



Synthesis and Antimicrobial Activity of Benzothiazole

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ABSTRACT

Compounds having benzothiazole moiety possess diverse antimicrobial activities. In this study a series of 2-(6-substituted 1,3-benzothiazol-2-yl)-N-(4-halophenyl) hydrazine carbothioamide (5a-o) have been synthesized by refluxing equimolar quantity of 2-Hydrazino-6-substituted-1,3- benzothiazole (3a-e) and 4-substituted phenylisothiocyanate (4a-c). 2-Hydrazino-6- substituted-1,3- benzothiazole (3a-e) have been synthesized by refluxing of 6-substituted-1,3- benzothiazol-2-amine (2a-e) with hydrazine hydrate in the presence of con. Hydrochloric acid and ethylene glycol. 4-substituted phenylisothiocyanate (4a-c) were prepared by reaction of 4- substituted aromatic amines with carbon disulfide in the presence of ammonia. 2-(6- substituted 1-3- benzothiazol-2-yl)-N-(4-halophenyl) hydrazine carbothioamide (5a-o) yielded according to the scheme.

KEYWORDS: Antibacterial, Benzothiazole Derivatives, Synthesis

INTRODUCTION

Antibacterial resistance is a global public health problem that has hampered the effective prevention and treatment of wide range of bacterial diseases [1,2]. Antibacterial resistance is aggravated by the misuse or overuse of antibacterial agents in people and animal [3]. Some bacteria are multidrug resistant and the major examples are Staphylococcus aureus and Escherichia coli [3]. These multidrug resistant organisms have increased the cost of healthcare “via” prolonged stay in hospital and more intensive care [2]. World Health Organisation (WHO) reported that the death caused by methicillin resistant S. aureus infection is higher by 64% as against the non-methicillin resistant S. aureus infection [2].

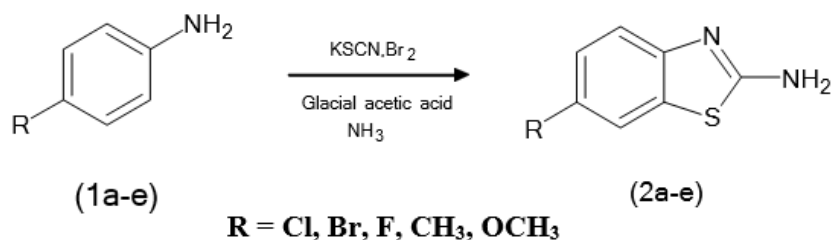
One of the WHO strategies for the control of antimicrobial resistance is to encourage investment in new medicine research and development [4]. In accordance with this recommendation many research team are engrossed in the synthesis of new antimicrobial drug with better efficacy and lower toxicity [2,5]. The most exploited derivatives are sulphonamides, thiourea and benzothiazole [6]. The antimicrobial, antioxidant, antiviral and antitumor properties of thiourea derivatives have been reported [3, 6]. Despite the vast number of antimicrobial agent available for the treatment of microbial infection, the problems of antimicrobial resistance is yet to be resolved. This study aims to synthesize benzothiazole derivatives into one structure that may have improved antibacterial property.

EXPERIMENTAL SECTION

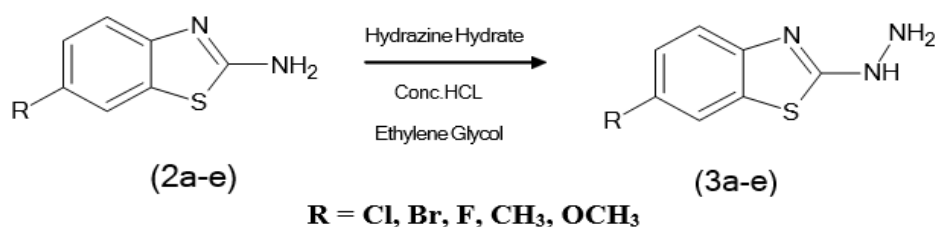
Materials and Methods: The chemicals used were of analytical grade and used without further purification. Melting points were determined with an open capillary melting point apparatus and are uncorrected. Reaction completion was monitored with thin layer chromatography (TLC) using silica gel-G (Marck 60). All the compounds were purified by column chromatography using silica gel mesh 120-160 (Marck). Infrared spectrophotometer was recorded on FT-IR (KBr) cm^{-1} at National Research Institute for Chemical Technology Zaria (NARICT) with Shimadzu FT-IR 8400s as described by Chinaka and Coworkers. [7]

Procedure For Preparation Of Compounds:

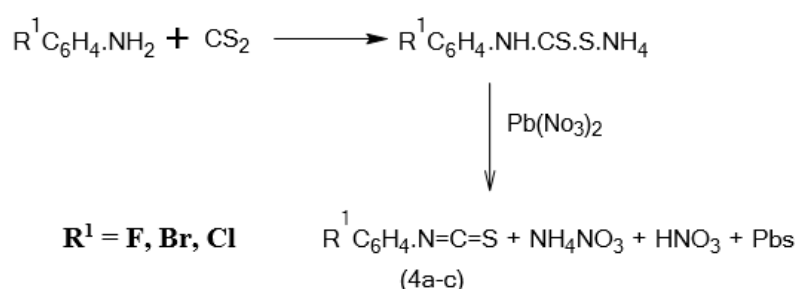
Procedure for synthesis of 6-substituted-1,3-benzothiazol-2- amine(2a-e): Glacial acetic acid (150 ml) precooled to 5 °C were added to potassium thiocyanate (0.06 mol) and 4-substituted aniline (0.06 mol) (1a). The mixture was placed in a freezing mixture of ice and mechanically stirred while bromine (0.02 Mol) in 10 ml glacial acetic acid was added from a dropping funnel at such rate that the temperature does not rise beyond 0-5 °C. After all the bromine has been added (110 min), the solution was stirred for an addition 2 hour at 0-10 °C. The residue was filtered and dissolved in hot water (150 ml). The solution was filtered and the filtrate was neutralized with a conc. ammonia solution to pH 6. The precipitates were collected and crystallized with ethanol. [8]



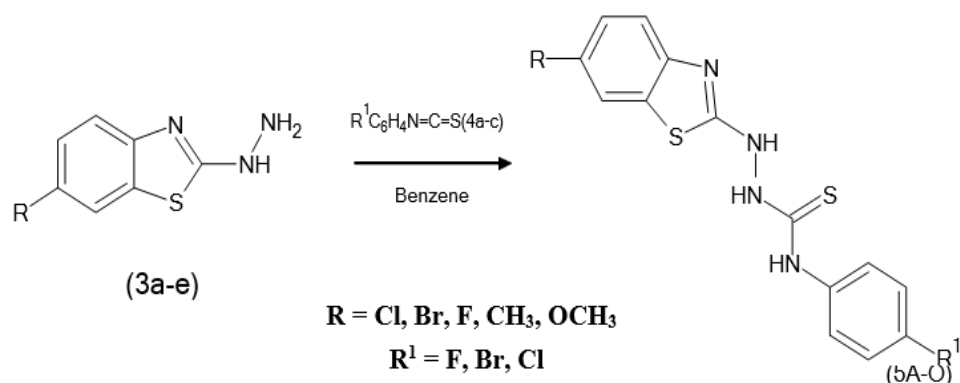
Procedure for synthesis of 2-hydrazino-6-substituted-1, 3-benzothiazole(3a-e): Conc. Hydrochloric acid (10 ml) was added drop by drop with stirring to hydrazine hydrate (10.0g, 0.2 Mol) at 5-10 °C followed by ethylene glycol (40-50 ml). Thereafter, 6-substituted-1,3-benzothiazol-2-amine (0.01 Mol) (2a-e) was added in portion and the resultant mixture refluxed for two hours and cooled. The crystalline solid separated was filtered, washed with water and recrystallization from ethanol. [9]



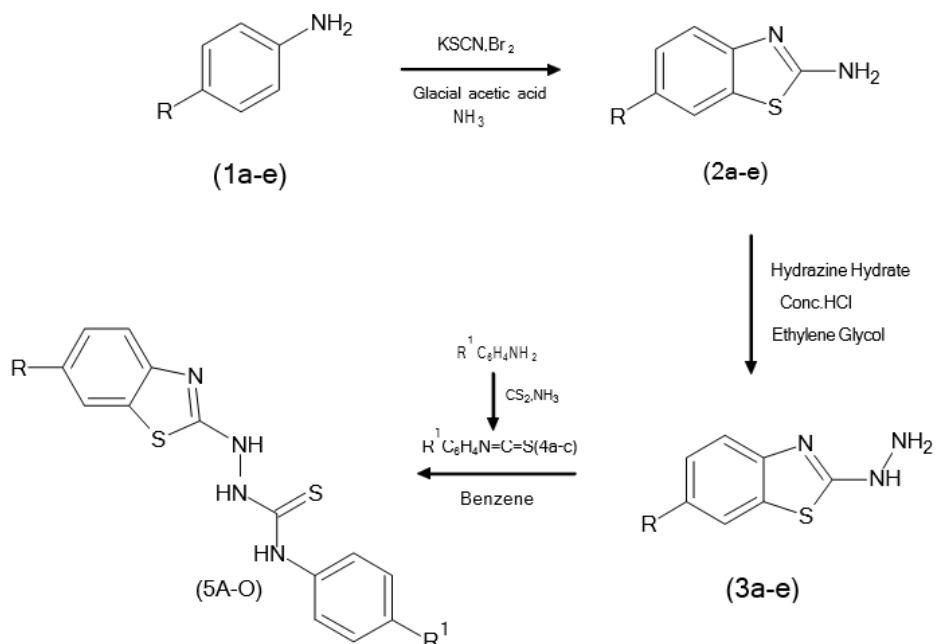
Procedure for synthesis of p-substituted phenyl isothiocyanate (4a-c): Add 50 ml of conc. ammonia solution slowly with stirring to a solution of 0.26 Mol of p-substituted aniline, 0.396 moles of carbon disulphide and 50 ml of rectified spirit at 10-15 °C. Considerable heat is evolved; cool the flask in a freezing mixture from few times so that temperature does not rise above 30 °C. The original milky suspension becomes clear and intermediate dithiocarbamate soon crystallizes out. Allow to stand overnight, filter the crystals, wash with ether, dissolve in 1500 ml water and stir mechanically while a solution of 0.262mol of lead nitrate in 200 ml of water is slowly added. Continue the stirring for 30 minutes, and isolate the p-substituted phenyl isothiocyanate by steam distillation into a receiver containing 5ml of 0.5M sulfuric acid; if the substances solidifies in the condenser, stop the cooling water awaiting the solid has melted and run into the receiver. Filter the cold solid product, wash with little water and dry in air upon filter paper. [10]



Procedure for synthesis of 2-(6-substituted-1,3-benzothiazol-2-yl)-N-(4-halophenyl) hydrazine carbothioamide (5A-O) : An equimolar mixture of 2-hydrazino-6-substituted-1,3-benzothiazole (3a-e) and p-substituted phenyl isothiocyanate (4a-c) in benzene (50 ml) and refluxed for three to six hours. A white product gradually separated out. It was filtered hot, dried and crystallization in methanol. [11]



SCHEME-I



Where,

R¹ = F

R¹ = Br

R¹ = Cl

R = Cl, Br, F, CH₃, OCH₃ (5a-e)

R = Cl, Br, F, CH₃, OCH₃ (5f-j)

R = Cl, Br, F, CH₃, OCH₃ (5k-o)



Table 1. Physical Data of Compounds (5A-O)

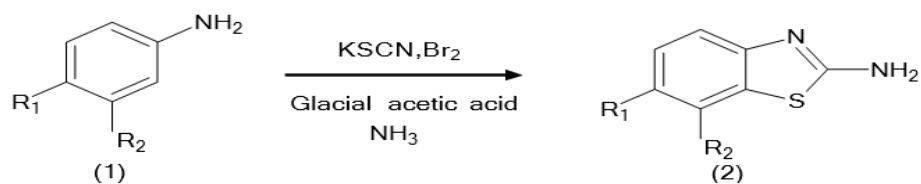
1. Comp	2. R	3. R1	4. M.pt 5. (°C)	6. Yield 7. (%)	8. *Rr	9. Calculated 10. LogP# value	11. Mol. Formula 12. (Mol. Weight)
13. 5A	14. Cl	15. F	16. 127	17. 97	18. 0.33	19. 4.80 ± 0.66	20. C ₁₄ H ₁₀ ClFN ₄ S ₂ (352.84)
21. 5B	22. Br	23. F	24. 140	25. 94	26. 0.36	27. 5.06 ± 0.68	28. C ₁₄ H ₁₀ BrFN ₄ S ₂ (397.29)
29. 5C	30. F	31. F	32. 142	33. 92	34. 0.32	35. 4.34 ± 0.68	36. C ₁₄ H ₁₀ F ₂ N ₄ S ₂ (336.38)
37. 5D	38. CH ₃	39. F	40. 133	41. 95	42. 0.38	43. 4.75 ± 0.65	44. C ₁₅ H ₁₃ FN ₄ S ₂ (332.42)
45. 5E	46. OCH ₃	47. F	48. 141	49. 90	50. 0.33	51. 4.20 ± 0.92	52. C ₁₅ H ₁₃ FN ₄ OS ₂ (348.42)
53. 5F	54. Cl	55. Br	56. 135	57. 95	58. 0.30	59. 5.60 ± 0.66	60. C ₁₄ H ₁₀ BrClN ₄ S ₂ (413.74)
61. 5G	62. Br	63. Br	64. 138	65. 94	66. 0.34	67. 5.78 ± 0.68	68. C ₁₄ H ₁₀ Br ₂ N ₄ S ₂ (458.19)
69. 5H	70. F	71. Br	72. 135	73. 92	74. 0.34	75. 5.06 ± 0.68	76. C ₁₄ H ₁₀ BrFN ₄ S ₂ (397.29)
77. 5I	78. CH ₃	79. Br	80. 130	81. 96	82. 0.36	83. 5.47 ± 0.65	84. C ₁₅ H ₁₃ BrN ₄ S ₂ (393.32)
85. 5J	86. OCH ₃	87. Br	88. 137	89. 94	90. 0.35	91. 4.92 ± 0.92	92. C ₁₅ H ₁₃ BrN ₄ OS ₂ (409.32)
93. 5K	94. Cl	95. Cl	96. 132	97. 96	98. 0.30	99. 5.43 ± 0.64	100. C ₁₄ H ₁₀ Cl ₂ N ₄ S ₂ (369.29)
101. 5L	102. Br	103. Cl	104. 139	105. 94	106. 0.35	107. 5.60 ± 0.66	108. C ₁₄ H ₁₀ BrClN ₄ S ₂ (413.74)
109. 5M	110. F	111. Cl	112. 140	113. 93	114. 0.33	115. 4.88 ± 0.66	116. C ₁₄ H ₁₀ ClFN ₄ S ₂ (352.84)
117. 5N	118. CH ₃	119. Cl	120. 128	121. 95	122. 0.39	123. 5.29 ± 0.63	124. C ₁₅ H ₁₃ ClN ₄ S ₂ (348.87)
125. 5O	126. OCH ₃	127. Cl	128. 139	129. 93	130. 0.34	131. 4.75 ± 0.89	132. C ₁₅ H ₁₃ ClN ₄ OS ₂ (364.87)

* Benzene: Ethanol (9): (1),

Table 2. Spectral Data of Representative Compounds (2A, 3A, 5A, 5D, 5J, 5L)

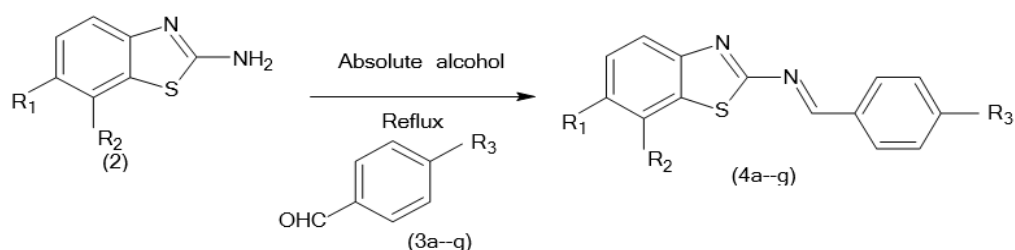
133. Comp.	134. R	135. R1	136. IR Spectral Data (cm ⁻¹)
137. 2A	138. Cl	139. -	140. 3452 (1 ⁰ N-H), 3081 & 814 (C-H Ar), 1280 (C-N), 1631 (C=N), 1530 (C=C Ar), 1440 (thiazole), 713(C-Cl)
141. 3A	142. Cl	143. -	144. 3316, 3200 & 1595 (1 ⁰ & 2 ⁰ N-H), 3065 & 855 (C-H Ar), 1260 (C-N), 1644 (C=N), 1552 (C=C Ar), 1455 (thiazole), 716 (C-Cl)
145. 5A	146. Cl	147. F	148. 3120 & 1560 (2 ⁰ N-H), 2995 & 825 (C-H Ar), 1266 (C-N), 1615 (C=N), 1510 (C=C Ar), 1443 (thiazole), 1220 (C=S), 1112 (C-F), 726 (C-Cl)
149. 5D	150. Me	151. F	152. 3200 & 1581 (2 ⁰ N-H), 3091 & 827 (C-H Ar), 2931 & 1385 (CH ₃), 1320 (C-N), 1615 (C=N), 1537 (C=C Ar), 1220 (C=S), 1095 (C-F)
153. 5J	154. OMe	155. Br	156. 3227 & 3100 (2 ⁰ N-H), 3089 & 820 (C-H Ar), 2950 & 1395 (CH ₃), 1047 (C-O), 1274 (C-N), 1605 (C=N), 1540 (C=C Ar), 1492 (thiazole), 1222 (C=S), 617 (C-Br)
157. 5L	158. Br	159. Cl	160. 3365 & 3176 (2 ⁰ N-H), 2998 & 800 (C-H Ar), 1280 (C-N), 1618 (C=N), 1530 (C=C Ar), 1195 (C=S), 698 (C-Cl), 595 (C-Br)

Procedure for synthesis of Di-substituted-1,3-benzothiazol-2- amine (2): To glacial acetic acid (150 ml) precooled to 5 °C were added to potassium thiocyanate (0.06 mol) and disubstituted aniline (0.06 mol) (1a). The mixture was placed in a freezing mixture of ice and salt are mechanically stirred while bromine (0.02 Mol) in 10 ml glacial acetic acid was added from a dropping funnel at such rate that temperature does not rise beyond 0-5 °C. After all the bromine has been added (105 min), the solution was stirred for an addition 2 hour at 0-10 °C. The residue was filtered and dissolved in hot water (150 ml). The solution was filtered and filtrate was neutralized with a conc. ammonia solution to pH 6. The precipitates were collected and crystallized with ethanol. [12, 13]



5. $\text{R}_1 = \text{F}, \text{R}_2 = \text{Cl}$.
6. $\text{R}_1 = \text{Cl}, \text{R}_2 = \text{Cl}$.
7. $\text{R}_1 = \text{H}, \text{R}_2 = \text{Cl}$.
8. $\text{R}_1 = \text{H}, \text{R}_2 = \text{Br}$.
9. $\text{R}_1 = \text{H}, \text{R}_2 = \text{CH}_3$.
10. $\text{R}_1 = \text{H}, \text{R}_2 = \text{OCH}_3$

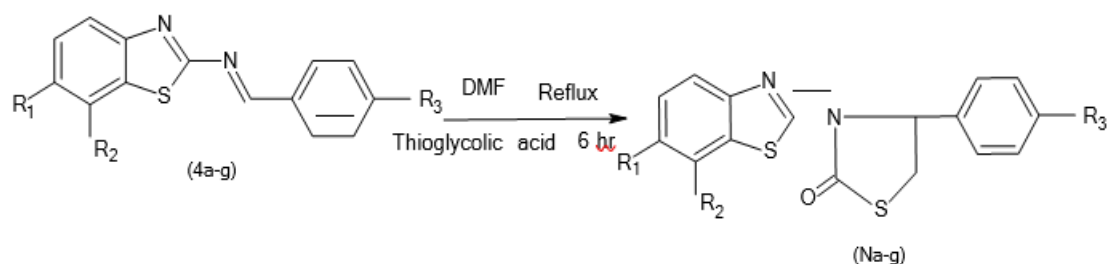
Procedure For Synthesis of Schiff Base (4a-g): 2-Amino-6-fluoro-7-chloro-benzothiazole 1.84 g (0.01 mole) and 4-dimethylamino benzaldehyde 1.49 g (0.01mole) was dissolved in 50 ml absolute alcohol. To this solution a small amount of anhydrous zinc chloride was added. The reaction mixture was refluxed for 18-20 hours on a water bath. It was cooled and poured into compressed ice. The solid product was obtained and product washed with water and recrystallized from ethanol. [14, 15]



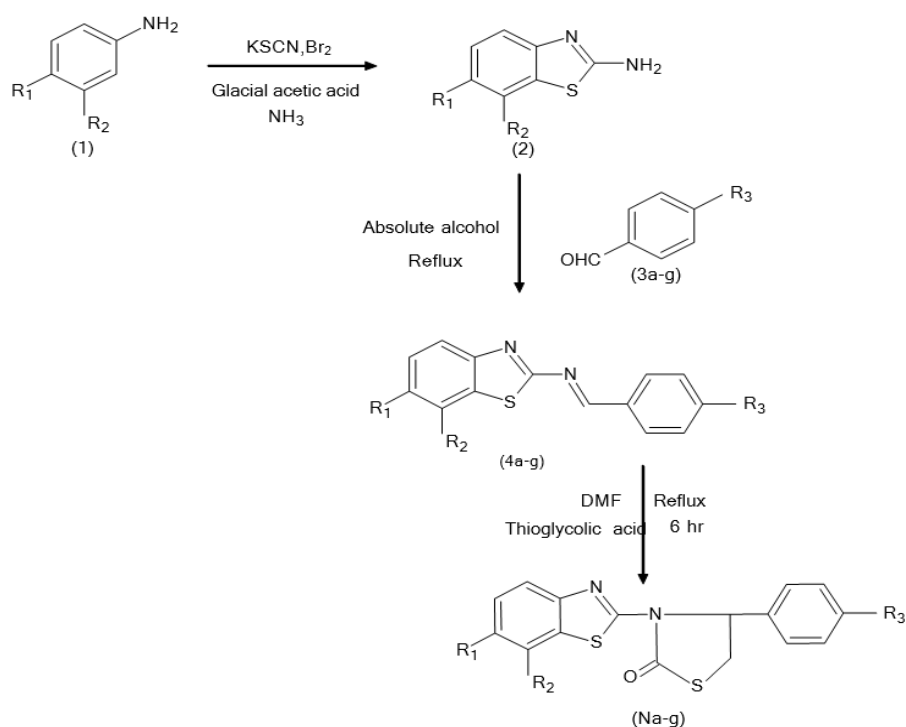
5. $\text{R}_1 = \text{F}, \text{R}_2 = \text{Cl}$.
6. $\text{R}_1 = \text{Cl}, \text{R}_2 = \text{Cl}$.
7. $\text{R}_1 = \text{H}, \text{R}_2 = \text{Cl}$.
8. $\text{R}_1 = \text{H}, \text{R}_2 = \text{Br}$.
9. $\text{R}_1 = \text{H}, \text{R}_2 = \text{CH}_3$.
10. $\text{R}_1 = \text{H}, \text{R}_2 = \text{OCH}_3$

$\text{R}_3 = \text{Dimethyle amine}, 4\text{-Cl}, 4\text{-H}, 4\text{-OH}, 4\text{-NO}_2, 4\text{-OCH}_3, 2\text{-OH}$

Procedure for 3-(6, 7-substituted-1,3-benzothiazol-2-yl)-4-(4- substituted phenyl)-1,3-thiazolidin-2-one derivatives (Na-g): Schiff bases (4a-h) (0.1 M) were dissolved individually in 50 ml DMF in a 100 ml round bottom flask fitted with a double surface reflux condenser. Thioglycolic acid (0.1 M) was added carefully to it and the reaction contents were subjected to a gentle reflux over a water bath for 6 hrs. The reaction was continuity monitored for its completeness using TLC techniques. after 6-8 hrs the reaction contents were cool down, the resultant product was separating and subjecting to recrystallise with alcohol. [16, 17]



SCHEME II- Synthesis Depicting Schematic Representation of Benzothiazole Derivatives



N= 5, 6, 7, 8, 9, 10.

5. R₁ = F, R₂ = Cl. R₃ = a= Dimethyle amine, b= Para Cl, c= Para -H, d= Para -OH, e = Para - NO₂, f = Para -OCH₃, g= 2- OH.
6. R₁ = Cl, R₂ = Cl. R₃ = a= Dimethyle amine, b= Para - Cl, c = Para -H, d= Para -OH, e= Para - NO₂, f= Para -OCH₃, g= 2- OH.
7. R₁ = H, R₂ = Cl. R₃ = a= Dimethyle amine, b= Para - Cl, c= Para -H, d= Para -OH, e= Para - NO₂, f= Para -OCH₃, g= 2- OH.
8. R₁ = H, R₂ = Br. R₃ = a= Dimethyle amine, b= Para - Cl, c= Para -H, d= Para -OH, e= Para - NO₂, f= Para -OCH₃, g= 2- OH.
9. R₁ = H, R₂ = CH₃. R₃ = a= Dimethyle amine, Para =4- Cl, c= Para -H, d= Para -OH, e= Para - NO₂, f= Para -OCH₃, g= 2- OH.
10. R₁ = H, R₂ = OCH₃. R₃ = a= Dimethyle amine, b= Para - Cl, c= Para -H, d= Para -OH, e= Para - NO₂, f= Para -OCH₃, g= 2- OH.



Table 3. Physical Properties of Benzothiazole Derivatives (5a-10g)

161. Co mp	162. R ₁	163. R ₂	164. R ₃	165. M .P (°C)	166. Yield (%)	167. * R _r	168. SOLUBILITY
169. 5a	170. F	171. Ch loro	172. Dim ethyl amine	173. 1 81	174. 63	175. 0 .53	176. DMSO, Chloroform
177. 5b	178. F	179. Ch loro	180. 4-Cl	181. 1 63	182. 62	183. 0 .55	184. DMSO, Chloroform
185. 5c	186. F	187. Ch loro	188. 4-H	189. 1 75	190. 67	191. 0 .48	192. DMSO, Chloroform
193. 5d	194. F	195. Ch loro	196. 4-H	197. 1 68	198. 67	199. 0 .52	200. DMSO, Chloroform
201. 5e	202. F	203. Ch loro	204. 4-NO ₂	205. 1 76	206. 76	207. 0 .49	208. DMSO, Chloroform
209. 5f	210. F	211. Ch loro	212. 4-OCH ₃	213. 1 74	214. 58	215. 0 .44	216. DMSO, Chloroform
217. 5g	218. F	219. Ch loro	220. 2-H	221. 1 53	222. 65	223. 0 .48	224. DMSO, Chloroform
225. 6a	226. Ch loro	227. Ch loro	228. Dim ethyl amine	229. 1 79	230. 53	231. 0 .46	232. DMSO, Chloroform
233. 6b	234. Ch loro	235. Ch loro	236. 4-CL	237. 1 64	238. 67	239. 0 .52	240. DMSO, Chloroform
241. 6c	242. Ch loro	243. Ch loro	244. 4-H	245. 1 60	246. 52	247. 0 .54	248. DMSO, Chloroform
249. 6d	250. Ch loro	251. Ch loro	252. 4-H	253. 1 69	254. 53	255. 0 .44	256. DMSO, Chloroform
257. 6e	258. Ch loro	259. Ch loro	260. 4-NO ₂	261. 1 63	262. 60	263. 0 .42	264. DMSO, Chloroform
265. 6f	266. Ch loro	267. Ch loro	268. 4-OCH ₃	269. 1 59	270. 57	271. 0 .44	272. DMSO, Chloroform
273. 6g	274. Ch loro	275. Ch loro	276. 2-H	277. 1 54	278. 53	279. 0 .54	280. DMSO, Chloroform
281. 7a	282. H	283. Ch loro	284. Dim ethyl amine	285. 1 77	286. 54	287. 0 .57	288. DMSO, Chloroform
289. 7b	290. H	291. Ch loro	292. 4-Cl	293. 1 68	294. 46	295. 0 .52	296. DMSO, Chloroform
297. 7c	298. H	299. Ch loro	300. 4-H	301. 1 57	302. 66	303. 0 .56	304. DMSO, Chloroform
305. 7d	306. H	307. Ch loro	308. 4-OH	309. 1 61	310. 57	311. 0 .33	312. DMSO, Chloroform
313. 7e	314. H	315. Ch loro	316. 4-NO ₂	317. 1 53	318. 66	319. 0 .45	320. DMSO, Chloroform
321. 7f	322. H	323. Ch loro	324. 4-OCH ₃	325. 1 63	326. 55	327. 0 .49	328. DMSO, Chloroform
329. 7g	330. H	331. Ch loro	332. 2-OH	333. 1 52	334. 56	335. 0 .63	336. DMSO, Chloroform
337. 8a	338. H	339. Br	340. Dim ethyl amine	341. 1 72	342. 58	343. 0 .58	344. DMSO, Chloroform
345. 8b	346. H	347. Br	348. 4-Cl	349. 1 68	350. 54	351. 0 .47	352. DMSO, Chloroform
353. 8c	354. H	355. Br	356. 4-H	357. 1 59	358. 56	359. 0 .66	360. DMSO, Chloroform
361. 8d	362. H	363. Br	364. 4-OH	365. 1 65	366. 63	367. 0 .54	368. DMSO, Chloroform
369. 8e	370. H	371. Br	372. 4-NO ₂	373. 1 58	374. 59	375. 0 .47	376. DMSO, Chloroform



377.	8f	378.	H	379.	Br	380.	4-OCH ₃	381.	1	382.	64	383.	0.39	384.	DMSO, Chloroform
385.	8g	386.	H	387.	Br	388.	2-OH	389.	1	390.	65	391.	0.57	392.	DMSO, Chloroform
393.	9a	394.	H	395.	CH ₃	396.	Dimethyl amine	397.	1	398.	56	399.	0.48	400.	DMSO, Chloroform
401.	9b	402.	H	403.	CH ₃	404.	4-chloro	405.	1	406.	57	407.	0.68	408.	DMSO, Chloroform
409.	9c	410.	H	411.	CH ₃	412.	4-Hydrogen	413.	1	414.	64	415.	0.57	416.	DMSO, Chloroform
417.	9d	418.	H	419.	CH ₃	420.	4-Hydroxy	421.	1	422.	60	423.	0.62	424.	DMSO, Chloroform
425.	9e	426.	H	427.	CH ₃	428.	4-Nitro	429.	1	430.	65	431.	0.62	432.	DMSO, Chloroform
433.	9f	434.	H	435.	CH ₃	436.	4-Methoxy	437.	1	438.	54	439.	0.54	440.	DMSO, Chloroform
441.	9g	442.	H	443.	CH ₃	444.	2-OH	445.	1	446.	54	447.	0.46	448.	DMSO, Chloroform
449.	10a	450.	H	451.	OC H ₃	452.	Dimethyl amine	453.	1	454.	53	455.	0.38	456.	DMSO, Chloroform
457.	10b	458.	H	459.	OC H ₃	460.	4-chloro	461.	1	462.	59	463.	0.35	464.	DMSO, Chloroform
465.	10c	466.	H	467.	OC H ₃	468.	4-Hydrogen	469.	1	470.	57	471.	0.65	472.	DMSO, Chloroform
473.	10d	474.	H	475.	OC H ₃	476.	4-Hydroxy	477.	1	478.	60	479.	0.54	480.	DMSO, Chloroform
481.	10e	482.	H	483.	OC H ₃	484.	4-Nitro	485.	1	486.	50	487.	0.47	488.	DMSO, Chloroform
489.	10f	490.	H	491.	OC H ₃	492.	4-Methoxy	493.	1	494.	59	495.	0.58	496.	DMSO, Chloroform
497.	10g	498.	H	499.	OC H ₃	500.	2-OH	501.	1	502.	65	503.	0.48	504.	DMSO, Chloroform

*Benzene (9) : Ethanol (1)

Table 4. Spectral Data of Representative Compounds (SCHEME-II) (5a-10g)

505.	Comp	506.	R ₁	507.	R ₂	508.	R ₃	509.	IR Spectral Data (cm ⁻¹)
510.	5b	511.	F	512.	Cl	513.	Cl	514.	3452 (1 ^o N-H), 3085 & 815 (C-H Ar), 1280 (C-N), 1634 (C=N), 1530 (C=CAr), 1440 (thiazole), 715 (C-Cl), 1112 (C-F), 1680 (C=O)
515.	6b	516.	Cl	517.	Cl	518.	Cl	519.	3316, 3200 & 1595 (1 ^o & 2 ^o N-H), 3065 & 858 (C-H Ar), 1263 (C-N), 1644 (C=N), 1552 (C=C Ar), 1450 (thiazole), 716 (C-Cl), 1675 (C=O)
520.	7b	521.	H	522.	Cl	523.	Cl	524.	3120 & 1560 (2 ^o N-H), 2995 & 825 (C-H Ar), 1266 (C-N), 1615 (C=N), 1510 (C=C Ar), 1443 (thiazole), 1220 (C=S), 726 (C-Cl), 1675 (C=O)
525.	7d	527.	H	528.	Br	529.	4-chloro	530.	3200 & 1581 (2 ^o N-H), 3091 & 827 (C-H Ar), 2931 & 1385 (CH ₃), 1320 (C-N), 1615 (C=N), 1537 (C=C Ar), 1220 (C=S), 617 (C-Br), 1680 (C=O)
531.	8b	532.	H	533.	Br	534.	Cl	535.	3227 & 3100 (2 ^o N-H), 3089 & 820 (C-H Ar), 2950 & 1395 (CH ₃), 1047 (C-O), 1274 (C-N), 1605 (C=N), 1540 (C=C Ar), 1492 (thiazole), 1222 (C=S), 617 (C-Br), 1685 (C=O)



536. 8e	537. H	538. Br	539. NO ₂	540. 3365 & 3176 (2° N-H), 2998 & 800 (C-H Ar), 1280 (C-N), 1618 (C=N), 1530 (C=C Ar), 1195 (C=S), 698 (C-Cl), 595 (C-Br), 1670(C=O)
541. 9f	542. H	543. CH ₃	544. OCH ₃	545. 3316, 3200 & 1595 (1° & 2° N-H), 3065 & 860 (C-H Ar), 1263 (C-N), 1647(C=N), 1550 (C=C Ar), 1454 (thiazole), 1680 (C=O)
546. 10d	547. H	548. OCH ₃	549. OH	550. 3227 & 3100 (2° N-H), 3089 & 820 (C-H Ar), 2950 & 1395 (CH ₃), 1047 (C-O), 1274 (C-N), 1605 (C=N), 1540 (C=C Ar), 1492 (thiazole), 1222 (C=S), 1675 (C=O)

ANTIMICROBIAL ACTIVITY

In vitro testing is primarily of value as a screening procedure. Compounds of a promise are then subjected to in-vitro test to determine the possible practical usefulness of the drug in question. For the present work efficacy of compounds was determined against *Staphylococcus aureus* (Gram positive) and *Escherichia coli* (Gram negative). Two concentrations of test compound were prepared, i.e. 50 & 100 mcg/ml in DMF. [18]

Subculture process: The strain cultured on nutrient agar media were further subcultures in peptone water (1%) for drug vulnerability testing. Using a sterilized platinum loop, a lapful of colony of microorganism was taken and inoculated into the sterile. Plugged test tubes containing peptone water under aseptic condition. These inoculated test tubes for each microorganism were then inoculated at 37 °C for 3 hours. [19, 20]

Protocol

- Inoculum's of respective test organisms was mixed with nutrient agar (1% v/v) and after mixing 20 ml of this seeded, medium was poured into a Petri dish of 100 mm diameter.
- After the setting of medium one hole/well was made in each plate and different concentration of test compounds was placed in each of the cavities.
- The plates were kept in cold for one hour and then incubated at 37°C for one hour.
- The diameter of zones of inhibition formed around the cups after 24 hours were measured.
- DMF was used as solvent for all compounds as well as control. [21, 22]

RESULTS AND DISCUSSION

2-(6-substituted-1,3-benzothiazol-2-yl)-N-(4-halophenyl) hydrazine carbo thioamide derivatives were synthesized by reaction of 6-substituted aniline (1a-e) with potassium thiocyanate and bromine in presence of glacial acetic acid and ammonia which yield it substituted 2 amino benzothiazole derivatives which on reaction with hydrazine hydrate (2a-e) in presence of conc hydrochloric acid and ethylene glycol yield it substituted 2 hydrazylbenzothiazole derivatives (3a-e). Which on reaction with substituted phenyl iso thiocyanate derivatives in presence of benzene yield it the final product(5A-O).

3-(6, 7-substituted-1,3-benzothiazol-2-yl)-4-(4-substituted phenyl)-1,3-thiazolidin-2- one derivatives (Na-g) derivatives were synthesized by reaction of disubstituted aniline (1) with potassium thiocyanate and bromine in presence of glacial acetic acid and ammonia which yield it disubstituted 2 amino benzothiazole derivatives(2) which on reaction with substituted benzaldehyde (3a-g) in presence of absolute alcohol yield it schiff base (4a-g) which on reaction with thioglycolic acid in presence of dimethyl formamide yielded the final product(Na-g).

Antibacterial Activity: Antibacterial activity was done by cup-plate method. The results of antibacterial data are summarized in table.



Table 5: Antibacterial activity of Benzothiazole

551. Compound s	552. Antibacterial Activity (Zone of Inhibition)				
	553. <i>E.coli</i> Conc.100mcg/ ml	554. <i>P. aeruginosa</i> Conc.100 mcg/ml	555. <i>B. substilis</i> Conc.100mcg/ml	556. <i>S. aureus</i> Conc.100mcg / ml	
557.	563.	564.	565.	566.	
562. 5a	20	18	20	22	
567. 5b	21	19	18	20	
572. 5c	19	18	19	19	
577. 5d	20	19	20	17	
582. 5e	20	18	22	23	
587. 5f	21	21	19	20	
592. 5g	22	18	17	25	
597. 6a	22	21	22	24	
602. 6b	21	22	21	19	
607. 6c	22	20	20	20	
612. 6d	21	22	18	21	
617. 6e	19	22	22	18	
622. 6f	24	22	17	19	
627. 6g	21	18	24	18	
632. 7a	19	23	18	24	
637. 7b	22	24	21	23	
642. 7c	18	20	17	18	
647. 7d	22	24	21	19	
652. 7e	19	18	18	18	
657. 7f	22	23	21	19	
662. 7g	23	23	21	20	
667. 8a	19	22	22	23	
672. 8b	22	23	21	22	
677. 8c	18	19	18	18	
682. 8d	23	21	23	21	
687. 8e	21	20	19	23	
692. 8f	22	23	21	21	
697. 8g	19	20	20	23	
702. 9a	22	22	23	21	
707. 9b	22	21	24	26	
712. 9c	21	23	19	18	
717. 9d	18	17	18	19	
722. 9e	19	20	21	22	
727. 9f	21	26	22	24	
732. 9g	22	24	21	23	
737. 10a	18	19	17	18	
742. 10b	22	18	19	21	
747. 10c	22	24	22	21	
752. 10d	21	22	19	23	
757. 10e	21	20	20	22	
762. 10f	22	21	21	23	
767. 10g	21	22	23	26	
772. Std (Ciprofloxacin)	773. 26	774. 31	775. 28	776. 30	

All synthesized compounds showed antibacterial activity against *E.coli*, *P. aeruginosa*, *S.aureus* and *B. substilis*. The synthesized compounds 5a, 5f,5g,6a,6b,6f,6g,7b, 7d, 7f,7g,8b,8d,8f,9a, 9b, 9c, 9f, 9g, 10b, 10e, 10f & 10g have shown good activity against *E. coli* and the synthesized compounds6d,6e,6f,7a, 7b,7d, 7f, 7g, 8a, 8b, 8d, 8f, 9a, 9b, 9c, 9f , 9g, 10c,10d&10g showed good activity against *P. Aeruginosa* and the synthesized compounds 5a, 5e, 6a, 6c, 6e, 6g, 7b, 7d, 7f, 7g, 8a, 8d, 8f, 9b, 10c & 10g showed good



activity against *S. aureus*. Synthesized compounds 5a, 5c, 5g, 6a, 6c, 7a, 7b, 8a, 8b, 8d, 8e, 8f, 8g, 9b, 9f, 9g, 10d, 10f & 10g showed good activity against *B. Substilis* that compared with standard drug of ciprofloxacin.

Antibacterial activity was done by cup-plate method. The results of antibacterial data are summarized in table.

Table 6: Antibacterial activity of Benzothiazole Derivatives (5A-5O)

Compounds	Antibacterial Activity (Zone of Inhibition)			
	Co			
	<i>E.coli</i>	<i>P. aeruginosa</i>	<i>B. substilis</i>	<i>S. aureus</i>
	Conc.100mcg/ml	Conc.100mcg/ml	Conc.100mcg/ml	Conc.100mcg/ml
5A	20	21	22	21
5B	17	19	21	19
5C	18	21	20	18
5D	19	18	21	18
5E	18	22	21	20
5F	20	21	20	20
5G	17	20	19	18
5H	18	23	21	20
5I	19	20	20	18
5J	18	22	21	20
5K	20	21	22	20
5L	19	22	21	20
5M	20	22	16	18
5N	18	21	23	19
5O	17	21	21	18
Streptomycin	24	23	24	24

The synthesized compounds shows antibacterial activity against *E. coli*, *P. aeruginosa*, *S. aureus* and *B. substilis*. The synthesized compounds 5A, 5F, 5K, and 5M have shown good activity against *E. coli* and the compounds 5A, 5C, 5E, 5F, 5G, 5H, 5I, 5J, 5K, 5L, 5M, 5N and showed good activity against *P. aeruginosa* and the compounds 5A, 5B, 5C, 5D, 5E, 5F, 5H, 5I, 5J, 5K, 5L, 5N and 5O showed good activity against *S. aureus*. The Synthesized compounds 5A, 5B, 5E, 5F, 5H, 5J, 5K, and 5L showed good activity against *B. substilis* that compared with standard drug of streptomycin.

CONCLUSION

In present work, a series of substituted benzothiazole based derivative were synthesized and all the synthesized compounds were evaluated for their Antibacterial activity. Melting point apparatus and are uncorrected. The purity of the synthesized compounds was ascertained by TLC on silica gel G coated plates and visualized by using Iodine vapour. Developing solvents were benzene : ethanol (9: 1). The structure of the synthesized compounds was confirmed by their spectral data. Infra red spectra (IR) were recorded in Thermo IR 200 spectrophotometer (KBr). All the synthesized compounds have comparable activities so it can be calculated that change in substituents at position 6 and position 4' in 2-(6- substituted-1,3-benzothiazol-2-yl)-N-(4-halophenyl)hydrazine carbo thioamide and change in substituents at position 6 and 7 and at 4' position in 3-(6, 7-substituted-1,3- benzothiazol-2-yl)-4-(4-substituted phenyl)-1,3-thiazolidin-2-one does not effect antibacterial activity.

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