



Antioxidant Potential of Novel 2-[2, 4-Bis (Arylamino) Thiazol-5-Oyl] Benzothiazoles

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Abstract:

A series of 2-[2, 4-bis (aryl/alkylamino) thiazol-5-oyl] benzothiazole derivatives were synthesized from 1-aryl-3-(N,N'-diarylamidino) thioureas and 2-(2-bromoacetyl) benzothiazole with triethylamine. Their structures were established on the basis of IR, ¹H NMR, ¹³C NMR and mass spectral analyses. Antioxidant activities of synthesized compounds have been evaluated by DPPH free radical scavenging activity.

Keywords: Benzothiazole, arylamino, amidinothiourea, DPPH, antioxidant activity.

1. INTRODUCTION

A marine alga is one of the richest sources of known and novel bioactive compounds. Several of these unique compounds have shown pharmacological activities for many of the deadly diseases.¹ Dendrodoine 5-[3-(N, Ndimethylamino-1,2,4-thiadiazolyl) -3-indolylmethanone is an alkaloid and extracted from the marine algae dendrodoa grossularia²⁻⁴. It possess a 1,2,4-thiadiazole unit a rarity among natural products.¹ It was noted that, substitution of thiazole ring in place of the thiadiazole ring would provide additional opportunities for introducing structural diversity. Benzothiazole analogs of dendrodoine derivatives have attracted a great deal of interest due to their biological and commercial importance. Heterocyclic compounds analogues and derivatives have attracted wide attention due to their useful biological and pharmacological properties. Benzothiazole is among the usually occurring heterocyclic nuclei in many marine as well as natural plant products⁵. Benzothiazole is a privileged bicyclic ring system with multiple applications. It is known to exhibit a wide range of biological properties including anticancer, antimicrobial, and antidiabetic, anticonvulsant, anti-inflammatory, antiviral, antitubercular activities⁶⁻¹⁰. A large number of therapeutic agents are synthesized with the help of benzothiazole nucleus. During recent years there have been some interesting developments in the biological activities of benzothiazole derivatives¹³. These compounds have special significance in the field of medicinal chemistry due to their remarkable pharmacological potentialities. Antioxidants have the ability of protecting organisms from damage caused by free-radical induced oxidative stress. Accordingly, the synthesis and the results of bioactivity of many diaminothiazole analogs of dendrodoine have reported. The present work describes the synthesis of some dendrodoine analogs and evaluation of antioxidant activity by DPPH scavenging method.

2. EXPERIMENTAL

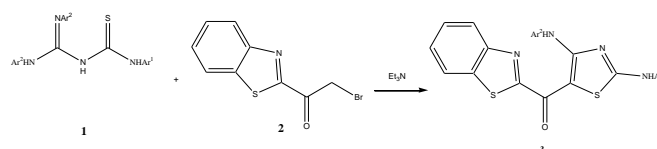
2.1. Materials and methods

The reagents and solvents used were of AR grade. All chemicals were purchased from Merck Specialities Pvt Ltd and

HiMedia Laboratories Pvt Ltd. The spectra were recorded on JEOL DPX 300 or DRX 300 NMR spectrometer (300 MHz for ¹H and 75 MHz for ¹³C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using argon/xenon, 6 kV, 10 mA as the FAB gas and *m*-nitrobenzyl alcohol as the matrix) for FAB mass spectra and Nicolet 400D FTIR spectrometer. Melting points were uncorrected.

2.2. General procedure for the synthesis of 2-[2,4-bis(arylamino)thiazol-5-oyl] benzothiazoles 3a-h

The reaction sequences employed for the synthesis of title compounds are shown in Scheme 1. 2-[2,4-bis (arylamino) thiazol-5-oyl] benzothiazoles 3a-h were prepared according to the following method (Abbs Fen Reji et al., 2009).



Scheme. 1. Synthetic route of molecules 3

Table.1.2-[2,4-bis(phenyl-aryl/alkylamino)thiazol-5-oyl] benzothiazole 3a-h

Compound	R
3a	Phenyl
3b	4-chlorophenyl
3c	4-methylphenyl
3d	4-methoxyphenyl
3e	4-ethoxyphenyl
3f	Ethyl
3g	n-propyl
3h	n-butyl

A solution of 1-aryl-3-(N,N'-diarylamidino) thiourea (1 mmol) in DMF (2ml) was added to a solution of 2-(2-bromoacetyl) benzothiazole (0.254g, 1m mol), which was prepared from 2-(1-hydroxyethyl) benzothiazole (Sawhney and singh, 1970; Gupta et al, 1980; Joshua and Rajasekharan, 1974; Hunter, 1925a,b, 1926) in DMF (2ml) . The reaction mixture was stirred well and triethylamine (0.15 ml, 1mmol) was added .The reaction mixture was warmed at 35-40°C for 10min. It was

then cooled and poured into ice-cold water with constant stirring. A yellowish orange precipitate thus obtained was filtered, washed with water and dried. The crude product was crystallized from methanol: water (2:1) and then from benzene: petroleum ether (1:1) to give a yellowish orange crystalline solid.

2-[2,4-Bis(Phenylamino)Thiazol-5-Oyl] Benzothiazole 3a

This was prepared and purified as per the above mentioned procedure. Yield 65% , m.p. 235-38°C Analysis: Found: C,64.31; H, 3.85; N, 13.25%; Calc. for $C_{23}H_{16}N_4OS_2$ (428.52): C64.46; H, 3.76; N, 13.08%; IR(KBr) cm^{-1} : 3433, 3272, 3198, 3048, 1626, 1600,1562, 1485, 1445, 1414, 1324, 1268, , 912, 757, 690 ; 1H NMR: (300 MHz, DMSO-d₆) δ 7.11-7.23 (m, 2H , 2ArH); 7.38-7.50 (m, 4H, 4ArH); 7.53-7.72 (m, 4H , H-5, H-6, 2ArH); 7.77 (d, 8.1Hz, 2H, 2ArH); 8.12 (d, 7.8Hz, 1H, H-4); 8.23 (d, 7.8Hz, 1H, H-7); 11.85 (s, 1H, NH). ^{13}C NMR; (75 MHz, DMSO-d₆) δ ; 91.1, 119.7, 120.1, 122.8, 123.7, 123.9, 124.3, 126.8, 127.0, 129.0, 135.9, 138.7, 138.9, 152.8, 163.6, 169.6, 170, 6, 172.1; FABMS: 429(MH⁺).

2-(2-CHLOROAMINO-4-PHENYLAMINOTHIAZOL-5-OYL) BENZOTHIAZOLE 3B

This was prepared and purified as per the above mentioned procedure. Yield 70% , m.p. 265-67°C Analysis: Found: C,52.243; H, 2.643; N, 14.65%; Calc. for $C_{17}H_{11}ClN_4OS_2$ (386.91): C,52.774; H, 2.8714; N, 14.484%; IR(KBr) cm^{-1} :3441, 3133, 2359, 1640, 1549, 1401, 703, 663, 393; 1H NMR: (300MHz, $CdCl_2$) δ ; 8.251 (s, 1H); 7.440-7.207 (m, 10H); 7.957 (s, 1H) .

2-(2-METHYLAMINO-4-PHENYLAMINOTHIAZOL-5-OYL) BENZOTHIAZOLE 3C

This was prepared and purified as per the above mentioned procedure. Yield 68% , m.p. 241 3°C Analysis: Found: C,58.543; H,3.786; N, 15.123%; Calc. for $C_{18}H_{14}N_4OS_2$ (366.49): C58.990;H, 3.858;N,15.2900%;IR(KBr) cm^{-1} : 3331, 3007, 2856, 2923, 1807, 1740, 1649, 1589, 1500, 1461, 1355, 1266, 1182, 1165, 1081, 1048, 998, 914, 880, 763, 730, 702 ; 1H NMR: (300MHz, $CdCl_2$) δ ; 8.108 (s, 2H); 7.531 (s, 1H); 7.321 (d, J= 7.2Hz , 3H); 7.066 (d, J= 7.8Hz, 3H); 2.928 (s, 3H); 2.529 (t, J= 1.8Hz , 2H) .

2-(2-METHOXYAMINO-4-PHENYLAMINOTHIAZOL-5-OYL) BENZOTHIAZOLE 3D

This was prepared and purified as per the above mentioned procedure. Yield 65% , m.p. 236-38°C Analysis: Found: C,58.543; H,3.786; N,15.123%; Calc. for $C_{18}H_{14}N_4O_2S_2$ (366.498): C58.990; H,3.858; N,15.2900% ;IR(KBr) cm^{-1} :3424, 3132, 2358, 1617, 1562, 1490, 1401, 1211, 1087, 1020, 819, 756, 724, 501; 1H NMR: (300MHz, $CdCl_2$) δ : 7.392.7.348 (m, 1H); 7.260 (s, 1H); 7.16 (d, J= 6.3Hz , 1H); 3.627-3.578 (m, 1H); 1.584-1.510 (m, 2H); 1.369-1.295 (m, 2H); 0.916 (t, J= 5.4Hz, 3H) .

2-(2-ETHOXYAMINO-4-PHENYLAMINOTHIAZOL-5-OYL) BENZOTHIAZOLE 3E

This was prepared and purified as per the above mentioned procedure. Yield 70% , m.p. 257-59°C Analysis: Found: C,57.342; H, 4.065; N, 14.322%; Calc. for $C_{19}H_{15}N_4O_2S_2$ (396.52): C57.551; H, 4.0753; N,14.1326%; IR(KBr) cm^{-1} : 3063, 2985, 2923, 2851, 2773, 2555, 2376, 2170, 2114, 1902, 1874, 1835, 1740, 1690, 1606, 1506, 1439, 1411, 1299, 1249, 1171, 1120, 1048, 919, 825, 802, 763, 707 ; 1H NMR: (300MHz, $CdCl_2$) δ : 7.418-6.855 (m, 13H); 4.047-3.978 (m, 1H); 1.435-1.377 (m, 2H) .

2-(2-ETHYLAMINO-4-PHENYLAMINOTHIAZOL-5-OYL) BENZOTHIAZOLE 3F

This was prepared and purified as per the above mentioned procedure. Yield 70% , m.p. 248-50°C Analysis: Found: C,59.543; H, 4.121; N, 14.564%; Calc. for $C_{19}H_{16}N_4OS_2$ (380): C59.971; H, 4.246; N,14.726%; IR(KBr) cm^{-1} : 3382, 3137, 1613, 1494, 1401, 1223, 752, 693; 1H NMR: (300MHz, $CdCl_2$) δ : 7.400 (d, J= 6.3Hz , 1H); 7.362-7.327 (m, 7H); 7.270 (d, J= 6.3Hz, 2H); 1.157 (t, J= 3.3Hz , 1H); 3.680-3.630 (m, 2H); 3.365-3.297(m, 1H); FABMS: 380(MH⁺).

2-(2-BUTYLAMINO-4-PHENYLAMINOTHIAZOL-5-OYL)BENZOTHIAZOLE 3G

This was prepared and purified as per the above mentioned procedure. Yield 65%, m.p. 255-56°C Analysis: Found: C, 60.765; H, 4.564; N, 14.212% ; Calc.for $C_{20}H_{18}N_4OS_2$ (394.5): C,60.883;H,4.607;N,14.726 % IR (KBr) cm^{-1} :3456, 3129, 1633, 1401, 533 ; 1HNMR :(300MHz, $CdCl_2$) δ : 8.14 (t, J= 11.4 Hz, 1 H); 7.993 (d, J= 8.1Hz, 1 H); 7.659 (d, J= 8.1 Hz , 1 H); 7.674-7.509 (m, 3 H); 7.487-7.254 (m, 5 H); 7.122 (d, J= 8.4 Hz , 1 H); 1.393 (d, J= 6.3 Hz, 2 H); 1.242-1.167 (m, 4 H); 1.095 (d, J= 6.6 Hz , 1 H); 0.967-0.850 (m, 1 H) .

2-(2-PROPYLAMINO-4-PHENYLAMINOTHIAZOL-5-OYL)BENZOTHIAZOLE 3H

This was prepared and purified as per the above mentioned procedure. Yield 70% , m.p. 257-59°C Analysis: Found: C,60.234; H, 4.323; N, 13.321%; Calc. for $C_{21}H_{20}N_4OS_2$ (408.491): C,60.277; H, 4.344; N, 13.392 %;IR(KBr) cm^{-1} : 3292, 3035, 2912, 2856, 2348, 2293, 2114, 2002, 1946, 1904, 1835, 1639, 1595, 1561, 1517, 1405, 1377, 1310, 1238, 1115,1059, 908, 819,786, 758, 707; 1H NMR: (300MHz, $CdCl_2$) δ : 8.14 (t, J= 11.4 Hz, 1 H); 7.993 (d, J= 8.1Hz, 1 H); 7.659 (d, J= 8.1 Hz , 1 H); 7.674-7.509 (m, 3 H); 7.487-7.254 (m, 5 H); 7.122 (d, J= 8.4 Hz , 1 H); 1.393 (d, J= 6.3 Hz, 2 H); 1.242-1.167 (m, 4 H); 1.095 (d, J= 6.6 Hz , 1 H); 0.967-0.850 (m, 1 H) .

3. ANTIOXIDANT ACTIVITY

2.3.1. DPPH free radical scavenging activity

The free radical scavenging capacity was determined using DPPH. DPPH is a stable free radical due to delocalization of the spare electron over the whole molecule. The delocalization restricts the molecule from dimerising as would be the case with most other free radicals. The delocalization also gives rise to the deep violet colouration characterized by a strong absorption band at 517 nm. DPPH free radical can accept an electron or hydrogen radical and can be converted into a stable, diamagnetic molecule with the loss of the violet colour. This paired radical can undergo further reaction, which control the overall stoichiometry and the absorption decreases with respect to the number of electron take up. The DPPH solution (10- 5 M) was prepared by using 1 mg in 250 mL methanol. Benzothiazole solutions of different concentrations 0.1, 0.25, 0.5, 0.75 and 1 mM were prepared. DPPH solution (2.8 mL, 10- 5M) was mixed with benzothiazole sample solution (0.1mL) and decolouration was measured at 517 nm after incubation for 30 minutes in the dark (spectrophotometer). The control DPPH solution was prepared which contain the same volume without any synthesized compounds and 0.05 mL methanol was used as the blank. Butylated Hydroxy Anisole (BHA) was used as a reference standard and dissolved in DPPH.

4. RESULTS AND DISCUSSION

The structures of all the compounds were established on the basis of elemental analysis, IR, ¹H NMR, ¹³C NMR and mass spectral data. Antioxidant capacity of the compound was expressed as the free radical scavenging activity (IC₅₀) of DPPH radical. Test solutions were prepared with sample solutions of different concentrations and their absorbance were found out at 517 nm. Similarly the absorbance was found out for BHA solutions also. From the absorbance values the percentage inhibition was calculated.

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

Then the percentage of remaining DPPH was plotted against concentrations for different samples as well as BHA. The graph is shown below in fig.1

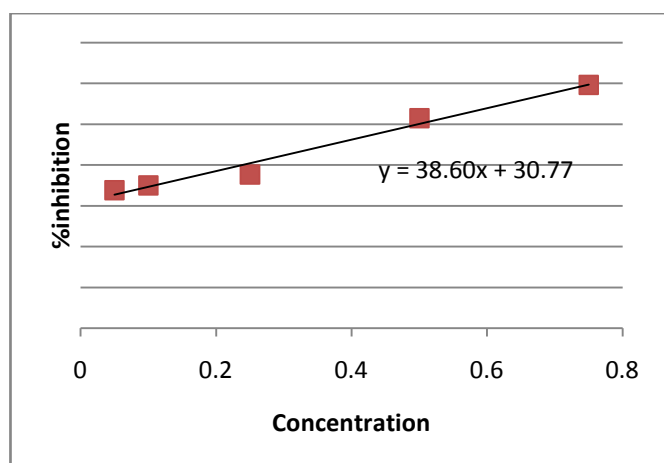


Figure. 1. DPPH radical scavenging activity of benzothiazole compound, 3d

Table.2. IC₅₀ value of different antioxidant activity

Compd.	IC ₅₀ value (µM)
3a	278
3b	498
3c	355
3d	530
3e	842
3f	423
3g	868
3h	412
BHA (Standard)	624

5. CONCLUSION

This study reports the successful synthesis of the benzothiazole compounds in good yield and characterized by IR, ¹H-NMR, ¹³C-NMR and mass spectral analysis. The antioxidant activity of the synthesized compounds was determined by DPPH free radical scavenging activity. The compounds **3a** and **3c** shows higher antioxidant dose than standard BHA antioxidant.

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