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Note

2-(2-Alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles: Synthesis and the effect of intra molecular H-bonding in ^{1}H NMR

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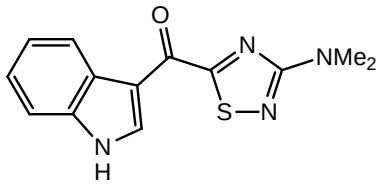
2-(2-Alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles, as the analogs of the cytotoxic marine alkaloid dendrodoine, is synthesized and characterized by elemental analysis, IR, NMR and mass spectral data. The thiourea derivatives provide four ring atoms for the thiazole ring construction and thus act as [C-N-C-S] synthons. The remaining carbon of the thiazole is sourced from 2-(2-bromoacetyl)-N-methylbenzimidazole. This [4+1] heterocyclization reaction is adopted for the synthesis of novel benzimidazole derivatives. The presence of two signals in the ^{1}H NMR spectrum arising from the NH_2 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.

Keywords: Analogs, dendrodoine, cytotoxic, thiazole, N-methylbenzimidazoles

Dendrodoine, 3-N,N-dimethylamino-5-indol-3-oyl-1,2,4-thiadiazole **1** is a marine alkaloid isolated[1] from the tunicate *Dendrodoa grossularia*. It contains a 1,2,4-thiadiazole unit, quite uncommon either in terrestrial or in marine natural products. Dendrodoine also belongs to the indole class of marine alkaloids. Dendrodoine has been reported to be cytotoxic to lymphoma cells L1210 in culture[1,2].

Benzimidazole shares several structural features with indole. In addition, benzimidazoles exhibit several significant biological activities just as indoles. The literature survey shows several examples of compounds having a benzimidazole ring which exhibit remarkable bioactivity[3-17]. The N-substituted benzimidazoles also show bioactivities that could make them potentially useful in the treatment of cancer and cardiovascular diseases[18]. The above survey amply demonstrates the significance of benzimidazole unit as a useful pharmacophore moiety. Such derivatives possess anticancer[3,4,14,15,18], anti-inflammatory[5,6,11,12], antibacterial[5,8-10,14,15], anti-fungal[5,8-10,14,15], antidiabetic[14,15] and anti-HIV activities[13-15]. On the basis of this observation it was decided to develop a route to diaminothiazoloyl-benzimidazoles as hitherto unreported analogs of dendrodoine by replacing the indole ring by a benzimidazole ring.



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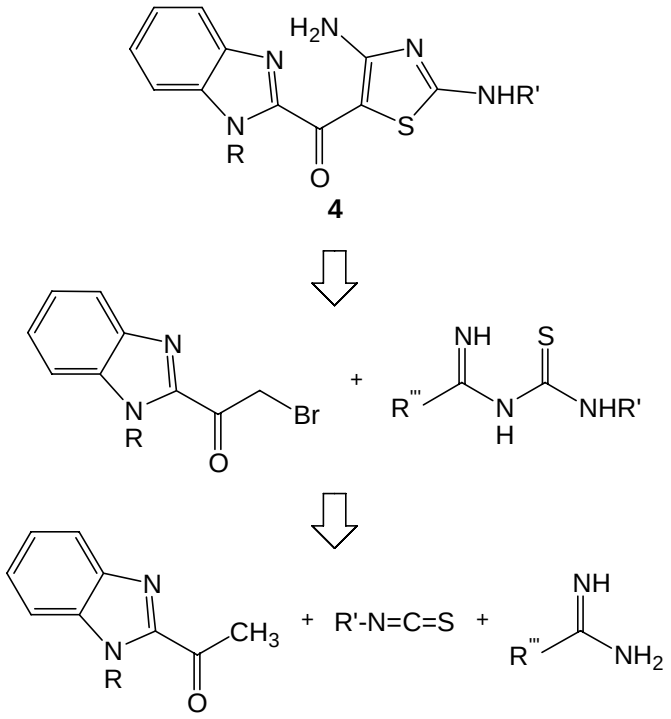
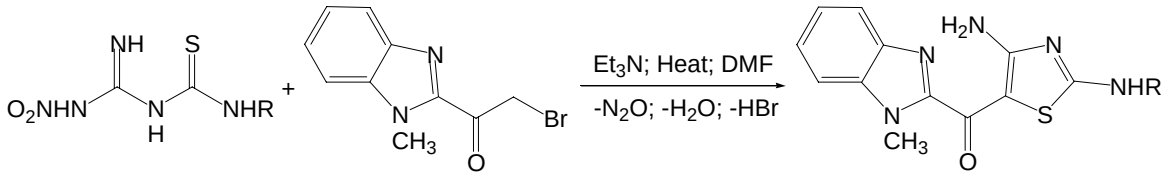
The route to the synthesis of novel analogs of dendrodoine was based on retrosynthesis, which is outlined in **Scheme I**.

Results and Discussion

The thiourea derivatives[19-21] **2a-e** 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)-N-methyl-benzimidazole. This [4+1] heterocyclization reaction is now adopted for the synthesis of novel benzimidazole derivatives. Thus the reaction of 1-ethyl-3-(N-nitroamidino)thiourea **2a** in N,N-dimethylformamide (DMF) with 2-(2-bromoacetyl)-N-methylbenzimidazole **3** afforded a yellow microcrystalline compound which showed up in the thin layer chromatogram (TLC) as a single fluorescent yellow spot, indicating the formation of only one major product (**Scheme II**). Based on the elemental analysis, the molecular composition of the compound was found to be $C_{14}H_{15}N_5OS$. The IR (KBr) spectrum shows the bands at 3333, 3237 and 3144 cm^{-1}, which have been identified as ν_{N-H} vibrations. The band at 3043 cm^{-1} is assignable to ν_{C-H} vibration of the aromatic system. The aliphatic ν_{C-H} bands are observed at 2967, 2875



Scheme I — Retrosynthesis of 2-(2-alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles **4**



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2a: R = -CH_2CH_3
2b: R = -$CH_2CH_2CH_3$
2c: R = -$CH(CH_3)_2$
2d: R = -$CH_2CH_2CH_2CH_3$
2e: R = -$CH_2CH{=}CH_2$

3

4

4a: R= -CH_2CH_3
4b: R = -$CH_2CH_2CH_3$
4c: R = -$CH(CH_3)_2$
4d: R = -$CH_2CH_2CH_2CH_3$
4e: R = -$CH_2CH{=}CH_2$

Scheme II — Synthetic route for molecule **4**

and 2800 cm^{-1}. The conjugated carbonyl group shows a band at 1620 cm^{-1}.

The ^1H NMR (300 MHz, DMSO-d_6) spectrum of the compound shows a three-hydrogen triplet at δ 1.16, which is due to the methyl group. The broad peak of two hydrogens, not well resolved, at δ 3.32 has been assigned to the methylene hydrogens. The methyl group of N-methylbenzimidazole ring appears as a singlet at δ 4.16. The multiplet at δ 7.23-7.41 is due to H-5 and H-6 of the N-methylbenzimidazole ring. The two one-hydrogen doublets at δ 7.62 and 7.70 arise from H-7 and H-4 of the N-methylbenzimidazole ring respectively. The broad peak at δ 8.05 has been attributed to the NH hydrogen of the NHR group. The two 4-NH_2 hydrogens appear as two broad singlets at δ 8.67 and 8.73.

The FAB MS shows strong MH^+ as well as M^+ peaks at *m/z* 302 and 301 respectively, which supports the molecular mass of the sample to be 301 in accordance with the elemental analysis data. The ^{13}C NMR gives fourteen peaks, thus accounting for all the fourteen carbon atoms. Based on the above evidence, the compound was identified as 2-(4-amino-2-ethylaminothiazol-5-oyl)-N-methylbenzimidazole **4a**.

The presence of two signals in the ^{1}H NMR spectrum of **4a** arising from the NH_2 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[22]. In those cases, the two hydrogens of the 4-NH_2 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[19-21]. An energy minimized structure obtained using MOPAC by the AM1 method is shown below in two different views (**Figure 1** and **2**).

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 benzimidazole ring due to the very close proximity as can be observed in **Figure 1** and **2**. Further, the 4-amino group may also have some amide like character since it can be viewed as a vinylogous amide -CO-C5=C4-NH_2, thus somewhat restricting the rotation along C4-[exocyclic N] bond. Such vinylogous amides as well as amides of the type Ar-CH=CH-CO-NH_2 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[23].

Figure 1 — Energy minimized structure of **4a**

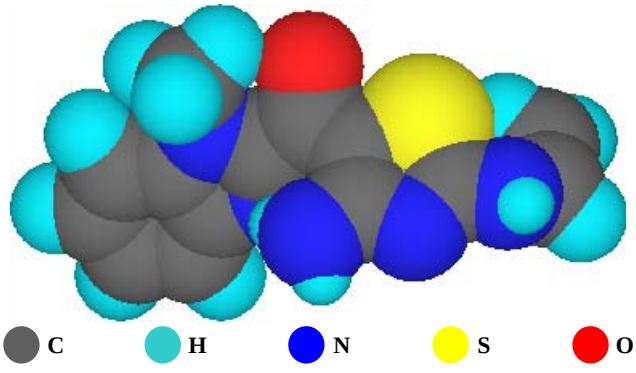

Figure 2 — Energy minimized structure of **4a**

In cases where DMSO-d_6 had been the NMR solvent, the 4-amino hydrogens appeared as two well separated signals in 2-(2-alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles **4a-e**. The absence of the separated amino hydrogen signals due to chemical exchange has been observed whenever $CDCl_3$ had been the NMR solvent. The hydrogens of the 4-NH_2 group were not seen, probably due to the chemical exchange with moisture in the $CDCl_3$ solvent.

Experimental Section

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 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. Elemental analysis was done at Central Drug Research Institute, Lucknow, India.

General procedure for the synthesis of 2-(2-alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles, 4a-e

A solution of 2-(2-bromoacetyl)-N-methylbenzimidazole **3** (0.254 g, 1 mmole) which was prepared from 2-(1-hydroxyethyl)benzimidazole[24,25], in DMF (2 mL) was added to a solution of 1-alkyl-3-(N-nitroamidino)thiourea (1 mmole) in DMF (2 mL). The reaction mixture was stirred well and triethylamine (0.15 mL, 1 mmole) 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. The yellow precipitate thus obtained was filtered, washed with water and dried. The crude product was purified from methanol-water (2:1) and then from benzene-petroleum ether (1:1) to give a yellow micro crystalline solid.

2-(4-Amino-2-ethylaminothiazol-5-oyl)-N-methylbenzimidazole, 4a

Yield 50%, m.p. 208-14°C. Anal. Found: C, 55.92; H, 5.15; N, 23.45. Calcd for $C_{14}H_{15}N_5OS$ (301.37): C, 55.79; H, 5.02; N, 23.24%. IR (KBr): 3333, 3237, 3144, 3043, 2967, 2875, 2800, 1620, 1552, 1531, 1445, 1404, 1336, 1243, 1138, 1091, 1047, 946, 743, 612 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.16(t,

J = 7.2 Hz, 3H, CH_3), 3.32(broad, 2H, CH_2), 4.16(s, 3H, N-CH_3), 7.23-7.41(m, 2H, H-5, H-6), 7.62(d, J = 8.1 Hz, 1H, H-7), 7.70(d, J = 8.1 Hz, 1H, H-4), 8.05 (broad, 1H, NH), 8.67(broad, 1H, NH), 8.73(broad, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 14.60, 32.24, 43.42, 98.40, 110.08, 121.02, 122.92, 124.38, 127.36, 136.87, 141.47, 167.34, 172.74, 176.35; FABMS: *m*/z 302 (MH^+), 301 (M^+).

2-[4-Amino-2-(*n*-propyl)aminothiazol-5-oyl]-N-methylbenzimidazole, 4b

Yield 50%, m.p. 187°C. Anal. Found: C, 57.28; H, 5.52; N, 22.10. Calcd for $C_{15}H_{17}N_5OS$ (315.39): C, 57.11; H, 5.43; N, 22.21%. IR (KBr): 3342, 3252, 3157, 3033, 2967, 2932, 2866, 1620, 1526, 1438, 1330, 1236, 1094, 936, 737, 616 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.90(t, J = 7.35 Hz, 3H, CH_3), 1.57(sextet, J = 7.1 Hz, 2H, CH_2), 3.27(broad, 2H, CH_2), 4.17(s, 3H, N-CH_3), 7.23-7.40(m, 2H, H-5, H-6), 7.63(d, J = 7.5 Hz, 1H, H-7), 7.70(d, J = 7.8 Hz, 1H, H-4), 8.10(broad, 1H, NH), 8.70(broad, 1H, NH), 8.76(broad, 1H, NH); FABMS: *m/z* 316 (MH^+), 315 (M^+).

2-[4-Amino-2-(isopropyl)aminothiazol-5-oyl]-N-methylbenzimidazole, 4c

Yield 52%, m.p. 229-30°C. Anal. Found: C, 57.01; H, 5.58; N, 22.43. Calcd for $C_{15}H_{17}N_5OS$ (315.39): C, 57.11; H, 5.43; N, 22.21%. IR (KBr): 3326, 3218, 3157, 2962, 1627, 1593, 1558, 1518, 1445, 1371, 1330, 1239, 1162, 1088, 939, 737 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 1.18(d, J = 6.6 Hz, 6H, $2CH_3$), 3.48(broad, 1H, CH), 4.16(s, 3H, N-CH_3), 7.21-7.39(m, 2H, H-5, H-6), 7.62(d, J = 8.1 Hz, 1H, H-7), 7.69(d, J = 7.8 Hz, 1H, H-4), 8.04(broad, 1H, NH), 8.62(broad, 1H, NH), 8.76(broad, 1H, NH); FABMS: *m/z* 316 (MH^+), 315 (M^+).

2-[4-Amino-2-(*n*-butyl)aminothiazol-5-oyl]-N-methylbenzimidazole, 4d

Yield 70%, m.p. 175-76°C. Anal. Found: C, 58.18; H, 5.97; N, 21.03. Calcd for $C_{16}H_{19}N_5OS$ (329.42): C, 58.33; N, 5.81; N, 21.26%. IR (KBr): 3336, 3252, 3151, 3063, 2935, 2867, 1620, 1549, 1438, 1336, 1155, 1101, 928, 898, 743, 614 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6): δ 0.88(t, J = 7.35 Hz, 3H, CH_3), 1.33(sextet, J = 7.32 Hz, 2H, CH_2), 1.53(quintet, J = 7.05 Hz, 2H, CH_2), 3.47(broad, 2H, CH_2), 4.15(s, 3H, N-CH_3), 7.23-7.40(m, 2H, H-5, H-6), 7.62(d, J = 7.8 Hz, 1H, H-7), 7.69(d, J = 7.8 Hz, 1H, H-4), 8.04 (broad, 1H, NH), 8.68(broad, 1H, NH), 8.70(broad, 1H, NH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 13.64, 19.94, 31.21, 32.22, 45.18, 95.45, 110.07, 120.99, 122.91, 124.36, 127.35, 136.86, 141.46, 167.31, 172.72, 176.32; FABMS: *m/z* 330 (MH^+), 329 (M^+).

2-[2-Allylamino-4-aminothiazol-5-oyl]-N-methylbenzimidazole, 4e

Yield 65%, m.p. 180-82°C. Anal. Found: C, 57.63; H, 4.90; N, 22.14. Calcd for $C_{15}H_{15}N_5OS$ (313.38): C, 57.49; H, 4.82; N, 22.35%. IR (KBr): 3349, 3238, 3157, 3041, 2934, 2858, 1617, 1542, 1525, 1493, 1444, 1333, 1243, 1088, 933, 737, 614 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$): δ 4.02(s, 2H, CH_2), 4.25(s, 3H, N-CH_3), 5.20-5.41(m, 2H, CH_2), 5.85-6.04(m, 1H, CH), 6.42(broad, 1H, NH), 7.22-7.50(m, 3H, H-5, H-6, H-7), 7.86(d, J = 7.8 Hz, 1H, H-4); ^{13}C NMR (75 MHz, $CDCl_3$): δ 32.26, 47.60, 96.20, 110.05, 118.06, 121.14, 122.96 124.42, 127.44, 132.65, 136.94, 141.56, 167.08, 173.03, 176.15; FABMS: *m/z* 314 (MH^+), 313 (M^+).

Conclusion

The replacement of a thiazole ring and benzimidazole ring in place of the 1,2,4-thiadiazole ring and indole ring respectively in dendrodoine **1** results in 2-(2-alkylamino-4-aminothiazol-5-oyl)-N-methylbenzimidazoles **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 ^{1}H NMR spectrum of arising from the NH_2 hydrogens due to the involvement of a strong hydrogen bond with a ring-nitrogen of the benzimidazole ring due to the very close proximity has been observed.

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