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Potential Alkylating Agents Derived from Benzimidazole and Benzothiazole

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Abstract □ Several benzimidazole and benzothiazole alkylating agents, bearing structural modification of certain drugs, were synthesized and evaluated for anticancer activity. Among the products, the dihydrochloride salt of 2-[*p*-[2-(bis(2-chloroethyl)amino)ethoxy]phenyl]benzimidazole (VI) exhibited a high antileukemic activity in P-388 lymphocytic leukemia.

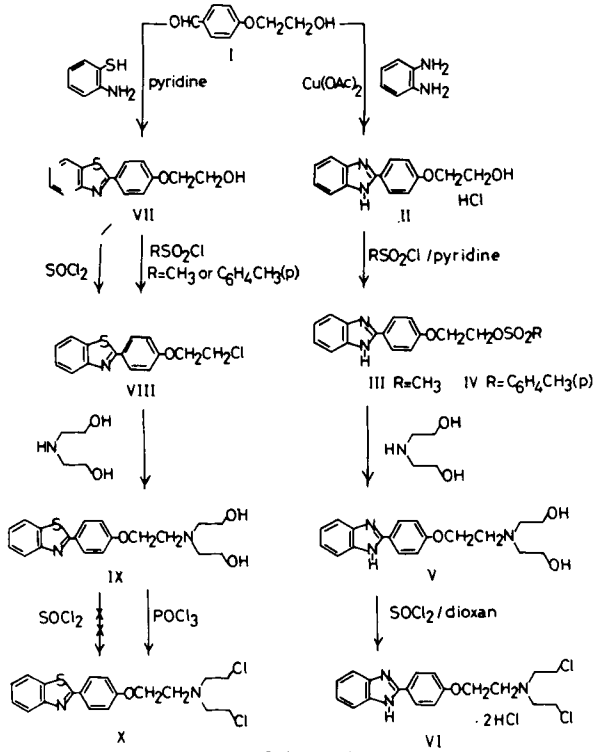
Keyphrases □ Alkylating agents—derived from benzimidazole and benzothiazole, potential □ Benzimidazole—potential alkylating agents, benzothiazole □ Benzothiazole—potential alkylating agents, benzimidazole

The studies of benzimidazole alkylating agents reported the production of a variety of compounds (1–5) of which 4 - [2 - [5(6) - bis - (2-chloroethyl)amino]benzimidazolyl]-butyric acid[1] (6) and 2-[bis(2-chloroethyl)aminoethyl]-benzimidazole[2] (7, 8) are the most effective and clinically useful anticancer agents. In a previous investigation of the effect of structural modification on the anticancer activity of these compounds, several benzimidazole-2-thioethylsulfonic esters and nitrogen mustard derivatives were synthesized and evaluated for antileukemic properties (9). In continuation of these studies, this study describes the preparation of several new benzimidazole and benzothiazole alkylating agents (III, IV, VI, and X) and reports on the results of their evaluation against P-388 lymphocytic leukemia (Scheme I).

RESULTS AND DISCUSSION

Chemistry—*p*-(2-Hydroxyethoxy)benzaldehyde (I), prepared by etherification of *p*-hydroxybenzaldehyde with ethylene chlorohydrin (10) in the presence of sodium methoxide, was reacted with *o*-phenylenediamine and copper acetate, in accordance with the modified Weidenhagen reaction (11), to give 2-[*p*-(2-hydroxyethoxy)-phenyl]-benzimidazole hydrochloride (II). This was reacted with methanesulfonyl chloride or *p*-toluenesulfonyl chloride in pyridine to produce the corresponding sulfonic esters (III and IV). The *p*-toluenesulfonic ester (IV) was fused with excess diethanolamine and the produced 2-[*p*-[2-(bis-(2-hydroxyethyl)amino)ethoxy]phenyl]benzimidazole (V) converted into the dihydrochloride salt of the nitrogen mustard 2-[*p*-[2-(bis-(2-chloroethyl)amino)ethoxy]phenyl]benzimidazole (VI) by boiling with thionyl chloride in dioxane.

The reaction of *p*-(2-hydroxyethoxy)benzaldehyde (I) with o-aminothiophenol in pyridine gave 2-[*p*-(2-hydroxyethoxy)phenyl]benzothiazole (VII). This, on treatment with *p-toluenesulfonyl* chloride or methanesulfonyl chloride, yielded 2-[*p*-(2-chloroethoxy)phenyl]benzothiazole (VIII) rather than the corresponding sulfonic esters. Compound VIII was also obtained when the hydroxybenzothiazole derivative



Scheme I

[1] Cytostasan, Imet 3393, A.
[2] Benzimidazole mustard NSC 23891, B.

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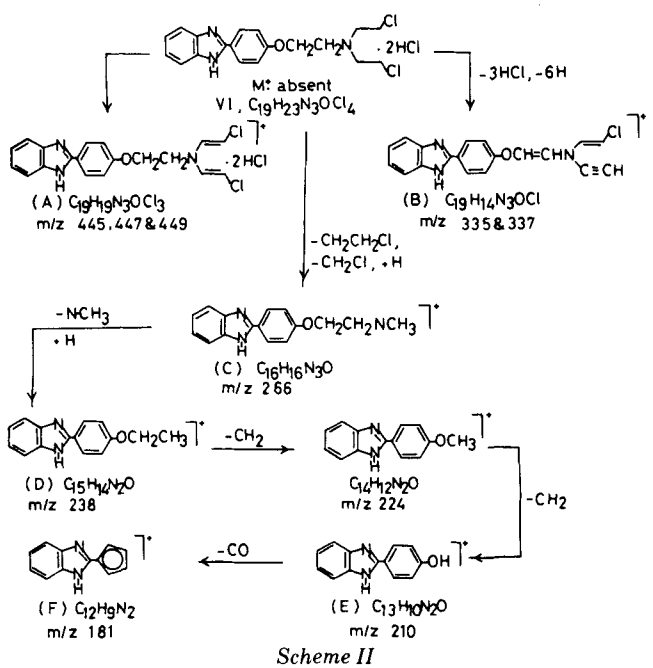
(VII) was treated with thionyl chloride in chloroform. It was then fused with diethanolamine to form the dihydroxyethylaminobenzothiazole derivative (IX) which on reaction with excess phosphorous oxychloride yielded the required nitrogen mustard, 2-[*p*-[2-(bis(2-chloroethyl)amino)ethoxy]phenyl]benzothiazole (X). The products were identified by microanalysis, IR and UV spectra and for representative examples by PMR and mass spectra.

The mass spectrum of the benzimidazole nitrogen mustard (VI) indicated the absence of the molecular ion peak at *m/z* 449. However, it showed that the molecule underwent a successive elimination of two pairs of hydrogens to give Ion A at *m/z* 445 and at 447 and 449 (for M+2 and M+4, respectively) (Scheme II). It also showed that Compound VI lost 3 moles of hydrogen chloride and six hydrogens to form Ion B at *m/z* 335 and 337 (for M+2). In an alternative fragmentation pathway, Compound VI eliminated a chloroethyl and a chloromethyl group and accepted a hydrogen to give Ion C at *m/z* 266. This, on further elimination of a methylamino moiety and acceptance of a hydrogen, gave Ion D at *m/z* 238. The successive removal of two methylene groups from Ion D led to formation of 2-(*p*-hydroxyphenyl)benzimidazole, Ion E, at *m/z* 210. The latter lost carbon monoxide to yield 2-cyclopentadienylbenzimidazole, Ion F, at *m/z* 181. The base peak was identified at *m/z* 28 corresponding to a carbon monoxide, an ethylene, or —N—CH_2 ion. The mass spectrum of benzothiazole nitrogen mustard (X) showed the molecular ion peak at *m/z* 394, and at 396 and 398 (for M+2 and M+4, respectively). The cleavage of a chlorine ion from Compound X gave the ion at *m/z* 359 and 361 which successively cleaved a methylene and a chloromethylamino fragment giving the ion at *m/z* 254. This in turn lost two successive methylene groups to form the 2-(*p*-hydroxyphenyl)benzothiazole ion at *m/z* 227, which on elimination of carbon monoxide gave the 2-cyclopentadienylbenzothiazole ion at *m/z* 198. The base peak, as shown in the data in the Experimental section, was shown at *m/z* 154, and at 156 and 158 (for M+2 and M+4, respectively) corresponding to the bis(2-chloroethyl)aminomethyl ion. The spectra of both Compounds VI and X have also shown the ions corresponding to the reported fragmentation of the heterocyclic rings (12–15).

Anticancer Screening—The products were evaluated against P-388 lymphocytic leukemia in mice (9). The activities were measured as the ratio of the mean survival time of the test animals to that of the control animals, expressed as a percentage (T/C %). The nitrogen mustard (VI) was the only product which exhibited T/C % values of 189, 144, and 132 when administered in doses of 12.5, 6.25, and 3.13 mg/kg of body weight, respectively.

As revealed from the reported studies of the benzimidazole nitrogen mustards, the majority of active products (1, 3, 4, 7) either retained the methylene group of 2-[bis(2-chloroethyl)aminoethyl]benzimidazole[2] or in only a few cases replaced it by phenyl or styryl moieties having the alkylating function directly attached to their benzene rings. In the present investigation, the high antileukemic activity of Product VI has demonstrated the efficacy of the *p*-ethoxyphenyl function as an additional carrier chain for alkylating groups. To confirm this finding, the compounds in preparation now for other structural activity relationship studies of alkylating agents have been designed to contain this chain.



Scheme II

EXPERIMENTAL[3]

2-[*p*-(2-Hydroxyethoxy)phenyl]benzimidazole Hydrochloride (II)—A solution of copper acetate monohydrate (6 g, 30 mmoles) in water (25 ml) was added to the solution of *o*-phenylenediamine (1.6 g, 14.8 mmoles) and *p*-(2-hydroxyethoxy)benzaldehyde (I) (2.42 g, 14.5 mmoles) in ethanol (10 ml) and the mixture, developing an immediate green precipitate, was heated under reflux for 30 min. The product was filtered, washed with water until the washing became colorless, and dissolved by heating under reflux in 2 *N* HCl solution (50 ml) for 2 hr. After cooling, the deposited shiny dark brown crystals were filtered and crystallized from ethanol (charcoal) giving the required product (II) as small needles melting at 272–274°. Yield: 3.2 g (76%). IR (mineral oil): 3460–3320 (OH), 1620 and 1610 (C=N), 1575 and 1500 (C=C, Ar), 1555 (δ NH), 1300 (δ OH), 1260 and 1045 cm^{-1} (—C—O—C—, asym and sym). UV λ_{max} (ethanol) (log ε): 255 (4.124), 312 (4.467), and at 325 nm (sh) (4.222).

Anal.—Calc. for $C_{15}H_{15}N_2O_2Cl$: N, 9.62; Cl, 12.2. Found: N, 10.00; Cl, 12.00.

2-[*p*-[2-(*p*-Toluenesulfonyloxy)ethoxy]phenyl]benzimidazole (IV)—*p*-Toluenesulfonyl chloride (5.5 g, 28.8 mmoles) was added to a cooled (ice-salt) solution of the benzimidazole derivative (II) (2.8 g, 9.6 mmoles) in dry pyridine (25 ml), and the mixture was stirred during cooling for 6 hr to form a white precipitate. Ice cold water (10 ml) was added dropwise and stirring was continued until the precipitate dissolved, and an orange solution was obtained. Further addition of water (100 ml) separated a solid which was filtered, washed with water, and crystallized from ethanol giving the sulfonic ester (III) melting at 155–157°. Yield: 2.87 g (74%). IR (mineral oil): 1605 (C=N), 1580, 1490 (C=C, Ar), 1560 (δ OH), 1340, 1170 (SO_2, asym and sym), 1250 and 1030 cm^{-1} (—C—O—C—).

Anal.—Calc. for $C_{22}H_{20}N_2O_4S$: C, 64.70; H, 4.94; N, 6.86. Found: C, 64.70; H, 5.20; N, 6.70.

Mass spectrum: *m/z* (relative abundance %) 408 (M^+) (1), 407 (6), 390 (2), 328 (5), 327 (6), 326 (29), 264 (2), 263 (7), 262 (35), 235 (5), 199 (14), 157 (6), 156 (11), 155 (100), 139 (10), 107 (11), 105 (11), 92 (12), 91 (96), 90 (5), 89 (6), 78 (13), 65 (17), 44 (9).

2-[*p*-[2-(Methanesulfonyloxy)ethoxy]phenyl]benzimidazole (III)—By reacting methanesulfonyl chloride (1.18 g, 10.3 mmoles) with the benzimidazole derivative (II) (1 g, 3.4 moles) in dry pyridine (15 ml), in the same manner as described for the synthesis of compound IV, the required methanesulfonic ester (III) was obtained as small white shiny crystals melting at 206–208° (ethanol). Yield: 750 mg (96%).

IR (mineral oil): 1610 (C=N), 1580, 1490 (C=C, Ar), 1540 (δ NH), 1330, 1100 (SO_2 asym and sym), 1260 and 1040 cm^{-1} (—C—O—C—). UV λ_{max} (ethanol) (log ε): 252 (4.182), 312 (4.507), and at 325 nm (sh) (4.262).

Anal.—Calc. for $C_{16}H_{16}N_2O_4S$: C, 57.83; H, 4.85; N, 8.43; S, 9.63. Found: C, 57.80; H, 4.80; N, 8.30; S, 9.70.

2-[*p*-[2-(Bis(2-hydroxyethyl)amino)ethoxy]phenyl]benzimidazole (V)—Excess diethanolamine (1 g, 9.5 mmoles) was added to the *p*-toluenesulfonic ester (IV) (1.7 g, 4.1 mmoles) and the mixture was heated at 120–130° (external temperature) for 1 hr. After cooling, the pale yellow solution was diluted with water (100 ml) to separate a white precipitate which was filtered and washed with water (4 × 50 ml) and crystallized from aqueous ethanol to yield the dihydroxy-ethylamino derivative (V) as white amorphous powder melting at 185–187°. Yield: 900 mg (90%). IR (mineral oil): 3375 (OH), 1605 (C=N), 1595, 1490 (C=C, Ar), 1540 (δ NH), 1240 and 1060 cm^{-1} (—C—O—C—).

Anal.—Calc. for $C_{19}H_{23}N_3O_3$: C, 66.84; H, 6.79; N, 12.31. Found: C, 67.00; H, 6.70; N, 12.30.

2-[*p*-[2-(Bis(2-chloroethyl)amino)ethoxy]phenyl]benzimidazole Dihydrochloride (VI)—Thionyl chloride (2 ml) was added dropwise to a hot and stirred solution of Compound V (650 mg, 2.6 mmoles) in dioxane (25 ml) to form a white precipitate. This soon dissolved as the reflux started, and fine white crystals began to form and increased in volume during reflux for 2 hr. Filtration followed by successive washing of the product with hot dioxane and dry acetone gave the

[3] All melting points are uncorrected. IR spectra were measured on a Beckman 4210 IR spectrophotometer. UV spectra were measured on a Beckman 24 spectrophotometer. PMR spectra were measured on a Varian A60, and mass spectra on an AEI-MS-50.

dihydrochloride salt of the nitrogen mustard VI, which softened with darkening at 245° and completely melted with decomposition at 283–285°. Yield: 920 mg (97%). IR (mineral oil): 3110 (NH), 1640, 1610 (C=N), 1590, 1510 (C=C, Ar), 1550 (δ NH), 1260 and 1065 cm^{-1} (—C—O—C—).

Anal.—Calc. for $C_{19}H_{23}N_3O\,Cl_4$: C, 50.50; H, 5.09; N, 9.31; Cl, 31.48. Found: C, 50.60; H, 4.70; N, 8.90; Cl, 31.50.

Mass spectrum: *m/z* (relative abundance) (M^+ absent) 449 (4), 447 (12), 445 (32), 379 (1), 378 (3), 337 (4), 335 (13), 266 (17), 238 (11), 237 (25), 236 (38), 235 (36), 224 (17), 223 (47), 211 (54), 210 (92), 209 (38), 181 (32), 180 (22), 129 (12), 127 (18), 121 (8), 120 (20), 119 (26), 112 (30), 107 (13), 105 (37), 100 (16), 99 (38), 97 (11), 93 (12), 91 (36), 84 (15), 78 (28), 77 (35), 72 (10), 70 (29), 65 (33), 64 (34), 63 (38), 58 (29), 57 (42), 56 (57), 55 (52), 52 (39), 44 (20), 42 (81), 38 (41), 28 (100).

2-[*p*-(2-Hydroxyethoxy)phenyl]benzothiazole (VII)—A solution of *o*-aminothiophenol (730 mg, 5.8 mmoles) in pyridine (5 ml) was added to the solution of *p*-(2-hydroxyethoxy)benzaldehyde (I) (970 mg, 5.8 mmoles) in pyridine (5 ml) and the mixture was heated on a water bath for 1 hr. After cooling, the product was poured onto water (100 ml), and the yellowish white emulsion so obtained was left overnight to deposit a whitish precipitate. This was filtered, washed with water (3 × 50 ml) and crystallized from ethanol (charcoal) to deposit the required product (VII) as small whitish shiny crystals melting at 157–159°. Yield: 1.28 g (81%). IR (mineral oil): 3200 (OH), 1595, 1570 (C=N mixed with C=C, Ar), 1305 (δ OH), 1245 and 1040 cm^{-1} (—C—O—C—). UV λ_{max} (ethanol) (log ε): 322 nm (4.447).

Anal.—Calc. for $C_{15}H_{13}NO_2S$: C, 66.41; H, 4.83; S, 11.78. Found: C, 65.90; H, 4.70; S, 11.40.

2-[*p*-(2-Chloroethoxy)phenyl]benzothiazole (VIII)—p-*Toluenesulfonyl Chloride or Methanesulfonyl Chloride*—The sulfonyl chloride derivative (11 mmoles) was added to a solution of Compound VII (1 g, 3.6 mmoles) in dry pyridine (25 ml), and the orange clear solution was stirred at ~60–70° (external temperature) for 1 hr. The final dark mixture was left for 3 days at room temperature and then diluted with ice cold water (100 ml). The separated buffer product was filtered, washed with water (3 × 100 ml) and crystallized from ethanol (charcoal) to give colorless shiny scales melting at 144–145°. This was found to be 2-[*p*-(2-chloroethoxy)phenyl]benzothiazole. Yield: 70–80%.

Phosphorous Oxychloride—Phosphorous oxychloride (10 ml) was added to the hydroxy derivative (VII) (2.15 g, 7.9 mmoles) and the mixture heated under reflux for 1 hr. The dark brown solution was evaporated *in vacuo*, to remove excess phosphorous oxychloride, and the residue was dissolved in hot ethanol, treated with sodium hydrogen carbonate (2 g), and left overnight. The alcoholic solution was filtered, concentrated, and cooled to give a white precipitate of the chloro derivative (VIII) which melted at 143–145° (ethanol). Yield: 1.8 g (73%). Product VIII obtained from all experiments did not show melting point depression and showed superimposability in IR and UV spectra. IR (mineral oil): 1600, 1575 (C=N and C=C, Ar), 1250 and 1040 cm^{-1} (—C—O—C— asym and sym). UV λ_{max} (ethanol) (log ε): 320 nm (4.551).

Anal.—Calc. for $C_{15}H_{12}NOSCl$: C, 62.10; H, 4.10; N, 4.80; S, 11.00. Found: C, 62.40; H, 4.50; N, 4.80; S, 11.10.

PMR: δ ($CDCl_3$) 3.83 (t, 2H, CH_2Cl, J = 7 Hz), 4.28 (t, 2H, CH_2O, J = 7 Hz), 6.90–8.19 (m, 8H, Ar—H) ppm.

Mass spectrum: *m/z* (relative abundance %) 291 (M^+) (47), (M+2 at 293), 292 (7), 290 (23), 289 (100), 228 (5), 227 (22), 226 (19), 199 (4), 198 (11), 197 (4), 154 (5), 108 (9), 69 (7), 63 (9).

2-[*p*-[2-(Bis(2-hydroxyethyl)amino)ethoxy]phenyl]benzothiazole (IX)—Excess diethanolamine (1 g, 9.5 mmoles) was added to the chloro derivative (VIII) (0.5 g, 1.17 mmoles), and the mixture was heated at 110–120° (external temperature) for 30 min. After cooling, chloroform (50 ml) was added and the mixture was shaken with water (2 × 100 ml). The aqueous layer was again extracted with chloroform (2 × 50 ml), and the combined chloroform extracts were washed with water (3 × 100 ml) until free from diethanolamine, dried (anhydrous Na_2SO_4), and evaporated. The produced viscous oil was dissolved in benzene, treated with light petroleum (bp 60–80°) until a permanent turbidity developed, scratched, and stored in a refrigerator. The deposited brown solid was crystallized from a benzene–light petroleum mixture to give the required product (IX), as a creamy amorphous powder melting at 77–79°. Yield: 420 mg (99.7%). IR (mineral oil): 3400–3220 (OH), 1600, 1575 (C=N and C=C, Ar), 1300 (δ OH), 1245 and 1085 cm^{-1} (—C—O—C—). UV λ_{max} (ethanol) (log ε): 322 nm (4.397).

Anal.—Calc. for $C_{19}H_{22}N_2O_3S$: C, 63.67; H, 6.19; N, 7.82. Found: C, 63.30; H, 6.20; N, 7.40.

2-[*p*-[2-(Bis(2-chloroethyl)amino)ethoxy]phenyl]benzothiazole (X)—Phosphorous oxychloride (5 ml) was slowly added to the dihydroxyethylamino derivative (IX) (580 mg, 1.62 mmoles) while being cooled in ice, and the mixture was allowed to warm slowly to room temperature and then heated under reflux for 1 hr. Excess phosphorous oxychloride was evaporated *in vacuo* and the black viscous residue decomposed by addition of crushed ice. Water (50 ml) and a few drops of 10% aqueous HCl solution were then added, and the mixture was heated, filtered while hot, cooled, and rendered alkaline with sodium bicarbonate. The crude buffer product so obtained exhibited two spots on TLC and could not be purified by repeated crystallization from ethanol. Therefore, it was purified on a column of silica gel[4] (10 g) using chloroform as the eluent. Evaporation of chloroform gave 200 mg (31%) of the nitrogen mustard X, which on crystallization from methanol separated as shiny white crystals melting with decomposition at 90–91°. IR (mineral oil): 1600, 1570 (C=N and C=C, Ar), 1245 and 1070 cm^{-1} (—C—O—C— asym and sym). UV λ_{max} (ethanol) (log ε): 321 nm (4.416).

Anal.—Calc. for $C_{19}H_{20}N_2OSCl_2$: C, 57.70; H, 5.06; N, 7.08; S, 8.10; Cl, 17.90. Found: C, 57.60; H, 5.30; N, 6.60; S, 8.50; Cl, 17.50.

PMR δ ($CDCl_3$): 2.85–3.25 [*m*, 6H, $N(CH_2)_3$], 3.55 (t, 4H, 2 × —CH_2Cl, J = 7 Hz), 4.15 (t, 2H, O—CH_2—, J = 7 Hz), 6.90–8.20 (m, 8H, Ar—H)ppm.

Mass spectrum: *m/z* (relative abundance %) 398 (5), 397 (6), 396 (31), 395 (11), 394 (39), 359 (2), 347 (3), 345 (11), 254 (3), 240 (2), 227 (5), 226 (5), 210 (12), 198 (5), 172 (8), 170 (8), 168 (11), 158 (14), 156 (80), 154 (100), 65 (5), 63 (14), 56 (12), 42 (10), 32 (8), 28 (30).

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[4] Kieselgel 100 E. Merck; 70–230 mesh, ASTM.