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Antibacterial Activity of New Benzimidazole Moiety Synthesis via a Acid chloride and Related Heterocyclic Chalcones

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Abstract

Aims: Pharmacological studies of benzimidazole derivatives including antibacterial activity have been accomplished. Methods: Fast and efficient one-step synthesis of a novel [1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one(**TBIO**) substrate and a several(3Z)-3-[(*substituted*phenyl) methylidene][1,3]thiazolo[3,2a]Benzi-midazol-2(3H)-one(**1a–k**),substitution[1,3]thia-zolo[3,2a]benzimidazol-2(3H)-one (**2a-c**), 5-phenylfuran-2-carbaldehyde derivatives (**B**), (3Z)-3-{[5-(*subsititution*phenyl)furan-2-yl]methylidene}[1,3]thiazo-lo[3,2a]benzimidazole-2(3H)-one(**3a-m**)and chalcones of TBIO(**4a–c**) were synthesized and evaluated for antibacterial activity with the positive control streptomycin.

Results: The structures of the newly prepared compounds were characterized by FT- IR, ^{1}H-NMR and mass spectral data. All synthesized compounds show different antibacterial activity against *Klebsiella sp., Escherichia coli, Staphylococcus aureus,* and *Staphylococcus epidermidis* were identified.

Conclusion More than thirty newly compounds were synthesis from novel substrate and studied its Anti-microbial activity showed unique activity comparing with streptomycin as positive control.

Keywords; antibacterial activity, benzimidazole, cyclocondensation, chalcones, (TBIO).

INTRODUCTION

In general, during the past few decades the lower of sensitivity to anti-microbial agents in Special use has been increasing, and the resistance to various drugs is more common for various microorganisms, particularly for Gram-positive bacteria and several intractable fungi. Many benzimidazole and imidazole derivatives containing heterocycle moiety and natural products have been synthesized for their anti-HIV,[1] antibacterial,[2][3] antifungal,[4],5] insecticidal, [6] anticancer [7] and anti-inflammatory,[8] activities. However, benzimidazole derivatives have particular importance as α-glucosidase inhibitor, [9] nticorrosion, [10] optical and fluorometric pH sensor [11]. As imidazole complexes have great antibacterial activity[12],[13],14]the benzimidazole complexes also have higher activity[15]. Furthermore, our Present work shows that benzimidazole derivatives display good antibacterial activity. We decided to synthesis a series of benzimidazoles carrying the deferent's groups and with additional substitution at the position C-1 with alkyl group While C-2 by sulphur atom conjugated to carbonyl group. There are several methods to prepare benzimidazole derivatives by using condensation of 1,2-phenylenediamines with aldehydes [16], aromatic acid derivatives, [17] and Carbon disulphide[18]. A series of benzimidazole derivatives has been synthesis by using 2-mercaptobenzimidazole (2MBI), Chloroacetyl chloride and Specific conditions to obtain the novel benzimidazole moiety.

EXPERIMENTAL SECTION

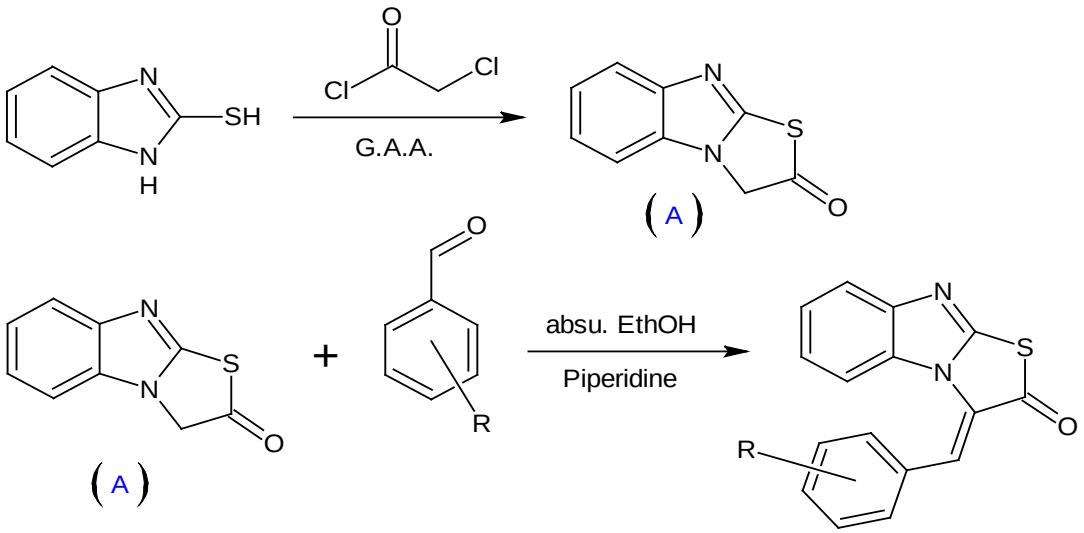
Materials and Methods

2-mercaptobenzimidazole (2MBI), Chloroacetyl chloride, glacial acetic acid and all aromatic aldehydes, aromatic amine and acid chloride are providing from Sigma Aldrich company, were used without purification. Melting points was registered by using digital Stuart scientific SMP30. Fourier transform infrared (FT-IR) Spectra Measurements was recorded by FT-IR-8400S – SHIADZU. ^{1}H-NMR spectra was registered on Burker 300MHz. The purity of the products was achieved by TLC using n-hexane-ethylacetate (9:1) as eluent and the spots were detected by (Gelman sciences LTD. U.K. device). Mass spectra were recorded on two different devices (Shimadzu model GCMSQP 1000 EX) and (VARIAN 3900).

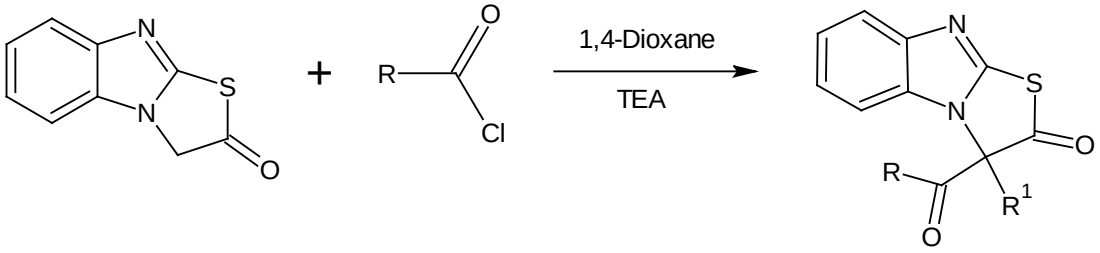
Synthesis of Heterocyclic Compounds (Schemes 1, 2, 3)

1. Synthesis of [1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (TBIO) (**A**).

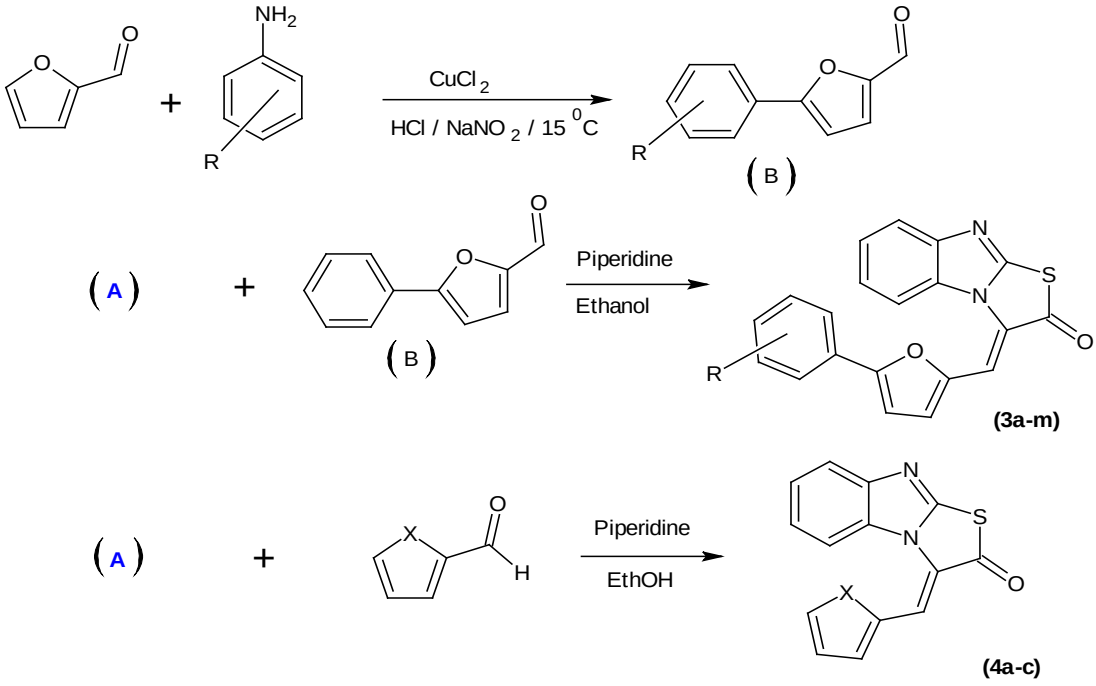
To solution of (0.1mol, 15gm) 2-mercaptobenzimidazole, (100ml) glacial acetic acid in a 250ml RBF was add dropwise (0.15mol, 11.9ml) Chloroacetyl chloride by using dropping funnel in 15 ^{0}C with good stirring by magnetic stirrer for 10min. After 1h of stirring the temperature gradually raise to 120 ^{0}C for 12h. Completion of the reaction was detected by (TLC), after cooling to R.T. the reaction mixture was poured onto (500ml) crushed -ice and stirred for 1 h. The separated precipitate were filtered and washed with distilled water, dried, and crystallized from benzene to afford the white crystals; yield: 89%. m. p.: 150– 152 ^{0}C; FT-IR : 1737.92 (C=O), 698.25 (C-S), 1610.61 (C=N) and 2924.18, 2966.62 (CH_2) cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ= 7.876, 7.852 (d, 1H, ArH), 7.606, 7.581 (d, 1H, ArH), 7.401-7.295 (m, 2H, ArH), 4.615 (s, 2H, N–CH_2-C=O) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (190) 100%.



Scheme 1 : Synthesis of (**TBIO**) and has chalcones, were **R**= *p*-Nitro, *p*-OH, *m*-CH_3 ,*p*-Cl ,$N(CH_3)_2$,*m*-OH , *p*-CHO , H, *p*-OCH_3 ,3,4-dimethoxy and *o*-Cl.

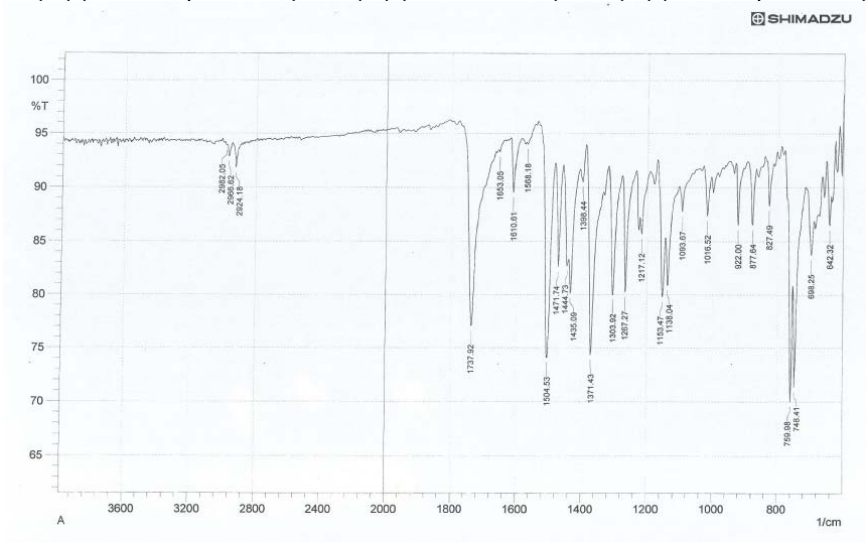


Scheme 2 : Synthesis of (**2a-c**). Were **2a** = {[R= CH_3 , R^1 = $COCH_3$]}, **2b** = {[R= *p*-Methoxy phenyl , R^1= *p*-Methoxy benzoyl]} and **2c** = {[R= phenyl, R^1= benzoyl]}.

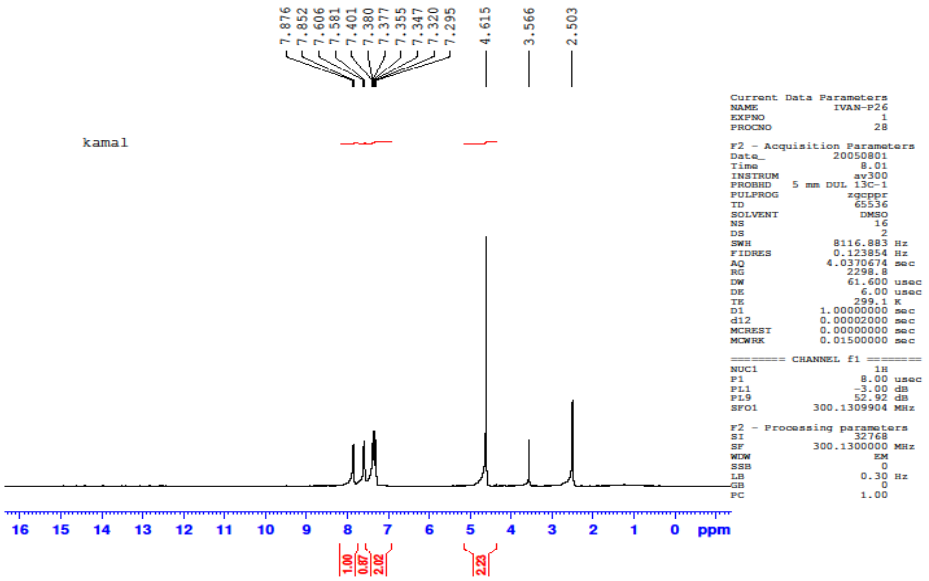


Scheme 3: Synthesis of 5-phenylfuran-2-carbaldehyde derivatives (**B**). Were **R**= *p*-Cl, *p*-Br, *p*-NO_2, 2,4-dichloro, *o*-NO_2, *o*-Cl, *m*-Cl, *p*-$COCH_2CH_3$, *p*-OH, *p*-$COCH_3$, *m*-Br, *m*-CH_3, *p*-COOH. (**3a-m**) and (**4a-c**).

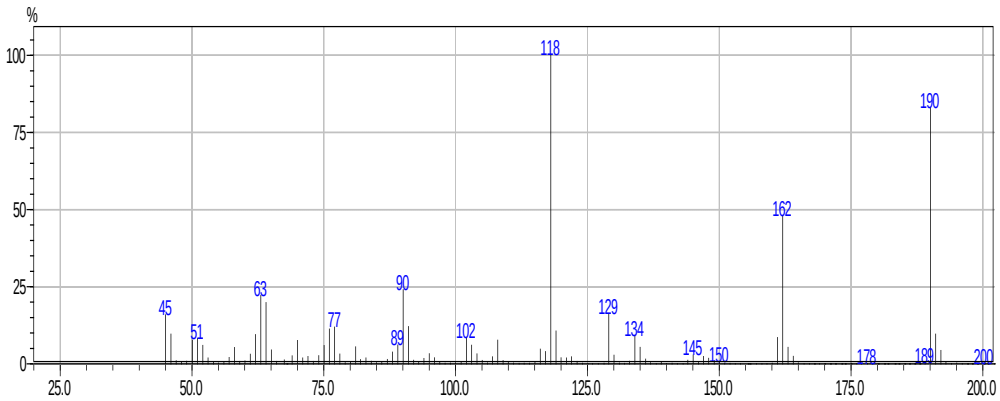
(**Figures** 1): (a) FT-IR Spectra of (TBIO). (b) ^{1}H NMR of (TBIO). (c) Mass Spectra of (TBIO).



(a) FT-IR Spectra of (TBIO).



(b) 1H NMR of (TBIO).



(c) Mass Spectra of (TBIO).

2. General procedures for chalcones of TBIO **(1a–k)**.
A solution of (0.01 mol) TBIO, (20 drops) Piperidine in 30 ml ethanol was stirring for 30 min in 50 ^{o}C. The (0.01 mol) of appropriate aldehyde added to solution and heated by reflux for 10 h. Products were filter and wash with Distilled water, recrystallized from alcohol to give pure chalcones.

2.1.Synthesis of (3Z)-3-[(4-nitrophenyl)methylidene][1,3]thiazolo[3,2-a]benzimid-azol-2(3H)-one (**1a**). Yellow crystals, Yield, 84% mp 285-287 ^{o}C ; FT-IR : 1716.70 (C=O), 1608.69 (C=N) and 1342.50, 1514.17 (NO_2) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 8.528-8.425 (d, 2H, ArH), 8.389-8.108 (m, 1H, ArH), 8.042-8.008 (m, 3H, ArH), 7.877 (s, 1H, C=CH), 7.431 (d, 2H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 323.

2.2. Synthesis of (3Z)-3-[(4-chlorophenyl)methylidene][1,3]thiazolo[3,2 a]benzimid-azol-2(3H)-one (**1b**). Yellow crystals, Yield, 74% mp 253-254 ^{o}C ; FT-IR : 1714.77 (C=O), 1604.83 (C=N) and 1055.10 (Ar-Cl), 812.06 (*p*-substitution) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 8.075 (d, 1H, ArH), 7.723,7.699 (d, 1H, ArH), 7.598-7.516 (q, 4H, ArH), 8.039 (s, 1H, C=CH), 7.429-7.381 (m, 2H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 313.5 (M^{+} 1).

2.3. Synthesis of (3Z)-3-[(3-methylphenyl)methylidene][1,3]thiazolo[3,2-a]benzimid-azol-2(3H)-one (**1c**). Yellow crystals, Yield, 66% mp 193-194 ^{o}C ; FT-IR : 1722.49 (C=O), 1606.76 (C=N) and 2920.32 (CH_3) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.062,8.051 (d, 1H, ArH), 7.708,7.683 (d, 1H, ArH), 7.444-7.409 (m, 4H, ArH), 8.041 (s, 1H, C=CH), 7.385 (d, 1H, ArH), 7.343-7.282 (m, 1H, ArH), 2.671,2.461 (s, 3H, CH_3) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 292.

2.4. Synthesis of (3Z)-3-{[4-(dimethylamino)phenyl]methylidene}[1,3]thiazolo [3,2-a]benzimidazol-2(3H)-one (**1d**). Orange crystals, Yield, 81% mp 241-242 ^{o}C ; FT-IR : 1705.13 (C=O), 1614.47 (C=N) and 2918.40 ($N(CH_3)_2$), 808.20 (*p*-substitution) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ= 8.085,8.062 (d, 1H, ArH), 7.995 (s, 1H, C=CH), 7.703,7.678 (d, 1H, ArH), 7.547,7.517 (d, 2H), 7.416-7.282 (m, 2H, ArH), 6.780,6.750 (d, 2H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 321.

2.5. Synthesis of (3Z)-3-[(4-hydroxyphenyl)methylidene][1,3]thiazolo[3,2-a] benzimidazol-2(3H)-one (**1e**). Bright yellow crystals, Yield, 67% mp 318-319 ^{o}C ; FT-IR : 1720.56 (C=O), 1610.61 (C=N), 829.42 (*p*-substitution) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 10.490 (s, 1H, OH), 7.964-7.939 (d, 1H, ArH), 7.685,7.661 (d, 1H, ArH), 7.640,7.612 (d, 2H, ArH), 8.017 (s, 1H, C=CH), 7.433-7.345 (m, 2H, ArH) 6.693,6.964 (d, 2H, ArH) ppm. Mass spectrum (MS, 70 eV): m/z = 294.

2.6. Synthesis of (3Z)-3-[(3-hydroxyphenyl)methylidene][1,3]thiazolo[3,2-a] benzimidazol-2(3H)-one (**1f**). Pale yellow crystals, Yield, 66% mp 247-248 ^{o}C ; FT-IR : 1732.13 (C=O), 1610.61 (C=N), 854.49 (*p*-substitution) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 9.940 (s, 1H, OH), 7.949-7.921 (d, 1H, ArH), 7.682-7.654 (d, 1H, ArH), 7.429-7.345 (m, 3H, ArH), 7.991 (s, 1H, C=CH), 7.181,7.155 (d, 1H, ArH), 7.122 (s, 1H, ArH) 6.960-6.928 (d, 1H, ArH) ppm. Mass spectrum (MS, 70 eV): m/z = 294.

2.7. Synthesis of 4-[(Z)-(2-oxo[1,3]thiazolo[3,2-a]benzimidazol-3(2H)-ylidene) methyl]Benzaldehyde (**1g**). Yellow crystals, Yield, 74% mp 253-254 ^{o}C ; FT-IR : 1718.63 (C=O), 1606.76 (C=N) and 1705.13 (C=O aldehyde), 2739.01,2821.95 (H-C=O aldehyde) 815.92 (*p*-substitution) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 10.114-10.077 (s, 1H, H-C=O aldehyde), 8.035,7.994 (d, 3H, ArH), 7.968,7.834 (d, 1H, ArH), 7.737,7.709 (d, 1H, ArH), 8.171 (s, 1H, C=CH), 7.491,7.362 (m, 3H, ArH), ppm. Mass spectrum (MS, HI, 70 eV): m/z = 306.

2.8. Synthesis of (3Z)-3-benzylidene[1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one(**1h**). Bright yellow crystals, Yield,68% mp 200-202 ^{o}C ; FT-IR : 1732.13 (C=O), 1614.47 (C=N) ; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.715,7.690 (d, 1H, ArH), 7.658,7.635 (d, 2H, ArH), 8.094 (s, 1H, C=CH), 7.578-7.504 (m, 3H, ArH), 7.443-7.345 (m, 2H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 278.

2.9. Synthesis of (3Z)-3-[(4-methoxyphenyl)methylidene][1,3]thiazolo[3,2-a] benzimidazol-2(3H)-one (**1i**). Yellow crystals, Yield, 90 % mp 210-212 ^{o}C ; FT-IR : 1708.99 (C=O), 1612.54 (C=N), 1074.39, 1103.32 (C-O-C), 2928.04,2978.19 (CH_3) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 7.731, 7.710 (d, 1H, ArH), 7.427-7.163 (dd, 3H, ArH), 7.127-7.038 (m, 2H, ArH), 7.027-7.701 (d, 2H, ArH) 7.759 (s, 1H, C=CH) 3.872 (s, 3H, OCH_3), ppm. Mass spectrum (MS, HI, 70 eV): m/z = 308.

2.10. Synthesis of (3Z)-3-[(3,4-dimethoxyphenyl)methylidene][1,3]thiazolo[3,2-a] benzimidazol-2(3H)-one (**1j**). Yellow crystals, Yield, 94% mp 243-244 ^{o}C ; FT-IR : 1707.06 (C=O), 1608.69 (C=N), 1138.04, 1159.26 (C-O-C), 2835.45, 2931.90 (OCH_3) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.058, 8.031 (d, 1H, ArH), 7.692,7.667 (d, 1H, ArH), 7.414-7.314 (m, 3H, ArH), 7.118,7.113 (s, 1H, ArH), 7.016,6.988 (d, 1H, ArH), 8.011 (s, 1H, C=CH) 3.979, 3.964 (s, 6H, $[OCH_3]_2$), ppm. Mass spectrum (MS, HI, 70 eV): m/z = 338.

2.11. Synthesis of (3Z)-3-[(2-bromophenyl)methylidene][1,3]thiazolo[3,2-a] benzimidazol-2(3H)-one (**1k**). Yellow crystals, Yield, 62 % mp 190-192 ^{o}C ; FT-IR : 1732.13 (C=O), 1612.54 (C=N) and 1153.47 (Ar-Br), cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ= 7.901 (d, 1H, ArH), 7.845,7.837 (d, 1H, ArH),

7.799-7.623 (m, 2H, ArH), 7.994 (s, 1H, C=CH), 7.422-7.378 (m, 2H, ArH), 7.311, 7.056 (d, 2H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 357.

3. General procedures for compounds - *substitution*[1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**2a-c**).

A mixture containing (TBIO) (0.01 mol), (0.3 mol) triethylamine and (30 ml) dioxane was stirred for 1h. In cold conditions (0.015 mol) acid chloride were added progressively, after 10h of continuous stirring in R.T. mixture of reactants were added to crushed ice and stirred further for 1/2h, the precipitate gained was filtered and to be free from chloride, repeated washing with distilled water is necessary. The dried product was eventually recrystallized with ethanol.

3.1. Synthesis of 3,3-diacetyl[1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**2a**). Red powder, Yield, 64 % mp 199-202 ^{o}C ; FT-IR : 1714.77 (C=O), 1612.54 (C=N), 1670.41, 1633.76 for (C=O acytyl), 2856.67, 2945.40 (CH_3) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.067, 8.001 (d, 1H, ArH), 7.976,7.942 (d, 1H, ArH), 7.886-7.668 (m, 1H, ArH), 7.619-7.363 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 274.

3.2. Synthesis of 3-benzoyl[1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one(**2b**). Yellow powder, Yield, 60 % mp 218-220 ^{o}C ; FT-IR : 1730.21 (C=O), 1612.54.76 (C=N), 1705.13 (C=O benzyl) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.023, 8.002 (d, 2H, benzyl ArH), 7.680,7.611 (m, 1H, benzyl ArH), 7.553 (m, 2H, benzyl ArH), 7.522 (d, 1H, ArH), 7.642 (d, 1H, ArH), 7.277 (m, 1H, ArH) 7.181 (m, 1H, ArH), 5.858 (s, 1H, CH) ppm. Mass spectrum (MS, 70 eV): m/z = 294.

3.3. Synthesis of 3-(4-methoxybenzoyl)[1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**2c**). Yellow powder, Yield, 54 % mp 241-243 ^{o}C ; FT-IR : 1726.35 (C=O), 1610.61 (C=N), 1708.99 (C=O benzyl), 2839.31, 2939.61 (CH_3), 1026.16, 1263.42 (C-O) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.265, 8.123 (d, 2H, ArH), 7.844 (d, 1H, benz ArH), 7.689-7.531 (d, 1H, benz ArH), 7.318,7.210 (m, 1H, benz ArH), 7.011,6.982 (m, 1H, benz ArH), 6.899, 6.797 (d, 2H, ArH) 6.142 (s, 1H, CH), 3.697 (s, 1H, OCH_3) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 324.

4. General procedures for compounds 5-phenylfuran-2-carbaldehyde derivatives (**B**).

The purposed compound (scheme 3) was prepared and purified by method that approbate with procedure correspond to reference[19]. The Physiochemical properties of the prepared compounds are listed in (table1).

5. General procedures for compounds (3Z)-3-{[5-(***subsititution***phenyl)furan-2-yl]methylidene}[1,3]thiazolo[3,2-a]benzimidazole-2(3H)-one (**3a-m**).

(0.01 mol) of (TBIO) was dissolved in minimum amount of ethanol (only 5-(4-nitrophenyl)furan-2-carbaldehyde in dioxane) with (0.02 mol) piperidine and stirring for 0.5h in 50 ^{0}C. The (0.01 mol) a substituted furan-2-carbaldehyde were added to a mixture (Scheme 3). Mostly, orange to yellow solids was formed during 1-24 h. The solids was collected by filtration and washed several times with cold ethanol, recrystallized from water/ethanol solvents to getting pure compound.

Table 1: Physiochemical properties of 5-phenylfuran-2-carbaldehyde derivatives(B).

Entry	R	m.p. oC	Yield %	color
1	p-Cl	130–132	67	Dark brown
2	p-Br	154–156	59	Dark brown
3	p-NO2	202–205	62	Dark orange
4	2,4-dichloro	121-123	79	Yellow
5	o-NO2	80-81	73	Dark orange
6	o-Cl	72-74	58	Dark brown
7	m-Cl	104-106	64	Dark brown
8	p-COOCH2CH3	125-127	88	Dark red
9	p-OH	166-168	52	Dark orange
10	p-COCH3	177-179	67	Yellow
11	m-Br	116-119	81	Dark brown
12	m-CH3	98-100	85	Dark brown
13	p-COOH	296-298	55	Yellow

5.1. Synthesis of (3*Z*)-3-{[5-(4-chlorophenyl)furan-2-yl]methylidene}[1,3]thiazolo [3,2-*a*]benzimidazol-2(3*H*)-one(**3a**). Yellow crystals, Yield 61 % mp 241-243 ^{o}C ; FT-IR : 1712.85 (C=O), 1612.54 (C=N), 1051.24 (Ar-Cl), 3037.99 (=C-H Ar), 3111.28 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.174, 8.149 (d, 1H, ArH), 7.931(s, 1H, C=C-H chalcone), 7.810,7.758 (d, 2H, ArH), 7.729,7.699 (d, 1H, ArH), 7.587,7.482 (d, 2H, furf.), 7.454-7.331 (m, 2H, ArH) 7.084, 6.997 (d, 1H, ArH), 6.985, 6.888 (d, 1H, Ar) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (378) 100% , 379 (M+1).

5.2. Synthesis of (3*Z*)-3-{[5-(4-bromophenyl)furan-2-yl]methylidene}[1,3]thiazolo [3,2-*a*]benzimidazol-2(3*H*)-one (**3b**). Yellow crystals, Yield 85 % mp 255-256 ^{o}C ; FT-IR : 1720.56 (C=O), 1612.54 (C=N), 1047.38 (Ar-Br), 3018.70 (=C-H Ar), 3117.07 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.693 (d, 2H, ArH), 7.899(s, 1H, C=C-H chalcone), 7.611 (d, 2H, ArH), 7.769, 7.789 (d, 1H, ArH), 7.530,7.547 (d, 2H, furf.), 7.251-7.261 (m, 1H, ArH), 7.580, 6.591 (d, 1H, Ar), 7,211, 7.145 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (423), 424 (M+1), 425 (M+2).

5.3. Synthesis of (3*Z*)-3-{[5-(4-nitrophenyl)furan-2-yl]methylidene}[1,3]thiazolo[3,2 *a*]benzimidazole-2(3*H*)-one (**3c**). Red crystals, Yield 89 % mp 322-323 ^{o}C ; FT-IR : 1716.70 (C=O), 1610.61 (C=N), 1330.93, 1516.10 (Ar-NO_2), 3039.91 (=C-H Ar), 3130.57 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 8.343, 8.155 (d, 2H, ArH), 7.803 (s, 1H, C=C-H chalcone), 8.126,8.073 (d, 2H,

ArH), 8.018,7.966 (d, 1H, ArH), 7.651,7.592 (d, 2H, furf. ArH), 7.542-7.403 (m, 1H, ArH), 7.803, 7.720 (d, 1H, ArH), 7.157, 7.122 (m, 1H, Ar) ppm. Mass spectrum (MS, HI, 70 eV): m/z = 389.

5.4. Synthesis of (3*Z*)-3-{[5-(2,4-dichlorophenyl)furan-2-yl]methylidene}[1,3]
thiazolo[3,2-*a*]benzimidazol-2(3*H*)-one (**3d**). Pink crystals, Yield 87 % mp 261-262 ^{o}C ; FT-IR : 1712.85 (C=O), 1604.83 (C=N), 1087.89 (Ar-Cl), 3053.42 (=C-H Ar), 3121.93, 3178.79 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.412, 7.429 (d, 1H, ArH), 7.821(s, 1H, C=C-H chalcone), 7.241,7.250 (m, 1H, ArH), 7.211,7.125 (m, 1H, ArH), 7.701 (s, 1H, ArH), 7.361 (d, 1H, furf.), 7.361 (d, 1H, furf.), 7.651,7.661 (d, 1H, ArH) 7.572, 7.611 (d, 1H, ArH), 7.541, 7.543 (d, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (413), 414 (M+1).

5.5. Synthesis of (3*Z*)-3-{[5-(2-nitrophenyl)furan-2-yl]methylidene}[1,3]thiazolo[3,2-*a*]benzimi daz-ol-2(3*H*)-one (**3e**). Dark red crystals, Yield 81 % mp 313-314 ^{o}C ; FT-IR : 1712.85 (C=O), 1614.47 (C=N), 1379.15, 1516.10 (NO_2), 3037.99 (=C-H Ar), 3140.22 (=C-H furf.), 783.13 (*ortho*-sub.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.872, 7.854 (d, 2H, ArH), 7.725(s, 1H, C=C-H chalcone), 7.700,7.674 (t, 2H, ArH), 7.354,7.342 (d, 2H, ArH), 7.238,7.227 (d, 2H, furf.), 7.208 (m, 1H, ArH), 6.824, 6.812 (d, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (389).

5.6. Synthesis of (3*Z*)-3-{[5-(2-chlorophenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimddazol-2(3*H*)-one (3f). Yellow crystals, Yield 74 % mp 280-282 ^{o}C ; FT-IR : 1714.77 (C=O), 1612.54 (C=N), 1055.10 (Ar-Cl), 3059.20 (=C-H Ar), 3130.57 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.711, 7.718 (d, 1H, ArH), 7.821(s, 1H, C=C-H chalcone), 7.610,7.619 (d, 1H, ArH), 7.381,7.392 (m, 2H, ArH), 7.362 (d, 1H, furf.), 7.371 (d, 1H, furf.), 7.572-7.579 (d, 2H, ArH), 7.242, 7.249 (m, 1H, Ar), 7.215, 6.228 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (378) 100%, 379 (M+1).

5.7. Synthesis of (3*Z*)-3-{[5-(3-chlorophenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimidazol-2(3*H*)-one (**3g**). Yellow crystals, Yield 73 % mp 293-294 ^{o}C ; FT-IR : 1716.70 (C=O), 1610.61 (C=N), 1031.95 (Ar-Cl), 3041.84 (=C-H Ar), 3157.58 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.443 (s, 1H, ArH), 8.378 (s, 1H, C=C-H chalcone), 7.952,7.959 (d, 1H, ArH), 7.490,7.521 (d, 1H, ArH), 7.529 (d, 2H, furf.), 7.544,7.453 (m, 1H, ArH), 7.570, 7.582 (d, 2H, Ar), 7.241, 7.249 (m, 1H, Ar), 7.217, 7.147 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (378), 379 (M+1).

5.8. Synthesis of Ethyl 4-{5-[(*Z*)-(2-oxo[1,3]thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ylidene)methyl]furan-2-yl}benzoate (**3h**). Yellow crystals, Yield 87 % mp 215-216 ^{o}C ; FT-IR : 1710.92 (C=O), 1608.92 (C=N), 1699.99 (C=O benzocain), 2899.11, 2883.98 (OCH_2CH_3), 3030.27 (=C-H Ar), 3134.43 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.193, 8.165 (d, 2H, ArH), 8.068, 8.038 (d, 1H, ArH), 7.896 (s, 1H, C=C-H chalcone), 7.727, 7.701 (d, 2H, furf.), 7.701, 7.634 (d, 1H, ArH), 7.417-7.280 (m, 2H, ArH), 7.926, 6.852 (d, 2H, ArH), 4.479- 4.409 (q, 2H, CH_2), 1.482- 1.434 (t, 3H, CH_3) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (416) 100%.

5.9. Synthesis of (3*Z*)-3-{[5-(4-hydroxyphenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimidazol-2(3*H*)-one (**3i**). Yellow crystals, Yield 62 % mp 310-312 ^{o}C ; FT-IR : 1716.99 (C=O), 1617.75 (C=N), 3432.22 (Ar-OH), 3017.929 (=C-H Ar), 3131.21 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.054, 8.024 (d, 2H, ArH), 7.899 (s, 1H, C=C-H chalcone), 7.778,7.732 (d, 2H, ArH), 7.679,7.658 (d, 1H, ArH), 7.592,7.553 (d, 2H, furf.), 7.387-7.354 (m, 1H, ArH) 7.210, 7.077 (m, 1H, Ar), 7.540, 7.501 (d, 1H, ArH), 10.546 (s, 1H, OH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (360).

5.10. Synthesis of (3*Z*)-3-{[5-(4-acetylphenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimidazol-2(3*H*)-one (**3j**). Yellow crystals, Yield 85 % mp 266-268 ^{o}C ; FT-IR : 1715.93 (C=O), 1611.65 (C=N), 1701.79 (C=O acetyl), 3022.75 (=C-H Ar), 3129.12 (=C-H furf.), 2854.64, 2933.11 (CH_3) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.069, 8.021 (d, 2H, ArH), 7.811 (s, 1H, C=C-H chalcone), 8.001, 7.897 (d, 2H, ArH), 7.563,7.552 (d, 1H, ArH), 7.536,7.527 (d, 1H, ArH), 7.526, 7.513 (d, 2H, furf.), 7.266-7.206 (m, 1H, ArH), 7.195, 7.106 (m, 1H, Ar) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (386).

5.11. Synthesis of (3*Z*)-3-{[5-(3-bromophenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimidazol-2(3*H*)-one (**3k**). Yellow crystals, Yield 80 % mp 240-242 ^{o}C ; FT-IR : 1713.68 (C=O), 1616.55 (C=N), 1041.33 (Ar-Br), 3014.99 (=C-H Ar), 3118.09 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.231 (d, 1H, ArH), 7.893 (s, 1H, C=C-H chalcone), 7.453,7.423 (s, 1H, ArH), 7.674,7.605 (d, 1H, ArH), 7.435-7.346 (m, 1H, ArH), 7.521 (d, 2H, furf.), 7.570, 7.566 (d, 1H, ArH), 7.544, 7.538 (d, 1H, ArH), 7.249, 7.241 (m, 1H, ArH), 7.216, 7.168 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (423), 425 (M+2).

5.12. Synthesis of (3*Z*)-3-{[5-(3-methylphenyl)furan-2-yl]methylidene}[1,3]thiazolo
[3,2-*a*]benzimidazol-2(3*H*)-one (**3l**). Yellow crystals, Yield 57 % mp 194-196 ^{o}C ; FT-IR : 1717.34 (C=O), 1608.47 (C=N), 2862.12, 2976.95 (Ar-CH_3), 3048.11 (=C-H Ar), 3173.23 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 7.979, 7.971 (d, 1H, ArH), 7.821 (s, 1H, C=C-H chalcone), 7.789,7.781 (s, 1H, ArH), 7.499,7.491 (m, 1H, ArH), 7.188,7.182 (d, 1H, ArH), 7.529 (d, 2H, furf.), 7.579, 6.571 (d, 1H, ArH), 7.549, 7.541 (d, 1H, ArH), 7.278, 7.264 (m, 1H, ArH), 7.217, 7.175 (m, 1H, ArH), 2.385, 2.279 (s, 3H, Ar-CH_3) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (343) 100%.

5.13. Synthesis of 4-{5-[(*Z*)-(2-oxo[1,3]thiazolo[3,2-*a*]benzimidazol-3(2*H*)-ylidene) methyl]furan-2-yl}benzoic acid (**3m**). Yellow crystals, Yield 85 % mp 320-322 ^{o}C ; FT-IR : 1722.64 (C=O), 1610.66 (C=N), 1706.33 (C=O carboxyl), 2600.22, 3500.87 (OH carboxyl), 3013.84 (=C-H Ar), 3133.21 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 12.516 (s, 1H, OH), 8.178, 8. 116 (d, 2H, ArH), 7.853 (s, 1H, C=C-H chalcone), 8.128, 8.115 (d, 2H, ArH), 7.689, 7.673 (d, 1H, ArH), 7.529, 7.521 (d, 2H, furf.), 7.549-7.537 (d, 1H, ArH), 7.364, 6.357 (m, 1H, ArH), 7.218, 6.178 (m, 1H, ArH) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (388) 100%.

6. General procedures for chalcones of TBIO **(4a–c)**.
(0.01 mol) of (TBIO) was dissolved in (25 ml) of ethanol with (0.02 mol) piperidine and stirring for 0.5h. The (0.01 mol) of (furan-2-carbaldehyde, 1H-pyrrole-2-carbaldehyde, thiophene-2-carbaldehyde) was added to a mixture (Scheme 3). In all cases, a yellow solid was formed during 1 - 24h. The solid was collected by filtration and washed several times by cold ethanol, after drying the solid were recrystallized from ethanol.

6.1. Synthesis of (3Z)-3-[(furan-2-yl)methylidene][1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**4a**). Yellow crystals, Yield 91 % mp 265-266 ^{o}C; FT-IR: 1716.70 (C=O), 1606.76 (C=N), 1066.67, 1085.96 (C-O-C), 3041.84 (=C-H Ar), 3144.07 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.031 (d, 1H, furf.), 7.812, (s, 1H, C=C-H chalcone), 7.681, 7.656 (d, 1H, furf.), 7.380, 7.353 (d, 2H, ArH), 7.300, 7.258 (m, 1H, ArH), 6.715, 6.633 (t, 1H, ArH), 6.628, 6.622 (m, 1H, furf.) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (268) 100%.

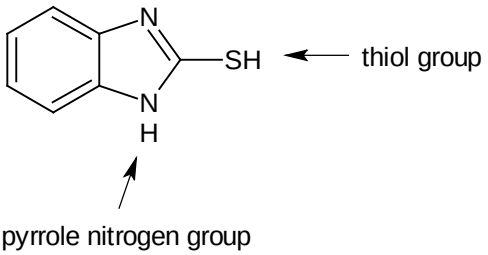
6.2. Synthesis of (3Z)-3-[(1H-pyrrol-2-yl)methylidene][1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**4b**). Yellow crystals, Yield 93 % mp 277-279 ^{o}C; FT-IR: 1712.85 (C=O), 1610.61 (C=N), 3068.85 (=C-H Ar), 3111.28 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, $CDCl_3$): δ = 8.491, (s, 1H, C=C-H chalcone), 8.225-8.041 (d, 1H, furf.), 8.017, 8.013 (d, 1H, furf.), 7.730, 7.713 (d, 1H, ArH), 7.690, 7.666 (d, 1H, ArH), 7.513, 7.359 (m, 2H, ArH), 7.312, 7.256 (d, 1H, furf.) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (284) 100%.

6.3. Synthesis of (3Z)-3-[(thiophen-2-yl)methylidene][1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (**4c**). Yellow crystals, Yield 87 % mp 325-327 ^{o}C; FT-IR: 1714.77 (C=O), 16014.47 (C=N), 3151.79 (NH), 3076.56 (=C-H Ar), 3111.11 (=C-H furf.) cm^{-1}; ^{1}H-NMR (300 MHz, DMSO-d_6): δ = 12.019 (s, 1H, NH), 7.947, 7.821 (d, 1H, furf.), 7.970 (s, 1H, C=C-H chalcone), 7.668, 7.611 (d, 1H, furf.), 7.405, 7.385 (d, 1H, ArH), 7.365-7.070 (m, 2H, ArH), 6.701, 6.585 (d, 1H, ArH), 6.548, 6.541 (t, 1H, furf.) ppm. Mass spectrum (MS, HI, 70 eV): m/z = (267) 100%.

Evaluation of antimicrobial activity
The bacteria strains were used to evaluate the antibacterial activity are; (Gram-positive; *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram-negative; *Klebsiella sp*, *Escherichia coli*). By using agar diffusion method. The solutions of synthesis compounds which used to test the antimicrobial activity were in concentrations 500,250, 125, 62.5 μg cm^{-3} for each compound and DMSO as solvent. Streptomycin was used as a positive control to compare the antibacterial activities with activities of synthesis compounds. Determine of (MIC) Minimum inhibitory concentration have been done for all compounds. After spread the bacteria *Klebsiella sp., Escherichia coli*, *Staphylococcus aureus*, and *Staphylococcus epidermidis* on agar plates with a specified quantity of test compounds they incubated at 37 ^{0}C for 24 h. The growth of bacterial cells and zone size inhibition was observed on agar plates and measured.

RESULTS AND DISCUSSION

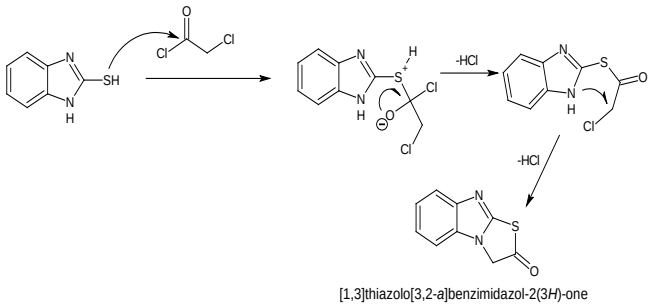
The novel benzimidazole moiety derivatives have been synthesis by achieving appropriate conditions. Many different organic compounds can be prepared from (TBIO) by exploiting different active groups (methylene and carbonyl) groups. In this work a different chalcones have been synthesis by condensation the precursor (TBIO) with heterocyclic and aromatic aldehyde. Synthesis the novel chalcones which have diverse groups expected to gate an elevated and various biological activity. We take advantage of the presence two hydrogen donor position, proton of pyrrole nitrogen and thiol proton which different in dissociation constant. The pyrrole nitrogen (PKa = 10.24) While (PKa= 4.91) for thiol group [18]. On the basic principles of dissociation constant that Compounds with a low PKa have a higher percentage of deprotonation, this will lead to a higher reactivity [20]. This deprotonation gives thiol group a negative charge and therefore increases reactivity and making the thiol much more reactive towards electrophiles. Depending on difference in PKa value between thiol group (lower value) and pyrrole nitrogen group (highest value) the thiol group much more reactive than pyrrole nitrogen group. (Formula 1).



Formula 1: 2-mercaptobenzimidazole (2MBI), Contain two hydrogen donor position.

On the other hand, the second reactant compound is Chloroacetyl chloride which has very active group (acid chloride) comparing with alkyl chloride, So When two compounds react in acidic medium and required temperature that give no doubt for obtain the desired product (TBIO) and prevents the production of other products as shown by mechanism.(Scheme 4). All compounds that synthesis was characterized by spectroscopic method (^{1}H-NMR, Mass spectra, FT-IR) and

gave satisfactory data for the proposed structures. In ^{1}H NMR (DMSO-d_6 , $CDCl_3$) spectrum of compounds except for (TBIO), the demise of a singlet from δ 4.615 ppm of (N–CH_2-C=O) clearly confirm that hydrogen atoms has been loss by reaction with aldehydes. The IR spectrum of all synthesized compound exhibited shifting the stretching band in 1737.92 cm^{-1} (TBIO) to lower value in the range of 1732-1705 cm^{-1} and that by increasing the conjugation to carbonyl group with double bond of chalcones. The structural of newly compounds was proven by its mass spectral studies. The mass spectra expose the exactly molecular ion that identical with molecular formula of synthesized compounds. The cyclocondensation reaction of chloroacetylchloride and 2-mercaptobenzimidazole without catalyst in acidic organic solvent give (TBIO) with a good yield (89 %). The FT-IR spectrum of (TBIO) in 4000-600 cm^{-1} range which is shown in (Figure 1), the carbonyl of five-membered ring is observed at 1737.92 cm^{-1} as a very strong band, that band provide a strong evidence of bonding the carbonyl group with Sulfur atom[21, 22] and There is no other option like pyrrole nitrogen [23, 24, 25] to form γ-lactam. All chalcones was obtained by using basic catalyst piperidine to give pure and high yield. However, this reaction without the appropriate catalyst the reaction well have longer time, poor yield and incomplete of reaction have been observed.



Scheme 4: the mechanism of preparing ([1,3]thiazolo[3,2-a]benzimidazol-2(3H)-one (TBIO).

Evaluation of antimicrobial activity

Antimicrobial activity of the synthesized compounds (31 compounds) were checked in different concentrations against Gram-positive; *Staphylococcus aureus*, *Staphylococcus epidermidis* and Gram-negative; *Klebsiella sp*, *Escherichia coli.* The minimum inhibition concentration (MIC, μg cm^{-3}) values of newly synthesized compounds are mention in (table 2). Different inhibition zones size against tested bacterial strains was observed, the result showed that synthesis compounds in low concentrations have high activity than high concentrations. In general the data for antibacterial activity have display that most of the synthesized compounds have antibacterial activity best than that of positive control streptomycin, However the activity against gram-positive bacteria better than that gram-negative as in (1b, 1f, 1j, 3b) compounds. The 3d and 3h compounds revealed excellent and highest activity against all kinds of bacteria and that mention the activity of 2,4-dichloro and *p*-OCH_2CH_3 substituent in the phenyl ring respectively. The synthesized compounds (3a-m) in general have high activity comparing with (1a-k) compounds, this is due to the presence of the furan ring.

Table 2: MIC (μg cm^{-3}) values of synthesis compounds (A-4c) against various bacterial strains.

Compound	Gram-positive		Gram-negative	
	Staphylococcus aureus	*Staphylococcus epidermidis*	*Klebsiella sp*	*Escherichia coli*
A	13.4	38.3	4.8	5.2
1a	17.8	19.5	7.50	9.9
1b	18.5	54.9	2.77	0
1c	37.5	34.7	6.24	17.5
1d	23.6	22.1	1.55	19.2
1e	9.3	19.5	7.39	12.1
1f	63.7	44.9	0	0
1g	54.9	34.7	8.55	2.5
1h	42.8	43.9	0	1.55
1i	52.5	54.5	6.25	18.5
1j	19.6	33.8	3.8	0
1k	75	97.4	11.3	15.75
2a	37.5	88.3	37.5	55.6
2b	47.7	75	55.5	65.8
2c	28.9	76.4	13.6	45.5
3a	46.2	86.3	22.5	59.5
3b	18.7	69.5	0	0
3c	43.0	95.5	15.4	79.7
3d	>100	75	>100	>100
3e	86.4	94.4	53.5	85.5
3f	74.9	75	13.6	74.6
3g	2.6	78.8	11.5	0
3h	75	>100	45.8	80.5
3i	54.5	68.9	0	43.5
3j	76.9	85.8	43.7	37.5
3k	84.4	36.6	76.4	18.5
3l	85.9	72.5	33.2	15.8
3m	59.8	68.5	5.7	30.6
4a	77.4	73.9	3.7	3.9
4b	83.4	83.0	0	0
4c	68.2	62.9	2.5	45.5
Streptomycin	2.15	2.27	4.66	4.38

CONCLUSION

In this study, novel (TBIO) was prepared by a simple and rapid modification method, by means of a strategy involving direct cyclocondensation of the 2-mercaptobenzimidazole with a chloroacetylchloride, we realized the chemoselective cyclocondensation of 2-mercaptobenzimidazole with acid chloride in acidic environment. Following the various new substituted chalcone has been synthesis depending on activity of methylene group in (TBIO). A structure of the synthesized compounds was illustrated on the basis of different spectroscopic methods. All synthesis compounds were identified in vitro as antibacterial activity against *Staphylococcus aureus, Staphylococcus epidermidis, Klebsiella sp and Escherichia coli* strains, the activity of most synthesized compounds showed higher almost 50 times for gram-positive and 10 times for gram-negative respectively, than that of streptomycin. The (3d) compound

revealed excellent and broad spectrum antibacterial activity.

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REFERENCES

1. X. Bi, X. Meng, G. Chen, B. Chen, and P. Zhao, "Manganese oxide catalyzed synthesis of anti-HIV N-substituted benzimidazoles via a one-pot multistep process," *Catal. Commun.*, vol. 116, pp. 27–31, 2018.
2. S. M. Ali, S. A. Kadhem, A. Jabar, K. Atia, and R. I. Al-bayti, "Journal of Global Pharma Technology Synthesis , Characterization and Antibacterial Studies of Some New Imidazole Derivatives," vol. 3026, no. 1, pp. 123–125, 2018.
3. S. A. Kadhem, S. M. Ali, A. Jabar, K. Atia, R. H. Salih, and R. A. Abdulrazaq, "Synthesis and study of biological activities of compounds derived from new Imidazole derivative," *J. Pharm. Sci. Res.*, vol. 10, no. 11, pp. 2818–2824, 2018.
4. Y. N. Wang, R. R. Y. Bheemanaboina, G. X. Cai, and C. H. Zhou, "Novel purine benzimidazoles as antimicrobial agents by regulating ROS generation and targeting clinically resistant Staphylococcus aureus DNA groove," *Bioorganic Med. Chem. Lett.*, vol. 28, no. 9, pp. 1621–1628, 2018.
5. S. Uzun, Z. Esen, E. Koç, N. C. Usta, and M. Ceylan, "Novel purine benzimidazoles as antimicrobial agents by regulating ROS generation and targeting clinically resistant Staphylococcus aureus DNA groove," *J. Mol. Struct.*, vol. 1178, pp. 450–457, 2019.
6. A. Kamil *et al.*, "Antimalarial and insecticidal activities of newly synthesized derivatives of Benzimidazole," *Pak. J. Pharm. Sci.*, 2015.
7. E. Łukowska-Chojnacka, P. Wińska, M. Wielechowska, M. Poprzeczko, and M. Bretner, "Synthesis of novel polybrominated benzimidazole derivatives - Potential CK2 inhibitors with anticancer and proapoptotic activity," *Bioorganic Med. Chem.*, vol. 24, no. 4, pp. 735–741, 2016.
8. R. Abraham, P. Prakash, K. Mahendran, and M. Ramanathan, "A novel series of N-acyl substituted indole-linked benzimidazoles and naphthoimidazoles as potential anti inflammatory, anti biofilm and anti microbial agents," *Microb. Pathog.*, vol. 114, no. 2018, pp. 409–413, 2018.
9. N. K. N. A. Zawawi, M. Taha, N. Ahmat, N. H. Ismail, A. Wadood, and F. Rahim, "Synthesis, molecular docking studies of hybrid benzimidazole as α-glucosidase inhibitor," *Bioorg. Chem.*, vol. 70, pp. 184–191, 2017.
10. A. Popova, E. Sokolova, S. Raicheva, and M. Christov, "AC and DC study of the temperature effect on mild steel corrosion in acid media in the presence of benzimidazole derivatives," *Corros. Sci.*, 2003.
11. Z. Li, L. J. Li, T. Sun, L. Liu, and Z. Xie, "Benzimidazole-BODIPY as optical and fluorometric pH sensor," *Dye. Pigment.*, 2016.
12. Z. N. Al-Saadi and K. R. H. Al-Jorani, "Synthesis, characterization and anti-methicillin resistant staphylococcus aureus (Mrsa) evaluation of 4-bromo-2-(4,5-diphenyl-1h-imidazol-2-yl) phenol [br-hpi] and its complexes with co^{ii}, cu^{ii} metal ions," *J. Pharm. Sci. Res.*, vol. 10, no. 11, pp. 2866–2871, 2018.
13. *Mohammed F.Al-Marjani and AbdulJabar K. Atia Maysoon A.A. Al-Soodani , Abdulwahab H. M. Ali, "Synthesis and Biological activity of some complexes of (2-phenyl-4-arylidine imidazole- 5-one) with some transition metal ions," *Int. J. Adv. Res.*, vol. 2, no. 3, pp. 399–408, 2014.
14. E. A. Of, "SYNTHESIS, CHARACTERIZATION, AND ENZYME ACTIVITY OF Co(II), Ni(II), Cu(II), Pd(II), Pt(IV) AND Cd(II) COMPLEXES WITH 2-THIOXOIMIDAZOLIDIN-4-ONE DERIVATIVE," *Acta Chim. Pharm. Indica*, vol. 6, no. 3, pp. 80–91, 2016.
15. A. A. El-Sherif, "Synthesis, solution equilibria and antibacterial activity of Co(II) with 2-(aminomethyl)-benzimidazole and dicarboxylic acids," *J. Solution Chem.*, vol. 39, no. 10, pp. 1562–1581, 2010.
16. Q. Guan, Q. Sun, L. Wen, Z. Zha, Y. Yang, and Z. Wang, "The synthesis of benzimidazoles *via* a recycled palladium catalysed hydrogen transfer under mild conditions," *Org. Biomol. Chem.*, vol. 16, no. 12, pp. 2088–2096, 2018.
17. H. A. Ibrahim, F. M. Awadallah, H. M. Refaat, and K. M. Amin, *Molecular docking simulation, synthesis and 3D pharmacophore studies of novel 2-substituted-5-nitro-benzimidazole derivatives as anticancer agents targeting VEGFR-2 and c-Met*, vol. 77. 2018.
18. K. Anandarajagopal, R. N. Tiwari, K. G. Bothara, J. Anbu Jeba Sunilson, C. Dineshkumar, and P. Promwichit, "2-Mercaptobenzimidazole Derivatives: Synthesis and Anticonvulsant Activity.," *Adv. Appl. Sci. Res.*, vol. 1, no. 2, pp. 132–138, 2010.
19. I. H. R. Tomi, A. H. R. Al-Daraji, A. M. Abdula, and M. F. Al-Marjani, "Synthesis, antimicrobial and docking study of three novel 2,4,5-triarylimidazole derivatives," *J. Saudi Chem. Soc.*, vol. 20, pp. S509–S516, 2016.
20. D. H. A. Bianchi and G. R. M. M. Haenen, "The paradoxical influence of the pKa on the reactivity of thiols and its biological relevance," *MaRBLe Res. Pap.*, vol. 2, pp. 222–231, 2014.
21. S. Breda, I. Reva, and R. Fausto, "Molecular structure and vibrational spectra of 2(5H)-furanone and 2(5H)-thiophenone isolated in low temperature inert matrix," *J. Mol. Struct.*, vol. 887, no. 1–3, pp. 75–86, 2008.
22. A. Gilbert, "Photochemistry of Aromatic Compounds.," *Photochemistry*, vol. 33, pp. 155–193, 2002.
23. J. Sun, J. J. Liu, W. Zhou, F. J. Guo, X. Y. Wang, and H. L. Zhu, "4-Hydroxy-3-(naphthalen-1-ylmethyl)thiophen-2(5H)-one as inhibitors of tyrosyl-tRNA synthase: Synthesis, molecular docking and antibacterial evaluation," *J. Mol. Struct.*, vol. 1056–1057, no. 1, pp. 104–109, 2014.
24. H. J. Rong, Y. F. Cheng, F. F. Liu, S. J. Ren, and J. Qu, "Synthesis of γ-Lactams by Mild, o-Benzoquinone-Induced Oxidation of Pyrrolidines Containing Oxidation-Sensitive Functional Groups," *J. Org. Chem.*, vol. 82, no. 1, pp. 532–540, 2017.
25. N. A. Magnus *et al.*, "Additives promote noyori-type reductions of a β-keto-γ-lactam: Asymmetric syntheses of serotonin norepinephrine reuptake inhibitors," *J. Org. Chem.*, vol. 78, no. 11, pp. 5768–5774, 2013.