 90(4.31%), 77(31.31%), 63(3.57%).

General procedure for preparation of 2-(1H-benzo[d]imidazol-2-ylthio)acetohydrazide(7), 2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide(8) and 2[2-(4 Methoxy phenyl)-1H-benzo[d]imidazol-1-yl] acetohydrazide(9):

A mixture of hydrazine hydrate 80% (0.05 mol, 0.25 ml) and ethyl 2-(1H-benzo[d]imidazol-2-ylthio)acetate **(4)** or ethyl 2-(1H-benzo[d][1,2,3]triazol-1-yl)acetate **(5)** or ethyl 2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetate **(6)** (0.0015 mol) in absolute ethanol (20 ml) were refluxed for 4 h. The reaction mixture

was cooled and poured into water. The crude product was filtered off and recrystallized from ethanol to give the desired hydrazides. [22]

2-(1H-benzo[d]imidazol-2-ylthio) acetohydrazide 7:

Mp: 143-145˚C, (yield 65%). IR (cm^{-1}): 745(C-S), 1643(C=O), NH_2 (3146), 3261(N-H). Mass spectrum: m/z(%): 225(M^++3, 0.19%), 222(12.60%), 200(1.03%), 191(12.42%), 175(0.21%), 163(7.16%).

2-(1H-benzo[d][1,2,3]triazol-1-yl)acetohydrazide 8:

Mp: 162-165˚C, (yield 60%). IR (cm^{-1}): 1542(N=N), 1652(C=O), 3060(NH_2), 3309(N-H). Mass spectrum: m/z(%): 191(M^+, 29.54%), 177(0.20%), 160(0.65%), 147(2.52%), 133(12.39%), 120(29.60%).

2[2-(4 Methoxy phenyl)-1H-benzo[d]imidazol-1-yl] acetohydrazide 9:

Mp: 180-183˚C, (yield 88%). IR (cm^{-1}): 1246(C-O-C), 1611(C=N), 1693(C=O), 3229(NH_2), 3333(NH). Mass spectrum: m/z(%): 296(M^+, 75.43%), 281(1.01%), 265(12.51%), 237(100%), 222(33.79%), 206(10.56%), 194(21.35%), 167(2.47%), 148(1.32%), 129(6.81%), 119(0.62%), 103(4.83%), 90(3.47%), 77(23.54%), 63(2.92%), 51(10.56%).

General procedure for preparation of 2-(1H-benzo[d]imidazol-2-ylthio)-N'-(substituted benzylidene) acetohydrazide (10-11) , 2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(substitutedbenzylidene) acetohydrazide(12-13) and (E)-N'-(substituted benzylidene)-2-(2-(4-methoxy phenyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide(14-15):

A mixture of acetohydrazides **(7-9)** (0.01 mol) and appropriate aromatic aldehyde (0.01 mol) in methanol (20 ml) in the presence of catalytic amount of glacial acetic acid was refluxed for 5 h. The solvent was removed under reduced pressure and the product recrystallized from chloroform. [24]

2-(1H-benzo[d]imidazol-2-ylthio)-N'-(4-methoxybenzylidene) acetohydrazide 10:

Mp: 128-130˚C, (yield 80%). IR (cm^{-1}): 743(C-S), 1249(O-CH_3), 1598(C=O), 3412(N-H). Mass spectrum: m/z (%): 341(M^++1, 0.71%), 328(0.24%), 313(0.22%), 299(0.26%), 268(4.41%), 256(1.31%).

2-(1H-benzo[d]imidazol-2-ylthio)-N'-(2-hydroxybenzylidene) acetohydrazide 11:

Mp: 158-160˚C, (yield 65%). Mass spectrum: m/z (%): 326 (M^+, 0.63%), 315(0.69%), 293(0.58%), 270(1.66%), 264(0.91%), 240(100%).

2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(4-methoxybenzylidene) acetohydrazide 12:

Mp: 141-144˚C, (yield 65%). IR (cm^{-1}): 1251(OCH_3), 1682(C=O), 3432(N-H). Mass spectrum: m/z (%): 309(M^+, 28.08%), 296(31.15%), 285(36.15%), 277(30.00%), 252(29.23%), 226(34.62%), 214(29.23%).

Mp: 168-171˚C, (yield 65%). IR (cm^{-1}): 1692(C=O), 3392(N-H), 3746(OH). Mass spectrum: m/z(%): 295(M^+,57.05%), 282(55.77%), 275(40.38%), 265(51.92%), 241(50.00%), 226(38.46%).

2-(2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)-N'-(3-nitrobenzylidene) acetohydrazide 14:

Mp: 158-160˚C, (yield 60%) IR (cm^{-1}): 1251(O-CH_3), 1527(NO_2), 1698(C=O), 3405(NH). Mass spectrum: m/z(%): 429(M^+, 100%), 237(19.16%), 193(10.41%), 103(20.08%), 77(63.21%).

N'-(4-methoxybenzylidene)-2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide 15:

Mp: 140-143˚C, (yield 70%) IR (cm^{-1}): 1254(O-CH_3), 1675(C=O), 3407(N-H). Mass spectrum: m/z(%): 414(M^+, 48.71%), 398(5.38%), 331(6.81%), 237(100%), 222(28.53%), 194(23.18%).

General procedure for preparationof 2-(1H-benzo[d]imidazol-2-ylthio)-N-(3-chloro-2-(substitutedphenyl)-4-oxoazetidin-1-yl)acetamide(16-17) , 2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-(supstituted phenyl)-4-oxoazetidin-1-yl)acetamide(18-19) and N-(3-chloro-2-(substituted phenyl)-4-oxoazetidin-1-yl)-2-(2-(4-methoxy phenyl)-1H-benzo[d]imidazol-1-yl)acetamide (20-21):

2-Chloroacetyl chloride (1.13 ml, 0.01 mol) was added drop wise to a mixture of 2-(1H-benzo[d]imidazol-2-ylthio)-N'-(substituted benzylidene) acetohydrazide **(10-11)** or 2-(1H-benzo[d][1,2,3]triazol-1-yl)-N'-(substitutedbenzylidene) acetohydrazide **(12-13)** or (E)-N'-(4-methoxybenzylidene)-2-(2-(supstituted phenyl)-1H-benzo[d]imidazol-1-yl) acetohydrazide **(14-15)** (0.01 mol), Et_3N (1 ml, 0.01 mol) and methanol for 2 h. The well-stirred reaction mixture was refluxed for 5 h. The reaction mixture was cooled and excess of solvent was evaporated under reduced pressure and the product recrystallized from chloroform. [24]

2-(1H-benzo[d]imidazol-2-ylthio)-N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl) acetamide 16:

Mp: 160-162˚C, (yield 55%). IR (cm^{-1}): 750(C-Cl), 1248(OCH_3), 1612(C=O), 1720 (C=O), 613(C-S). Mass spectrum: m/z(%): 416(M^+, 13.31%), 386(16.44%), 362(13.89%), 219(21.72%), 196(19.57%), 69(100%).^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 2.51(s,3H,OCH_3), 3.83(s,2H,CH_2-S), 5.07(d,1H,CH-Cl), 5.54(d,1H,CH-Ph), 7.07-7.74(m,8H,Ar-H), 12(s,2H,2NH). Elemental analysis calculated for $C_{19}H_{17}ClN_4O_3S$: C, 54.74; H, 4.11 ; N, 13.44 . Found: C, 54.33; H, 4.49; N, 13.13.

2-(1H-benzo[d]imidazol-2-ylthio)-N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide 17:

Mp: 195-198˚C, (yield 60%) IR (cm^{-1}): 740(C-Cl), 1625(C=O), 1717 (C=O), 3412(O-H). Mass spectrum: m/z(%): 402(M^+, 57.41%), 392(50.93%), 377(58.33%), 324(67.59%), 223(80.56%), 166(79.63%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 4.2(d,1H,CH-Cl), 4.8(d,1H,CH-Ph), 6.94(s,2H,CH_2-S), 6.96-7.70(m,8H,Ar-H), 11.02-11.11(s,2H,2NH), 12.23(s,1H,OH). Elemental analysis calculated for $C_{18}H_{15}ClN_4O_3S$: C, 53.67; H, 3.75; N, 13.91. Found: C, 53.34; H, 4.09; N, 14.29.

2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)acetamide 18:

Mp: 160-163˚C, (yield 60%). IR (cm^{-1}): 617(C-Cl), 1247(OCH_3), 1601(C=O), 1739 (C=O), 3417(N-H). Mass spectrum: m/z (%): 386(M^++1, 9.45%), 385(16.18%), 368(14.18%), 353(14.18%), 331(15.82%), 307(12.91%). Elemental analysis calculated for $C_{18}H_{16}ClN_5O_3$: C, 56.04; H, 4.18; N, 18.15. Found: C, 56.42; H, 4.55; N, 17.87.

2-(1H-benzo[d][1,2,3]triazol-1-yl)-N-(3-chloro-2-(2-hydroxyphenyl)-4-oxoazetidin-1-yl)acetamide 19:

Mp: 113-115˚C, (yield 60%). IR (cm^{-1}): 745(C-Cl), 1618(C=O), 1729 (C=O), 3420(N-H), 3736(OH), Mass spectrum: m/z(%): 372(M^++1, 0.15%), 371(0.22%), 350(0.18%), 344(0.20%), 322(0.19%), 240(7.76%), 223(0.67%).^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 1.16(s, 2H, CH_2-CO), 5.6 (d, 1H, CH-Cl), 6.93(d, 1H, CH-Ph), 6.96-7.70(m, 8H, Ar-H), 8.99(s, 1H, N-H), 11.11(s, 1H, OH). Elemental analysis calculated for $C_{17}H_{14}ClN_5O_3$: C, 54.92; H, 3.80; N, 18.84. Found: C, 55.28; H, 3.46; N, 18.52.

N-(3-chloro-2-(3-nitrophenyl)-4-oxoazetidin-1-yl)-2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetamide 20:

Mp: 253˚C, (yield 55%) IR (cm^{-1}): 744(C-Cl), 1522(NO_2), 1608(C=O), 1699 (C=O), 3423(N-H). Mass spectrum: m/z(%): 509(M^++4, 9.40%), 381(1.o1%), 327(9.49%), 270(9.68%), 204(17.88%), 80(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.82(s, 2H, CH_2-CO), 3.86(s, 3H, OCH_3), 5.24(d, 1H, CH-Cl), 5.69(d, 1H, CH-Ph), 7.16-8.54(m, 12H, Ar-H), 12.17(s, 1H, N-H). Elemental analysis calculated for $C_{25}H_{20}ClN_5O_5$: C, 59.35; H, 3.98; N, 13.84. Found: C, 59.72; H, 3.58; N, 13.49.

N-(3-chloro-2-(4-methoxyphenyl)-4-oxoazetidin-1-yl)-2-(2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)acetamide 21:

Mp: 147-150˚C, (yield 65%) IR (cm^{-1}): 747(C-Cl), 1606(C=O), 1692(C=O), 3419(N-H). Mass spectrum: m/z(%): 490(M^+, 30.72%), 367(43.67%), 325(43.07%), 251(42.17%), 135(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.01(s, 3H, OCH_3) 3.04(s, 3H, OCH_3), 3.83(s, 2H, CH_2-CO), 5.06(d, 1H, CH-Cl), 5.45(d, 1H, CH-Ph), 6.96-7.49(m, 12H, Ar-H), 11.73(s, 1H, N-H). Elemental analysis calculated for $C_{26}H_{23}ClN_4O_4$: C, 63.61; H, 4.72; N, 11.41. Found: C, 63.79; H, 5.06; N, 11.77.

General procedure for preparation of 2-(subsituted benzylidene) benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one (22-26):

A mixture of 1H-benzo[d]imidazole-2-thiol **(1)** (1.5g, 0.01 mol), 2-chloroacetic acid (0.95 ml, 0.01 mol), appropriate aromatic aldehyde (0.012 mol) and anhydrous sodium acetate (1.64 g, 0.02 mol) were refluxed for 3 h in a mixture of acetic anhydride (5 ml) and glacial acetic acid (5 ml). Obtained powders were filtered off, washed with methanol and recrystallized with acetic acid [(25)].

2-Benzylidene benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one 22:

Mp: 218-220˚C, (yield 65%). IR (cm^{-1}): 754(C-S), 1730(C=O). Mass spectrum: m/z(%): 278 (M^+,100%), 249(20.5%), 129(59,9%), 90(27.1%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 5.71(s, 1H, CH), 7.30-8.11(m, 9H, Ar-H). Elemental analysis calculated for $C_{16}H_{10}N_2OS$: C, 69.04; H, 3.62; N, 10.06. Found: C, 68.43; H, 3.36; N, 10.55.

2-(3-Nitrobenzylidene) benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one 23:

Mp: 216-218˚C, (yield 85%).IR (cm^{-1}): 745(C-S), 1507(NO_2), 1726(C=O). Mass spectrum: m/z(%): 323(M^+,100%), 277(17.9%), 249(18.8%), 190(24.2%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 7.29-7.84(m, 8H, Ar-H), 8.68(s, 1H, CH). Elemental analysis calculated for $C_{16}H_9N_3O_3S$: C, 59.44; H, 2.81; N, 13.00. Found: C, 59.78; H, 2.64; N, 13.37.

2-(4-Methoxybenzylidene) benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one 24:

Mp: 198-200˚C, (yield 80%). IR (cm^{-1}): 748(C-S), 1013(O-CH_3), 1721(C=O). Mass spectrum: m/z(%): 308(M^+, 1.1%), 208(30.1%), 190(71%), 118(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.86(s, 3H, OCH_3), 4.13(s, 1H, CH),7.09-8.08(m, 8H, Ar-H) . Elemental analysis calculated for $C_{17}H_{12}N_2O_2S$: C, 66.22; H, 3.92; N, 9.08. Found: C, 66.47; H, 3.64; N, 8.82

2-(2-Hydroxybenzylidene) benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one 25:

Mp: 219-221˚C, (yield 88%).IR (cm^{-1}): 749(C-S), 1722(C=O), 3417(O-H). Mass spectrum: m/z(%): 294(M^+,41.4%), 266(54.3%), 237(12,9%), 145(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 4.13(s, 1H, CH), 7.09-8.60 (m, 8H, Ar-H), 12.80(s,1H,OH). Elemental analysis calculated for $C_{16}H_{10}N_2O_2S$: C, 65.29; H, 3.42; N, 9.52. Found: C, 65.61; H, 3.72; N, 9.87.

2-(Furan-2-ylmethylene) benzo[d]thiazolo [3, 2-a] imidazol-3(2H)-one 26:

Mp: 240˚C, (yield 85%). IR (cm^{-1}): 754(C-S), 1373(C-N), 1718(C=O). Mass spectrum: m/z(%): 268 (M^+,100%), 240 (22.9%), 119(33.7%), 96(21.5%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 7.26-7.96 (m, 7H, Ar-H), 8.17(s, 1H, CH). Elemental analysis calculated for $C_{14}H_8N_2O_2S$: C,

62.67; H, 3.01; N, 10.44. Found: C, 62.98; H, 3.08; N, 10.61.

General procedure for preparation of 2-subsitutedphenyl-2H-benzo[d][1,3]thiazeto[3,2-a]imidazole (27-28):

An equimolar mixture of 1H-benzo[d]imidazole-2-thiol **(1)** (1.5 g, 0.01 mol), aromatic aldehyde (0.01 mol) and p-TsOH (0.5 g, 0.003 mol) in dry DMF (50 mL) was refluxed for 10–12 h, cooled, and poured onto crushed ice. The isolated product was crystallized from methanol [26]

2-(4-Methoxyphenyl)-2H-benzo[d][1,3]thiazeto[3,2-a]imidazole 27:

Mp: 270˚C, (yield 70%).IR (cm^{-1}): 709(C-S), 1261(O-CH_3). Mass spectrum: m/z (%): 271(M^++3, 0.4 %), 150(100%), 122(12.3%), 106(15.8%), 65(25,9%). Elemental analysis calculated for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 67.38; H, 4.22; N, 10.68.

2-(2H-benzo[d][1,3]thiazeto[3,2-a]imidazol-2-yl)phenol 28:

Mp: 275˚C, (yield 75%). IR (cm^{-1}): 708(C-S), 3439(O-H). Mass spectrum: m/z(%): 256 (M^++2, 11.9%), 176(21.4%), 150(100%), 122(26.2%), 106(47.6%), 309(1.36%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.30(s, 1H, CH), 7.08-7.14(m, 8H, Ar-H), 12.48(s, 1H, OH). Elemental analysis calculated for $C_{14}H_{10}N_2OS$: C, 66.12; H, 3.96; N, 11.02. Found: C, 66.51; H, 3.63; N, 11.59.

2H-benzo[d][1,3]thiazeto[3,2-a]imidazole-2-thione 29:

A mixture of 1H-benzo[d]imidazole-2-thiol **(1)** (1.5 g, 0.01mol) and carbon disulphide (1 ml) in pyridine (25 ml) was refluxed for 8 h then left to cool and poured on ice cold water . The solid obtained was filtered, washed with water, dried and recrystalized from ethanol. [27]

Mp: 220-222˚C, (yield 90%). IR (cm^{-1}): 738(C-S), 1176(C=S). Mass spectrum: m/z(%): 193(M^++2, 12.59%), 191(12.94%), 169(11.17%), 150(100%), 129(15.96%), 98(19.68%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 7.01-7.15(m, 4H, Ar-H). Elemental analysis calculated for $C_8H_4N_2S_2$: C, 49.98; H, 2.10; N, 14.57. Found: C, 49.57; H, 2.48; N, 14.75.

(1H-benzo[d]imidazol-2-yl) methanethiol 30:

A mixture of o-phenylenediamine (1 g, 0.01mol) was mixed with thioglycolic acid (0.9 ml, 0.01 mol) added to 4 N HCl (5 ml) and refluxed for 24 h. After completion of the reaction, the reaction mixture was cooled and neutralized with ammonia soln. The solid separated through filtration and recrystallized from acetone.[28]

Mp: 157˚C, (yield 75%). IR (cm^{-1}): 738(C-S), 2676(S-H), 3419(N-H). Mass spectrum: m/z(%): 164(M^+, 99.7%), 131(100%), 119(23.4%), 104(20.7%), 91(11.7%).

1H-[1,4]thiazino[4,3-a]benzimidazol-4(3H)-one 31:

A mixture of (1H-benzo[d]imidazol-2-yl) methanethiol **(30)** (1.64 g, 0.01 mol), 2-chloroacetic acid (0.95 ml, 0.01 mol) and sodium acetate (0.8 g, 0.01mol) was refluxed for 6 h. Reaction progress was monitored by TLC. Upon completion of reaction, the reaction mixture was cooled. The solid product was recrystallized from ethanol. [29]

Mp: 250˚C, (yield 60%). IR (cm^{-1}): 738(C-S), 1619(C=O). Mass spectrum: m/z(%): 204(M^+, 26.%1), 131(52.2%), 90(47.8%), 71(78.3%), 55(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.65-4.08(dd, 2H, CH_2-S), 5.20-5.80(dd, 2H, CH_2C=O), 6.96-7.85(m, 4H, Ar-H). Elemental analysis calculated for $C_{10}H_8N_2OS$: C, 58.80; H, 3.95; N, 13.72. Found: C, 58.46; H, 3.58; N, 13.43.

General procedure for preparation of 1-(substitutedphenyl-1,3-dihydrobenzo[d]thiazolo[3,4-a]imidazole 32-33:

An equimolar mixture of (1H-benzo[d]imidazol-2-yl)methanethiol **(30)** (1.64 g, 0.01 mol), aromatic aldehyde (0.01 mol) and p-TsOH (0.5 g, 0.003 mol) in dry DMF (50 mL) was refluxed for 10–12 h, cooled, and poured onto crushed ice. The isolated product was crystallized from methanol [26]

1-(4-Methoxyphenyl)-1,3-dihydrobenzo[d]thiazolo[3,4-a]imidazole 32:

Mp: 139-142˚C, (yield 60%). IR (cm^{-1}): 743(C-S), 1254(O-CH_3), 1601(C=N). Mass spectrum: m/z(%): 284(M^++2, 64.95 %), 269(56.70%), 252(75.26%), 250(53.61%), 227(68.04%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 2.27(s, 3H, OCH_3) 3.57-3.82(dd, 2H, CH_2), 7.06(s,1H,CH), 7.11-7.88(m, 8H, Ar-H). Elemental analysis calculated for $C_{16}H_{14}N_2OS$: C, 68.06; H, 5.00; N, 9.92. Found: C, 68.39; H, 4.77; N, 9.58.

2-(1, 3-Dihydrobenzo[d]thiazolo[3,4-a]imidazol-1-yl)phenol 33:

Mp: 132-135˚C, (yield 65%). Mass spectrum: m/z(%): 269(M^++1, 45.93%), 254(52.59%), 240(54.07%), 204(45.93%), 131(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm)= 5.61-5.64(dd, 2H, CH_2), 6.5(s, 1H, CH), 7.31-7.59(m, 8H, Ar-H), 10.20(s, 1H, OH). Elemental analysis calculated for $C_{15}H_{12}N_2OS$: C, 67.14; H, 4.51; N, 10.44. Found: C, 66.79; H, 4.18; N, 10.16.

5-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-oxadiazole-2-thiol 34:

A mixture of 2[2-(4 methoxy phenyl)-1H-benzo[d]imidazol-1-yl] acetohydrazide **(9)** (2.96 g, 0.01 mol), absolute ethanol (100 ml), carbon disulfide (1.14 ml, 0.015 mol), and potassium hydroxide (0.8 g, 0.015 mol) was heated under reflux for 4 h. Then the solvent was distilled off, and the residue was poured into 240 ml of water. The separated precipitate was filtered off, dried, and recrystallized from ethanol. [20]

Mp: 227-230˚C, (yield 85%). IR (cm^{-1}): 1262(C-O-C), 1606(C=N), 2330(SH). Mass spectrum: m/z(%): 338(M^+, 100%), 322(1.55%), 306(1.13%),

280(12.88%), 262(7.43%), 237(52.40%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.88(s, 3H, OCH_3), 6.06(s, 2H, CH_2), 7.22-8.04(m, 8H, Ar-H), 9.33(s, 1H, SH). Elemental analysis calculated for $C_{17}H_{14}N_4O_2S$: C, 60.34; H, 4.17; N, 16.56. Found: C, 60.21; H, 4.05; N, 16.36.

S-5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-yl 2-chloroethanethioate 35:

2-Chloroacetyl chloride (1.13 ml, 0.01 mol) was added drop wise to a mixture of 5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl)-1, 3, 4-oxadiazole-2-thiol **(34)** (3.38 g, 0.01 mol), Et_3N (1 ml, 0.01 mol) and methanol and stirred for 2 h. The well stirred reaction mixture was refluxed for 5 h. The reaction mixture was cooled and excess of solvent was evaporated under reduced pressure and the product recrystallized from chloroform. [24]

Mp: 106-108˚C, (yield 65%). IR (cm^{-1}): 740(C-Cl), 1248(O-CH_3), 1611(C=O). Mass spectrum: m/z(%): 416 (M^++2, 4.57%), 344(2.9%), 310(2.8%), 249(1.0%), 224(100%).

5-(5-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)thiazol-2-amine 36:

A mixture of S-5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl) - 1, 3, 4-oxadiazol-2-yl 2-chloroethanethioate **(35)** (8.3 g, 0.02 mol), absolute ethanol (50 ml) and thiourea (1.9 g, 0.025 mol) was refluxed for 12 h. After completion of the reaction (monitored by TLC), it was cooled and poured onto crushed ice. The separated solid was filtered, washed with sodium bicarbonate (2%) solution and recrystallized from ethanol. [30]

Mp: 115˚C, (yield 55%). IR (cm^{-1}): 743(C-S), 1164(C-O-C), 1248(O-CH_3), 3455(NH_2). Mass spectrum: m/z(%): 436(M^+, 3.02%), 410(31.72%), 403(15.41%), 265(74.02%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 2.60 (s, 2H, NH_2), 3.85 (s, 3H, OCH_3), 5.78 (s, 2H, CH_2), 7.11-7.83 (m, 9H, ArH). Elemental analysis calculated for $C_{20}H_{16}N_6O_2S_2$: C, 55.03; H, 3.69; N, 19.25. Found: C, 55.39; H, 3.24; N, 19.59.

5-(5-((2-(4-Methoxyphenyl)-1H-benzo[d]imidazol-1-yl)methyl)-1,3,4-oxadiazol-2-ylthio)oxazol-2-amine 37:

A mixture of S-5-((2-(4-methoxyphenyl)-1H-benzo[d]imidazol-1-yl) methyl) - 1, 3, 4-oxadiazol-2-yl 2-chloroethanethioate **(35)** (8.3 g, 0.02 mol), urea (1.5 g, 0.025 mol) and dry methanol (50 ml) was refluxed for 12 h. After completion of the reaction (monitored by TLC), it was cooled and poured onto crushed ice. The separated solid was filtered, washed with sodium bicarbonate (2%) solution and recrystallized from ethanol. [30]

Mp: 85˚C, (yield 50%). IR (cm^{-1}): 743(C-S), 1156 (C-O-C), 1249(O-CH_3), 3429(NH_2). Mass spectrum: m/z(%): 422 (M^++2, 32.25%), 406(22.9%), 394(30.22%),237(100%). ^{1}H-NMR (DMSO, 300 MHz): δ(ppm) = 3.30(s, 2H, NH_2), 3.85(s, 3H, OCH_3), 5.78(s, 2H, CH_2), 7.11-7.76(m, 9H, Ar-H). Elemental analysis calculated for $C_{20}H_{16}N_6O_3S$: C, 57.13; H, 3.84; N, 19.99. Found: C, 57.55; H, 3.63; N, 19.83.

2- Biological studies

2.1. Antimicrobial screening

The antimicrobial activities of the synthesized compounds were tested by the disk diffusion method [31] against different strains of Gram-positive bacteria *staphylococcus aureus* (ATCC 25923*), streptococcus aglactiae* (ATCC 29212) and *Bacillus subtilus* (ATCC 813106), Gram-negative bacteria *Escherichia coli* (ATCC 25922) and *Pseudomonas aureginosa* (ATCC 9027) and strain of fungus *Candida albicans* (ATCC 2091).

Paper disc agar diffusion method:-

A plate of 90 mm diameter containing the Muller Hinton agar for the growth of bacteria and the sabouraude dextrose agar for the growth of fungi were prepared and each plate was separately inoculated with different cultures of the test bacteria and fungi by swabbing aseptically on the whole surface of the agar with cotton wool. A 6 mm diameter filter paper disc was impregnated with 20 µl of tested compounds in dimethylsulfoxide. The discs were air dried and placed aseptically at the center of the plates. The plates were left in refrigerator for 1 hour before incubation to allow the extract to diffuse into the agar. Cefotaxime (0.050 mg) and Ampicillin (0.050 mg), were also impregnated onto the disc, air dried, and used as a positive control. The plate were incubated at the suitable temperature (37° C for bacteria and 25° C for fungi) the growth inhibition, was measured. Evaluated of the inhibitory properties was carried out in duplicates.

3.Results and Discussion

1-Chemistry

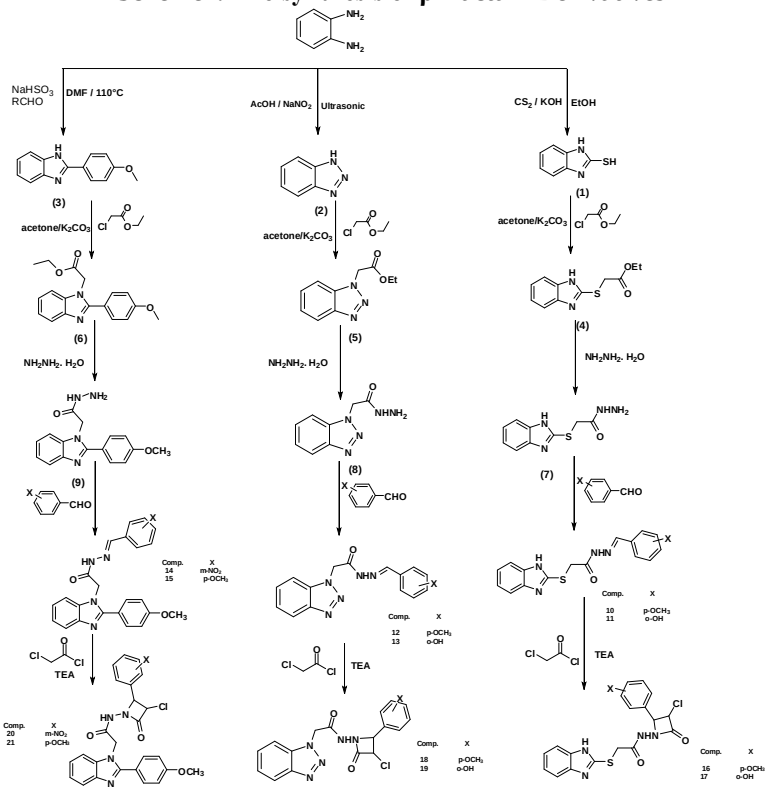
In scheme 1, o-phenylene diamine undergo three cyclization reactions with different methods to give benzimidazole and benztriazole derivatives, in the first cyclization [20] o-phenylenediamine was refluxed with carbon disulfide in the presence of KOH and EtOH to give benzimidazole thiol **1** In the second cyclization [21] o-phenylene diamine was irradiated with acetic acid and sodium nitrite in an ultrasonic cleaner to give benzotriazole **2** through diazotization reaction. In the third cyclization [22] oxidative condensation of o-phenylenediamine with sodium metabisulfite adduct of appropriate aldehydes in the presence of DMF to give benzimidazole **3**. Compounds **1-3** was alkylated [23] by refluxing with ethylchloroacetate to give the corresponding esters **4-6** which was approved by IR spectrum that showed the appearance of the band corresponding to C=O of ester at the range of 1643 -1745 cm^{-1}. These esters was allowed to react with hydrazine hydrate [22] to give corresponding

hydrazides **7-9** which showed in the IR spectrum the appearance of bands corresponding to NH_2 and NH at the range of 3146-3333 cm^{-1}. Hydrazides **7-9** were condensed [24] with different aldehydes to give different benzylidene derivative **10-15,** the IR spectra of these compounds showed the absence of band corresponding to NH_2. These benzylidene derivatives **10-15** were allowed to react with chloroacetyl chloride [24] in the presence of TEA to form the beta lactam bearing compounds **16-21.** The structure of these compounds was approved in IR and ^{1}H-NMR , in IR the band corresponding to C-Cl appeared at range of 740-750 cm^{-1} in addition to the two C=O of beta lactam ring and amide at the range of 1675-1739 cm^{-1} and 1601-1692 cm^{-1} respectively, while the ^{1}H-NMR spectrum showed two doublet signals for protons of CH-Cl and CH-Ph of beta lactam ring at the range of 5.6-5.24 δ (ppm) and 5.54-6.93 δ (ppm) respectively.

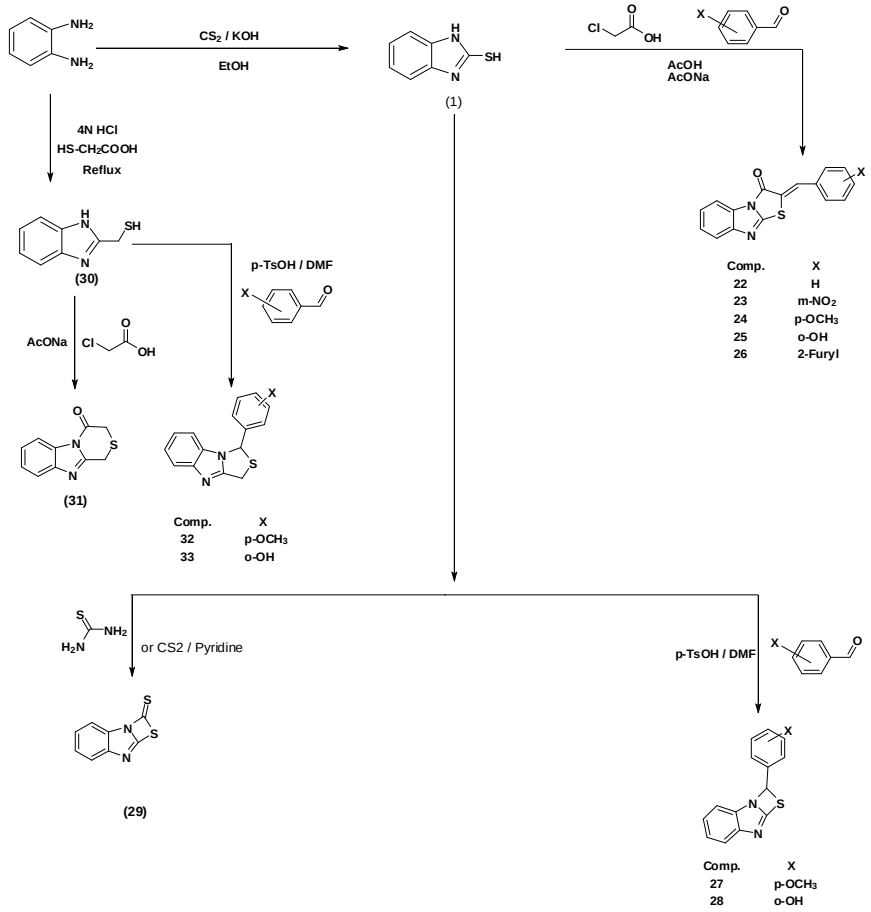
In scheme 2, benzimidazole thiol **1** was cyclocondensation [25] with appropriate aromatic aldehydes in the presence of chloroacetic acid to give thiazolo derivatives **22-26** which was confirmed in IR spectrum by the disappearance of band corresponding to S-H and appearance of amidic group band at range of 1718-1730 cm^{-1} and in ^{1}H-NMR spectrum by the appearance of single signal at 8.17 δ (ppm) for C=CH and absence of signal for S-H proton. On the other hand cyclization of benzimidazole thiol **1** with substituted aromatic aldehyde in the presence of p-TsOH and DMF [26] gave thiazeto derivatives **27-28** which showed in ^{1}H-NMR singlet signal at 3.30 δ (ppm) for CH of thiazito ring. Reaction of compound **1** with CS_2 [27] in the presence of pyridine gave thiazeto –thione derivative **29** which showed in IR spectrum the absorption band for C=S at 1167 cm^{-1} and disappearance of S-H band. Refluxing of o-phenylene diamine with thioglycolic acid [28] gave (1H-benzo[d]imidazol-2-yl) methanethiol **30** which upon refluxing with chloroacetic acid [29] gave thiazino derivative **31** which showed in IR spectrum the amidic C=O absorption band at 1619 cm^{-1} and in ^{1}H-NMR spectrum two doublet of doublet signal at range of 3.65-4.08 and 5.20-5.80 δ (ppm). Condensation of compound **30** with appropriate aldehydes [26] in the presence of p-TsOH and DMF gave thiazolo derivatives **32-33**, the success of the reaction was approved from IR and ^{1}H-NMR spectra where the S-H disappeared from both spectra and in ^{1}H-NMR spectrum showed doublet of doublet signals at range of 3.57-3.82 and 5.61-5.64 δ (ppm) for CH of thiazole ring.

In scheme 3, cyclization [20] of benzimidazole hydrazide **9** with carbon disulphide in alkaline medium afforded, after acidic treatment, oxadiazole -2-thiol **34** which was subsequently reacted with 2-chloro acetyl chloride [24] in the presence of triethyl amine to produce the corresponding S- alkyl oxadiazole **35** which upon refluxing [30] with urea and thiourea gave thiazolo and oxazolo compounds **36-37** respectively which was confirmed in both IR and ^{1}H-NMR spectra, where in IR spectrum showed the absence of carbonyl absorption band and appearance of NH_2 absorption band at range of 3455 and 3429 cm^{-1} , while in ^{1}H-NMR spectrum showed singlet signal at 2.60-3.30 δ (ppm) for protons of NH_2.

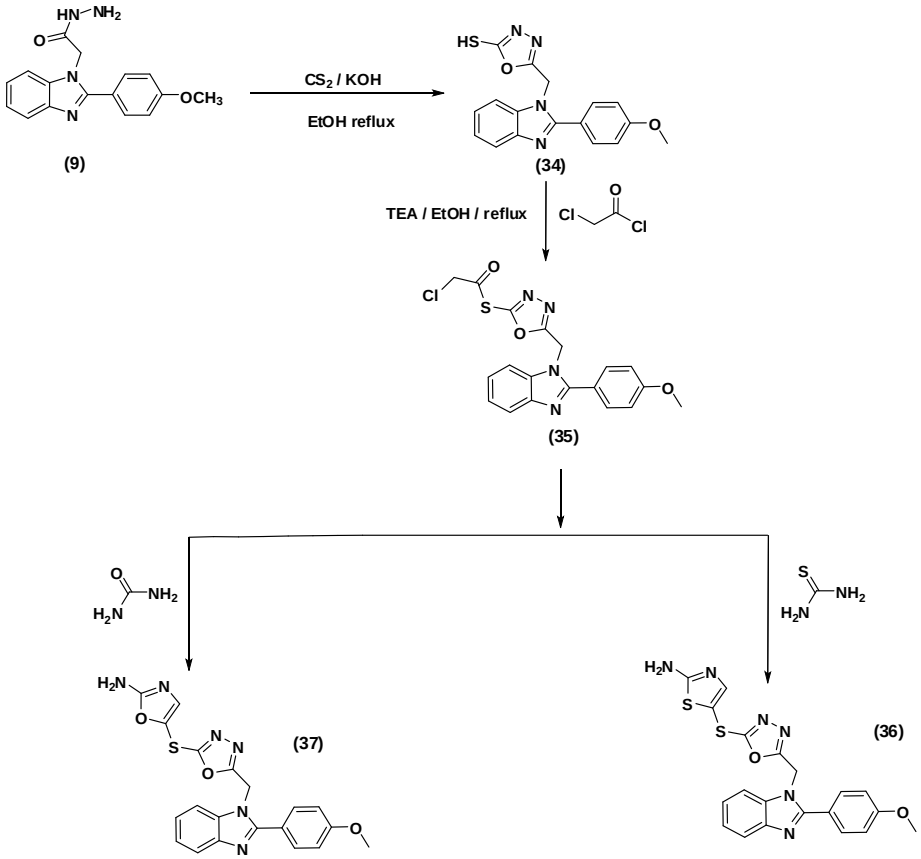
Scheme1. The synthesis of β-Lactam Derivatives



Scheme2. The synthesis of Benzimidazole-2-thiol Derivatives



Scheme3. The synthesis of Benzimdazole Derivatives



2- Biological results

Antimicrobial screening

The antimicrobial activities of compounds **16-29**, **31- 33**, **36** and **37** were tested by the disk diffusion method. From the data it is clear that compounds **16-19** showed intermediate activity against both Gram positive and Gram negative bacteria and this compounds have been substituted at position 4 of beta-lactam ring with either *o*-hydroxy or *p*-methoxy phenyl moiety. Substitution on the N atom of beta-lactam ring with 2-(1H-benzo[d]imidazole-2-ylthio)acetamide and 2(1H-benzo[d][1, 2, 3triazol-1-yl]acetamide moiety (**16**, **17**, **18** and **19**) increased the activity against both Gram positive and Gram negative bacteria while substitution with 2-(2(4-methoxy phenyl)-1H benzo[d]imidazole-1-yl)acetamide moiety**(20 - 21)** led to reduction of antibacterial activity this may be due to steric hindrance. Compound **16** and **17** have the same moiety on N atom of beta-lactam ring but different phenyl moiety at position 4 thus the different in their activity were due to the substitution on the phenyl moiety at position 4 where the substitution with p-methoxy group in compound **16** seemed to decrease activity against Gram positive and shown good activity against Gram negative bacteria while o-hydroxy group of compound **17** showed intermediate activity against both Gram positive and Gram negative bacteria. Compounds **18** and **19** have the same moiety on N atom of beta-lactam ring but different phenyl moiety at position 4 thus the different in their activity were due to the substitution on the phenyl moiety at position 4 where p-methoxy group of compound **18** seemed to increase the activity against Gram positive bacteria and decrease activity against Gram negative bacteria while o-hydroxy group of compound **19** led to increase the activity against only *s.aureus* and reduce activity against other tested organisms. Compound **22**, **23**, **24**, **25** and **26** were benzylidene derivatives with different substitution (H, *m*-NO_2, *p*-OCH_3, *p*-OCH_3, *p*-OH and 2-furyl respectively) all of these compounds showed no activity against *S. aureus*. Compound **24** with *p*-methoxy moiety had the greatest activity against both Gram positive and Gram negative especially *Bacillus* and *E.coli* followed by compound **23** which had *m*-NO_2 substitution. Compound **27** and **28** have intermediate activity against all tested organisms. Compound **29** was more active against Gram positive than Gram negative bacteria.Compound **31**, **32** and **33** have intermediate activity against all tested organisms. Compound **36** and **37** being the most active compounds of all synthesized compounds; both had good activity against all tested organisms and more potent than ampicillin and cefotaxime activity against *Bacillus*, *E.coli* and *S. aureginosa*. The activity may be contributed to the oxazole and thiazole moiety on the benzimidazole nucleus. **(Table 1).**

Table1. Antimicrobial Activity of tested compounds using disk diffusion method

	Gram positive bacteria			***Gram negative bacteria***	
Comp.	***staphylococcus aureus***	***Bacillus***	***Streptococcus aglactiae***	***Escherichia coli***	***Pseudomonas aureginosa***
16	12(I)	14(I)	14(I)	18(I)	16(I)
17	14(I)	16(I)	12(I)	18(I)	14(I)
18	20(I)	18(I)	12(I)	14(I)	16(I)
19	18(I)	10(I)	10(I)	14(I)	12(I)
20	6(R)	6(R)	6(R)	6(R)	6(R)
21	6(R)	10(I)	12(I)	6(R)	12(I)
22	6(R)	6(R)	12(I)	6(R)	8(R)
23	6(R)	20(I)	6(R)	20(I)	10(I)
24	6(R)	22(S)	18(I)	24(S)	20(I)
25	6(R)	10(I)	6(R)	6(R)	12(I)
26	6(R)	10(I)	10(I)	6(R)	12(I)
27	6(R)	18(I)	16(I)	16(I)	20(I)
28	12(I)	18(I)	14(I)	18(I)	12(I)
29	18(I)	18(I)	16(I)	14(I)	16(I)
31	6(R)	16(I)	12(I)	16(I)	14(I)
32	16(I)	18(I)	18(I)	16(I)	16(I)
33	18(I)	16(I)	16(I)	14(I)	14(I)
36	16(I)	22(S)	22(S)	24(S)	24(S)
37	18(I)	24(S)	20(I)	24(S)	18(I)
cefotaxime	18(I)	18(I)	20(I)	20(I)	22(S)
Ampicillin	22(S)	20(I)	22(S)	20(I)	24(S)
DMSO	6(R)	6(R)	6(R)	6(R)	6(R)

R= Resist (Inhibition Zone Less Than 10 mm), I= Intermediate (Inhibition Zone Less Than 10-20 mm), S= Sensitive (Inhibition Zone More Than 20 mm)

Conclusions:

Compounds **24**, **36** and **37** showed high activity against Gram-positive bacteria and Gram-negative bacteria while other compounds showed intermediate activities against Gram positive and

Gram negative bacteria, finally all synthesized compounds **show no** anticandidal activities

Conflict of interest statement

The authors declare that there are no conflicts of interest.

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