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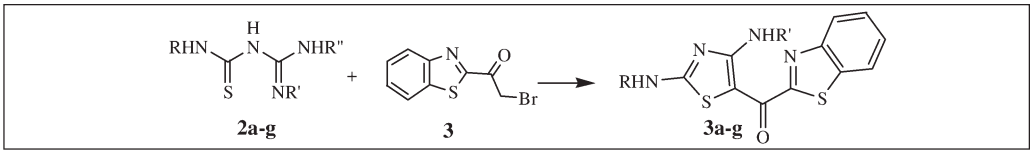

The synthesis of 2-(4-amino-2-alkylaminothiazol-5-oyl)benzothiazoles and 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles as benzothiazoloylthiazole analogs of the cytotoxic marine alkaloid dendrodoine is reported. The highly decorated thiazole ring assembly was achieved using 2-bromoacetybenzothiazole to supply the C5 ring carbon and amidinothioureas of the type $R^1NH—CS—NH—C(=NHR^2)—(NHR^3)$ to provide the four ring atoms [C4—N3—C2—S1] in a [4+1] thiazole ring construction strategy. The antibacterial activity of these new analogs is reported.

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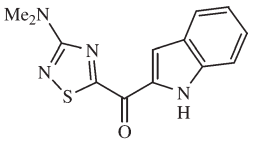
INTRODUCTION

A recent review [1] on marine pigments highlights the rich variety of colored molecules that can be found in marine organisms. These pigments have structures that in many instances have no counterpart in any terrestrially derived molecules. Many among these are alkaloidal pigments. One among these, the pale yellow, bisheterocyclic, cytotoxic alkaloid dendrodoine, 3-*N*,*N*-dimethylamino-5-indol-3-oyl-1,2,4-thiadiazole 1, isolated from the tunicate *Dendrodoa grossularia* [2], is considered unique in being the first and only naturally occurring 1,2,4-thiadiazole derivative [1]. It is reported to be cytotoxic to lymphoma cells L1210 in culture [2,3].



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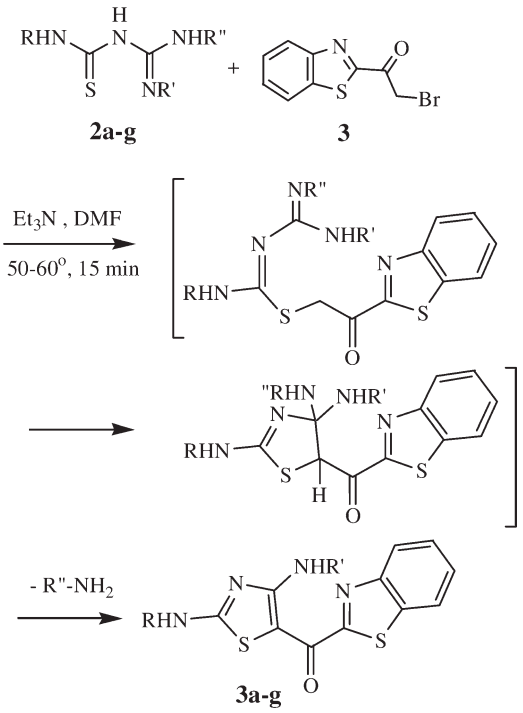
We have recently been interested in synthesizing [4] and cytotoxicity screening [5] of thiazole analogs of dendrodoine in the light of its reported cytotoxicity and the difficulty in its synthesis [6]. Two approaches were adopted by us; in the first, to overcome the limited opportunity for substitution positions in the 1,2,4-thiadiazole ring, it was replaced by a 1,3-thiazole ring [4a]. In the second, the indoloyl unit was varied to other benzofused heterobicyclic rings [7]. This allowed us to introduce much structural diversity leading to a large portfolio of dendrodoine analogs. We were also enthused by the recently reported *in vitro* cytotoxicity of bis(indolyl)thiazoles [8] and indolylthiazoles [9]. Further, noting the remarkable cytotoxic activity of benzothiazole derivatives as reviewed recently [10,11], we decided to extend our work on the synthesis and bioactivity screening of dendrodoine analogs to 2-(2,4-diaminothiazol-5-oyl)benzothiazoles.

RESULTS AND DISCUSSION

Several modifications of the classic Hantzsch 2-aminothiazole synthesis have recently been developed for the direct ring assembly of highly decorated thiazole derivatives. Among such methods, the use cyanothioureas [12,13] RNH—CS—NH—CN, our reports [14–16] on the use of amidinothioureas RNH—CS—NH—C(=NH)—NH_2 and RNH—CS—NH—C(=NH)—$NHNO_2$, or the recent use of *S*-alkyldithiobiurets [17] RNH—CS—NH—C(SR)—NH_2, as the source of the four [S1—C2—N3—C4] ring atoms for the thiazole ring construction are noteworthy. The remaining ring C5 atom could be sourced from α-haloketones, which reacted with the above thioureas to afford 4-amino-5-acyl-2-(substituted amino)thiazoles. Nevertheless, our report [14,16] on the use of amidinothioureas of the type $R^1NH—CS—NH—C(=NHR^2)—(NHR^3)$ seems to be the only direct ring synthesis of 5-acyl-2,4-bis(substituted amino)thiazoles. Based on these considerations, we have now chosen the reaction between the amidinothiourea derivatives **2a–g** and 2-(2-bromoacetyl)benzothiazole 3 to access hitherto unreported 2-(4-amino-2-alkylaminothiazol-5-oyl)benzothiazoles and 2-[2,4-bis(arylamino)thiazol-5-oyl]benzothiazoles.

Accordingly, the reaction of 1-ethyl-3-(*N*-nitroamidino)thiourea 2a in *N*,*N*-dimethylformamide (DMF) with 2-(2-bromoacetyl)benzothiazole 3 afforded a yellow

Scheme 1



2a, 4a: R = C_2H_5, R' = H, R"= NO_2;
2b, 4b: R = *n*-C_3H_7, R' = H, R"= NO_2;
2c, 4c: R = *n*-C_4H_9, R' = H, R"= NO_2;
2d, 4d: R = Allyl, R'= H, R"= NO_2;
2e, 4e: R = R'=C_6H_5, R"=H;
2f, 4f: R = R' = 4-ClC_6H_5, R"=H;
2g, 4g: R = R' = 4-MeC_6H_5, R"=H

crystalline compound which showed in the thin layer chromatogram a single fluorescent yellow spot. Based on the elemental analysis, the molecular composition of the compound was found to be $C_{13}H_{12}N_4OS_2$. The IR spectrum shows distinct bands at 3467, 3285, 3233, and 3175 cm^{-1}, which are ascribed to ν_{N-H} vibrations. The aliphatic C—H stretching bands were seen at 2972, 2928, and 2850 cm^{-1} and a strong band at 1623 cm^{-1} indicated the presence of a conjugated carbonyl group. The ^{1}H NMR spectrum consisted of a three-hydrogen triplet at δ 1.18, due to methyl hydrogens. The peak due to the methylene hydrogens could not be seen as it appeared to be submerged in the broad solvent-based peak. The multiplet at δ 7.45–7.62 was assignable to the H-5 and H-6 of the benzothiazole ring. The two one-hydrogen doublets at δ 8.07 and 8.16 were attributed to H-4 and H-7 of the benzothiazole ring, respectively. The broad peak at δ 8.39 was due to the NH hydrogen of the NHR group. The FAB MS showed a strong MH^+ peak at m/z 305. Based on these, the compound was formulated as 2-(4-amino-2-ethylaminothiazol-5-oyl)benzothiazole **4a**; the reaction steps involved in its formation

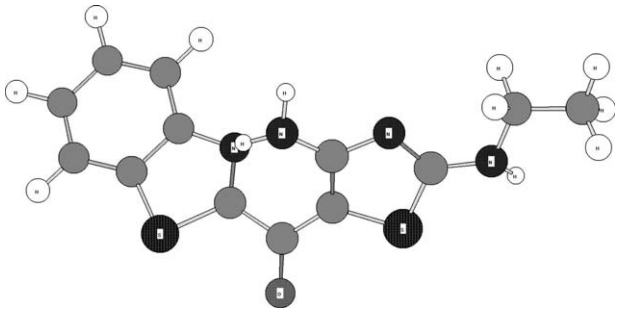


Figure 1. Energy minimized structure of **4a**.

is presented in Scheme 1. Three other thiazoloylbenzothiazoles **4b–d** were also synthesized. An interesting feature of the ^{1}H NMR spectrum of **4a–d** was the appearance of the two hydrogens of the 4-amino group as two well separated broad singlets. For example, in the case of **4a**, these hydrogens were seen at δ 8.78 and 8.94. The results of energy minimized computations on **4a** obtained using MOPAC by the AM1 method are shown in Figure 1. These computed structures showed that one of the two hydrogens of the amino group could be strongly hydrogen bonded to the ring nitrogen of the benzothiazole unit. In addition, the 4-amino group in **4a** could also be amide like as it could be viewed as a vinylogous amide —CO—C^5=C^4—NH_2, which would also impede the rotation of the C^4—N bond.

Next, 1-phenyl-3(*N*,*N*′-diphenylamidino)thiourea **2e** was reacted with **3** to obtain a deep yellow compound with molecular composition $C_{23}H_{16}N_4OS_2$. Based on the FAB-MS, ^{1}H and ^{13}C NMR spectra, the structure of the compound was assigned as 2-[2,4-bis(phenylamino)thiazol-5-oyl]benzothiazole **4e**. In a similar reaction, two other 2-[2,4-diarylaminothiazol-5-oyl]benzothiazoles **4f–g** were also obtained.

To assess the bioactivity, the benzothiazoles **4a–g** were screened against the bacterial strains *Escherichia coli, Salomonella typhi*, *Staphylococcus aureus*, and *Bacillus subtilis* and the results are shown in Table 1.

Table 1

Antibacterial activity of benzothiazoloylthiazoles **4a–g**.

Compound	*E. coli*	*S. typhii*	*S. aureus*	*B. subtilis*
4a	9	8	7	7
4b	7	7	NA	NA
4c	7	8	NA	NA
4d	10	10	NA	NA
4e	8	7	6	NA
4f	8	8	10	10
4g	6	8	NA	NA
Penicillin G	12	12	13	12

Values are in diameter of zone of inhibition (mm) and average of three replicates.
NA, Not active.

EXPERIMENTAL

Melting points are uncorrected and were determined by open capillary method using an immersion bath of silicon oil. Thin layer chromatography was performed using silica gel-G (E. Merck, India) coated on glass plates. The spots were visualized in iodine vapour or under UV light. 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 fot IR spectra. Reagents and solvents were from Merck India and Fluka. Elemental analysis was done at Central Drug Research Institute, India. The antibacterial acticity was evaluated by the Kirby-Baur method [18].

General procedure for the synthesis of 2-(2,4-diaminothiazol-5-oyl)benzothiazoles (4a–g). A solution of 2-(2-bromoacetyl)benzothiazole **3** (0.254 g, 1 mmol), obtained from 2-(1-hydroxyethyl)benzothiazole [19,20], in DMF (2mL) was added to 1-alkyl-3-(*N*-nitroamidino)thiourea (**2a–d**) or 1-aryl-3-(*N*,*N*′-diarylamidino)thiourea (**2e–g**) (1 mmol) in DMF (2 mL). The reaction mixture was stirred well and triethylamine (0.3 mL, 2 mmol) was added and warmed at 50–60°C for 15 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 by crystallization from methanol–water (2:1), then from benzene–petroleum ether (1:1) in the case of **4a–d**, and from ethanol–water (3:1) in the case of **4e–g**.

2-(4-Amino-2-ethylaminothiazol-5-oyl)benzothiazole (4a). Yield: 65%, m.p. 255–256°C; *Anal*. found: C, 51.41: H, 3.90: N, 18.55%; calcd. for $C_{13}H_{12}N_4OS_2$ (304.39): C, 51.29: H, 3.97: N, 18.41%; IR (KBr) ν: 3467, 3285, 3233, 3175, 3067, 2972, 2928, 2850, 1623, 1592, 1558, 1450, 1351, 1093, 882, 818, 757, 722cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ: 1.18(t, J = 7.0 Hz, 3H, CH_3), 3.35(br, 2H, CH_2), 7.45–7.62(m, 2H, H-5, H-6), 8.07(d, J = 7.8 Hz, 1H, H-4), 8.16(d, J = 7.8 Hz, 1H, H-7), 8.39(br, 1H, NH), 8.78(br, 1H, NH), 8.94(br, 1H, NH); FABMS: 305 (MH^+).

2-[4-Amino-2-n-propylaminothiazol-5-oyl]benzothiazole (4b). Yield: 63%, m.p. 211–213°C; *Anal*. found: C, 52.95: H, 4.58: N, 17.45%; calcd. for $C_{14}H_{14}N_4OS_2$ (318.42): C, 52.80: H, 4.43: N, 17.60%; IR (KBr) ν: 3360, 3218, 3134, 3067, 2967, 2933, 2867, 1639, 1592, 1552, 1506, 1472, 1357, 1155, 1093, 891, 823, 778, 683, 622cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.91(t, J = 7.4 Hz, 3H, CH_3), 1.58(sextet, J = 6.7 Hz, 2H, CH_2), 3.38(br, 2H, CH_2), 7.45–7.63(m, 2H, H-5, H-6), 8.06(d, J = 6.9 Hz, 1H, H-4), 8.16(d, J = 7.5 Hz, 1H, H-7), 8.40(br, 1H, NH), 8.79(br, 1H, NH), 8.95(br, 1H, NH); ^{13}C NMR: (75 MHz, , DMSO-d_6) δ: 11.3, 21.9, 39.2, 91.1, 122.8, 123.8, 126.4, 126.8, 135.8, 139.3, 153.1, 169.5, 170.6, 171.3; FABMS: 319 (MH^+).

2-[4-Amino-2-n-butylaminothiazol-5-oyl]benzothiazole (4c). Yield: 65%, m.p. 182–185°C; *Anal*. found: C, 54.33: H, 4.93: N, 16.59; calcd. for $C_{15}H_{16}N_4OS_2$ (332.44): C, 54.19: H, 4.85: N, 16.85%; IR (KBr) ν: 3352, 3279, 3198, 3162, 3050, 2962, 2917, 2858, 1634, 1600, 1539, 1465, 1357, 1309, 1152, 1081, 891, 818, 771, 737, 612cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 0.90(t, J = 7.4 Hz, 3H, CH_3), 1.35(sextet, J = 7.3 Hz, 2H, CH_2), 1.51(quintet, J = 7.1 Hz, 2H, CH_2), 3.33(br, 2H, CH_2), 7.45–7.64(m, 2H, H-5, H-6), 8.06(d, J = 7.8 Hz, 1H, H-4), 8.17(d, J = 7.5 Hz, 1H, H-7), 8.42(br, 1H, NH), 8.92(br, 1H, NH), 9.00(br, 1H, NH); FABMS: 333 (MH^+).

2-[2-Allylamino-4-aminothiazol-5-oyl]benzothiazole (4d). Yield: 63%, m.p. 254–255°C; *Anal*. found: C, 53.29: H, 3.91: N, 17.57%; calcd. for $C_{14}H_{12}N_4OS_2$ (316.40): C, 53.14: H, 3.82: N, 17.71%; IR (KBr) ν: 3486, 3299, 3238, 3083, 3050, 2967, 2933, 2894, 2842, 1626, 1599, 1565, 1506, 1458, 1322, 1094, 1013, 958, 891, 825, 764, 729cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 4.02(m, 2H, CH_2), 5.11–5.32(m, 2H, CH_2), 5.82–6.00(m, 1H, CH), 7.45–7.64(m, 2H, H-5, H-6), 8.07(d, J = 7.8 Hz, 1H, H-4), 8.17(d, J = 7.5 Hz, 1H, H-7), 8.43(br, 1H, NH), 8.77(br, 1H, NH), 9.09(br, 1H, NH); FABMS: 317 (MH^+).

2-[2,4-Bis(phenylamino)thiazol-5-oyl]benzothiazole, (4e). Yield: 65%, m.p. 235–238°C; *Anal*. found: C, 64.31: H, 3.85: N, 13.25%; calcd. for $C_{23}H_{16}N_4OS_2$ (428.52): C, 64.46: H, 3.76: N, 13.08%; IR (KBr) ν: 3433, 3272, 3198, 3048, 1626, 1600, 1562, 1485, 1445, 1414, 1324, 1268, 912, 757, 690cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6) 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, J = 8.1 Hz, 2H, 2ArH), 8.12(d, J = 7.8 Hz, 1H, H-4), 8.23(d, J = 7.8 Hz, 1H, H-7), 11.85(s, 1H, NH); ^{13}C NMR: (75 MHz, , DMSO-d_6) δ: 91.1, 119.7, 120.1, 122.8, 123.7, 123.9, 124.3, 126.8, 127.0, 129.0, 129.2, 135.9, 138.7, 138.9, 152.8, 163.6, 169.6, 170.6, 172.1; FABMS: 429 (MH^+).

2,4-Bis(4-chlorophenylamino)thiazol-5-oylbenzothiazole, (4f). Yield: 65%, m.p. 258–259°C; *Anal*. found: C, 55.69: H, 2.99: N, 11.41%; calcd. for $C_{23}H_{14}Cl_2N_4OS_2$ (497.42): C, 55.53: H, 2.84: N, 11.26%; IR (KBr) ν: 3428, 3275, 3207, 3066, 1631, 1572, 1497, 1424, 1324, 1269, 1221, 1186, 1095, 1021, 923, 826, 756, 628cm^{-1}; ^{1}H NMR: (300 MHz, DMSO-d_6) δ: 7.41-7.79(m, 10H, H-5, H-6, 8ArH), 8.08(d, J = 9 Hz, 1H, H-4), 8.20(d, J = 9 Hz, 1H, H-7), 11.76(s, 1H, NH); FABMS: 497 (MH^+).

2,4-Bis(4-methylphenylamino)thiazol-5-oylbenzothiazole, (4g). Yield: 63%, m.p. 221–224°C; *Anal*. found: C, 65.51: H, 4.58: N, 12.53%; calcd. for $C_{25}H_{20}N_4OS_2$ (456.57): C, 65.76: H, 4.42: N, 12.27%; IR (KBr) ν: 3400, 3266, 3200, 3117, 3062, 2928, 2840, 1617, 1607, 1572, 1490, 1434, 1324, 1221, 1021, 923, 828, 764, 731, 620cm^{-1}; ^{1}H NMR: (300 MHz, $CDCl_3$) δ: 2.30(s, 6H, $2CH_3$), 7.02–7.75(m, 10H, H-5, H-6, 8ArH), 8.10(d, J = 7.8 Hz, 1H, H-4), 8.21(d, J = 7.5 Hz, 1H, H-7), 11.86(s, 1H, NH); FABMS: 457 (MH^+).

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