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Synthesis, characterization & biological evaluation of some novel 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-imidazo[2,1-b]thiazole derivatives

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Abstract: An efficient and convenient procedure has been developed for the synthesis of some novel imidazo[2,1-b]thiazole derivatives like 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-N-arylimidazo[2,1-b] thiazole-2-carboxamide having 57-71% yield and aryl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate having 56-74% yield. The structures of the new compounds have been evaluated on the basis of FT-IR, ^{1}H NMR and Mass spectroscopy data. They have also been screened for their antimicrobial activities against various strains of bacteria and fungi.

Keywords: Antimicrobial activity, Imidazo[2,1-b]thiazole, imidazole, thiazole

Introduction:

Heterocyclic compounds are an important class in pharmaceutical chemistry. A wide variety of drugs, most of the vitamins, many natural products and biologically active compounds consist of heterocyclic compounds [1]. Imidazo[2,1-b]thiazole structure containing two fused five member rings with one nitrogen atom at the ring junction. Fused five member heterocyclic compounds are particularly versatile in the field of medicinal chemistry because of their different biological activities. [2]. The structure of imidazo[2,1-b]thiazole accept different kind of substitution reaction, therefore in the last few decade the research in this field has generated various patents with various therapeutic applications [3]. The chemical structure of imidazo[2,1-b]thiazole is describe in **(Figure 1)**.

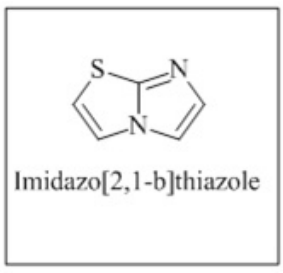


Figure 1: Chemical structure of imidazo[2,1-b] thiazole

Imidazo[2,1-b]thiazole and its derivatives have been attracted in the field of medicinal chemistry because of their wide ranging of biological activities [4, 5]. The same type of parent molecule i.e. thiazolo[2,3-b]quinazoline derivatives are anti-breast cancer and anti angiogenic agents [6]. Levamisole is a member of Imidazo[2,1-b] thiazole class of drug with trade name Ergamisol is an anthelmintic and immunomodulatory drug [7], Imidazo[2,1-b]thiazole derivatives also reported as anti-infectious [8], Mycobacterium tuberculosis pantothenate synthetase (MTB PS) [9], DHFR inhibitors [10], antitubercular [11], anthelmintic and anti-inflammatory [12], cardio depressant [13], antiviral [14], anticancer [15], acetyl cholinesterase inhibitor [16], The chemical structures of these bioactive molecules containing imidazo[2,1-b]thiazole skeleton are represented in (**Figure 2)**.

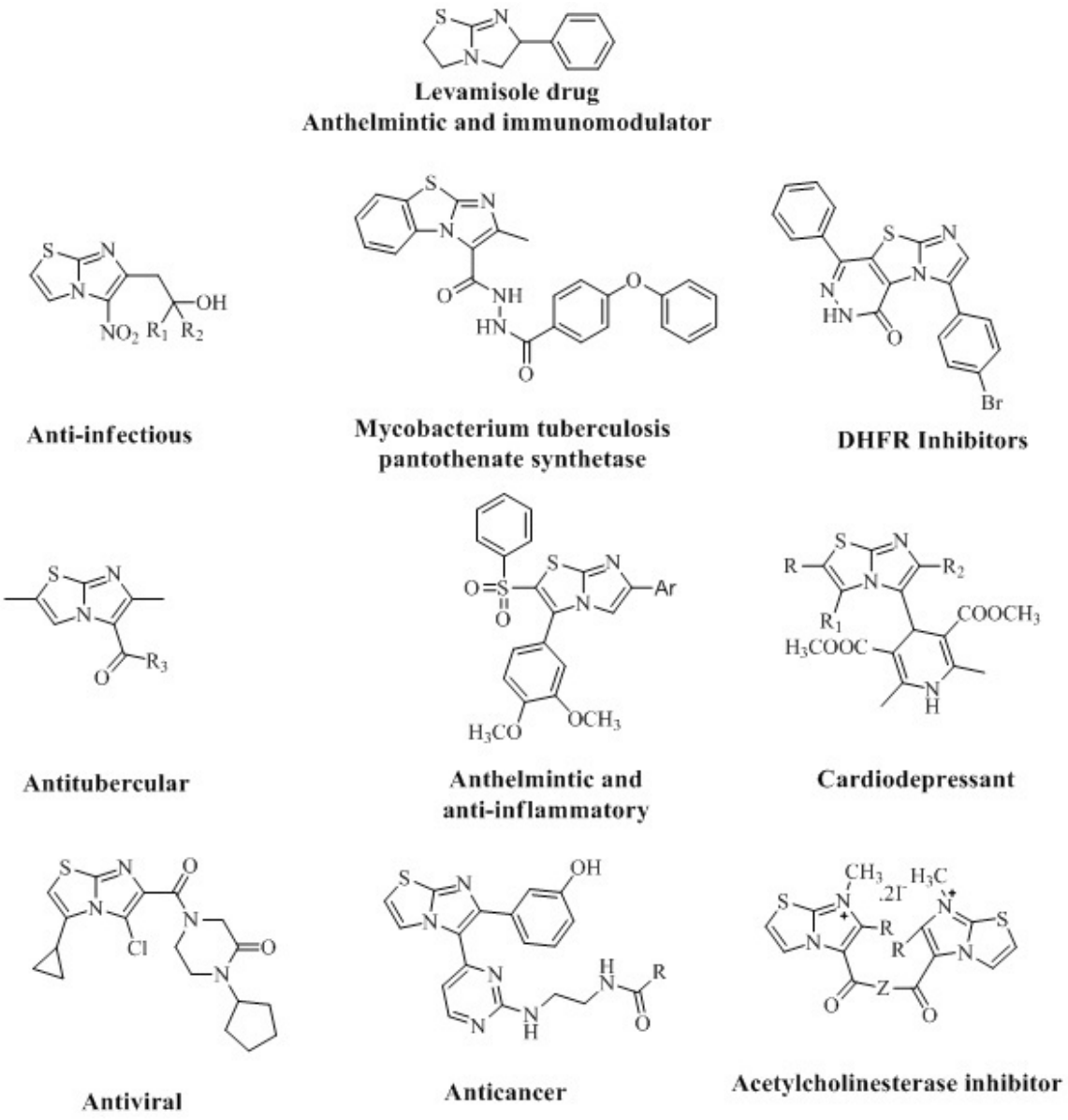


Figure 2: Chemical structures of bioactive molecules containing imidazo2,1-b]thiazole compound.

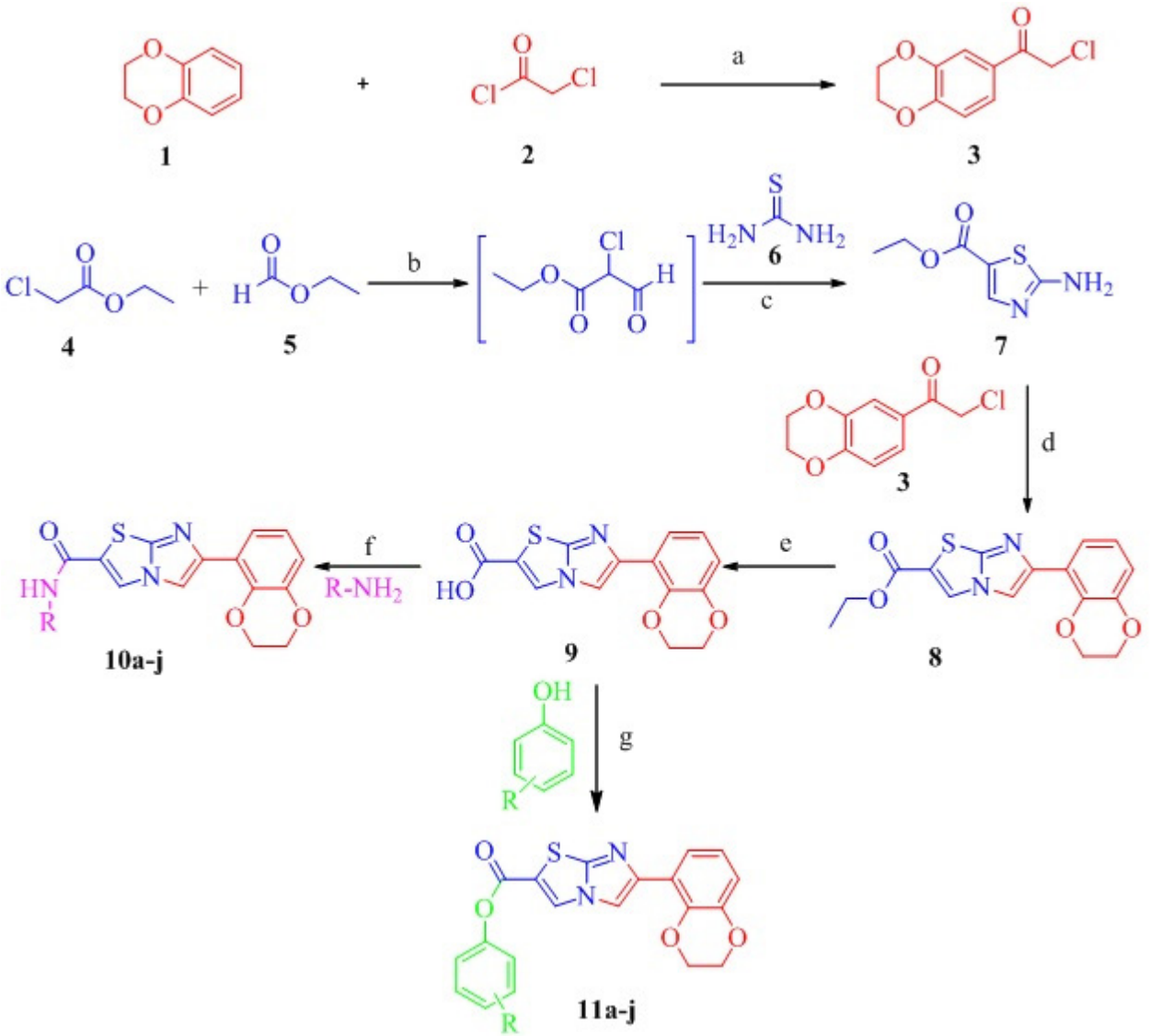
The imidazo[2,1-b]thiazole ring was also synthesized by microwave-assisted solvent free Groebkee-Blackburne-Bienayme reaction catalyzed by H_3PO_4/Al_2O_3 [17]. The main objective of the study was to synthesize the novel imidazo[2,1-b]thiazole derivatives in view to study their biological activity. Based on literature, versatile method for synthesis of novel 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-2-methylimidazo[2,1-b]thiazole derivative is describe in **(Scheme 1).**

General synthetic scheme:

Reagents: (a) $AlCl_3$, DCM, 0-10°C; (b) Sodium methoxide, Toluene, 0-5°C; (c) Conc. HCl, reflux; (d) DMF, 90-100°C; (e) Ethanol, aqueous NaOH, RT; (f) EDC.HCl, HOBT, TEA, DCM, RT; (g) EDC.HCl, HOBT, TEA, DCM, RT.

Reaction Mechanism:

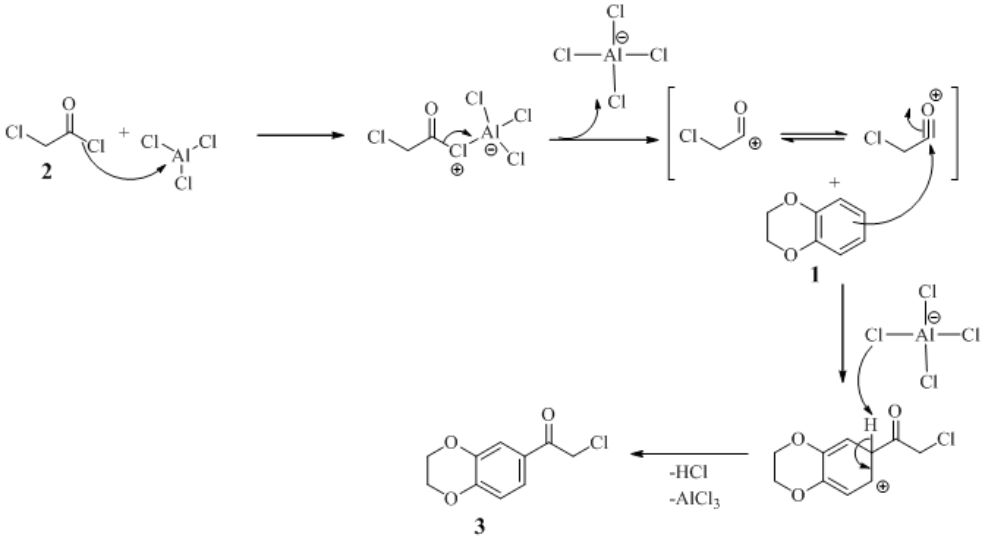
Plausible reaction mechanism of synthesis



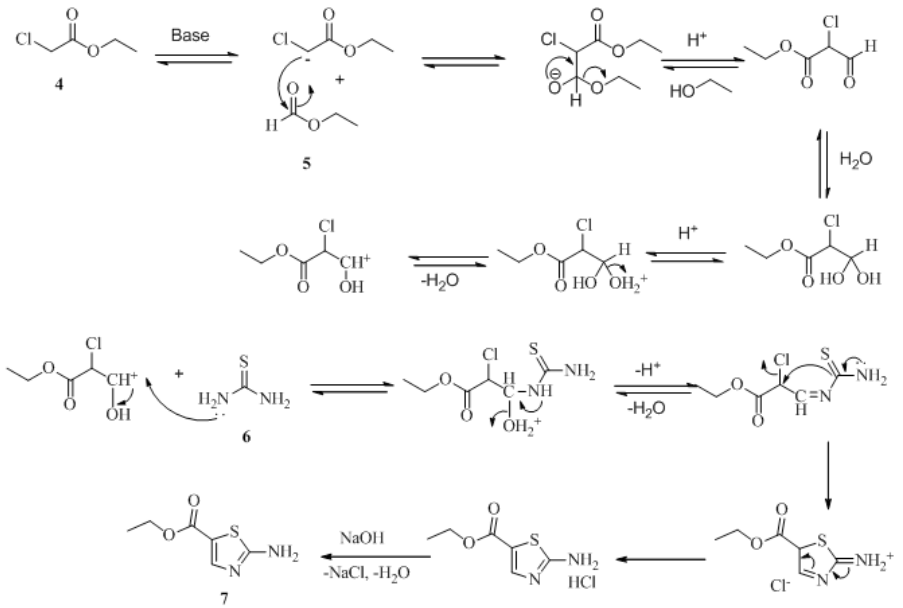
Scheme 1: Reaction scheme for synthesis of 10a-j and 11a-j

of compound **3, 7, 8, 9, 10a-j** and **11a-j** are describe in **(Scheme 2, Scheme 3, Scheme 4, Scheme 5** and **Scheme 6)** respectively.

A reaction occurs between the Lewis acid ($AlCl_3$) and the chloroacetyl chloride. A complex is formed and the Chloroacetyl chloride loses a chloride ion, forming an acylium ion which is stabilized by resonance. The acylium ion (RCO^+) goes on to execute an electrophilic attack on the aromatic ring of 2,3-dihydrobenzo[b][1,4]dioxine **(1)**. The aromaticity of the ring is temporarily lost as a complex is formed. The intermediate complex is now deprotonated, restoring the aromaticity to the ring and 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl) ethanone **(3)** is obtained via the Friedel-Crafts acylation reaction.

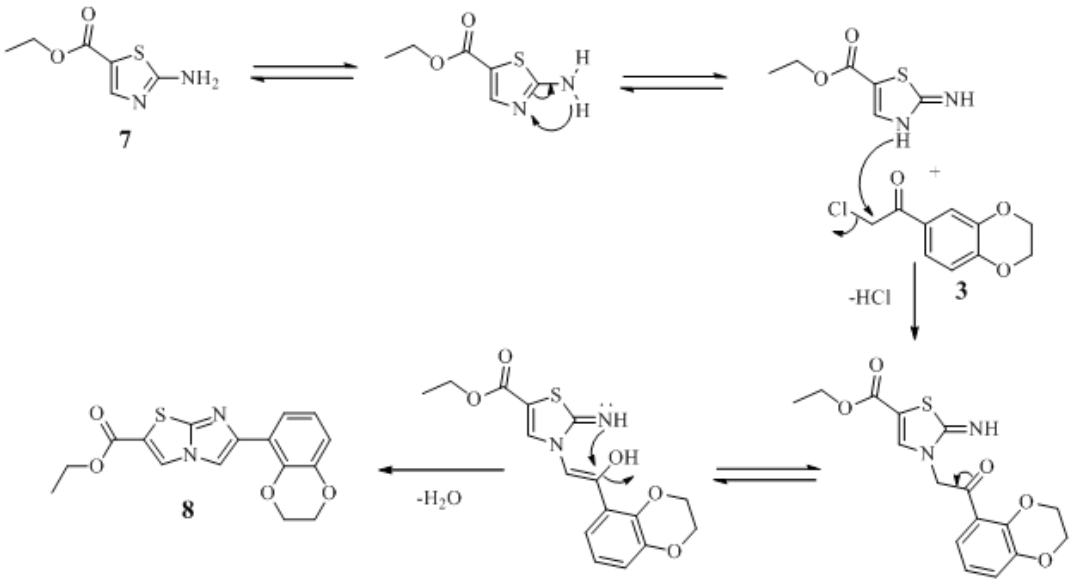


Scheme 2: Plausible mechanism for synthesis of compound **3**

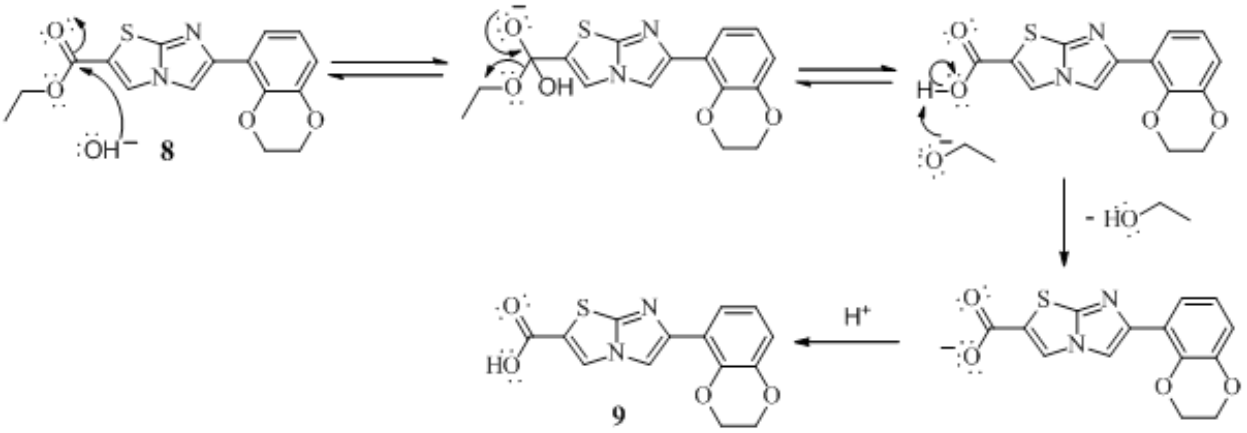


Scheme 3: Plausible mechanism for synthesis of compound **7**

In the first step of the mechanism, α-proton of ethyl chloroacetate is removed by a strong base (sodium methoxide), resulting in the formation of an enolate anion. Next, the carbonyl carbon of the ethyl formate is nucleophilically attacked by the enolate anion. The ethoxy group is then eliminated and Con. HCl is added to acidify reaction mass in which the enolate is neutralized. The formation of the thiazole ring is actually a two-step process; in the first step carbocation generated in acidic medium which is reacted with NH_2 group of thioamide and water is then eliminated. In second step intramolecular cyclization occurs and formation of ethyl 2-aminothiazole-5-carboxylate (**7**) [18]. Imidazo[2,1-b]thiazole was prepared in a single step simply by heating the appropriate α -haloketone with a 2-aminothiazole in a suitable solvent [19]. In the first step of the mechanism alkylation of the ethyl 2-aminothiazole-5-carboxylate (**7**) by 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl) ethanone (**3**) occurs on the ring nitrogen rather than the amino group to give intermediate which is insitu cylized and water is then eliminated and form imidazo[2,1-b]thiazole (**8**) [20].

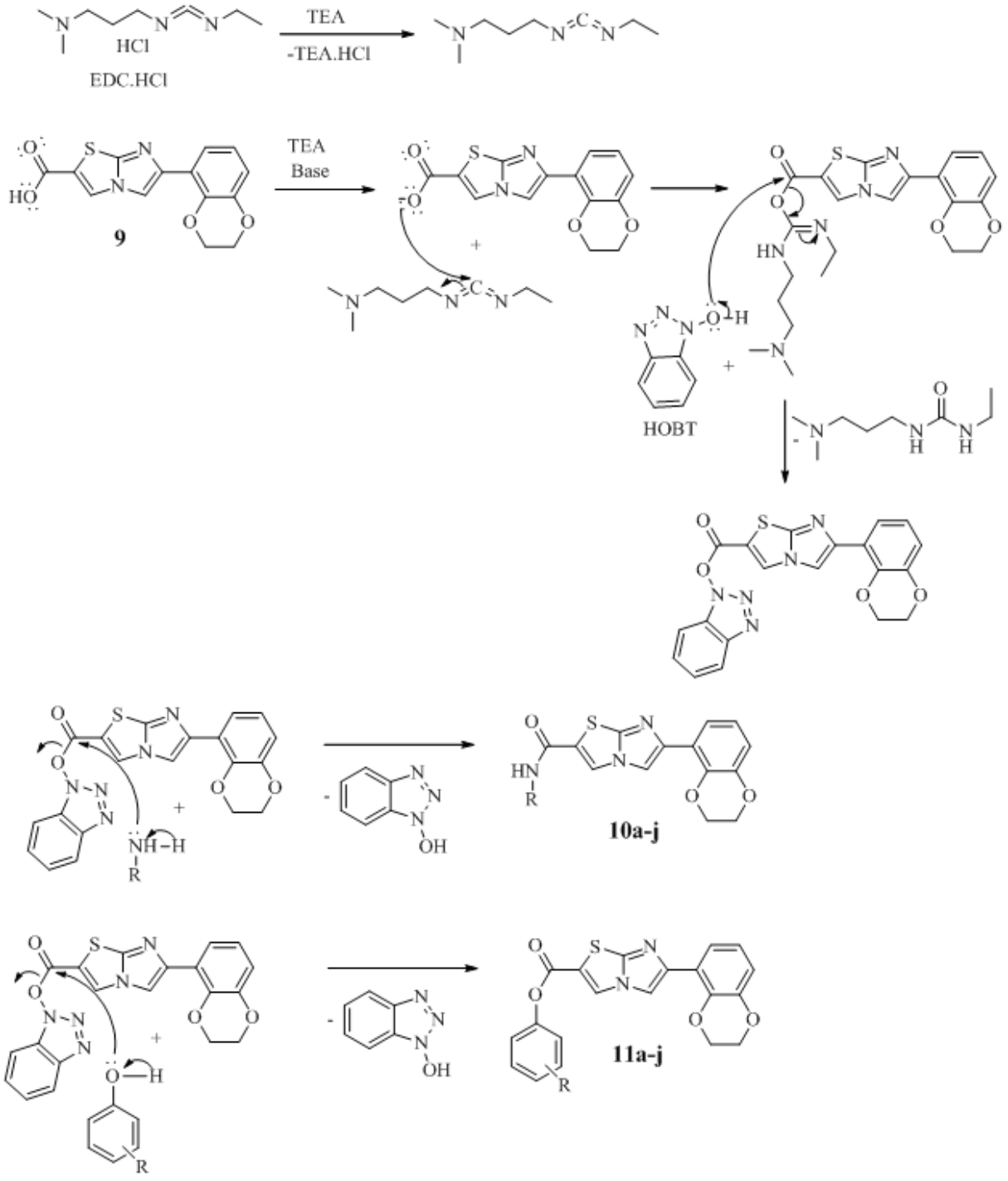


Scheme 4: Plausible mechanism for synthesis of compound **8**



Scheme 5: Plausible mechanism for synthesis of compound **9**

In the first the first step of the mechanism hydroxide nucleophiles attacks at electrophilic carbonyl carbon of the ester group **(8)**, breaking the π bond and creating the tetrahedral intermediate. In second step ethoxide group is eliminated, leading to the formation of carboxylate anion. In third step acidic work up would allow the carboxylic acid **(9)** to be obtained from the reaction.



Scheme 6: Plausible reaction mechanism for synthesis of compound **10a-j** and **11a-j**

The acid **9** will react with the carbodiimide (EDC) to produce the key intermediate: the O-acylisourea, which will react with nucleophiles such as hydroxybenzotriazole (HOBT) that reacts faster than the competing acyl transfer and generates an intermediate, which will react with the substituted amine/ phenol to give the desired amide **10a-j** and ester **11a-j**.

Materials and methods:

All chemicals were purchased from laboratory grade and used without further purification. The progress of the reaction was monitored by analytical TLC on precoated plates (silica gel 60, F_{254}) and visualized with UV light. Melting points were recorded on Spectral Lab melting point (Model no. Check Melt-2). NMR spectra were recorded using DMSO-d_6 as a solvent on a Bruker 400 MH and chemical shifts are expressed in parts per million (ppm) related to internal standard TMS. IR spectra were determined on a "IR Affinity-1S" (Shimadzu). Mass spectrometry data were recorded on LC/ MS (Waters): electro spray (+) ionization, mass ranges 100-800 Da, 20-V cone voltage, and Xterra MS C18 column (2.1 mm x 50 mm x 3.5 µm).

Experimental Procedure:

Preparation of 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone (3):

To a stirred solution of 2,3-dihydrobenzo[b] [1,4]dioxine **1** (50.0 g, 0.3672 mole) was dissolve in dichloromethane (500 ml) and anhydrous aluminum chloride (53.9 g, 0.4039 mole) was added in reaction mixture at 0-10°C. Chloroacetyl chloride **2** (45.6 g, 0.4039 mole) was added slowly into reaction mixture at 0-10°C. Reaction mixture was stirred for 2 hours at 0-10°C. The progress of reaction was monitored by TLC. After completion of reaction, water (500 ml) was added into reaction mixture and product was extracted in dichloromethane. Evaporate the solvent from organic layer and this crude compound was purified in ethyl acetate (250 ml) and resulting solid was filtered, wash with ethyl acetate and dried in under vacuum at 40-50°C to give pure 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone **3** (65.0 g), yield 83.24%.

Preparation of ethyl 2-aminothiazole-5-carboxylate (7):

To a stirred solution of ethyl chloroacetate (50.0 g, 0.408 mol) and ethyl formate (30.3 g, 0.408 mol) was dissolve in toluene (500 ml). Sodium methoxide (26.5 g, 0.489 mol) was added slowly into reaction mixture at 0-5°C, Reaction mixture was maintained at 0-5°C for 2 hr. Then, the reaction mixture was stirred at room temperature for another 3 hr. The progress of reaction was monitored by TLC. After completion of reaction, reaction mass was quenched with water and layers were separated. The aqueous phase was acidified with concentrated hydrochloric acid. In this acidified solution, thiourea (34.2 g, 0.448 mol) was added and reaction was heated at refluxed for 2.5 hr. The progress of reaction was monitored by TLC. After completion of reaction, the reaction mixture was cooled and neutralized with 2 N sodium hydroxide solution and resulting solid was filtered and dried in under vacuum at 40-50°C to give ethyl 2-aminothiazole-5-carboxylate **7** (50.0 g), yield 71.42%.

Preparation of ethyl 6-(2,3-dihydrobenzo[b] [1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate (8):

To a stirred solution of 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone **3** (50.0 g, 0.2351 mole) and ethyl 2-aminothiazole-5-carboxylate **7** (44.5 g, 0.2586 mole) in N,N-

dimethylformaide (50 ml). Reaction mixture was heated at 90-100°C for 4 hours. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, water (500 ml) was added into reaction mixture and resulting solid was filtered at 25-35°C, wash with water and this crude compound was crystallization in methanol (250 ml) and resulting solid was filtered, wash with methanol and dried in under vacuum at 40-50°C to give pure ethyl 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate **8** (54.0 g), yield 69.51%. Mass: m/z 331.2 $[M+H]^+$.

Preparation of 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylic acid (9):

To a stirred solution of ethyl 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl) imidazo[2,1-b]thiazole-2-carboxylate **7** (50.0 g, 0.1513 mole) in ethanol (250 ml), 1N sodium hydroxide solution (225 ml, 0.1513 mol) was added drop wise into reaction mixture. The resulting reaction mixture was stirred at room temperature for 3 hours. The progress of reaction was monitored by TLC. After completion of reaction, water (250 ml) was added and the reaction mixture was wash with dichloromethane (250 ml) and separate organic layer and aqueous layer. Acidified the aqueous layer with 1 N hydrochloric acid and resulting solid was filtered at 25-35°C, wash with water and dried in under vacuum at 40-50°C to give pure 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylic acid **9** (40.0 g), yield 87.91%. Mass: m/z 303.0 $[M+H]^+$.

General procedure for synthesis of substituted 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-substituted-N-arylimidazo[2,1-b]thiazole-2-carboxamide (10 a-j):

To a stirred solution of 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylic acid **9** (1.0 g, 0.0033 mol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (0.92 g, 0.0048 mol) and 1-hydroxybenzotriazole (0.64 g, 0.0048 mol) in dichloromethane (10 ml). Substituted aryl amine (0.32 g, 0.0036 mol) was added into reaction mixture. Triethylamine (0.65 g, 0.0064 mol) was added slowly into reaction mixture and resulting reaction mixture was stirred at room temperature for 5 hours. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, water was added into reaction mixture and reaction mixture was stirred at room temperature for 1 hour, solid was precipitated out and resulting solid was filtered, wash with dichloromethane and this crude compound was purified by isopropyl alcohol (10 ml) and resulting solid was filtered, wash with isopropyl alcohol and dried in under vacuum at 40-50°C to give pure substituted 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-substituted-N-arylimidazo[2,1-b]thiazole-2-carboxamide **10a-j** (0.70 g), 57-71%. The yield and physical properties are reported in **Table-1**.

General procedure for synthesis of substituted aryl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl) imidazo[2,1-b]thiazole-2-carboxylate (11a-j):

To a stirred solution of 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylic acid **9** (1.0 g, 0.0033 mol), N-(3-dimethylaminopropyl)-N′-ethylcarbodiimide hydrochloride (0.92 g, 0.0048 mol) and 1-hydroxybenzotriazole (0.64 g, 0.0048 mol) in dichloromethane (10 ml). Substituted phenol (0.32 g, 0.0036 mol) was added into reaction mixture. Triethylamine (0.65 g, 0.0064 mol) was added slowly into reaction mixture and resulting reaction mixture was stirred at room temperature for 5 hours. The progress of reaction was monitored by thin layer chromatography. After completion of reaction, water was added

into reaction mixture and reaction mixture was stirred at room temperature for 1 hour, solid was precipitated out and resulting solid was filtered, wash with dichloromethane and this crude compound was purified by isopropyl alcohol (10 ml) and resulting solid was filtered, wash with isopropyl alcohol and dried in under vacuum at 40-50°C to give pure substituted aryl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl) imidazo[2,1-b]thiazole-2-carboxamide **11a-j** (0.80 g), 56-74%. The yield and physical properties are reported in **Table-2**.

Spectral & physical data:

2-Chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone (3):

Off white Solid; **^{1}H NMR (400 MHz, $CDCl_3$):** 4.28-4.34 (4H, m), 4.63 (2H, s), 6.92-6.94 (1H, d), 7.47-7.50 (2H, m) ppm; **MS:** m/z 213.0 $[M+H]^+$

6-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)-N-(2,4-dimethylphenyl)imidazo[2,1-b]thiazole-2-carboxamide (10d):

Off white Solid; M.p.: 235-237°C, Yield: 70%. **^{1}H NMR (400 MHz, DMSO-d_6):** 2.20 (3H, s), 2.28 (3H, s), 4.27 (4H, s), 6.88-6.90 (1H, d), 7.03-7.05 (1H, d), 7.10 (1H, s), 7.18-7.20 (1H, d), 7.33-7.36 (2H, m), 8.31 (1H, s), 8.79 (1H, s) 10.10 (1H, s) ppm; **MS:** m/z 406.1 $[M+H]^+$, **IR Cm^{-1}:** 3225, 3093, 2978, 1658, 1566, 1458, 1288, 1057, 817.

6-(2,3-Dihydrobenzo[b][1,4]dioxin-5-yl)-N-(1-phenylethyl)imidazo[2,1-b]thiazole-2-carboxamide (10f):

White Solid; M.p.: 242-244°C, Yield: 63.0%. **^{1}H NMR (400 MHz, DMSO-d_6):** 1.48-1.49 (3H, d), 4.26 (4H, s), 5.10-5.14 (1H, m), 6.87-6.89 (1H, d), 7.23-7.27 (1H, t), 7.31-7.40 (6H, m), 8.27 (1H, s), 8.74 (1H, s), 9.07-9.09 (1H, d) ppm; **MS:** m/z 406.1 $[M+H]^+$, **IR Cm^{-1}:** 3325, 3140, 2978, 1635, 1573, 1481, 1273, 1057, 879.

N-Benzyl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxamide (10g):

Off white Solid; M.p.: 196-198°C, Yield: 64%. **^{1}H NMR (400 MHz, DMSO-d_6):** 4.26 (4H, s), 4.47-4.49 (2H, d), 6.87-6.89 (1H, d), 7.26-7.38 (7H, m), 8.26 (1H,s), 8.62 (1H, s), 9.26-9.29 (1H, t) ppm; **MS:** m/z 392.2 $[M+H]^+$, **IR Cm^{-1}:** 3371, 3078, 2978, 1635, 1573, 1489, 1296, 1064, 879.

Phenyl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate (11a):

Cream Solid; M.p.: 206-208°C, Yield: 74%. **^{1}H NMR (400 MHz, DMSO-d_6):** 4.27 (4H, s), 6.89-6.91(1H, d), 7.32-7.39 (5H, m), 7.47-7.51 (2H, t), 8.22 (1H, s), 9.03 (1H, s) ppm; **MS:** m/z 379.1 $[M+H]^+$, **IR Cm^{-1}:** 3086, 2978, 1728, 1558, 1489, 1327, 1242, 1057, 887, 732.

4-Methoxyphenyl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate (11b):

Cream Solid; M.p.: 254-256°C, Yield: 67%. **^{1}H NMR (400 MHz, DMSO-d_6):** 3.78 (3H, s), 4.27 (4H, s), 6.89-6.91 (2H, d), 7.00-7.02 (2H, d), 7.23-7.25 (2H, d), 7.35-7.38 (2H, d), 8.22 (1H, s), 9.01 (1H, s) ppm; **MS:** m/z 409.1 $[M+H]^+$, **IR Cm^{-1}:** 3093, 2978, 1728, 1550, 1496, 1327, 1242, 1057, 864, 732.

2-Chlorophenyl-6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate (11c):

Cream Solid; M.p.: 196-198°C, Yield: 59%. **^{1}H NMR (400 MHz, DMSO-d_6):** 4.27 (1H, s), 6.90-6.92 (1H, d), 7.37-7.40 (3H, m), 7.42-7.51

(1H, dt), 7.53-7.55 (1H, dd), 7.66-7.68 (1H, dd), 8.24 (1H, s), 9.12 (1H, s) ppm; **MS:** m/z 413.0 & 415.1$[M+H]^+$, **IR Cm^{-1}:** 3086, 2978, 1728, 1558, 1481, 1319, 1280, 1203, 1057, 879, 740.

Table-1: Characteristics physical data of Compound 10a-j

Compound	Substitution R-NH_2	Color	M.P. (°C)	Yield
10a	Aniline	Cream	198-200°C	57.0
10b	4-Methoxy aniline	Cream	202-204°C	71.0
10c	4-Fluoro aniline	White	189-191°C	68.0
10d	2,4-Dimethyl aniline	Off white	235-237°C	70.0
10e	3- Methyl aniline	Cream	182-184°C	65.0
10f	1-Phenylethyl amine	White	242-244°C	63.0
10g	Benzyl amine	Off white	196-198°C	64.0
10h	2-Fluro aniline	Cream	220-222°C	67.0
10i	3-Methoxy aniline	Cream	209-211°C	60.0
10j	3,4-Dichloro aniline	Cream	225-227°C	62.0

Table-2: Characteristics physical data of Compound 11a-j

Compound	Substitution R	Color	M.P. (°C)	Yield
11a	-H	Cream	206-208°C	74.0
11b	4-OCH_3	Cream	254-256°C	67.0
11c	2-Cl	Cream	196-198°C	59.0
11d	4-CH_3	Cream	178-180°C	61.0
11e	4-F	Cream	157-159°C	67.0
11f	2,6-Dibromo	Cream	211-213°C	70.0
11g	2,6-Dimethyl	Cream	201-203°C	68.0
11h	4-CN	Cream	185-187°C	58.0
11i	3-NO_2	Yellow	215-217°C	62.0
11j	5-F,2-NO_2	Yellow	223-225°C	56.0

Biological activities:

Antibacterial and antifungal activities:

The newly synthesized compounds were analyzed for their in vitro antibacterial activity against gram negative Escherichia coli and Pseudomonas aeruginosa, gram positive Staphylococcus aureus and Bacillus subtilis and antifungal activity against Aspergillus paraciticus and Rhizopus by micro broth dilution method. The standard strains used for screening antibacterial and antifungal activities were procured from Atmiya Institute of Pharmacy in vitro testing Laboratory, Rajkot, Gujarat, India. The MIC values are given in **Table-3** and **Table-4**. The standard drugs used for antibacterial activity were Streptomycin, Ampicillin and Nystatin for antifungal activity. 1000 µg/ml, 500 µg/ml, 250 µg/ml, 125 µg/ml and 62.5 µg/ml, concentrations of the synthesized drugs were taken.

The newly synthesized compounds were analyzed for their in vitro antibacterial and antifungal activity. The title compounds **10a-j** and **11a-j** were evaluated for antimicrobial activity against *S. aureus, B. subtilis* (Gram-positive bacteria), *P. aeruginosa, E. coli* (Gram negative bacteria) and *A. paraciticus* and *Rhizopus* (fungi). The antimicrobial and antifungal screening results presented in **Table 3** and **Table 4**. Compound **10i** (3-methoxy aniline)**, 10j** (3,4-dichloroaniline)**, 11b** (4-methoxyphenol), **11c** (2-chlorophenol) and **11g (**2,6-dimethylphenol**)** displayed better activity for gram positive, gram negative bacteria and fungi. Whereas, compounds **10e** (3- methyl aniline) and **10f** (1-phenylethyl amine) exhibited better activity against gram positive and gram negative bacteria but not able not inhibit fungi. Compound **11f** (2,6-dibromophenol) are exhibited mainly antifungal activity.

On careful analysis of antimicrobial activities of amide **10a-j** and ester **11a-j** provides some lead molecule with good antibacterial and anti

Table-3: Antibacterial and antifungal activity of 10a-j

Compound Codes	Antibacterial MIC (µg/ml)				Antifungal MIC (µg/ml)	
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Rhizopus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
10a	1000	1000	1000	1000	1000	1000
10b	1000	1000	1000	1000	500	500
10c	125	125	125	125	1000	1000
10d	62.5	62.5	62.5	62.5	62.5	1000
10e	250	250	250	500	1000	1000
10f	62.5	62.5	500	125	1000	1000
10g	1000	1000	1000	1000	1000	1000
10h	1000	1000	1000	1000	62.5	1000
10i	250	250	250	250	250	500
10j	250	250	1000	125	62.5	62.5

Figure 4: Antibacterial and antifungal activity, Minimum Inhibition Concentration (Graphical form) of **10a-j**

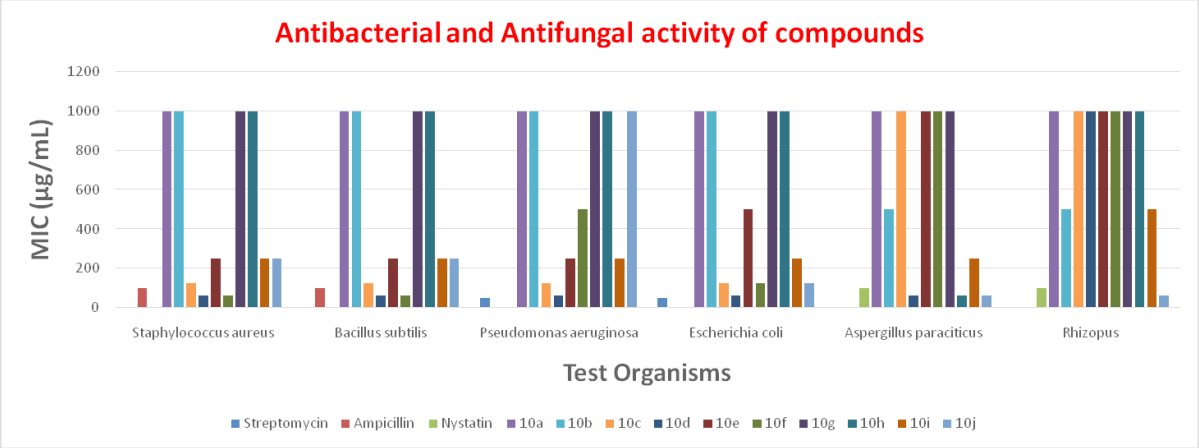
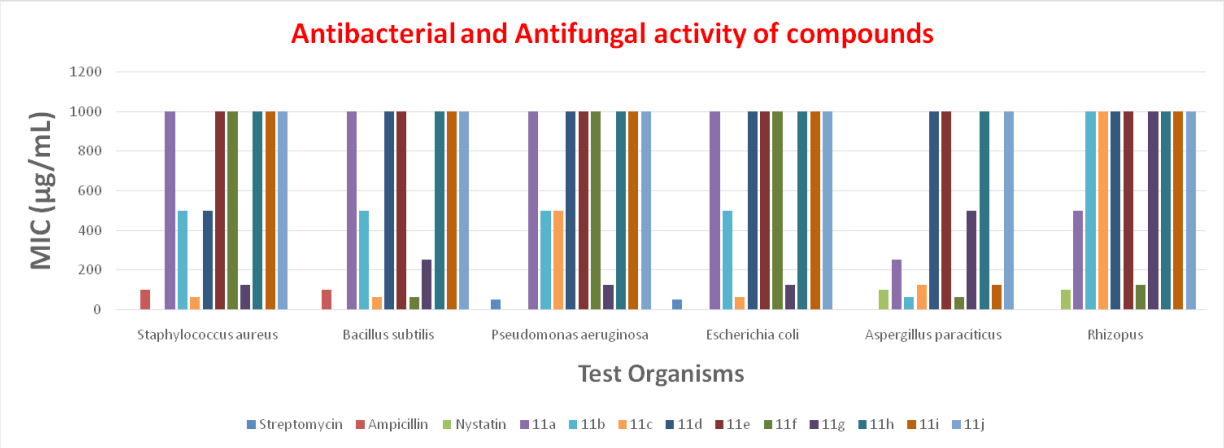


Table-4: Antibacterial and antifungal activity of 11a-j

Compound Codes	Antibacterial MIC (µg/ml)				Antifungal MIC (µg/ml)	
	Staphylococcus aureus	*Bacillus subtilis*	*Pseudomonas aeruginosa*	*Escherichia coli*	*Aspergillus paraciticus*	*Rhizopus*
Streptomycin			50	50		
Ampicillin	100	100				
Nystatin					100	100
11a	1000	1000	1000	1000	250	500
11b	500	500	500	500	62.5	1000
11c	62.5	62.5	500	62.5	125	1000
11d	500	1000	1000	1000	1000	1000
11e	1000	1000	1000	1000	1000	1000
11f	1000	62.5	1000	1000	62.5	125
11g	125	250	125	125	500	1000
11h	1000	1000	1000	1000	1000	1000
11i	1000	1000	1000	1000	125	1000
11j	1000	1000	1000	1000	1000	1000

Figure 5: Antibacterial activity and antifungal activity, Minimum Inhibition Concentration (Graphical form) of **11a-j**



fungal activity. It was demonstrated that in both the case electron donating group on phenyl ring may serve as good agents in medicinal chemistry. The result from **Table 3** and **Table 4** shows that methoxy group and dimethyl group increases of antimicrobial potency in both types of compound. On other hand electron withdrawing substituent's on phenyl ring such as nitro group and cyano group shows poorly active against gram positive, gram negative bacteria and fungi.

Results and discussion:

Various methodologies and process have been described for the synthesis of ethyl 6-phenylimidazo[2,1-b]thiazole-2-carboxylate. During the study of literature, we found that 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl) imidazo[2,1-b]thiazole-2-carboxylic acid are versatile intermediate or scaffold. Thus, we first synthesized 6-(2,3-dihydrobenzo[b] [1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylic acid **9**.

As describe in synthetic **Scheme 1**, ethyl chloroacetate **4** is reacted with ethyl formate **5** in the presence of sodium methoxide in toluene at 0-5°C to give intermediate ethyl 2-chloro-3-oxopropanoate which is insitu reacted with thiourea **6** in the presence of concentrated hydrochloric acid in water at refluxed temperature to give ethyl 2-aminothiazole-5-carboxylate **7**, which is reacted with 2-chloro-1-(2,3-dihydrobenzo[b][1,4]dioxin-6-yl)ethanone **3** in N,N-dimethylformamide at 90-100°C to give novel ethyl 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)imidazo[2,1-b]thiazole-2-carboxylate **8.** This ester was hydrolyzed in the presence of aqueous sodium hydroxide in ethanol to give 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl) imidazo[2,1-b]thiazole-2-carboxylic acid **9.**

This acid scaffold **9** then converted into amide by the reaction of different substituted aromatic amine in the presence of EDC.HCl, HOBT and triethylamine in DCM at RT to give novel 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-substituted-N-arylimidazo[2,1-b]thiazole-2-carboxamide **10**.

This acid Scaffold **9** then converted into ester by the reaction of different substituted aromatic phenol in the presence of EDC.HCl, HOBT and triethylamine in DCM at RT to give novel 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-substituted-N-arylimidazo[2,1-b]thiazole-2-carboxamide **11**.

Conclusion:

In summary, we have developed an efficient and convenient procedure for the preparation of 6-(2,3-dihydrobenzo[b][1,4]dioxin-5-yl)-2-methylimidazo[2,1-b]thiazole derivative. The structure of all newly synthesized compound **10a-j** and **11a-j** was established on the basis of spectral analysis like IR, ^{1}H NMR, and LC-Mass spectroscopic analysis.

All the synthesized compounds were analyzed for their antimicrobial activity. The investigation of antimicrobial and antifungal screening data revealed that compounds **10d, 10i, 10j, 11b, 11c** and **11g** are broad spectrum compound which can inhibit the growth of gram-positive, gram-negative bacteria as well as fungi. Compounds **10c, 10e** and **10f** are potentially efficient against both gram-positive and gram-negative bacteria but not able to inhibit fungi. Compound **11f** exhibited mainly antifungal activity. Whereas rest of the compounds is also potent compound, gives narrow spectrum action against pathogenic microbes.

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