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Synthesis of biologically active benzothiazole substituted thiazolidinone derivatives via cyclization of unsymmetrical imines

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Novel benzothiazole substituted thiazolidinone derivatives are synthesized through cyclisation of unsymmetrical imine with mercaptoacid in the presence of $SnCl_2.2H_2O$ and evaluated their inhibition ability against *Proteus mirabilis, Staphylococcus aureus, Salmonella typhi and Klebsiella pneumoniae.*

Keywords: Unsymmetrical imine, benzothiazole, thiazolidinone, cyclization, antibacterial activity

In recent years, there has been considerable interest in the synthesis of substituted thiazolidinone derivatives due to their biological and pharmacological activities[1]. Especially, 4-thiazolidinone motifs are having many interesting activity profiles namely COX-1 inhibitors[2], inhibitors of the bacterial enzyme MurB[3], non-nucleoside inhibitors of HIV-RT[4] and anti-histaminic agents[5]. The methodology involves an one-pot three-component condensation or a two step synthesis is the most simple and efficient method despite numerous different protocols have been reported for the synthesis of 4-substituted thiazolidinone derivatives. This reaction proceeds through imine formation in the first step followed by an attack of sulfur nucleophile on the imine carbon and finally intramolecular cyclization with the elimination of water. The later step seems to be critical for obtaining high yields of 4-thiazolidinones.

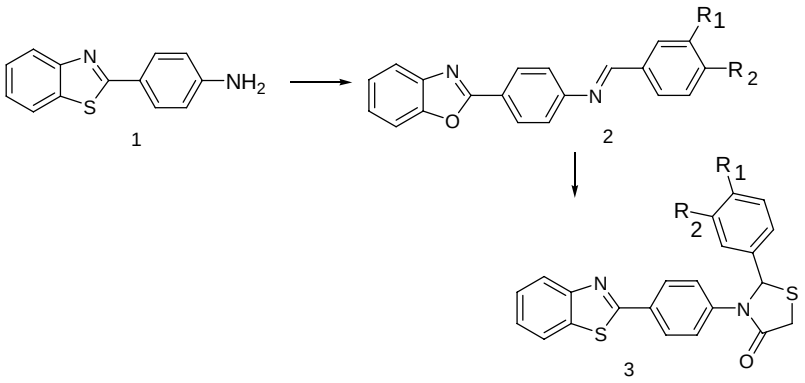
Several protocols reported using anhydrous $ZnCl_2$, sodium sulphate, ionic liquid and dicyclohexyl carbodiimide limits the large scale application, requires high temperature and prolong reaction time. Variety of applications of thiazolidinone in the biological studies necessitated us to take up the development of convenient and simple synthetic protocols.

The presence of two or more different heterocyclic moieties in a single molecule often enhances the biocidal profile remarkably. Hence, benzothiazole moiety with C-4 position of thiazolidinone is focused to fuse and this moiety is having potent biological properties such as antitumor[6], antimicrobial[7], LTD_4 receptor antagonist[8] like orexin[9] (**Figure 1**).

Arylbenzothiazoles bearing a substituent at C-2 are of great interest as this structural framework has proved to be an important class of bicyclic privileged substructures owing to their utility as imaging agents for β-amyloid, as chemiluminescent agents, anti-tumour agents, calcium channel antagonists, anti-tuberculotics, antiparasitics and also as photo-sensitizers [10–17].

Recently, $SnCl_2.2H_2O$ has been used as an alternative to Lewis acidic ionic liquids[18], due to non-toxic, melts near RT and has negligible vapour pressure. $SnCl_2.2H_2O$ has been utilized for various acid catalyzed reactions such as imino-Diels-Alder reaction, Fischer indole synthesis, Michael addition of indole to α,β-unsaturated ketone and the formation bis-indolylmethane derivatives. Hence, we here in report a convenient and facile synthesis of benzo-thiazole substituted thiazolidinone derivatives using $SnCl_2.2H_2O$ as a catalyst (**Scheme I**). The reaction proceeds through imine formation of benzothiazole substituted aniline and substituted aldehydes followed by the addition of mercapto acid in the presence of ecobenign tin chloride dehydrate at 45ºC for 30 – 40 min.

Firstly, the catalyst effect was evaluated on the formation of desired product with high yield and short reaction time. The results are summarized in **Tables I**



Scheme I

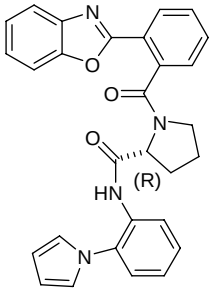


Figure 1 – Orxin receptor

Table I— Effect of Catalyst

S.No	Catalyst	Time (min)	Compound(Entry6) (yield 5)
1	SnCl2	30	81
2	BF3OEt	120	Trace
3	TiCl4	150	32
4	No catalyst	24	Trace

and **II**. Experiments showed that tin chloride dihydrate at 45ºC was found to be the best of choice. The quantity of catalyst and the solvent effect for the reaction was evaluated and found that 20 mole% is optimum in toluene.

The scope of the substrate in the reaction under the optimized reaction conditions was investigated and the results were summarized in **Table II**. The reaction was amenable to a wide variety of substituted ketenes. The nature of functional groups in the aromatic ring of the aldehyde exerted a great influence on the final product. An increase in the yield was observed with aryl aldehydes bearing electron-donating group. Moreover, the removal of water moiety from the intermediate is the rate-determining step. The H-bonding interaction of N atom in the benzothiazole moiety with hydroxyl group favours the removal of water and the desired product in good yield with shorter reaction time (**Figure 2**).

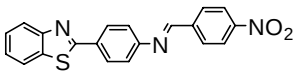
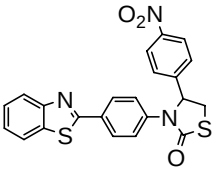
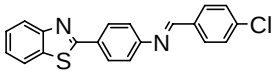
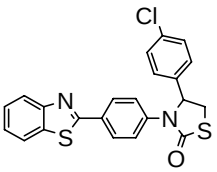
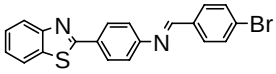
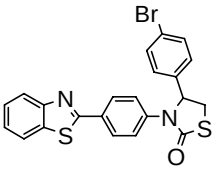
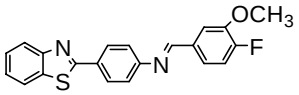
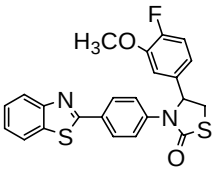
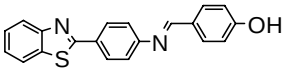
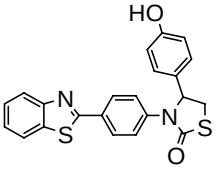
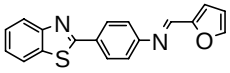
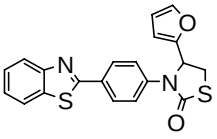
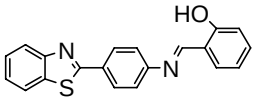
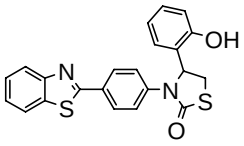
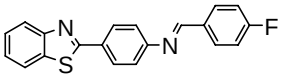
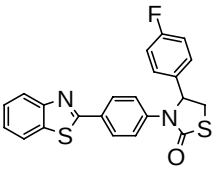
Biological Study

The treatment of infectious diseases still remains an important and challenging problem because of a combination of factors including emerging infectious diseases and the increasing number of multi-drug resistant microbial pathogens with a particular relevance for gram positive bacteria[19–23]. The therapeutic problem has achieved increasing importance in hospitalized patients, in immuno suppressed patients with AIDS or undergoing anticancer therapy and organ transplants. In spite of a large number of antibiotics and chemotherapeutics available for medical use, at the same time the emergence of old and new antibiotic resistance created in the last decades, there is a substantial medical need for new classes of antibacterial agents. A potential approach to overcome the resistance problem is to design innovative agents with a different mode of action so that no cross-resistance with the present therapeutically can occur[24].

Results and Discussion

All the eight compounds were tested each at 50, 100 and 150 µL concentration to find out their efficacy in inhibiting the growth of the four human pathogenic bacteria. The synthetic compounds efficiently inhibited the growth of *Proteus mirabilis, Staphylococcus aureus and Salmonella typhi followed by Klebsiella pneumoniae*. Streptomycin was used as a standard drug. From the **Table III** , it is evident that the halogenated (Cl, Br and F) compounds 2, 3, 4 and 8 were effective inhibitors towards the growth of the four human pathogens in comparison with the

Table II —Synthesis of thiazolidinone

Entry	Unsymmetrical imine	Product	Yield (%)
1			75
2			62
3			81
4			53
5			67
6			81
7			64
8			72

synthetic compounds (1, 5, 6 and 7). But, the effect of *Klebsiella pneumoniae* is minimum when compared to the other tested bacteria as shown in **Table III**. A positive correlation existed between the concentration of the compound and the inhibitory action against the pathogens tested. Streptomycin concentration (10 µL/disc) inhibited the growth of *Staphylococcus aureus* by 22 mm, *Klebsiella pneumoniae* by 18 mm, *Salmonella typhi* by 17 mm and *Proteus mirabilis* by 18 mm respectively.

The bacterial screening of the benzothiazole substituted thiazolidinone derivatives were analysed against *Proteus mirabilis*, *Staplhylococcus aureus*, *Salmonella typhi* and *Klebsiella pneumoniae* by disc diffusion method. All the eight compounds were tested the inhibition ability against human pathogens each at 50, 100 and 150 µL concentration. A positive correlation existed between the concentration of the compound and the inhibitory action against the pathogens tested. Among the eight compounds, compound Entry 8 showed significant activity against the tested bacteria, namely *Proteus mirabilis, Salmonella typhia and Klebsiella pneumoniae*. The compound (**Entry 3**) shown more inhibitory activity than other compounds on *Staphylococcus aureus*. The standard antibiotic disc (Streptomycin concentration (10µL/disc) inhibited the growth of *Staphylococcus aureus* by 22 mm, *Klebsiella pneumoniae* by 18 mm, *Salmonella typhi* by 17 mm and *Proteus mirabilis* by 18 mm respectively. The diameter of inhibition zone for each concentration against all the test bacteria is depicted in **Table III**.

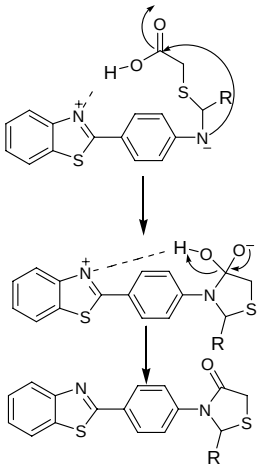


Figure 2 — Hydrogen bonding mechanism

Experimental section

General procedure: To the substituted imine (0.01 mmole) dissolved in toluene was added $SnCl_2$ (0.05 mmole) as a catalyst under nitrogen atm. The reaction-mixture was stirred at RT for 1 hr and then added thioglycollic acid (0.01 mmole). The mixture was refluxed for 12 hr, cooled to RT, solvent was evaporated at reduced pressure and the residue was dissolved in dichloromethane. The organic layer was washed with $NaHCO_3$ (10%) and finally with brine solution, dried over Na_2SO_4 and evaporated to dryness at reduced pressure. Crude was purified by column chromatography on silica gel with hexane/chloroform (2:8 v/v).

3-[4-(1,3-Benzothiazol-2-yl)phenyl]-2-(4-nitro-phenyl)-1,3-thiazolidin-4-one. (Entry 1, **Table II**) yield 67%; yellow solid; m.p. 193- 96ºC; IR (KBr, cm^{-1}): 3461, 1645,1487, 1365, 835 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.83-7.91 (m, 4H, ArH), 7.50-7.31 (m, 7H, ArH), 7.99-7.97 (d, 1H, *J* = 10 Hz, ArH), 8.05-8.03 (d, 1H, *J* = 5 Hz, ArH), 8.01-8.00 (d, 1H, *J* = 10 Hz, ArH), 6.73-6.71 (d, 1H, *J* = 10 Hz,

Table III — Testing of antibacterial activity

	Zone of inhibition- diameter in mm (percentage)											
	Proteous mirbilis			*Staphylococcus*			*Salmonella typhi*			*Klebsiella pneumoniae*		
Compd	50 µg/ mL	100 µg/ mL	150 µg/ mL	50 µg/ mL	100 µg/ mL	150 µg/ mL	50 µg/ mL	100 µg/ mL	150 µg/ mL	50 µg/ mL	100 µg/ mL	150 µg/ mL
1	4.7 (5.2)	6.8 (7.5)	8.5 (9.5)	4.6 (5.1)	6.5 (7.2)	8.3 (9.2)	4.3 (4.7)	6.4 (7.1)	7.3 (8.1)	4.0 (4.5)	5.7 (6.3)	6.7 (7.4)
2	6.2 (6.8)	8.2 (9.1)	10.2 (11.3)	5.0 (5.5)	6.9 (7.9)	9.4 (10.4)	4.8 (5.3)	6.5 (7.2)	8.7 (9.6)	4.6 (5.1)	6.3 (7.0)	8.4 (9.3)
3	6.6 (7.3)	8.3 (9.2)	11.2 (12.4)	6.5 (7.2)	8.1 (9.0)	10.9 (12.1)	6.3 (7.0)	7.5 (8.3)	10.4 (11.5)	6.0 (6.6)	7.2 (8.0)	10.2 (11.3)
4	5.4 (6.0)	6.7 (7.4)	8.4 (9.3)	5.0 (5.5)	6.5 (7.2)	8.0 (8.8)	4.6 (5.1)	6.0 (6.6)	7.9 (8.7)	4.2 (4.6)	5.8 (6.4)	6.9 (7.6)
5	5.3 (5.8)	6.4 (7.1)	7.7 (8.5)	5.1 (5.6)	6.3 (7.0)	8.4 (7.3)	4.3 (3.3)	5.3 (5.8)	7.3 (8.1)	3.4 (3.7)	4.5 (5.0)	6.0 (6.6)
6	5.0 (5.5)	6.8 (7.5)	7.5 (8.3)	4.9 (5.4)	6.2 (6.8)	7.3 (8.1)	4.1 (4.5)	5.4 (6.0)	7.0 (7.7)	3.9 (4.3)	4.7 (5.2)	6.5 (7.2)
7	5.3 (5.8)	6.4 (7.1)	7.8 (8.6)	5.2 (5.7)	6.2 (6.8)	7.5 (8.3)	4.8 (5.3)	6.0 (6.6)	8.2 (7.2)	4.2 (4.6)	5.6 (6.2)	7.2 (8.0)
8	7.2 (8.0)	9.6 (10.6)	11.8 (13.0)	6.9 (7.6)	8.4 (9.3)	10.2 (11.3)	6.4 (7.1)	8.2 (9.1)	11.0 (12.2)	6.1 (6.7)	7.9 (8.7)	10.2 (11.6)

ArH),4.00 (s, 2H, SCH_2CON), 3.51 (s, 1H, NCH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 157.5, 149.6, 134.2, 129.7, 125.1, 124.8, 122.9, 120.7, 117.9 , 113.8, 60.0, 31.0 ; ESI-MS, *m/z*: 452.6 (M+ Na)+ Anal. Calcd. for $C_{22}H_{15}N_3O_3S_2$: C, 61.45; H, 4.26; N, 9.35. Found: C, 61.26; H, 4.21; N, 9.68%.

3-[4-(1,3-Benzothiazol-2-yl) phenyl]-2-(4-chlorophenyl)-1, 3-thiazolidin-4-one. (Entry 2, **Table II**), yield 73%; yellow solid; m.p. 153- 55ºC; IR (KBr): 3456, 1727, 1604, 1487, 1175 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$): δ 7.29-7.65 (m, 5H, ArH), 7.82-7.83 (d, 1H, J= 5 Hz, ArH), 7.77-7.88 (d, 1H, J = 5 Hz, ArH), 7.96-7.98 (d, 1H, J = 10 Hz, ArH), 8.06-8.07 (d, 1H, J = 5 Hz, ArH), 8.13-8.15 (d, 1H, ArH), 8.23-8.25 (d, 1H, J = 10 Hz, ArH), 6.71-6.72 (d, 1H, *J* = 5 Hz, ArH), 3.97 (s, 2H, SCH_2CON), 2.99 (s, 1H, NCH); ^{13}C NMR ($CDCl_3$, 75MHz): δ 168.6 ,154.3, 149.3, 129.2,128.7,126.1, 124.5, 122.5, 121.7, 121.5, 114.8, 63.0,33.0, ESI-MS, *m/z*: 423.0 (M+ Na)+ Anal. Calcd for $C_{22}H_{15}ClN_2OS_2$: C, 62.47; H, 3.57; N, 6.62. Found: C, 62.59; H, 3.60; N, 6.68%.

3-[4-(1,3-Benzothiazol-2-yl)phenyl]-2-(4-bromophenyl)-1,3-thiazolidin-4-one. (Entry 3, **Table II**), 87% yield; yellow solid; m.p. 181-83ºC; IR (KBr): 3457, 1724, 1604, 1431, 1174 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$): δ 7.82-7.93 (m, 4H, ArH), 7.53-7.51 (m, 7H, ArH), 7.98-7.97 (d, 1H, *J* = 10 Hz, ArH), 8.06-8.05 (d, 1H, *J* = 5 Hz, ArH), 8.12-8.11 (d, 1H , *J*= 10 Hz, ArH), 6.72-6.74 (d, 1H, *J*= 10 Hz, ArH), 4.01 (s, 2H, SCH_2 CON), 3.63 (s, 1H, NCH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 169.8, 157.5, 149.6, 134.2, 129.7, 125.1, 124.8, 122.9, 120.7, 117.9, 113.8, 60.0, 31.0; ESI-MS, m/z: 466.4 (M+ Na^+)'; Anal. Calcd for $C_{22}H_{15}BrN_2OS_2$: C, 56.53; H, 3.23; N, 5.99. Found: C, 56.67; H, 3.28; N, 6.02 %.

3-[4-(1,3-Benzothiazol-2-yl)phenyl]-2-(4-fluoro-3-methoxyphenyl)-1,3-thiazolidin-4-one. (Entry 4, **Table II**), yield 97%; yellow solid; m.p. 173-75ºC; IR (KBr): 3391, 1732, 1604, 1487, 759 cm^{-1} ^1H NMR (500 MHz, $CDCl_3$): δ 7.29-8.55 (m, 8H, ArH), 7.87-7.89 (d, 2H, *J*= 10 Hz, ArH), 6.71-6.73 (d, 2H, *J* = 10 Hz, ArH), 3.91 (s, 2H, SCH_2CON), 3.43 (s, 1H, NCH) 3.5(s, 3H OCH_3); ^{13}C NMR (75 MHz, $CDCl_3$): δ 168.6, 154.3, 149.3, 129.2, 128.7, 126.1, 124.5, 123.9, 122.5, 121.7, 121.5, 114.8, 63.0, 59.9, 32.0 ; ESI-MS *m/z* 436.5 (M+ Na+) Anal. Calcd for $C_{23}H_{15}FN_2O_2S_2$: C, 63.58; H, 3.48; N, 6.45. Found: C, 63.69; H, 3.41; N, 5.69%.

3-[4-(1,3-Benzothiazol-2-yl)phenyl]-2-(4-hydroxyphenyl)-1,3-thiazolidin-4-one. (Entry 5, **Table II**) Yield 77%; yellow solid; m.p. 153- 55ºC; IR (KBr): 3390, 1727, 1487, 1309, 1226, cm^{-1} ^1H NMR (500 MHz, $CDCl_3$): δ 7.28-8.55 (m, 8H, ArH), 7.85-7.83 (d, 2H, *J*= 10 Hz, ArH), 6.71-6.73 (d, 2H, *J* = 10 Hz, ArH), 3.91 (s, 2H, SCH_2CON), 2.93 (s, 1H, NCH),5.3(s, OH); ^{13}C NMR (75MHz, $CDCl_3$):δ 168.6, 154.3, 149.3,129.2, 128.7, 126.1, 124.5, 123.9, 122.5, 121.7, 121.5, 114.8, 60.0, 32.0; ESI-MS: *m/z* 404.5 (M+ Na+) Anal. Calcd for $C_{22}H_{16}N_2O_2S_2$: C, 65.32; H, 3.99;N, 6.93. Found: C, 65.45; H, 4.02; N, 6.89%.

3-[4-(1,3-Benzothiazol-2-yl)phenyl]-2-(4-flurophenyl)-1,3-thiazolidin-4-one. (Entry 8, **Table II**), Yield 94%; yellow solid; m.p. 163-65ºC; IR (KBr) 3391, 1732, 1604, 1487, 1174, 759 cm^{-1} ^1H NMR (300 MHz, DMSO-d_6,): δ 8.17-8.14 (d, 3H, ArH), 8.08-7.92 (m, 3H, ArH), 7.78-7.57 (m, 3H, ArH), 7.51-7.50 (d, 3H, *J* = 3 Hz, ArH), 7.48-7.45 (t, 1H, *J* = 3 Hz ,ArH), 6.69-6.67 (d, 1H, *J* = 6 Hz, ArH), 8.7 (S, 1H, *J* = 3 Hz, N=CH); ^{13}C NMR (75MHz, $CDCl_3$): δ 187.4, 163.1, 158.0, 131.1, 130.5, 129.3, 129.0, 128.7, 126.7, 122.7, 122.2, 122.0, 113.6, 113.4; ESI-MS, *m/z*: 377.3 (M+ Na+). Anal. Calcd. for $C_{22}H_{15}FN_2S_2O$: C, 65.00; H, 3.72; N, 6.89. Found: C, 65.24; H, 3.80; N, 6.96%.

In conclusion, we have described a simple and ecobenign protocol for the synthesis of benzothiazole substituted thiazolidinone derivatives is described and evaluated their antibacterial property against *Proteus mirabilis*, *Stahylococcus aureus*, *Salmonella typhi* and *Klebsiella pneumoniae*.

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