ORIGINAL ARTICLE

Synthesis and the influence of intramolecular H-bonding in NMR spectra of novel analogs of dendrodoine: Diaminothiazoloylbenzothiazoles

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Abstract
2-(4-Amino-2-arylaminothiazol-5-oyl)benzothiazoles, as the novel analogs of the cytotoxic marine alkaloid dendrodoine, are synthesized and characterized by elemental analysis, IR, NMR and mass spectral data. The thiourea derivatives provide four ring atoms for the thiazole ring construction and thus act as [C–N–C–S] synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)benzothiazoles. This [4+1] heterocyclization reaction is adopted for the synthesis of novel benzothiazole derivatives. The presence of two signals in the 1H NMR spectrum arising from the NH2 hydrogens shows that the two hydrogens are not exchanging rapidly on the chemical shift time scale and they are in two different chemical environments due to H-bonding.

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1. Introduction

Dendrodoine, 3-[(N,N-dimethylamino)-1,2,4-thiadiazol-5-oyl]indole I is a marine alkaloid isolated (Heitz et al., 1980) from the tunicate Dendrodoa grossularia. It contains a 1,2,4-thiadiazole unit, quite uncommon either in terrestrial or in marine natural products (Fig. 1). Dendrodoine also belongs to the indole class of marine alkaloids. Dendrodoine has been reported to be cytotoxic to lymphoma cells L1210 in culture (Heitz et al., 1980; Helbecque et al., 1987). Though its synthesis has been reported (Hogan and Sainsbury, 1984), further studies on it or on its analogs have not appeared. It was noted that the substitution of a thiazole ring in place of the thiadiazole ring in I would provide additional opportunities for introducing structural diversity on I. Thiazole moiety is present in a variety of natural and synthetic biomolecules. Recent studies on the in vitro cytotoxicity of thiazole derivatives include reports on the significant cytotoxic activity of bis(indolyl)thiazoles (Jiang and Gu, 2000) and indolylthiazoles (Moody et al., 1997).
Benzothiazole shares several structural features with indole. In addition, benzothiazoles exhibit several significant biological activities just as indoles. The literature survey shows several examples of compounds having a benzothiazole ring which exhibit remarkable bioactivity. The above survey amply demonstrates the significance of benzothiazole unit as a useful pharmacophore moiety. Such derivatives possess antitumor (Takeshi et al., 2000a,b; Alexander et al., 2000a,b; Geoffrey et al., 2000; Hutchinson et al., 2001; Abbs Fen Reji et al., 2008; Kok et al., 2008), anti-inflammatory ( Sharma et al., 1998; Murugan et al., 1999), antibacterial (Murugan et al., 1999; Kabeer et al., 2001) and antifungal (Kabeer et al., 2001; Margita et al., 1995, 1997; Milan et al., 1999, 2000) activities. On the basis of this observation we decided to develop a route to 2-(4-amino-2-arylaminothiazol-5-oyl)benzothiazoles as hitherto unreported analogs of dendrodoine by replacing the indole ring by a benzothiazole ring.

The route to the synthesis of novel analogs of dendrodoine was based on retrosynthesis, which is outlined in Scheme 1.

2. Experimental

2.1. Materials and methods

Reagents and solvents were from Merck India and Fluka. The spectra were recorded on JEOL DRX 300 or DPX 300 NMR spectrometer (300 MHz for $^1$H and 75 MHz for $^{13}$C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using Ar-Gon/Xenon, 6 kV, 10 mA as the FAB gas and Nicolet 400D FTIR spectrometer. Melting points are uncorrected.

2.2. General procedure for the synthesis of

2.2. 2-(4-amino-2-arylaminothiazol-5-oyl)benzothiazoles 4a–d

A solution of 2-(2-bromoacetyl)benzothiazole (0.254 g, 1 mmol) which was prepared from 2-(1-hydroxyethyl)benzothiazole (Sawhney and Singh, 1970; Gupta et al., 1980; Joshua and Rajasekharan, 1974; Hunter, 1925a,b; Hunter, 1926) in DMF (2 mL) was added to a solution of 2-amino-3-(N-nitrosoamino)thiourea 2a–e (1 mmol) in DMF (2 mL). The reaction mixture was stirred well and triethylamine (0.15 mL, 1 mmol) was added. The reaction mixture was warmed at 35–40°C for 5 min. 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 crystallised from methanol–water (2:1) and then from benzene–petroleum ether (1:1) to give a yellowish orange crystalline solid.

Yield 60%, m.p. 293–95°C Analysis: Found: C, 57.75; H, 3.50; N, 15.69%; Calc. for C$_{17}$H$_{12}$N$_4$O$_5$S$_2$ (354.43): C, 57.93; H, 3.43; N, 15.90%; IR (KBr) cm$^{-1}$: 3454, 3285, 3137, 3103, 3050, 1625, 1599, 1566, 1526, 1499, 1445, 1356, 1237, 1188, 1034, 891, 749, 690; $^1$H NMR: (300 MHz, DMSO-d$_6$) $\delta$: 7.12(t, $J = 7.35$ Hz, 1H, 1ArH), 7.40(t, $J = 7.8$ Hz, 2H, 2ArH), 7.49–7.65(m, 2H, H-5, H-6), 7.72(d, $J = 8.1$ Hz, 2H, 2ArH), 8.09(d, $J = 8.1$ Hz, 1H, H-4), 8.20(d, $J = 7.8$ Hz, 1H, H-7), 8.64(br, 1H, NH), 8.76(br, 1H, NH), 8.76(br, 1H, NH), 11.08 (s, 1H, NH); $^{13}$C NMR: (75 MHz, DMSO-d$_6$) $\delta$: 91.1, 119.4, 122.9, 123.7, 123.9, 126.6, 126.9, 129.1, 135.9, 139.3, 152.9, 168.7, 169.6, 170.6, 171.3; FABMS: 353 (MHI$^+$.)

2.3. 2-(4-Amino-2-phenylaminothiazol-5-oyl)benzothiazole 4a

Yield 60%, m.p. 293–95°C Analysis: Found: C, 57.75; H, 3.50; N, 15.69%; Calc. for C$_{17}$H$_{12}$N$_4$O$_5$S$_2$ (354.43): C, 57.93; H, 3.43; N, 15.90%; IR (KBr) cm$^{-1}$: 3454, 3285, 3137, 3103, 3050, 1625, 1599, 1566, 1526, 1499, 1445, 1356, 1237, 1188, 1034, 891, 749, 690; $^1$H NMR: (300 MHz, DMSO-d$_6$) $\delta$: 7.12(t, $J = 7.35$ Hz, 1H, 1ArH), 7.40(t, $J = 7.8$ Hz, 2H, 2ArH), 7.49–7.65(m, 2H, H-5, H-6), 7.72(d, $J = 8.1$ Hz, 2H, 2ArH), 8.09(d, $J = 8.1$ Hz, 1H, H-4), 8.20(d, $J = 7.8$ Hz, 1H, H-7), 8.64(br, 1H, NH), 8.76(br, 1H, NH), 8.76(br, 1H, NH), 11.08 (s, 1H, NH); $^{13}$C NMR: (75 MHz, DMSO-d$_6$) $\delta$: 91.1, 119.4, 122.9, 123.7, 123.9, 126.6, 126.9, 129.1, 135.9, 139.3, 152.9, 168.7, 169.6, 170.6, 171.3; FABMS: 353 (MHI$^+$.)

2.4. 2-(4-Amino-2-(4-chlorophenylamino)thiazol-5-oyl)benzothiazole 4b

Yield 59%, m.p. 335–38°C Analysis: Found: C, 52.57; H, 2.79; N, 14.65%; Calc. for C$_{17}$H$_{12}$ClN$_4$O$_5$S$_2$ (386.88): C, 52.77; H, 2.87; N, 14.48%; IR (KBr) cm$^{-1}$: 3461, 3272, 3210, 3136, 3083, 1634, 1605, 1526, 1492, 1465, 1357, 1256, 1189, 1093, 892, 825, 757, 667; $^1$H NMR: (300 MHz, DMSO-d$_6$) $\delta$: 7.44(d, $J = 9$ Hz, 2H, 2ArH), 7.51–7.67(m, 2H, H-5, H-6), 7.76(d, $J = 8.7$ Hz, 2H, 2ArH), 8.10(d, $J = 7.8$ Hz, 1H, H-4), 8.21(d, $J = 7.8$ Hz, 1H, H-7), 8.69(br, 1H, NH), 8.72(br, 1H, NH), 11.18 (s, 1H, NH); FABMS: 387 (MHI$^+$.)

2.5. 2-(4-Amino-2-(4-methoxyphenylamino)thiazol-5-oyl)benzothiazole 4c

Yield 63%, m.p. 254–55°C Analysis: Found: C, 56.30; H, 3.75; N, 14.80%; Calc. for C$_{18}$H$_{14}$N$_4$O$_5$S$_2$ (382.46): C, 56.52; H, 3.69; N, 14.65%; IR (KBr) cm$^{-1}$: 3455, 3293, 3187, 3067, 2931, 2842, 1617, 1537, 1468, 1324, 1261, 1186, 1102, 1026, 897, 828, 755, 728, 690; $^1$H NMR: (300 MHz, DMSO-d$_6$) $\delta$: 3.76(s, 3H, OCH$_3$), 6.98(d, $J = 9$ Hz, 2H, 2ArH), 7.47–7.66(m, 4H, H-5, H-6, 2ArH), 8.08(d, $J = 7.8$ Hz, 1H, H-4),

![Figure 1](image-url) Dendrodoine.
8.19(d, J = 7.5 Hz, 1H, H-7), 8.57(br, 1H, NH), 8.78(br, 1H, NH), 10.92(s, 1H, NH); FABMS: 383 (MH+).

2.6. 2-[4-Amino-2-(4-ethoxyphenylamino)thiazol-5-oyl]benzothiazole 4e

Yield 60%, m.p. 282–85 °C Analysis: Found: C, 57.84; H, 3.73; N, 15.43%; Calc. for C_{17}H_{12}N_{4}O_{2}S_2 (366.46): C, 58.99; H, 3.85; N, 15.29%; IR (KBr) cm⁻¹: 3454, 3279, 3130, 3082, 2927, 2861, 1625, 1526, 1465, 1357, 1256, 1189, 1020, 831, 763, 729; ¹H NMR: (300 MHz, DMSO-d₆) δ: 7.49–7.68(m, 4H, H-5, H-6, 2ArH), 8.09(d, J = 6 Hz, 1H, H-7), 8.56(br, 1H, NH), 8.76(br, 1H, NH), 10.89(s, 1H, NH); FABMS: 367 (MH+).

2.7. 2-[4-Amino-2-(4-methylphenylamino)thiazol-5-oyl]benzothiazole 4f

Yield 65%, m.p. 282–85 °C Analysis: Found: C, 57.80; H, 4.18: N, 14.36%; Calc. for C_{17}H_{12}N_{4}O_{2}S_2 (366.46): C, 57.55; H, 4.07; N, 14.13%; IR (KBr) cm⁻¹: 3454, 3279, 3130, 3082, 2927, 2861, 1625, 1479, 1454, 1324, 1255, 1175, 1104, 1054, 899, 831, 763, 729; ¹H NMR: (300 MHz, DMSO-d₆) δ: 7.49–7.68(m, 4H, H-5, H-6, 2ArH), 8.08(d, J = 6 Hz, 1H, H-7), 8.56(br, 1H, NH), 8.76(br, 1H, NH), 10.89(s, 1H, NH); FABMS: 397 (MH+).

3. Results and discussion

For the synthesis of 2-(4-amino-2-arylaminothiazol-5-oyl)benzothiazoles 4, as the novel analogs of the cytotoxic marine alkaloid dendrodoine, [4+1] heterocyclization (Scheme 2) reaction is adopted. In this [4+1] heterocyclization thiourea derivatives (Rajasekharan et al., 1998; Devi and Rajasekharan, 2002) 2a-d provide four ring atoms for the thiazole ring construction and thus act as [C–N–C–S] skeletons of the 4-NH₂ group appear as a broad singlet. Moreover, in the case of the corresponding indole derivatives (Abbs Fen Reji et al., 1996). Two broad singlets due to one hydrogen each is seen at δ 8.64 and 8.76 are attributed to the two hydrogens attached to H-4 and H-7 of the benzothiazole ring respectively (Stevens et al., 1996). Two broad singlets due to one hydrogen each is seen on δ 8.64 and 8.76 are attributed to the two hydrogen doublets at δ 7.72. The two hydrogen doublets at δ 8.09 and 8.20 have been attributed to H-4 and H-7 of the benzothiazole ring respectively (Stevens et al., 1996). Two broad singlets due to one hydrogen each is seen at δ 8.64 and 8.76 are attributed to the two hydrogens attached to the nitrogen of the 4-NH₂ group. The one-hydrogen singlet at δ 11.08 has been ascribed to NH hydrogen of the NHR group.

In the ¹H NMR (300 MHz, DMSO-d₆) spectrum, the aromatic hydrogen para to NH group gives rise to a triplet at δ 7.12. The two-hydrogen triplet at δ 7.40 has been assigned to two aromatic hydrogens meta to NH group. The triplet at δ 7.49–7.65 is assignable to H-5 and H-6 of the benzothiazole ring. The two aromatic hydrogens in the ortho position of NH group produce a two-hydrogen doublet at δ 7.72. The two hydrogen doublets at δ 8.09 and 8.20 have been attributed to H-4 and H-7 of the benzothiazole ring respectively (Stevens et al., 1996). Two broad singlets due to one hydrogen each is seen at δ 8.64 and 8.76 are attributed to the two hydrogens attached to the nitrogen of the 4-NH₂ group. The one-hydrogen singlet at δ 11.08 has been ascribed to NH hydrogen of the NHAr group.

The FAB MS shows a strong MH+ peak at m/z 353, which confirms the molecular mass of the compound to be 352 in accordance with the elemental analysis data. The ¹³C NMR spectrum shows fifteen peaks, two of which appear to arise from two-carbon each, thus accounting for all the seventeen carbons. Based on the above data, the compound is formulated as 2-(4-amino-2-phenylthiazol-5-oyl)benzothiazole 4a.

From the results the reaction pathway can be depicted in Scheme 3.

The presence of two signals in the ¹H NMR spectrum of 4a at δ 6.78 and 8.64 arising from the NH₂ hydrogens shows that the two hydrogens are not exchanging rapidly on the chemical shift time scale and they are in two different chemical environments. This NMR observation is in contrast with that seen in the case of the corresponding indole derivatives (Abbs Fen Reji and Rajasekharan, 2008). In those cases, the two hydrogens of the 4-NH₂ group appear as a broad singlet. Moreover, such two different signals for the two amino hydrogens have not been observed in the case of aminothiazolyl phenyl or thienyl ketones (Rajasekharan et al., 1998; Devi and Rajasekharan, 2002). An energy minimized structure obtained using MOPAC by the AM1 method is shown below in two different ways (Figs. 2 and 3). These computed structures show that one of the two hydrogens of the amino group may be involved in a strong hydrogen bond with a ring-nitrogen of the benzothiazole ring due to the very close proximity as can be observed in the figures. Further,
Scheme 3  Mechanism for the formation of 4.

Figure 2  Energy minimized structure of 4a.

Figure 3  Energy minimized structure of 4a.
the 4-amino group may also have some amide like character since it can be viewed as a vinylogous amide –CO–C5–NH2, thus somewhat restricting the rotation along C4-[exocyclic N] bond. Such vinylogous amides as well as amides of the type Ar–CH=CH–CO–NH2 are known to show two amide NH signals each due to one hydrogen in a situation that is reminiscent of the non-equivalence of the two methyls in NMR spectrum of N,N-dimethylformamide (Sanders et al., 1989).

In cases where DMSO-d6 had been the NMR solvent, the 4-amino hydrogens appeared as two well separated signals in 2-(4-amino-2-arylaminothiazol-5-oyl)benzothiazole 4a–e. The absence of the amino hydrogen signals due to chemical exchange has been observed whenever CDCl3 had been the NMR solvent. The hydrogens of the 4-NH2 group were not seen, probably due to the chemical exchange with moisture in the CDCl3 solvent (Abbs Fen Reji and Rajasekharan, 2008).

4. Conclusion

The replacement of a thiazole ring and benzothiazole ring in place of the 1,2,4-thiadiazole ring and indole ring respectively in dendrodoine 1 results in 2-(4-amino-2-arylaminothiazol-5-oyl)benzothiazole 4a–e, as the analogs. To the best of knowledge, all the synthesized analogs of dendrodoine 1 are new and should have cytotoxic activity. The presence of two signals in the 1H NMR spectrum of arising from the NH2 hydrogens due to the involvement of a strong hydrogen bond with a ring-nitrogen of the benzothiazole ring due to the very close proximity has been observed.

References