Synthesis and *in vitro* anti-HIV Activity of Certain 2-(1*H*-Benzimidazol-2-ylamino)pyrimidin-4(3*H*)-ones and Related Derivatives

El-Sayed A. M. Badawey[a]* and Thomas Kappe[b]

[a] Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Alexandria, Alexandria, AR Egypt

[b] Institute für Organische Chemie, Karl Franzens Universität, Graz, Austria

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Summary

In an ongoing effort to develop novel non-nucleoside human immunodeficiency virus inhibitors, a series of substituted 2-(1*H*-benzimidazol-2-ylamino)pyrimidin-4(3*H*)-ones and related derivatives were synthesized via cyclocondensation of 2-guanidino-1*H*-benzimidazole with diethyl ethoxymethylenemalonate, substituted diethyl malonates, some β-keto esters and 2-acetylbutyrolactone. From these series of compounds, 2-(1*H*-benzimidazol-2-ylamino)-6-hydroxy-5-phenylpyrimidin-4(3*H*)-ones (**5f**, NSC 666286) was confirmed to have a moderate *in vitro* anti-HIV activity.

Introduction

The benzimidazole nucleus is an essential part of many medicinally useful drugs. For example, omeprazole, the 2-pyridylmethylsulfinylbenzimidazole derivative, is a useful drug in the treatment of peptic ulcer[1,2a]. Domperidone is a dopamine antagonist used for the symptomatic relief of acute nausea and vomiting[2b]. Pimobendan, the 2-(4-methoxyphenyl)benzimidazole derivative, is a non-glucosidic cardiotonic drug[2c,3]. Clemizole is an effective H-1 antihistaminic[2d], while KG-2413, the 2-(1,4-diazepinyl)benzimidazole derivative, is under clinical trial[4]. The benzimidazole derivatives, thiabendazole, triclabendazole, and mebendazole are effective anthelimintic agents[2e]. Chlormidazole is used in the treatment of fungal infection of the skin[2f]. Enviroxime is an active drug against rhinoviruses[2g]. Random screening of certain thiazolo[3,4-*a*]benzimidazoles for their anti-HIV activity, led to the discovery of 1-(2,6-difluorophenyl)-1*H*,3*H*-thiazolo[3,4-*a*]benzimidazole (NSC 625487) which is undergoing initial preclinical studies[5]. In this area of research, we have reported the synthesis and anti-HIV evaluation of several benzimidazoles that carry different thiazolyl and thiazolopyrimidine moieties at position-2 [6–8]. In such compounds, the benzimidazole nucleus is either linked directly at C-2 with the selected heterocyclic substituents or separated by one atom spacer. However, we failed to obtain a lead structure for medicinal chemical optimization. Recently, a lead benzoxazole derivative (L697,661, Figure 1) was found to be effective non-nucleoside specific HIV-1 reverse transcriptase inhibitor[9]. This compound, which comprises the isosteric benzoxazole nucleus linked at C-2 with a pyridone moiety through a two-atom spacer, is undergoing clinical trials[10]. According to this finding, and as a continuation of our interest in this area[6–8], we report here the synthesis and anti-HIV activity of some new substituted 2-(1*H*-benzimidazol-2-ylamino)pyrimidin-4(3*H*)-ones (Schemes 1,2). Compound **5f** (NSC 666286, Figure 1) as a model structure for such type of compounds comprises the isosteric benzimidazole, and pyrimidinone counter parts of (L697,661) separated by an NH linker. This compound was confirmed to have moderate anti-HIV activity. For this reason some of our previously reported 2-substituted-benzimidazoles[11,12] (**I** and **II**; Figure 1), which have close structural similarities to L697,661 and NSC 666286, respectively, were also selected by the NCI for anti-HIV testing. The antiviral activity recorded for the 2-(N^3-phenylguanidino)benzimidazole[13], may give some significance for the use of 2-guaindinobenzimidazole (**1**) as a starting material for the synthesis of the target compounds, particularly those with phenyl substituents **5f**, **6b**, and **9b**.

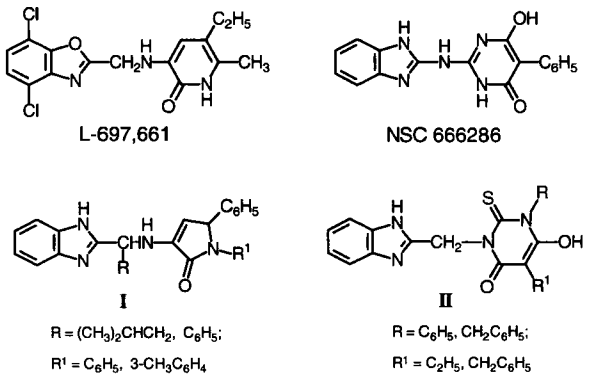

Figure 1

Results and Discussions

Chemistry

For the synthesis of the desired compounds, Schemes 1 and 2 were followed. Reacting 2-guanidinobenzimidazole (**1**) with diethyl ethoxymethylenemalonate in refluxing acetonitrile in presence of potassium carbonate afforded ethyl 2-benzimidazolylaminopyrimidine-5-carboxylate (**2**). Reinvestigation of this reaction in absence of potassium carbonate resulted, unexpectedly, in the formation of 2-amino-1,3,5-triazino[1,2-*a*]benzimidazole (**3**). It seems that the diethyl ethoxymethylene-malonate acts similar to triethyl orthofor-

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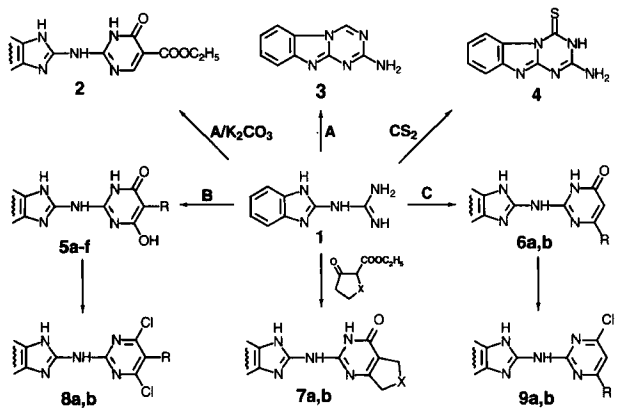
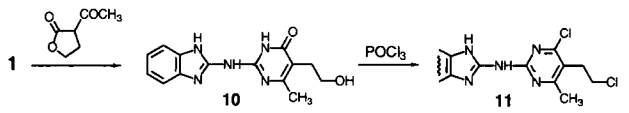


Scheme 1. **A** = EtO-CH=C($COOC_2H_5$)$_2$; **B** = R-CH($COOC_2H_5$)$_2$; **C** = R-$COCH_2COOC_2H_5$; for R see Tables 1 and 2. **7a**: X = CH_2. **7b**: X = $(CH_2)_2$.

mate in this cyclocondensation. The literature survey indicated that compound **3** could be also obtained from **1** and triethyl orthoformate[14]. The 4-thioxo analog (**4**) was obtained by reacting **1** with carbon disulfide in the presence of potassium hydroxide. The structures of both **3** and **4** were confirmed by ^{1}H NMR and ^{13}C NMR spectral data. The required 2-benzimidazolylaminopyrimidin-4(3*H*)-ones (**5,6**) were obtained in excellent yields upon condensing **1** with the selected substituted diethyl malonates or β-keto esters in diphenyl ether at 200–220 °C. Analogously, the 2-benzimidazolylaminocyclopenta[d]-pyrimidin-4(3H)-one (**7a**) and 2-benzimidazolylaminotetrahydroquinazolin-4(3*H*)-one (**7b**) were prepared from 1 and ethyl cyclopentanone-2-carboxylate and ethyl cyclohexanone-2-carboxylate, respectively. The chloropyrimidines **8** and **9** were obtained in high yields upon refluxing **5** and **6** with phosphorus oxychloride, respectively. Scheme 2, shows the synthesis of 2-(1*H*-benzimidazol-2-ylamino)-5-(2-hydroxyethyl)-6-methylpyrimidin-4(3*H*)-one (**10**) by condensing **1** with 2-acetylbutyrolactone in refluxing bromombenzene. Reacting **10** with phosphorus oxychloride resulted in the dichloro analog **11**.



Scheme 2

Biology

The designed compounds together with some of our previously reported benzimidazoles (**I**[11] and **II**[12], Figure 1), have been selected by NCI and evaluated for their effects on HIV-induced cytopathogenicity in a human T_4 lymphocyte cell line (CEM). Activity is expressed as % of protection which represents the percentage of surviving HIV-infected cells treated with test compound (at the indicated concentration) relative to the same uninfected untreated controls. The effective concentration 50% (EC_{50}%), represents the concentration of test agent resulting in 50% reduction of viral cytopathic effect. The 50% inhibitory concentration (IC_{50}%), represents the toxic concentration of drug resulting in 50% growth inhibition of normal, uninfected cells. The therapeutic index (TI) was determined by dividing (IC_{50}%) by (EC_{50}%). Among the tested compounds, only the 5-phenyl derivative **5f** (NSC 666286, Figure 1), viz. 2-(1*H*-benzimidazol-2-ylamino)-6-hydroxy-5-phenyl-pyrimidin-4(3*H*)-one, was confirmed to have moderate *in vitro* anti-HIV activity. It showed a good reduction of viral cytopathic effects ranging from 58.72% to 67.98% in four independent experiments. Of the previously reported benzimidazoles (**I**[11] and **II**[12], Figure 1), only the 3-phenyl derivative (**II**, R = C_6H_5; R1 = C_2H_5) was found to be less active than **5f**, where it reduces the viral cytopathic effect by 35%. In contrast to **5f** (NSC 666286, Figure 1), the 6-phenyl analog **6b** (Scheme 1) exhibited very weak activity. There is no precise explanation for this vari-

Table 1. Experimental data of substituted 2-(1*H*-benzimidazol-2-ylamino)pyrimidines (**5, 6, 8 & 9**).

Cpd	R	mp[a] °C	Yield %	Molecular formula	Elemental analyses
5a	CH_3	>350	91	$C_{12}H_{11}N_5O_2$	C, H, N
5b	C_2H_5	335	92	$C_{13}H_{13}N_5O_2$	C, H, N
5c	*n*-C_3H_7	>350	84	$C_{14}H_{15}N_5O_2$	C, H, N
5d	*n*-C_4H_9	315–317	85	$C_{15}H_{17}N_5O_2$	C, H, N
5e	$CH_2C_6H_5$	312–314	63	$C_{18}H_{15}N_5O_2$	C, H, N
5f	C_6H_5	338–340	78	$C_{17}H_{13}N_5O_2$	C, H, N
6a	CH_3	>350	93	$C_{12}H_{11}N_5O$	C, H, N
6b	C_6H_5	>350	82	$C_{17}H_{13}N_5O$	C, H, N
8a	CH_3	>350	96	$C_{12}H_9Cl_2N_5$	C, H, Cl, N
8b	C_2H_5	320–321	95	$C_{13}H_{11}Cl_2N_5$	C, H, N
9a	CH_3	330–333	93	$C_{12}H_{10}ClN_5$	C, H, Cl, N
9b	C_6H_5	300–301	96	$C_{17}H_{12}ClN_5$	C, H, N

[a] Recrystallized from dimethylformamide.

Table 2. ^{1}H NMR spectral data of substituted 2-(1*H*-benzimidazol-2-ylamino)pyrimidines (**5, 6, 8 & 9**).

Cpd	*R*	4 ArH of benzimidazole	H at C-5
5a	1.65s (CH_3)	6.9dd, 7.1dd	–
5b	1.0t, 2.35q (C_2H_5)	7.2dd, 7.4dd	–
5c	0.9t, 1.5m, 2.3t (*n*-C_3H_7)	7.2dd, 7.3dd	–
5d	0.9t, 1.4m, 2.35t (*n*-C_4H_9)	7.2dd, 7.4dd	–
5e	3.65s (CH_2-benzyl)	7.1–7.4m (9 Ar*H*)	–
5f	C_6H_5 (with other Ar*H*)	7.1–7.6m (9 Ar*H*)	–
6a	2.2s (CH_3)	7.1dd, 7.4dd	5.6
6b	7.55m, 8.0m (C_6H_5)	7.1dd, 7.4dd	6.25
8a	2.35s (CH_3)	7.1dd, 7.5dd	–
8b	1.1t, 2.9q (C_2H_5)	7.1dd, 7.5dd	–
9a	2.55s (CH_3)	7.1dd, 1.5dd	7.1
9b	7.6m, 8.3m (C_6H_5)	7.1dd, 7.5dd	7.8

ation in activity, but the only difference is that structure **6b** is lacking the malonyl residue which characterizes the pyrimidine moiety of compounds **5f** and (**II**, R = C_6H_5; R^1 = C_2H_5). The remaining compounds failed to counteract the cytopathic effects of HIV since the cell growth of HIV-infected cells remained between 13–16%. Owing to their weak anti-HIV activity, it is difficult to clarify the relationship between the molecular structure and biological activity. The recorded IC_{50}% and EC_{50}% for **5f** were $>2.00 \times 10^{-4}$ and 1.38×10^{-4}, respectively, however the resulting therapeutic index (TI) is more than 1.45 which is not sufficient for further *in vivo* testing as compared with AZT (TI = $> 3.89 \times 10^{-2}$, Table 3)..

Table 3. *In vitro* anti-HIV activity of compound **5f** (NSC 666286) and AZT.

Cpd	Protection %	IC_{50} (Molar)	EC_{50} (Molar)	TI (IC/EC)
5f	67.98	$> 2.00 \times 10^{-4}$	1.38×10^{-4}	> 1.45
AZT	111.76	$> 1.00 \times 10^{-6}$	2.57×10^{-9}	$> 3.89 \times 10^{-2}$

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Experimental Part

Chemistry

Melting points: Gallenkamp apparatus, uncorrected.– The IR (KBr): Perkin-Elmer 298.– The ^1H NMR: Varian Gemini 200 spectrometer, TMS internal standard, δ (ppm), [D_6]DMSO, 200 MHz.– ^{13}C NMR: Bruker AM 360 instrument. Microanalyses: Carlo Erba 1106 analyzer, all values of C, H, Cl, N are within ± 0.4 of the theoretical percentages.

*Ethyl 2-(1H-benzimidazol-2-ylamino)-3H-4-oxopyrimidine-5-carboxylate (**2**)*

This compound was prepared by refluxing a stirred solution of 2-guanidinobenzimidazole (**1**) (1.75 g, 10 mmol) and diethyl ethoxymethylenemalonate (2.0 ml, 10 mmol) in acetonitrile (25 ml) in the presence of anhydrous potassium carbonate (1.4 g, 10 mmol) for 10 h. After cooling, a yellowish product was filtered, suspended in water, and acidified with hydrochloric acid to pH 3. Yield 1.2 g (40.1%), mp 317–320 °C (DMF).– IR: ν = 3300–2500 cm^{-1} bm, 1690 s, 1650 m, 1620 , 1550 s, 1470 s.– ^1H NMR: δ =1.4 (t, 3H, CH_3), 4.2 (q, 2H, CH_2), 7.2 (dd, 2 ArH), 7.4 (dd, 2 ArH), 8.5 (s, 1 H at C-6 of pyrimidine), 11.5 (bs, NH), 12.5 (bs, 2 NH). Anal. ($C_{14}H_{13}N_5O_3$).

*2-Amino-1,3,5-triazino[1,2-a]benzimidazole (**3**)*

It was prepared by refluxing a stirred solution of **1** (1.75 g, 10 mmol) and diethyl ethoxymethylenemalonate (2.0 ml, 10 mmol) in acetonitrile (25 ml) for 5 h. After cooling, the product was filtered and dried. Yield 1.8 g (97.3%), mp 300–301 °C (DMF).– IR: ν = 3300 cm^{-1} m, 3150 bm, 1680 w, 1630 s, 1600 s, 1480 s.– ^1H NMR: δ = 7.25 (t,1 Ar*H* at C-8), 7.4 (t, 1 Ar*H* at C-7), 7.55 (d, 1 Ar*H* at C-9), 7.7 (bs, 2H, NH_2), 8.05 (d, 1 Ar*H* at C-6), 9.1 (s, 1 Ar*H* at C-4).– ^{13}C NMR: δ 113, 119, 122, 127, (C-6, C-7, C-8, C-9), 128 (C-2), 146, 151, 154 (C-10a, C-9a, C-5a), 163 (C-4). Anal. ($C_9H_7N_5$).

*2-Amino-1,3,5-triazino[1,2-a]benzimidazole-4(3H)-thione (**4**)*

A solution of 2-guanidinobenzimidazole (**1**) (1.75 g, 10 mmol) and potassium hydroxide (0.56 g, 10 mmol) in dimethylformamide was treated with carbon disulfide (0.6 ml, 10 mmol) and the reaction mixture was stirred at 60 °C for 24 h. After cooling and addition of water, the mixture was neutralized with hydrochloric acid and the product was filtered and dried. Yield 1.0 g (46.1%), mp 320 °C (DMF/H_2O).– IR: ν = 3300 cm^{-1} s, 3150 bm, 1670 s, 1470 s.– ^1H NMR: δ = 7.2–7.5 (m, 3H, 3 Ar*H* at C-7, C-8, C-9), 7.6 (bs, 2H, N*H*2), 9.3 (d, 1 Ar*H* at C-6).– ^{13}C NMR: δ 112, 117, 122, 126, (C-6, C-7, C-8, C-9), 128 (C-2), 131, 152, 160 (C-10a, C-5a, C-9a), 176 (C=S). Anal. ($C_9H_7N_5S$).

*2-(1H-Benzimidazol-2-ylamino)-6-hydroxy-5-substituted-pyrimidin-4(3H)-ones (**5a–f**)*

2-Guanidinobenzimidazole (**1**) (1.75 g, 10 mmol) and the appropriate substituted diethyl malonate (12 mmol) was heated with diphenyl ether at 200–220 °C for 1–2 h. After cooling, the product was filtered, washed with hot toluene followed by diethyl ether and dried.– IR: ν = 3500–2500 cm^{-1} bm, 1650 w-m, 1630–1620 s-m, 1570–1550 s, 1500 w. Experimental data: see Table 1.– ^1H NMR spectral data: see Table 2.

*2-(1H-Benzimidazol-2-ylamino)-6-substituted-pyrimidin-4(3H)-ones (**6a,b**)*

It was prepared as described for **5** from **1** (1.75 g, 10 mmol) and the appropriate β-keto ester (12 mmol).– IR: ν = 3500–2500 cm^{-1} bm, 1650 w-m, 1640–1620 s-m, 1560–1540s. Experimental data: see Table 1.– ^1H NMR spectral data: see Table 2.

*2-(1H-Benzimidazol-2-ylamino)-6,7-dihydro-3H,5H-cyclopenta[d]pyrimidin-4-one (**7a**)*

As described for **5**, from **1** (1.75 g, 10 mmol) and ethyl cyclopentanone-2-carboxylate (12 mmol). Yield 2.3 g (86.1%), mp >350 °C (DMF).– IR: ν = 3300–2200 cm^{-1} bm, 1650 m, 1630 s,1580 w,1550 s.– ^1H NMR: δ = 2.0 (m, 2H, CH_2), 2.6 (t, 2H, CH_2), 2.8 (t, 2H, CH_2), 7.1 (dd, 2 Ar*H*), 7.4 (dd, 2 Ar*H*). Anal.($C_{14}H_{13}N_5O$).

*2-(1H-Benzimidazol-2-ylamino)-5,6,7,8-tetrahydroquinazolin-4(3H)-one (**7b**)*

As described for **5**, from **1** (1.75 g, 10 mmol) and ethyl cyclohexanone-2-carboxylate (12 mmol). Yield 2.0 g (71.2%), mp >350 °C (DMF).– IR: ν = 3300–2200 cm^{-1} bm, 1650 m, 1625 s,1560 s.– ^1H NMR: δ = 1.7 (m, 4H, 2 CH_2), 2.25 (t, 2H, CH_2), 2.45 (t, 2H, CH_2), 7.1 (dd, 2 Ar*H*), 7.35 (dd, 2 Ar*H*). Anal. ($C_{15}H_{15}N_5O$).

*2-(1H-Benzimidazol-2-ylamino)-4,6-dichloro-5-substituted-pyrimidines (**8a,b**)*

The appropriate **5** (10 mmol) was refluxed with phosphorus oxychloride (30 ml) for 5 h. The excess phosphorus oxychloride was removed under vacuum and the residue was treated with ice-water, neutralized with sodium carbonate, and the product was filtered, washed with water and dried.– IR: ν = 3320–3310 cm^{-1} m, 1640 s, 1610 w, 1570–1500m.

Experimental data: see Table 1.– ^1H NMR spectral data: see Table 2.

*2-(1H-Benzimidazol-2-ylamino)-6-chloro-4-substituted-pyrimidines (**9a,b**)*

As described for **8**, from the appropriate **6** (10 mmol) and phosphorus oxychloride (30 ml).– IR: ν = 3320–3310 cm^{-1} m, 1640 s, 1620 w, 1570–1490 w-s.

Experimental data: see Table 1.– ^1H NMR spectral data: see Table 2.

*2-(1H-Benzimidazol-2-ylamino)-5-(2-hydroxyethyl)-6-methylpyrimidin-4(3H)-one (**10**)*

2-Guanidinobenzimidazole (**1**) (1.75 g, 10 mmol) and 2-acetylbutyrolactone (1.3 ml, 12 mmol) was refluxed with bromobenzene (25 ml) for 5 h. After cooling, the product was filtered, washed with toluene, and dried. Yield 2.4 g (84.2%), mp 315–317 °C (DMF).– IR ν cm^{-1}: 3600–3300 m, 3200–2200 bm, 1670 m, 1620 s, 1600 w, 1560 m, 1470 w.– ^1H NMR: δ = 2.25 (s,

3H, CH_3), 2.5 (t, 2H, CH_2), 3.5 (m, 2H, CH_2), 4.65 (bs, O*H*), 7.1 (d, 2 Ar*H*), 7.4 (d, 2 Ar*H*), 12.5 (bs, 2 N*H*). Anal. ($C_{14}H_{15}N_5O_2$).

2-(1H-Benzimidazol-2-ylamino)-5-(2-chloroethyl)-6-chloro-4-methyl-pyrimidine (**11**)

As described for **8**, from **10** (1.43g, 5 mmol) and phosphorus oxychloride (20 ml). Yield: 1.4 g (86.7%), mp > 350 °C (DMF).– IR: ν = : 3300m, 3000–2200 cm^{-1} bm, 1650 m, 1610 m, 1570 m, 1510 m.– ^1H NMR: δ = 2.7 (s, 3H, CH_3), 3.2 (t, 2H, CH_2), 3.9 (m, 2H, CH_2), 7.1 (d, 2 Ar*H*), 7.5 (d, 2 Ar*H*), 11.6 (bs, 2N*H*). Anal. ($C_{14}H_{13}Cl_2N_5$).

Biology

The *in vitro* anti-HIV drug testing system was performed in the National Cancer Institute's Developmental Therapeutics Program, AIDS antiviral screening program, according to a reported procedure[15]. The assay involved the killing of T_4 lymphocytes by HIV. T_4 lymphocytes (CEM cell line) were exposed to HIV at a virus-to-cell ratio of approximately 0.05 and treated with the compounds, dissolved in dimethylformamide, at doses ranging from 10^{-8} to 10^{-4} M. A complete cycle of virus reproduction is necessary to obtain the required cell killing (incubation at 37 °C in a 5% carbon dioxide atmosphere for 6 days). Uninfected cells with the compound served as a toxicity control, and infected and uninfected cells without the compound served as basic controls. After incubation, the tetrazolium salt XTT is added to all wells, and cultures were incubated to allow formazan color development by viable cells. Formazan production was measured spectrophotometrically and possible protective activity was confirmed by microscopic detection of viable cells. The effect of each compound on cell growth of HIV-infected and uninfected cells was compared to that of untreated uninfected cells. All tests were compared with AZT as positive control carried out at the same time under identical conditions.

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