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Design, synthesis, characterization, bio-molecular docking studies, and biological activity of (4-amino-2-(aryl/alkylamino)thiazol-5-yl)(6-methylbenzo[d] thiazol-2-yl)methanone derivatives

A Yardily*[a], M Fathima Shahana[a], Jino Johnson[a], Shijula Lindry[a] & T F Abbs Fen Reji[b]

[a] Department of Chemistry and Research Centre, Scott Christian College (Autonomous) Nagercoil 629 003, India

[b] Department of Chemistry and Research Centre, Nesamony Memorial Christian College, Marthandam 629 165, India

(affiliated to Manonmaniam Sundaranar University, Abishekapatti, Tirunelveli, India)

E-mail: ayardily@gmail.com; abbsfen@gmail.com

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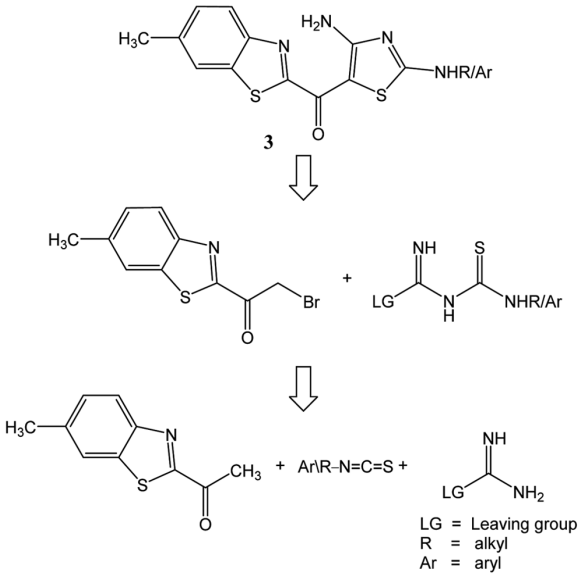
A series of novel (4-amino-2-(aryl/alkylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone compounds have been synthesized. They have been characterized by elemental analysis, IR, ^{1}H and ^{13}C NMR and mass spectral techniques. All the synthesized compounds have been screened for their antibacterial potential and show significant antibacterial activity. Among these (4-amino-2-(4-chlorophenyl)amino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone is more active. Moreover, the compound **3d** shows promising antioxidant activity activity. The compounds have been further evaluated for their potential for DNA cleavage and two compounds completely cleaved DNA. Two of the compounds have been evaluated for their anti-proliferative activity against breast cancer cell lines. The IC_{50} value of the compound (4-amino-2-(4-chlorophenyl)amino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone against the cell line MCF-7 is found to be 10 µg/mL. Four compounds have been docked towards 5077 receptor protein. Molecular docking shows very good interaction with protein. In this (4-amino-2-(4-methoxyphenyl)amino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone has the highest binding interaction with the protein.

Keywords: Dendrodoine, benzothiazoles, anti-bacterial activity, anti-proliferative activity, anti-oxidant activity, DNA cleavage

Marine algae are one of the richest sources of known and novel bioactive compounds. Several of these unique compounds have been shown to have pharmacological activity against many diseases. *Dendrodoa grossularia* is a marine algae which contains Dendrodoine (3-N,N-dimethylamino-5-indol-3-oyl-1,2,4-thiadiazole). It possesses a 1,2,4-thiadiazole unit, a rarity among natural products and it has been synthesized[1,2]. Thiazole analogue of dendrodoine derivatives indicates tremendous attraction due to their biological and pharmacological significance[3]. Compounds owning to a benzothiazole ring have increased the pharmacological interaction with a living organism and exhibit anti-inflammatory, anti-bacterial[4], anti-fungal[5] and anti-tumour activity[6]. Methyl-substituted benzothiazole compounds have good anti-bacterial and anti-fungal activities[7]. They also have good anti-malarial[8] and anti-cancer activity[9]. Based on these facts we decided to develop a new route to synthesize, (4-amino-2-(aryl/alkylamino)thiazol-5-yl)(6-methylbenzo[d] thiazol-2-yl)methanone which are hitherto analogues of dendrodoine, by using 6-methyl bezothiazole in the place of indole ring. From this approach, we compare the biological activities of various compounds. These novel analogues of dendrodoine were retrosynthesized (Scheme I).



Scheme I — Retrosynthesis of (4-amino-2-(aryl/alkylamino) thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone **3**

Experimental Section

All chemicals and solvents were purchased from Merck and Hi-Media with AR grade. The NMR (^{1}H-300MHz and ^{13}C NMR-75MHz) spectra were recorded on JEOL DRX 300 NMR spectrometer, For FAB mass spectra JEOL SX 102/DA-6000 mass spectrometer and Nicolet 400D FTIR spectrometer were used. The purity of the compounds were checked by TLC using silica gel coated on a glass plates. Melting points are determined by using digital melting point apparatus and uncorrected. All new compounds gave C, H and N analysis (CDRI, Lucknow).

General procedure for the synthesis of (4-amino-2-(aryl/alkylamino)thiazol-5-yl)(6-methylbenzo [d]thiazol-2-yl)methanone 3a-j

From the literature survey, synthesis of 2-(2-bromoacetylbenzothiazole obtained from 2-(1-hydroxyethyl) benzothiazole have been reported by Sawhney, Gupta *et al*.[10,11] But in our studies, we have attempted to synthesize solution of 2-(2-bromoacetyl-6-methylbenzothiazole (0.254 g, 1 mmol) obtained from 2-(1-hydroxyethyl)-6-methylbenzothiazole in DMF (2 mL) was added to the solution of 1-aryl/alkyl-3-(N-nitroamidino)thiourea **2a-j** (1 mmol) in DMF (2 mL). The reaction mixture was stirred well and added to triethylamine (0.3mL, 2mmol) and maintained at the temperature 50-60°C for 15 minutes in water bath. It was transferred into ice-cold water with constant stirring. The yellow-orange precipitate thus obtained. It was filtered, washed with water and dried. The crude product was purified and recrystallized by using methanol:water in the ratio of 2:1 to get pure yellow – orange crystalline solid.

Spectral analysis for the synthesized compounds 3a-j

(4-Amino-2-(phenylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3a: Yield 60%. m.p. 284–285 °C. Anal.found: C, 58.73; H, 3.90; N. 15.43%. Calcd. for $C_{18}H_{14}N_4OS_2$ (366.46): C, 58.99; H, 3.85; N, 15.29%. IR (KBr) cm^{-1} 3467, 3279, 3143 (υ_{N-H}), 3097(aromatic υ_{C-H}), 1630($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d$_6$) 2.46(s, 3H, CH$_3$), 7.12(t, 7.35 Hz, 1H, 1ArH), 7.33-7.45(m, 3H, H-5, 2ArH), 7.72(d, 7.8 Hz, 2H, 2ArH),7.90-8.00(m, 2H, H-4, H-7), 8.62(br, 1H, NH), 8.74(br, 1H, NH), 11.06(s, 1H, NH); FABMS: 367 (MH$^+$).

(4-Amino-2-(4-chlorophenyl)amino)thiazol-5-yl) (6-methylbenzo[d]thiazol-2-yl)methanone, 3b: Yield 63%. m.p. 350–353 °C. Anal.found: C, 53.75; H, 3.35; N, 13.82%. Calc. for $C_{18}H_{13}ClN_4OS_2$ (400.90): C, 53.92; H, 3.27; N, 13.98%. IR (KBr) cm^{-1} 3466, 3279, 3211 (υ_{N-H}), 3066 (aromatic υ_{C-H}), 1634($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d$_6$) 2.48(s, 3H, CH$_3$), 7.39-7.49(m, 3H, H-5, 2ArH), 7.76(d, 8.7 Hz, 2H, 2ArH), 7.92-8.02(m, 2H, H-4, H-7),8.67(br, 1H, NH), 8.70(br, 1H, NH), 11.17(s, 1H, NH); FABMS: 401 (MH$^+$).

(4-Amino-2-(4-methoxyphenyl)amino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3c: Yield 65%. m.p. 264–265°C. Anal.found: C, 57.70; H, 4.15; N, 14.34%. Calc. for $C_{19}H_{16}N_4O_2S_2$ (396.48): C, 57.55; H, 4.07; N, 14.13%. IR (KBr) cm^{-1} 3447, 3265, 3137 (υ_{N-H}), 3083(aromatic υ_{C-H}), 1631($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d$_6$) δ: 2.47(s, 3H, CH$_3$), 3.77(s, 3H, OCH$_3$), 6.98(d, 9 Hz, 2H, 2ArH), 7.42(d, 8.4 Hz, 1H, H-5), 7.58(d, 8.7 Hz, 2H, 2ArH), 7.90-8.01(m, 2H, H-4, H-7), 8.55(br, 1H, NH), 8.75(br, 1H, NH), 10.91(s, 1H, NH);^{13}C NMR (75 MHz, CDCl$_3$+DMSO-d$_6$) ɡ: 21.68, 21.72, 96.25, 114.08, 114.43, 115.00, 121.92, 122.23, 123.80, 128.49, 132.88, 136.63, 136.72, 151.64, 156.29, 169.24, 169.98; FABMS: 397 (MH$^+$).

(4-Amino-2-(4-ethoxyphenyl)amino)thiazol-5-yl) (6-methylbenzo[d]thiazol-2-yl)methanone, 3d: Yield 68%. m.p. 263–264 °C. Anal. found: C, 58.65; H, 4.54; N, 13.36%. Calc. for $C_{20}H_{18}N_4O_2S_2$ (410.51): C, 58.51; H, 4.42; N, 13.65%. IR (KBr) cm^{-1} 3464, 3277, 3144(υ_{N-H}), 3080(aromatic υ_{C-H}), 1631($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d$_6$) δ: 1.33(t, 6.9 Hz, 3H, CH$_3$), 2.47(s, 3H, CH$_3$), 4.02(quart, 6.9 Hz, 2H, CH$_2$), 6.96(d, 9 Hz, 2H, 2ArH), 7.41(d, 8.4 Hz, 1H, H-5), 7.57(d, 8.7 Hz, 2H, 2ArH), 7.90-7.99(m, 2H, H-4, H-7), 8.51(br, 1H, NH), 8.74(br, 1H, NH), 10.86(s, 1H, NH); FABMS: 411 (MH$^+$).

(4-Amino-2-(p-tolylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3e: Yield 60%. m.p. 312–313 °C. Anal. found: C, 59.81; H, 4.39; N, 14.57%. Calc. for $C_{19}H_{16}N_4OS_2$ (380.48): C, 59.97; H, 4.24; N, 14.73%. IR (KBr) cm^{-1} 3461, 3292, 3130, (υ_{N-H}), 3076, 3080(aromatic υ_{C-H}), 1630 ($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d$_6$) δ: 2.30(s, 3H, CH$_3$), 2.48(s, 3H, CH$_3$), 7.20(d, 8.1 Hz, 2H, 2ArH), 7.43(d, 8.4 Hz, 1H, H-5), 7.58(d, 8.4 Hz, 2H, 2ArH), 7.92-8.00(m, 2H, H-4, H-7), 8.55(br, 1H, NH), 8.71(br, 1H, NH), 10.95(s, 1H, NH); FABMS: 381 (MH$^+$).

(4-Amino-2-(ethylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3f: Yield 68%. m.p. 252–253 °C. Anal. found: C, 52.93; H, 4.30; N, 17.43%. Calc. for $C_{14}H_{14}N_4OS_2$ (318.42): C,

52.81; H, 4.43; N, 17.60%. IR (KBr) cm^{-1}: 3427(υ_{N-H}), 2919(aliphatic υ_{C-H}), 1603 ($\upsilon_{C=O}$); ^{1}H NMR: 0.84(t, 7.2 Hz, 3H, CH_3), 1.23(s, 3H, CH_3), 3.29(br, 2H, CH_2), 7.3-7.4(m, 3H, H-4, H-5, H-7), 8.22(br, 1H, NH), 8.25(br, 1H, NH), 8.4 (s, 1H, NH); FABMS: 319 (MH^+).

(4-Amino-2-(propylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3g: Yield 63%. m.p. 275–278 °C. Anal. found: C, 54.01; H, 4.91; N, 16.92%. Calc. for $C_{15}H_{16}N_4OS_2$ (332.45): C, 54.19; H, 4.85; N, 16.85%. IR (KBr) cm^{-1} : 3428(υ_{N-H}), 2920, (aliphatic υ_{C-H}), 1688($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d_6) 1.22(s, 3H, CH_3), 2.2(t, 7.2Hz,3H, CH_3) 2.26-2.35(sext,7.3Hz, 2H, CH_2), 4.24(quart, 7.4Hz, 2H, CH_2), 7.33-7.45(m, 3H, H-4, H-5, H-7), 8.07(br, 1H, NH), 8.25(br, 1H, NH), 8.31 (s, 1H, NH); FABMS: 333 (MH^+).

(4-Amino-2-(isopropylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3h: Yield 60%. m.p. 232–233 °C. Anal. found: C, 54.46; H, 4.34; N, 17.21%. Calc. for $C_{15}H_{16}N_4OS_2$ (332.45): C, 54.19; H, 4.85; N, 16.85%. IR (KBr) cm^{-1}: 3341(υ_{N-H}), 3042, (aromatic υ_{C-H}), 1648 ($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d_6) 1.18(d, 6.6Hz, 6H, $2CH_3$), 2.5(s, 3H, CH_3), 4.24(quart, 6.6Hz, 1H, CH), 7.96-8.07(m, 3H, H-4, H-5, H-7), 8.47(br, 1H, NH),8.64(br, 1H, NH), 10.17(s, 1H, NH); FABMS: 333 (MH^+).

(4-Amino-2-(butylamino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3i: Yield 66%. m.p. 219–220 °C. Anal. found: C, 55.36; H, 5.28; N, 16.23%. Calc. for $C_{16}H_{18}N_4OS_2$ (346.47): C, 55.47; H, 5.24; N, 16.17%. IR (KBr) cm^{-1} : 3427(υ_{N-H}), 1605($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d_6) 1.2(t, 7.2 Hz, 3H, CH_3), 2.1(sext, 6.9 Hz, 2H, CH_2), 2.74(quint, 7.2 Hz, 2H, CH_2), 3.34(br, 2H, CH_2),7.48-8.14(m, 3H, H-4, H-5, H-7), 8.57(br, 1H, NH), 8.78(br, 1H, NH),10.92(s, 1H, NH);FABMS: 347 (MH^+).

(2-(Allylamino)-4-aminothiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl)methanone, 3j: Yield 68%. m.p. 212–213 °C. Anal. found: C, 54.12; H, 4.82; N, 16.92%; Calc. for $C_{15}H_{14}N_4OS_2$ (330.43): C, 54.52; H, 4.27; N, 16.96%. IR (KBr) cm^{-1} : 3447(υ_{N-H}), 2918(aliphatic υ_{C-H}), 1604($\upsilon_{C=O}$); ^{1}H NMR: (300 MHz, DMSO-d_6) 0.84(d, 7.3Hz, 2H, CH_2), 2.15(s, 3H, CH_3), 2.26-2.34(m, 1H, CH), 2.52(d, 6.6 Hz,CH_2), 7.3-7.6(m, 3H, H-4,H-5,H-7), 8.62(br, 1H, NH), 8.72(br, 1H, NH), 9.13(s, 1H, NH).; FABMS: 331 (MH^+).

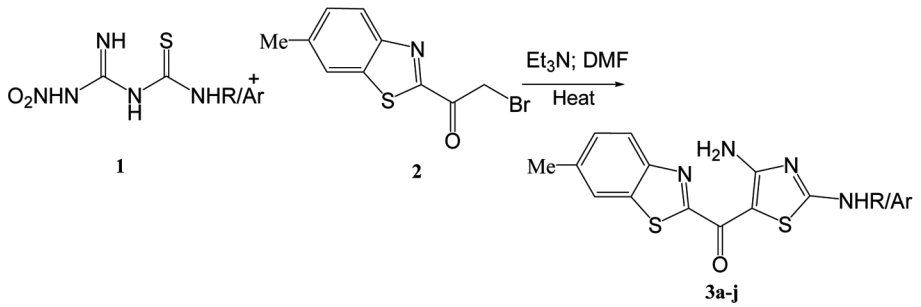
Results and Discussion

Chemistry

The synthesis of (4-amino-2-(aryl/alkylamino) thiazol-5-yl)(6-methylbenzo[d]thiazol-2yl)methanone **3a–j** which are novel analogues of the cytotoxic marine alkaloid dendrodoine, is similar to that reported by Yardily *et al*.[12] But in this studies instead of 2-(2-bromoacetyl)benzothiazole we used 2-(2-bromoacetyl)-6-methylbenzothiazole (Scheme II). For this, [4+1] hetero cyclization reaction was used, during which thiourea derivatives gave 4 ring atoms for the construction of a thiazole, consequently acting as [C-N-C-S] synthons[13-15]. The other one carbon (C-5) of the thiazole was sourced from 2-(2-bromoacetyl)-6-methylbenzothiazole **2**. A mixture of **2** in dimethylformamide (DMF) and 1-aryl/alkyl-3-(N-nitroamidino)thiourea **1** (Table I) in DMF was taken. The reaction mixture was stirred well and triethylamine was added and heated on a water bath at 50–60°C for 15 minutes. This led to a higher yield of the desired products, **3a–j**. The structures of all these compounds **3a–j** were elucidated from their spectral data (IR, ^{1}H-NMR and MS) and elemental analysis.

Table I — (4-amino-2-(aryl/alkylamino)thiazol-5-yl) (6-methylbenzo[d]thiazol-2-yl)methanone **3a–j**

Compd	Substituent	Compd	Substituent
3a	Phenyl	**3f**	Ethyl
3b	4-chlorophenyl	**3g**	n-propyl
3c	4-methoxyphenyl	**3h**	iso-propyl
3d	4-ethoxyphenyl	**3i**	n-butyl
3e	4-tolyl	**3j**	Allyl-



Scheme II — Synthetic route for the formation of benzothiazole derivatives **3a-j**

A mixture of 1-(4-chlorophenyl)-3-N-nitroamidino) thiourea (1 mmol) in DMF (2 mL), 2-(2-bromoacetyl)-6-methylbenzothiazole **2** in DMF (2 mL) was taken. The reaction mixture was heated on a water bath at 80–85 ·C for 5 min. To this, triethylamine (0.15 mL, 1 mmol) was added and the mixture was continuously heated along with stirring. The yellow crystalline compound was obtained. It was filtered, washed by using water and dried. The crude material was recrystallized by using methanol:water (2:1). Elemental analysis confirmed the molecular formula of the compound as $C_{18}H_{13}ClN_4OS_2$. Its IR (KBr) spectrum showed bands at 3466, 3279 and 3211 cm^{-1} which are assigned as secondary amine stretching. The absorption band at 3066cm^{-1} can be attributed to aromatic C-H stretching vibration. The conjugated carbonyl group gives rise to a vibrational frequency at 1634 cm^{-1}. The ^{1}H-NMR (300 MHz, DMSO-d_6) spectrum showed, the methyl group produces a three - hydrogen singlet at ɡ 2.48. The multiplet at ɡ 7.39-7.49 has been attributed to H-5 of the 6-methylbenzothiazole and other two aromatic hydrogens. The two hydrogen doublet ɡ 7.76 arises from the two aromatic hydrogens. The H-4 and H-7 of the 6-methylbenzothiazole ring appear as a multiplet at ɡ 7.92-8.02. The two 4-amino hydrogens appear as two well separated broad singlets at ɡ 8.67 and 8.70. It is due to the two hydrogens are not exchanging rapidly on the chemical shift time scale and they are in two different chemical environments. The presence of NH hydrogen of the NHAr group is seen at ɡ 11.17 as a one hydrogen singlet The Mass spectrum showed a strong MH^+ peak at m/z 401, which confirmed the molecular mass of the compound. From the above evidences, the compound was found to be (4-amino-2-(4-chlorophenyl) amino)thiazol-5-yl)(6-methylbenzo[d]thiazol-2-yl) methanone **3b**.

In Scheme III, the leaving group could be NH_2NO_2 group. Thus the required thiourea derivative provide the C-N-C-S atoms that go to the making of the thiazole ring. The remaining C-5 atom would come from α-haloketone with benzothiazole. In this reaction HBr is the another one eliminating group.

Biology

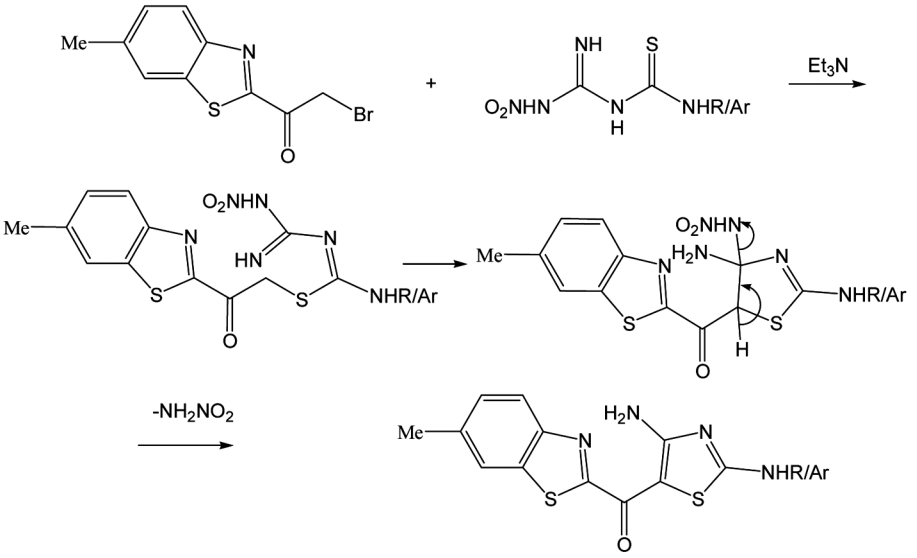
Anti-bacterial activity

To assess the bioactivity, the benzothiazoles **3a–j** were screened against the bacterial strains *Klebsiella pneumoniae*(MTCC 7407), *Pseudomonas aeruginosa* (MTCC 6538), *Salmonella typhi* (MTCC 733), *Bacillus subtilis*(MTCC 1134), *Streptococcus mutans* (MTCC 1936) and *Staphylococcus aureus* (MTCC 916) by using disc diffusion method[16].

For evaluating the antibacterial activity Penicillin G was used as the reference drug. Amongst the compounds tested for antibacterial activity, all the compounds showed moderate activity (Table II).

Anti-oxidant Assay (DPPH Free Radical-Scavenging activity)

The free radical scavenging activity of the compounds were determined by using 1,1-Diphenyl-2-picryl-hydrazyl (DPPH). DPPH 1 mg in 10^{-5} mol methanol was prepared in a 250-ml standard flask



Scheme III — Mechanistic pathway of the reaction **3a-j**

Table II — Anti-bacterial activity of compounds **3a–j**

Compd	Zone of inhibition(mm)					
	K.pneumoniae MTCC 7401	*P.aeruginosa* MTCC 6538	*S.typhi* MTCC 733	*B.subtilis* MTCC 1134	*S.mutans* MTCC 1936	*S.aureus* MTCC 916
3a	11	9	8	8	8	9
3b	13	11	10	13	14	12
3c	8	9	11	9	9	10
3d	9	10	11	9	9	8
3e	9	10	10	9	8	10
3f	8	8	9	8	8	8
3g	8	9	8	8	9	10
3h	9	9	9	8	8	8
3i	9	8	8	10	8	8
3j	8	9	8	9	9	8
Penicillin G	15	15	17	18	15	16

(control – 2.8 mL of this solution + 0.05 mL methanol). Benzothiazole solutions of different concentrations (0.1, 0.25, 0.5, 0.75, 1 mM) were prepared. BHA (standard) solutions of different concentrations (0.1, 0.25, 0.5, 0.75, 1 mM) were also prepared. The absorbance values of the control, test and standard solutions were recorded at 517 nm. From the absorbance values, % of inhibition was calculated. Then the % of inhibition was plotted against concentrations for different samples as well as BHA. From the graph, IC_{50} values were calculated. The IC_{50}values are lesser, higher the antioxidant capacity of the compounds. For each compound, five concentrations were employed and the Percentage inhibition was determined. The percentage inhibition of the antioxidant was expressed as,

$$\% \text{ inhibition} = \frac{\text{Control absorbance} - \text{Sample absorbance}}{\text{Control absorbance}} \times 100$$

The compound **3d** with group ethoxyphenyl showed very good activity compared to butylated hydroxyl anisole (BHA) at all the concentrations tested (Figure 1).

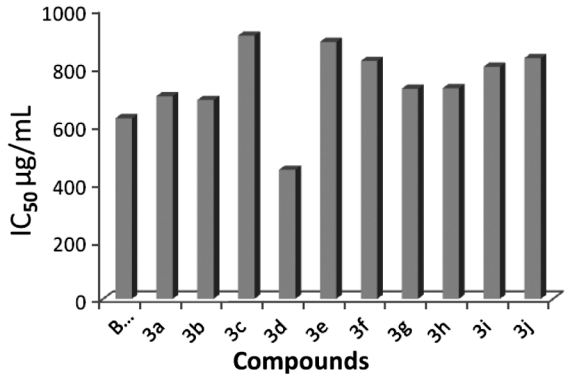


Figure 1 — Antioxidant activity of compounds **3a–j**

DNA cleavage activity

A number of studies have shown that the clinical efficacy of many drugs correlates with their ability to induce enzyme-mediated DNA cleavage. The inhibitory potency of the test compounds was assessed by comparing their potential for cleaving DNA with that of the control. Gel electrophoresis was used for the analysis of **3a, 3b, 3c, 3d, 3e** and **3h** having the groups phenyl, chlorophenyl, methoxyphenyl, ethoxyphenyl, methylphenyl and isopropyl respectively

The compounds were added separately to the calf thymus DNA sample. The sample mixtures were incubated at 37°C for 2 h and subjected to gel electrophoresis. Three hundred milligrams of agarose was dissolved in 25 mL of TAE buffer (4.84 g Tris base, pH 8.0, 0.5 M EDTA/1 L) by boiling. At ~55°C, the gel was poured into the gel cassette fitted with comb and allowed to solidify. The comb was removed and the gel placed in the electrophoresis chamber flooded with TAE buffer. The DNA samples (mixed with bromophenol blue dye at 1:1 ratio) were loaded carefully into the wells, along with standard DNA marker and a constant electricity of 100 V was maintained until the dye front reached the end of the gel. Then the gel was removed and stained with ETBR solution (10 µg/mL) for 10–15 min, and the bands observed under a UV transilluminator.

Results showed that the compounds **3a** and **3b** completely cleaved the DNA. The compounds **3e** & **3h** partially cleaved the DNA and the other samples were ineffective (Figure 2).

Anti-proliferative activity

The two benzothiazole compounds were screened for their anti-proliferative activity against the breast cancer cell line MCF-7 by the MTT method and IC_{50} values calculated. For evaluating the anti-proliferative activity, compound **3b** was the most active derivative against the breast cancer cell line, with an IC_{50} value of 10 µg/mL. The compound **3d** showed IC_{50} of > 100µg/mL.

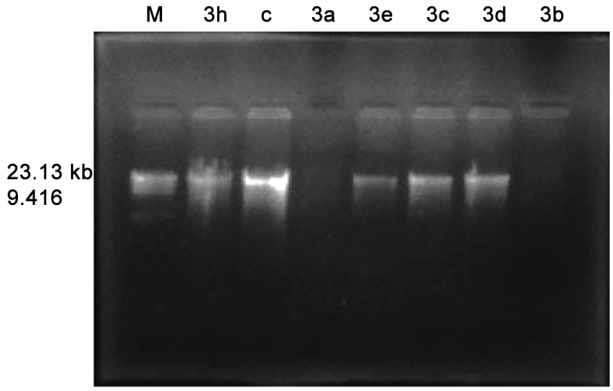


Figure 2 — DNA cleavage study of compounds

Molecular Docking Studies

Molecular docking is a well-established and regularly used approach in drug design. This studies were carried out to investigate the binding affinities of newly synthesized titled compounds and the protein receptor of *Klebsiella Pneumonia*(PDB code:5O77), which is downloaded from protein data bank in PDB format. *K. Pneumonia* (Bacteria), most commonly causes pneumonia and form broncho pneumonia and bronchitis in living beings. It is a gram-negative, encapsulated, non-motile bacterium that is found in the environment and has been associated with pneumonia in the alcoholic and diabetic patient population. The bacterium typically settles human mucosal surfaces of the oropharynx and gastrointestinal (GI) tract. Once the bacterium enters the body, it can show high degrees of virulence and antibiotic resistance[17].

The above synthesized compounds **3b, 3c, 3g, 3i** were docked with 5O77 receptor (inhibitor of KP) (Figure 3, Figure 4, Figure 5 and Figure 6) using Hex dock software and visualized by Discovery studio 3.5. Before that, the compounds was checked to obey

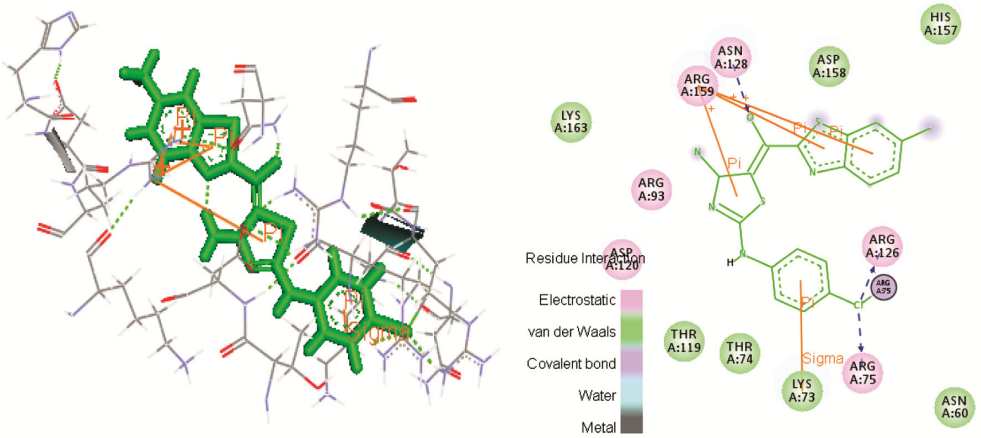


Figure 3 — 3D and 2D interaction of the compound **3b** and the protein 5O77

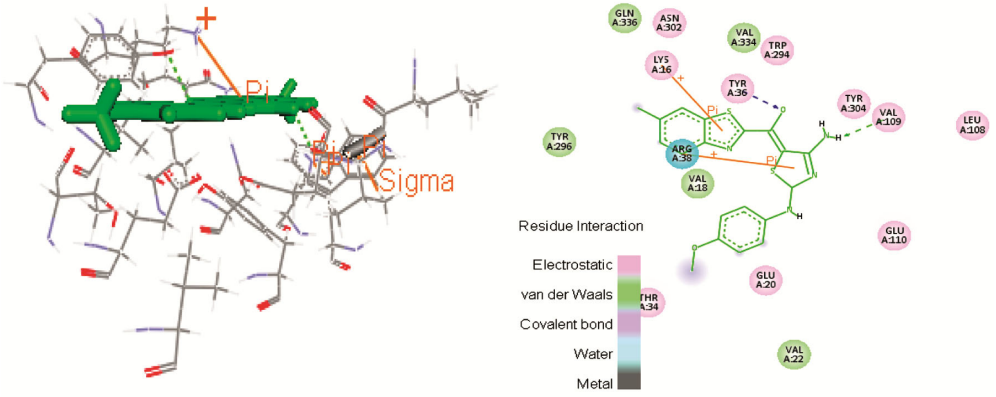


Figure 4 — 3D and 2D interaction of the compound **3c** with the protein receptor 5O77

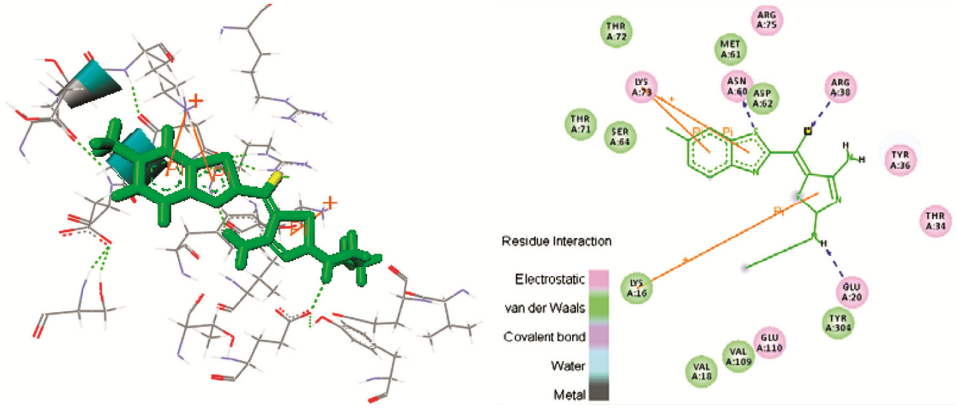


Figure 5 — 3D and 2D interaction of the compound **3g** witth the protein receptor 5O77

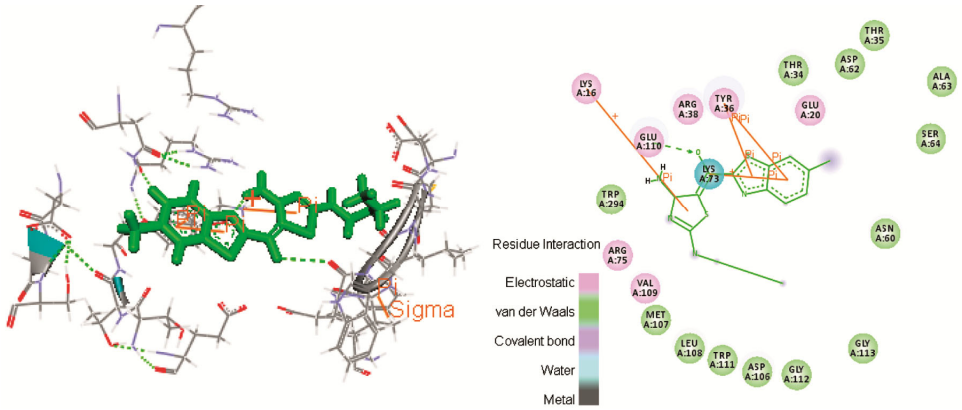


Figure 6 — 3D and 2D interaction of the compound **3i** with the protein receptor 5O77

Table III — LIPINSKI rule of five for the compounds

Compd	Mol. Wt < 500 Dalton	HB donor<5	HB acceptor <10	Log P <5	Mol. Refractivity 40-130
3b	400.50	3	5	5	109.05
3c	396.00	3	6	4.62	110.59
3g	332.00	3	5	3.69	93.09
3i	346.00	3	5	4.086	97.71

Table IV — Docking score and interaction of the compounds with the protein 5O77

Compd	Binding Energy (KJ/mol)	Active sites of interactions				
		π-σ interactions	π-cation interactions	π-π interactions	Electrostatic	Van der Waals
3b	−331.03	LYS A73	ASG A159	–	ARG A159, ASN A128, ARG A126, ARG A75. ARG A93, ASP A120	LYS A73, ASP A 158, THR A119, THR A74.
3c	−339.87	–	LYSA16, ARG A38.	–	TYR A36, VAL A 109, TYR A304	VAL A18, VAL A334, GLN A336, TYR A296.
3g	−300.88	–	LYS A73, LYS A16	–	ASN A60, GLU A20, ARG A38	ASP A 62, MET A61, SER A64, Lys A16
3i	−307.40	–	LYS A73, LYS A16	TYR A36, LYS A73	TYR A36, LYS A16, GLU A110, ARG A38	TRP A294

LIPINSKI rule of five for drug ability (Table III). The binding energy and interacting sites are tabulated (Table IV). The stability of the ligand-receptor arrangement was understood by hydrogen bonding, electrostatic and covalent interactions[18]. Lower the binding energy, higher will be the protein-ligand interaction and more antibacterial activity[19]. This study shows that the antibacterial activity of the methoxy substituted compound **3c** has more binding interaction with the protein (5O77).

Conclusion

The objectives of the present study were to synthesize novel benzothiazoles with the hope of discovering new structure leads serving as anti-bacterial, anti-oxidant, DNA cleavage and anti-proliferative agents. These compounds exhibited significant activity against the growth of bacteria. The results of the anti-bacterial studies revealed that the compounds **3a-j** were moderately active. The compound **3b** was found to exhibit very good anti-proliferative agent against the breast cancer cell line, MCF-7 and its IC_{50} value was 10 µg/mL. These results were further substantiated by the DNA cleavage and antioxidant property of these compounds. The test compounds **3a** and **3b** cleaved DNA completely. The compound **3d** revealed potent anti-oxidant activity when compared with BHA. The molecular docking suggests that, compounds-receptor systems are stabilized by π-cation, electrostatic and van der Waals interactions. Thus the study confirms the methylbenzothiazole with various substituents on aminothiazole ring could be usable as a antiproliferative drug in the future.

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