Synthesis of anticancer compounds 2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles

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Received 12 July 2011; accepted (revised) 7 March 2013

2-(2,4-Diaminothiazol-5-oyl)-N-methylbenzimidazoles have been 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 novel compounds show very good anticancer activity and moderate antibacterial activity.

Keywords: Dendrodoine, arylamino, thiazole, benzimidazoles, anticancer, antibacterial

For a natural product, either from terrestrial or from marine sources, dendrodoine 1, 3-N,N-dimethylamino-5-indol-3-oyl-1,2,4-thiadiazole, isolated from the “baked bean ascidian” or Dendrodoa grossularia, is unusual in that it incorporates a 1,2,4-thiadiazole ring. It has been shown to be cytotoxic in vitro and has been synthesized by a 1,3-dipolar cycloaddition of indoloyl cyanide to a nitrile sulfide obtained by the thermolysis of a 1,3,4-oxathiazol-2-one prepared from N,N-dimethylurea and chlorocarbonylsulphenyl chloride. This route is rather inflexible as it is confined solely to the preparation of 3-N,N-dialkylamino derivatives. In addition, the hetaroyl cyanides are difficult to access, thereby making the preparation of dendrodoine analogs with a variety of substituents difficult.

Moreover, the scope of the substituent manipulation in 1 is restricted due to the availability of only two carbons for substitution or functionalization in the 1,2,4-thiadiazole ring. Therefore the exchange of a 2-aminothiazole unit for the 3-amino-1,2,4-thiadiazole unit in dendrodoine seemed attractive.

Thus, the synthesis of several (2-N,N-dimethylaminothiazol-5-oyl) heterocyclics as thiazole analogs of dendrodoine and the cancer cell cytotoxicity of the indolyl derivative 2 at submicro molar concentration were reported recently.
modified suitably for accessing densely functionalized thiazole derivatives. For example, cyanothioureas of the type RNH-CS-NH-CN (Ref. 15), amidinothioureas of the type RNH-CS-NH-C(=NH)-NH2 (Ref. 16) or S-alkyldithiobiurets of the type RNH-CS-NH-C(SR)-NH2 (Ref. 17), reacts with α-haloketones to afford 4-amino-5-aroyl-2-(substituted amino)thiazoles. However, the use of amidinothioureas of the type R1NH-CS-NH-C(=NHR2)-(NHR2) (Ref. 5), as reported from this laboratory remains the only direct ring synthesis of 5-aroyl-2,4-bis(substituted amino)thiazoles. It is now reasoned that such amidinothiourea derivatives 6 would provide the four [S1-C2-N3-C4] ring atoms for the thiazole ring construction. The remaining ring atom C5 of the thiazole could be sourced from 2-(2-bromoacetyl)-N-methylbenzimidazole 5. This [4+1] heterocyclization reaction is now adopted for the synthesis of the novel N-methylbenzimidazole derivatives 7 (Scheme I).

Thus, the reaction of 3-(N-nitroamidino)-1-phenylthiourea 6a in N,N-dimethylformamide (DMF) with 2-(2-bromoacetyl)-N-methylbenzimidazole 5 afforded a compound which showed in the thin layer chromatogram (TLC) a single fluorescent yellow spot, indicating the formation of only one major product. Elemental analysis showed that the composition of the compound was C18H15N2OS. In the IR (KBr) spectrum, the peaks at 3474, 3400, 3233 and 3183 cm\(^{-1}\) arise from the \(\nu\)N-H vibration. The \(\nu\)C-H band of aromatic rings appears at 3050 cm\(^{-1}\). The bands at 2928 cm\(^{-1}\) and 2858 cm\(^{-1}\) are due to \(\nu\)C-H vibration of the aliphatic C-H group. The highly conjugated carbonyl group shows \(\nu\)C=O band at 1607 cm\(^{-1}\). The \(^1\)H NMR (300 MHz, DMSO-\(d_6\)) spectrum shows a three hydrogen singlet at \(\delta\) 4.19, which is assignable to the methyl group attached to nitrogen atom of the benzimidazole ring. A one-hydrogen triplet at \(\delta\) 7.08 has been assigned to one aryl hydrogen para to the NH group. The multiplet at \(\delta\) 7.26-7.44 has been attributed to H-5 and H-6 of the N-

### Table I — Physical characterisation data of 2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles 7a-e

<table>
<thead>
<tr>
<th>Compd</th>
<th>Ar</th>
<th>m.p. (°C)</th>
<th>Yield (%)</th>
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<tbody>
<tr>
<td>7a</td>
<td>[2]H5</td>
<td>165-66</td>
<td>95</td>
</tr>
<tr>
<td>7b</td>
<td>4-ClC6H4</td>
<td>143-45</td>
<td>90</td>
</tr>
<tr>
<td>7c</td>
<td>4-CH3OC6H4</td>
<td>148-49</td>
<td>98</td>
</tr>
<tr>
<td>7d</td>
<td>4-C2H5OC6H4</td>
<td>135-38</td>
<td>98</td>
</tr>
<tr>
<td>7e</td>
<td>4-CH3C6H4</td>
<td>184-86</td>
<td>93</td>
</tr>
</tbody>
</table>

Results and Discussion

The classic Hantzsch 2-aminothiazole synthesis from simple thioureas and α-haloketones has been
methylbenzimidazole ring and two aryl hydrogens meta to the NH group. The H-4 and H-7 of the N-methylbenzimidazole ring and two aryl hydrogens ortho to the NH group give rise to the multiplet at δ 7.60-7.76. The two broad singlets due to one-hydrogen each is seen at δ 10.82 and 8.69 and are attributed to the NH hydrogen of the NHAr group. The presence of two signals in the different chemical environments. The one hydrogen singlet at δ 10.82 is due to NH hydrogen of the NHAr group.

Table II — Antibacterial activity of N-methylbenzimidazoles 7a-e

<table>
<thead>
<tr>
<th>Compd</th>
<th>Bacterial strain vs Activity</th>
<th>I</th>
<th>II</th>
<th>III</th>
<th>IV</th>
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<tbody>
<tr>
<td>7a</td>
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<td>8</td>
<td>8</td>
<td>6</td>
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<tr>
<td>7c</td>
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<tr>
<td>7d</td>
<td></td>
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<td>10</td>
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</tr>
<tr>
<td>7e</td>
<td></td>
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<td>7</td>
<td>7</td>
<td>6</td>
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<tr>
<td>Penicillin G</td>
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<td>12</td>
<td>12</td>
<td>13</td>
<td>12</td>
</tr>
</tbody>
</table>

# values are diameter of zone of inhibition (mm) and average of three replicates.

Anticancer Activity

The cytotoxicity of the thiazoles 7a-e was subjected to a preliminary evaluation at a concentration of 10^-4M against a panel of three human tumor cell lines using the National Cancer Institute preliminary anticancer screen which included NCI-H460 (lung cancer), MCF7 (breast cancer) and SF268 (CNS cancer). The results revealed that the thizole 6c showed very good activity.

Antibacterial Activity

The newly synthesised compounds 7a-e have been screened for antibacterial activity against Escherichia coli (I), Salomonella typhi (II), Staphylococcus aureus (III) and Bacillus subtilis (IV).

The results show that 2-[4-amino-2-(4-methoxyphenylamino)thiazol-5-oyl]-N-methyl-benzimidazole 7e shows maximum activity against all bacteria. All compounds show good activity against I and II. The results are shown in Table II.

Experimental Section

Melting points are determined in open capillaries using an immersion bath of silicon oil and are uncorrected. 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 1H and 75 MHz for 13C NMR spectra), JEOL SX 102/DA-6000 mass spectrometer (using Argon/Xenon, 6 KV, 10 mA and m-nitrobenzyl alcohol as the matrix) for FAB mass spectra and Nicolet 400D FTIR spectrometer. All new compounds gave satisfactory C, H and N analysis (CDRI, Lucknow).

General procedure for the synthesis of 2-(4-amino-2-arylaminothiazol-5-oyl)-N-methylbenzimidazoles 7a-e

2-(2-bromoacetyl)-N-methylbenzimidazole 5 (0.254 g, 1 mmol) which was prepared from 2-(1-hydroxyethyl)benzimidazole20,21, in DMF (2 mL) was added to a solution of 1-aryl-3-(N-nitroamidino)-thiourea 6 (1 mmol) in DMF (2 mL). The reaction mixture was heated at 60°C on a water bath for 5 min. Triethylamine (0.15 mL, 1 mmol) was added and heating was continued for another 10 min (or irradiation by microwave radiation for 2 min). The reaction mixture was then cooled and poured into ice-cold water (60 mL) with stirring. The deep yellow precipitate obtained was filtered, washed with water, dried and purified by recrystallisation from methanol-water (2:1) to get pure deep yellow crystalline 7a-e.

2-(4-Amino-2-phenylaminothiazol-5-oyl)-N-methylbenzimidazole 7a

Anal. Found: C, 61.60; H, 4.40; N, 20.21. Calcd for C_{18}H_{15}N_{5}OS (349.41): C, 61.87; H, 4.33; N, 20.04%. IR (KBr): 3474, 3400, 3233, 3183, 3050, 2928, 2858, 1607, 1492, 1445, 1340, 1115, 939, 858, 751, 690 cm\(^{-1}\). \(^1\)H NMR (300 MHz, DMSO-d\(_6\)): \(\delta\) 4.19(s, 3H, N-CH\(_3\)), 7.08(t, J = 7.35 Hz, 1H, 1ArH), 7.26-
7.44 (m, 4H, H-5, H-6, 2ArH), 7.60-7.76 (m, 4H, H-4, NH), 10.82 (s, 1H, NH); \(^{13}\)C NMR (75 MHz, DMSO-\(d_6\)): \(\delta\) 32.2, 93.4, 111.1, 119.1, 120.1, 122.9, 123.3, 124.2, 129.1, 136.7, 139.6, 140.7, 147.6, 167.5, 170.9, 171.7; FABMS: \(m/z\) 350 (MH\(^+\)), 349 (M\(^+\)).

2-[4-Amino-2-(4-chlorophenylamino)thiazol-5-oyl]-N-methylbenzimidazole 7b
Anal. Found: C, 56.53; H, 3.57; N, 18.53. Calcd for C\(_{18}\)H\(_12\)ClN\(_2\)OS (383.86): C, 56.32; H, 3.68; N, 18.25%. IR (KBr): 3387, 3258, 3204, 3137, 3090, 1519, 1438, 1330, 1245, 1115, 1020, 841, 734 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.26-7.40 (m, 3H, 2H, 2ArH), 7.75 (d, J = 7.8 Hz, 2H, 2ArH), 7.75 (d, J = 7.8 Hz, 1H, H-4), 10.29 (s, 1H, NH); FABMS: \(m/z\) 384 (MH\(^+\)), 383 (M\(^+\)).

2-[4-Amino-2-(4-methoxyphenylamino)thiazol-5-oyl]-N-methylbenzimidazole 7c
Anal. Found: C, 60.28; H, 4.60; N, 18.25. Calcd for C\(_{19}\)H\(_{14}\)NO\(_2\)S (379.43): C, 60.14; H, 4.52; N, 18.46%. IR (KBr): 3467, 3267, 3216, 3067, 2892, 1604, 1580, 1519, 1438, 1330, 1245, 1115, 1032, 936, 837, 743 cm\(^{-1}\); \(^{1}\)H NMR (300 MHz, DMSO-\(d_6\)): \(\delta\) 7.05 (s, 3H, OCH\(_3\)), 4.18 (s, 3H, N-CH\(_3\)), 6.95 (d, J = 8.7 Hz, 2H, 2ArH), 7.23-7.45 (m, 2H, H-5, H-6), 7.55 (d, J = 8.7 Hz, 2H, 2ArH), 7.65 (d, J = 8.1 Hz, 1H, H-7), 7.70 (d, J = 8.1 Hz, 1H, H-4), 8.24 (broad, 1H, NH), 8.72 (broad, 1H, NH), 10.67 (s, 1H, NH); FABMS: \(m/z\) 380 (MH\(^+\)), 379 (M\(^+\)).

Acknowledgements
TFAFR acknowledges Tamil Nadu State Council for Science and Technology for financial assistance. The authors thank SAIF (CUSAT), Cochin; NIIST, Trivandrum and CDRI, Lucknow for spectral and analytical data. The authors thank Dr. D. Karunagaran, Department of Biotechnology, Indian Institute of Technology for anticancer studies.

References