Synthesis of Some New Imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones as Potential Antineoplastic Agents

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Some substituted imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones have been synthesized *via* the reaction of 2-aminoimidazole sulfate with some β-keto esters, diethyl ethoxymethylenemalonate and ethyl ethoxymethylenecyanoacetate. Several compounds were screened for their *in vitro* antineoplastic and anti-HIV activity but were inactive.

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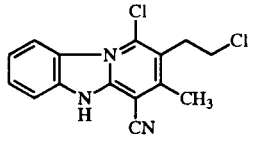
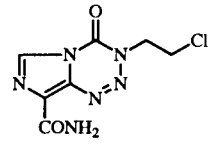
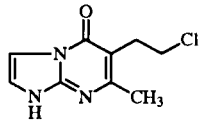
In a previous paper we have described the synthesis of some pyrido[1,2-*a*]benzimidazoles as potential antineoplastic and anti-HIV agents [1]. Of these derivatives, only the 1-chloro-2-(2-chloroethyl)-3-methylpyrido[1,2-*a*]-benzimidazole-4-carbonitrile (NSC 649900) (Figure 1) exhibited interesting *in vivo* antitumor activity against most of the cell lines of leukemia and some cell lines from colon, melanoma and renal cancer panels. However it showed marginal *in vitro* activity against P388 murine leukemia. In our search for other new lead compounds in this area, we have planned to explore the potential of some imidazo[1,2-*a*]pyrimidines (Schemes 1 and 2). Compounds **7** and **8** were of particular interest because their structures possess certain features in common with NSC 649900 and mitozolomide (Figure 1). As far as we know the latter compound is in phase-I clinical trials as a potential anticancer agent [2].



NSC 649900



Mitozolomide



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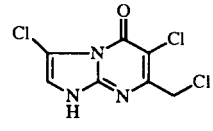

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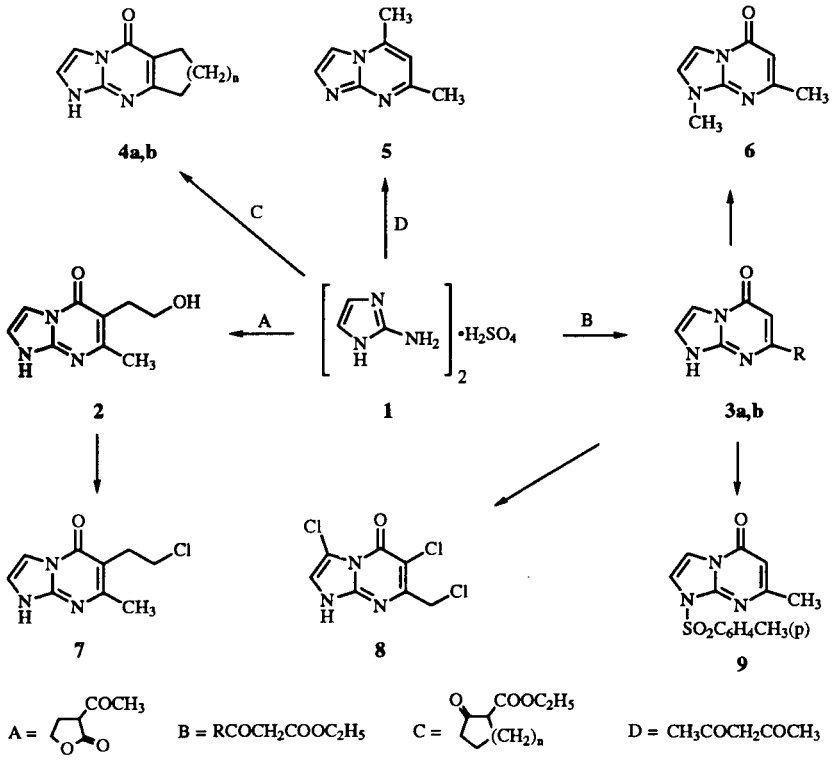
Figure 1

The most common synthetic procedure that has been employed for the preparation of imidazo[1,2-*a*]pyrimidines involved the condensation of 2-aminopyrimidine derivatives with α-halocarbonyl compounds [3-11]. On the other hand, only a few reports have appeared to describe the synthesis of the ring system by the condensation of 2-aminoimidazole or its salts with substituted diethyl malonates [12], reactive malonates [13], and ethyl acetoacetate or benzoylacetate in the presence of acetic acid [9], polyphosphoric acid or sodium hydroxide [14].

For the synthesis of the desired imidazo[1,2-*a*]pyrimidin-5-ones illustrated in Scheme 1, we have planned to effect the cyclocondensation of 2-aminoimidazole sulfate (**1**) with some selected β-keto esters in the presence of ammonium acetate. This modified Pechmann condensation was first described by Kappe and Mayer for the synthesis of some pyrono-coumarines and quinolines [15]. Later on, we have utilized this methodology successfully for the synthesis of many pyrido- and cyclopentapyrido-[1,2-*a*]benzimidazoles [1,16-17].

Thus reacting **1** with an equimolar quantity of 2-acetylbutyrolactone in the presence of two equivalents of ammonium acetate at 140° furnished 6-(2-hydroxyethyl)-7-methylimidazo[1,2-*a*]pyrimidin-5 (1*H*)-one (**2**). The 7-methyl and 7-phenyl derivatives **3a,b** were obtained from **1** and ethyl acetoacetate and ethyl benzoylacetate, respectively, under identical reaction conditions. Similarly, the cyclopenta- and cyclohexa[*d*]imidazo[1,2-*a*]pyrimidin-5(1*H*)-ones **4a,b** were prepared from **1** and ethyl 2-cyclopentanonecarboxylate or ethyl 2-cyclohexanonecarboxylate, respectively. In these reactions, ammonium acetate acted as a source of ammonia which converted the β-keto esters to the more reactive β-enamino congeners and liberated the 2-aminoimidazole base from its salt. In analogous manner, 5,7-dimethylimidazo[1,2-*a*]pyrimidine (**5**) was obtained by condensing **1** with acetylacetone in the presence of ammonium acetate. Refluxing compound **3a** with trimethyl phosphate gave the 1,7-dimethyl derivative **6**, the structure of which was confirmed by the nuclear Overhauser enhancement (nOe) study where the irradiation of the methyl group led to a positive nOe

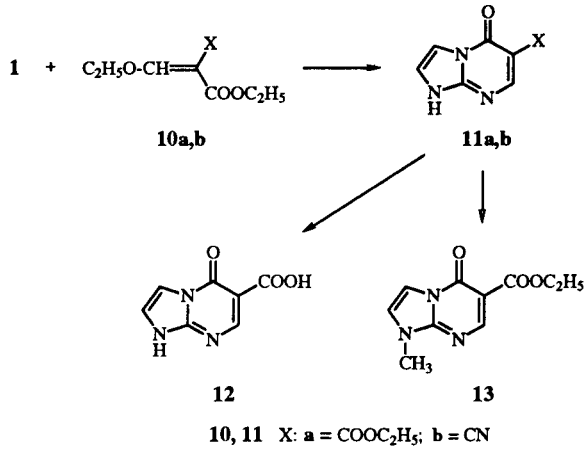
Scheme 1



which could be observed on the C-2 proton. This observation together with the absence of an interaction between the two methyl groups excluded N-8 methylation and hence the formation of the 7,8-dimethyl isomer. The 6-(2-chloroethyl)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**7**) resulted upon refluxing **3** with phosphorus oxychloride, whereas, the 7-chloromethyl-3,6-dichloroimidazo-[1,2-*a*]pyrimidin-5(1*H*)-one (**8**) was obtained by reacting **3a** with sulfuryl chloride at 60°. In the latter reaction the sulfuryl chloride effected both side chain and ring chlorination at C-3 and C-6 as revealed from the ^{1}H nmr and ^{13}C nmr spectral data of the product. A literature survey indicated that the electrophilic substitutions of some imidazo[1,2-*a*]pyrimidines could occur at C-3 [18], C-6 [12] or at both carbon atoms [19]. Reacting **3a** with tosyl chloride gave the 1-tosyl derivative **9**.

Scheme 2 outlines the synthetic approaches to ethyl 5-oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carboxylate (**11a**), 5-oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carbonitrile (**11b**) and 6-carboxylate **12**. Reacting **1** with diethyl ethoxymethylenemalonate (**10a**) or ethyl ethoxymethylenecyanoacetate (**10b**) in the presence of sodium methoxide resulted in the 6-ethyl carboxylate **11a** or the 6-carbonitrile derivative **11b**, respectively. Alkaline hydrolysis of compound **11a** gave the 6-carboxylic acid analogue **12** while its treatment with trimethyl phosphate afforded the 1-

Scheme 2



methyl derivative **13**. The structure of the latter compound was affirmed by the nuclear Overhauser enhancement (nOe) study where a positive nOe was observed on the C-2 proton because of the neighboring N-1 methyl group.

Compounds **2a,b**, **3**, **4a,b**, **7**, **8**, **9**, **10a** and **11** were selected by NCI to be screened for their *in vitro* anti-HIV as well as antineoplastic activity against 60 human cell lines derived from seven clinically isolated cancer types (lung, colon, melanoma, renal, ovarian, brain and

leukemia) according to a standard protocol [20]. Unfortunately, none of the tested compounds showed significant activity and further structural modifications of NSC 649900 will be the subject of the next publication.

EXPERIMENTAL

Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. The ir spectra were recorded on a Perkin-Elmer 298 spectrophotometer using samples in potassium bromide discs. The ^{1}H nmr spectra were recorded on a Varian Gemini 200 at 200 MHz using (DMSO-d_6, unless otherwise stated) with tetramethylsilane (TMS) as the internal standard. The ^{13}C nmr (360 MHz) spectra were performed on a Bruker AM 360 instrument.

General Method for the Synthesis of Imidazo[1,2-*a*]pyrimidin-5(1*H*)-one Derivatives **2-4**.

A mixture of 2-aminoimidazole sulfate (6.6 g, 50 mmoles), the appropriate β-keto ester (50 mmoles) and ammonium acetate (7.7 g, 100 mmoles) was heated in an oil bath at 140° until solidification of the mixture took place (3-5 hours). After cooling, the reaction mixture was treated with acetonitrile, filtered and the product was boiled with water to dissolve the inorganic salt and cooled.

6-(2-Hydroxyethyl)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**2**).

From 2-acetylbutyrolactone, the yield was 4.1 g (42%), mp 246-248° (ethanol); ir: ν 3400 s, 3300-2300 bm, 1660 s, 1630 w, 1570 m, 1510 m, 1450 w cm^{-1}; ^{1}H nmr: δ 2.3 (s, 3H, CH_3), 2.7 (t, J = 7 Hz, 2H, CH_2), 3.5 (t, J = 7 Hz, CH_2O), 4.6 (bs, 1H, OH), 7.3 (d, J = 2 Hz, 1H at C-2), 7.5 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_9H_{11}N_3O_2$: C, 55.95; H, 5.74; N, 21.75. Found: C, 55.81; H, 5.73; N, 21.71.

7-Methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**3a**).

From ethyl acetoacetate, the yield was 4.5 g (60%), mp 242-243° (water); ir: ν 3200-2100 bm, 1680 s, 1460 m, 1580 s, 1500 w, 1420 w cm^{-1}; ^{1}H nmr: (360 MHz) δ 2.3 (s, CH_3), 5.7 (s, 1H at C-6), 7.4 (d, J = 2 Hz, 1H at C-2), 7.55 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_7H_7N_3O$: C, 56.37; H, 4.73; N, 28.17. Found: C, 56.28; H, 4.78; N, 28.40.

7-Phenylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**3b**).

From ethyl benzoylacetate, the yield was 4.4 (42%), mp 293-295° (dimethylformamide); ir: ν 3200-2700 bm, 1650 s, 1550 m, 1490 w, 1450 m cm^{-1}; ^{1}H nmr (360 MHz): δ 6.4 (s, 1H at C-6), 7.54, 8.05 (2 m, 5 ArH), 7.55 (d, J = 2 Hz, 1H at C-2), 7.65 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_{12}H_9N_3O$: C, 68.24; H, 4.29; N, 19.89. Found: C, 68.31; H, 4.42; N, 20.08.

7,8-Dihydro-1*H*,6*H*-cyclopenta[*d*]imidazo[1,2-*a*]pyrimidin-5-one (**4a**).

From ethyl cyclopentanone-2-carboxylate, the yield was 6.5 g (74%), mp 307-310° (dimethylformamide); ir: ν 3200-2100 bm, 1670 s, 1610 w, 1530 s, 1470 w, 1440 m cm^{-1}; ^{1}H nmr: δ 2.0 (m, 2H at C-7), 2.7 and 2.85 (2 t, J = 7 Hz, 4H at C-6 and 8), 7.4 (d, J = 2 Hz, 1H at C-2), 7.6 (d, J = 2 Hz, 1H at C-3), 13.5 (bs, 1H, NH).

Anal. Calcd. for $C_9H_9N_3O$: C, 61.70; H, 5.18; N, 23.99. Found: C, 61.69; H, 5.26; N, 23.96.

6,7,8,9-Tetrahydro-1*H*-benzo[*d*]imidazo[1,2-*a*]pyrimidin-5-one (**4b**).

From ethyl cyclohexanone-2-carboxylate, the yield was 5.5 g (58%), mp 242° (ethanol); ir: ν 3200-2100 bm, 1680 s, 1640 m, 1580 s, 1540 w, 1450 m cm^{-1}; ^{1}H nmr; δ 1.7 (m, 4H at C-7 and 8), 2.40, 2.65 (2 t, J = 7 Hz, 4H at C-6 and 9), 7.4 (d, J = 2 Hz, 1H at C-2), 7.5 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_{10}H_{11}N_3O$: C, 63.48; H, 5.86; N, 22.21. Found: C, 63.60; H, 5.87; N, 22.19.

5,7-Dimethylimidazo[1,2-*a*]pyrimidine (**5**).

It was prepared as described above from **1** and acetylacetone but the product was obtained by extracting the aqueous solution with chloroform, yield 2.4 g (82%), mp 105° (benzene/petroleum ether); ir: ν 3600-2800 bm, 1630 s, 1530 s, 1450 m cm^{-1}; ^{1}H nmr: δ 2.5 (s, CH_3), 2.6 (CH_3), 6.85 (s, 1H at C-6), 7.65 (d, J = 2 Hz, 1H at C-2), 7.8 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_8H_9N_3$: C, 65.29; H, 6.16; N, 28.55. Found: C, 65.46; H, 6.11; N, 28.66.

1,7-Dimethylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**6**).

Compound **3a** (1.0 g) was refluxed with trimethyl phosphate (10 ml) for 1 hour in the presence of anhydrous sodium carbonate (0.1 g). After cooling the reaction mixture was alkalinized with sodium hydroxide (1 *N*), extracted with chloroform and the product was obtained after the removal of chloroform and addition of ether, yield 0.3 g (27%), mp 160-161° (acetonitrile); ir: ν 3100 m, 1680 s, 1570 s, 1530 w, 1450 w cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 2.35 (s, CH_3), 3.7 (s, NCH_3), 5.9 (s, 1H at C-6), 6.9 (d, J = 2 Hz, 1H at C-2), 7.5 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_8H_9N_3O$: C, 58.89; H, 5.56; N, 25.75. Found: C, 58.70; H, 5.43; N, 25.81.

6-(2-Chloroethyl)-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**7**).

It was prepared by refluxing **2** (1.0 g) with phosphorus oxychloride (15 ml) for 1 hour. The product was obtained after removal of phosphorus orychloride, addition of cold water and neutralization with sodium carbonate, yield 0.5 g (46%), mp 183-184° (acetonitrile); ir: ν 3000-2100 bm, 1675 s, 1630 s, 1580 s, 1440 w cm^{-1}; ^{1}H nmr: δ 2.4 (s, CH_3), 2.95 (t, J = 7 Hz, 2H, CH_2), 3.75 (t, J = 7 Hz, 2H, CH_2Cl), 7.4 (d, J = 2 Hz, 1H at C-2), 7.55 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_9H_{10}ClN_3O$: C, 51.07; H, 4.76; Cl, 16.75; N, 19.85. Found: C, 51.24; H, 4.83; Cl, 16.71; N, 20.01.

7-Chloromethyl-3,6-dichloroimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**8**).

To a stirred suspension of compound **3a** (1.49 g, 10 mmoles) in dioxane (10 ml), sulfuryl chloride (1.62 ml, 20 mmoles) was added dropwise and the reaction mixture was stirred at 50° for 1 hour. After cooling and addition of water the product was filtered and dried, yield 1.4 g (55%), mp >350° (ethanol); ir: ν 3300-2300 bm, 1690 s, 1570 s, 1480 s, 1400 m cm^{-1}; ^{1}H nmr: δ 4.65 (s, CH_2Cl), 7.8 (s, 1H at C-2); ^{13}C nmr: 44.2 (CH_2-Cl), 105.0 (C-6), 108.7 (C-2), 117.2 (C-3), 144.3 (C-7), 153.9 (C-8a), 156.0 (C-5).

Anal. Calcd. for $C_7H_4Cl_3N_3O$: C, 33.30; H, 1.60; N, 16.64. Found: C, 33.53; H, 1.75; N, 16.69.

1-Tosyl-7-methylimidazo[1,2-*a*]pyrimidin-5(1*H*)-one (**9**).

A solution of **3a** (0.75 g, 5 mmoles), triethylamine (0.69 ml, 5 mmoles) and tosyl chloride (0.95 g, 5 mmoles) in acetonitrile (20 ml) was stirred at room temperature for 1 hour. The product was obtained after removal of the solvent and addition of ether; yield 1.4 g (92%), mp 131-133° (acetonitrile); ir: ν 3110 m, 1670 s, 1590 s, 1520 s, 1420 m cm^{-1}; ^1H nmr (deuteriochloroform): δ 2.35 (s, CH_3), 2.45 (s, CH_3), 6.0 (s, 1H at C-6), 7.3, 8.2 (dd, 4 ArH), 7.4 (d, J = 2 Hz, 1H at C-2), 7.5 (d, J = 2 Hz, 1H at C-3).

Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.29; H, 4.45; N, 13.86.

Ethyl 5-Oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carboxylate (**11a**).

Compound **1** (13.2 g, 100 mmoles) was added to a well stirred solution of sodium methoxide (200 mmoles) in methanol (200 ml). Subsequently, diethyl ethoxymethylenemalonate (**10a**) (20.2 ml, 100 mmoles) was added and the reaction mixture was refluxed for 15 hours. After cooling, the product was filtered, dissolved in water, purified by heating with charcoal, filtered, cooled and acidified with hydrochloric acid to *p*H 4, yield 4.5 g (22%), mp 250-252° (ethanol); ir: ν 3300-2300 bm, 1720 s, 1640 s, 1590 m, 1520 s, 1420 s, cm^{-1}; ^1H nmr: δ 1.3 (t, J = 7 Hz, CH_3), 4.25 (q, J = 7 Hz, CH_2), 7.65 (d, J = 7 Hz, 1H at C-2), 7.8 (d, J = 7 Hz, 1H at C-3), 8.65 (s, J = 7 Hz, 1H at C-7).

Anal. Calcd. for $C_9H_9N_3O_3$: C, 52.17; H, 4.38; N, 20.28. Found: C, 51.96; H, 4.53; N, 20.26.

5-Oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carbonitrile (**11b**).

This was prepared from **1** (13.2 g, 100 mmoles) and ethyl (ethoxymethylene)cyanoacetate (**10b**) (16.92 g, 100 mmoles) as described for **11a**, yield 3.5 g (22%), mp 330-333° (dimethylformamide); ir: ν 3200-2400 bm, 2220 s, 1650 s, 1610 s, 1570 m, 1550 s cm^{-1}; ^1H nmr: δ 7.75 (d, J = 7 Hz, 1H at C-2), 7.8 (d, J = 7 Hz, 1H at C-3), 8.50 (s, 1H at C-7).

Anal. Calcd. for $C_7H_4N_4O$: C, 52.50; H, 2.52; N, 34.99. Found: C, 52.54; H, 2.52; N, 34.87.

5-Oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carboxylic Acid (**12**).

It was prepared by stirring **11a** (0.41 g, 2 mmoles) with a solution of (1 *N*) sodium hydroxide (15 ml) at 80° for 5 hours. The product was obtained after cooling and acidification of the reaction mixture with hydrochloric acid, yield 0.25 g (70%), mp 232-233° (dimethylformamide); ir: ν 3300-2000 bm, 1720 s, 1640 m, 1600 w, 1550 s, 1400 s cm^{-1}; ^1H nmr: δ 7.8 (d, J = 7 Hz, 1H at C-2), 7.95 (d, J = 7 Hz, 1H at C-3), 8.70 (s, 1H at C-7).

Anal. Calcd. for $C_7H_5N_3O_3$: C, 46.94; H, 2.81; N, 23.46. Found: C, 47.03; H, 3.32; N, 23.40.

Ethyl 1-Methyl-5-oxo-1*H*-imidazo[1,2-*a*]pyrimidine-6-carboxylate (**13**).

It was prepared from **11a** (0.41 g, 2 mmoles) and trimethyl phosphate (10 ml) as described for **6**, yield 0.2 g (45%), mp 180-182° (benzene); ir: ν 3100 s, 1725 s, 1640 s, 1580 s, 1530 s, 1480 s cm^{-1}; ^1H nmr: δ 1.3 (t, J = 7 Hz, 3H, CH_3), 3.75 (s, 3H, NCH_3), 4.2 (q, J = 7 Hz, 2H, CH_2), 7.7 (d, J = 7 Hz, 1H at C-2), 7.8 (d, J = 7 Hz, 1H at C-3), 8.7 (s, 1H at C-7).

Anal. Calcd. for $C_{10}H_{11}N_3O_3$: C, 54.30; H, 5.01; N, 19.00. Found: C, 53.97; H, 4.97; N, 19.04.

Acknowledgments.

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