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SYNTHESIS OF THE PYRIMIDINE ANALOG OF 4,5,6,7-TETRAHYDROIMIDAZO[4,5,1-*jk*][1,4]BENZODIAZEPIN-2(1*H*)ONE (TIBO) POTENTIAL FOR HIV-1 INHIBITION

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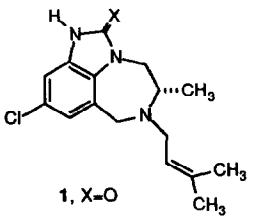
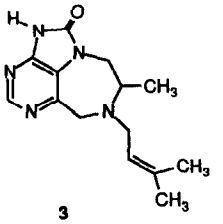
Abstract: Efficent synthesis of the pyrimidine TIBO analog **3**, starting from 9-benzyl-6- chloropurine and testing of its ability to inhibit the replication of the HIV-1 virus in MT-4 cells are described.

We have reported that members of a novel series of tetrahydro-imidazo[4,5,1-*jk*][1,4]-benzodiazepin-2(1*H*)one and -thione(TIBO), such as **1** and **2**, inhibit the replication of HIV-1[1,2], the main etiological agent of AIDS, but not of HIV-2, or of any other DNA or RNA viruses tested to date[3-5]. The unprecedented specificity of these compounds is believed to result from an interaction with reverse transcriptase, the unique viral enzyme responsible for translation of HIV-1 viral RNA into DNA which is incorporated into host cells genomic DNA. Previous studies have established that **2** inhibits the isolated reverse transcriptase[6]. In laboratory tests, TIBO derivatives inhibited reproduction of the HIV-1 virus at concentrations far below those toxic to uninfected cells. Compound **2** is currently being evaluated in clinical trials as another drug to add to anti-AIDS therapy. In the course of SAR studies to find even more potent analogs, phenyl substituents were varied and those studies will be published in the future. Additionally, substitution of heteroaromatics for the benzo portion of the TIBO structure was undertaken. This report describes the synthesis and anti-HIV-1 testing result of pyrimidine analog **3**, an example of that type of change.



1, X=O

2, X=S

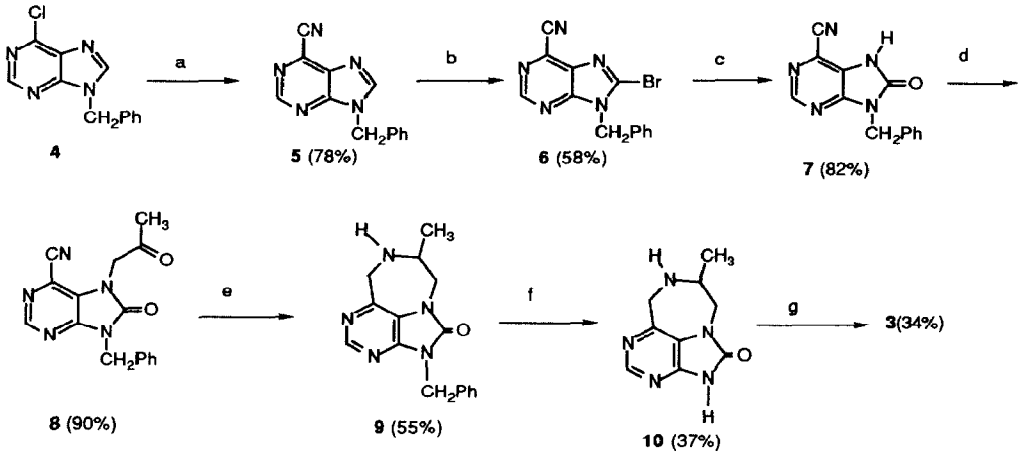


3

Synthesis of compound **3** is illustrated in Scheme 1[7]. Treatment of chloride **4**[9] with two equivalents of tetraethylammonium cyanide and trimethylamine[10] gave an excellent yield of cyanide **5** (mp 99-100.5°C). Bromination of **5** using excess NBS/$FeCl_3$ (cat.) yielded bromide **6** (mp 115-116°C). Other brominating conditions, such as Br_2/DMF, Br_2/THF-acetate buffer (pH 4), $C_6H_5CH_2N(CH_3)_3$+Cl-Br_2[11], NBS/H_2SO_4-H_2O(v/v 1:1)[12], failed to give or gave only traces of the desired bromide. Hydrolysis of bromide **6** with dilute

aqueous NaOH gave purinone **7** (mp 167-168.5°C)[13] in 82% isolated yield. Alkylation of **7** with chloroacetone afforded compound **8** (mp 124-126°C). Hydrogenation of the nitrile in **8** yielded a primary amine which subsquently underwent reductive amination with the ketone to affect ring closure to diazepine **9** in 55% yield. Debenzylation[15] of **9** with sodium and liquid ammonia gave compound **10** which was found to be too soluble in water to isolate from an aqueous work-up. Consequently, after quenching the debenzylation reaction with solid NH_4Cl, methanol was added and the solid was filtered off . The solvent was removed and the crude residue was chromatographed with CH_2Cl_2-CH_3OH-NH_4OH (100:10:1) to obtain compound **10**[16] as a colorless solid. Alkylation of **10** with dimethylallyl bromide gave the final target compound **3** (mp 155-158°C)[17-18].

Scheme 1



Reagents and Conditions: a, two equivalents of Et_4NCN/Me_3N in CH_3CN, 10°C to room temperature; b, NBS (10 fold excess)/$FeCl_3$(cat.) in $CHCl_3$, reflux; c, two equivalents of 0.1N aqueous NaOH in THF, 0°C; d, $ClCH_2COCH_3/Na_2CO_3$ in DMF, room temperature; e, H_2/Pd-C in HOAc-C_2H_5OH(v/v 1:1), 50°C; f, Na/liq.NH_3, -78°C; g, one equivalent of $(CH_3)_2C{=}CHCH_2Br$/ Na_2CO_3 in DMF, room temperature.

The anti-HIV-1 activity of this series was determined in MT-4 cells as described previously[20,21]. The cells were either infected with HIV-1 or mock infected and incubated in the presence of various concentrations of the test compounds to determine the concentration (IC_{50} values) that blocked viral replication and subsequent cell death by 50%. Compounds **1** and **2** had IC_{50}'s of 0.18 uM and 0.042 uM, respectively. Compound **3** at concentrations up to 2 uM showed no activity against HIV-1 virus replication. Replacement of the phenyl moiety of the benzodiazepine structure with a pyrimidine ring results in an inactive analog.

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References and Notes

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7. An alternative route to synthesis of **3** starting from 4,5-diamino-6-pyrimidinecarboxylic acid [8] was explored. Standard peptide coupling reaction of the pyrimidinecarboxylic acid and L-alanine methyl ester with DCC and 1-hydroxybenzotriazole in DMF gave **11.** Thermal (up to 200° C) ring cyclization of **11** was attempted and gave numerous components. Mass spectrum detected the molecular ion corresponding to **12** in the reaction mixture, but it could not be obtained in workable yields.

11 12

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13. We were unable to directly convert 6-chloro-9-benzyl-8-purione[14] to **7** using either KCN/DMSO or Et_4NCN/Me_3N.
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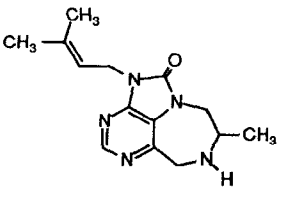
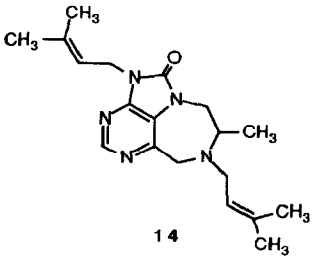
15. Debenzylation of **9** via hydrogenolysis using Pd-C or Pearlman's catalyst in HCl-EtOH at elevated temperature (75° C) was unsuccessful (no reaction). Other mild debenzylation reactions, such as $KOtBu/O_2$; NBS/CH_2Cl_2/light; TMSI, of **9** or the t-Boc protected derivative of **9**, were explored and failed to give the desired products.
16. Compounds (**5**, **7** and **8**) have satisfactory microanalytical and ^1H NMR spectral results. Compounds **6**, **9** and **10** have satisfactory mass and ^1H NMR spectral results.
17. We had tried the reverse reaction sequence that was alkylation of **9** first and then followed by debenzylation to the target molecule **3**. Na-NH_3 debenzylation of N-dimethylallyl compound **9** gave the desired compound **3**, but it was not a clean reaction.
18. Alkylation reaction also gave two minor side products, **13** and **14**, confirmed by HPLC-MS.



13



14

19. The analytical data for **3** are as follows: IR (KBr, cm^{-1}) 3054, 2969, 2922, 2854, 2747, 2655,1725 (C=O), 1622 (C=C), 1487, 1455, 1118; ^1H NMR ($CDCl_3$, ppm) 1.28(d, 3H), 1.52(s, 3H), 1.55(s, 3H), 3.15-3.22(d of d, 1H), 3.25-3.33(d of d, 1H), 3.52-3.60(m, 1H), 3.87-3.95(d of d, 1H), 3.98-4.02(d of d, 1H), 4.15-4.18(d, 1H), 4.2-4.25(d, 1H), 5.18-5.25(t, 1H), 8.55(s, 1H), 9.05(s, 1H); Calcd for $C_{14}H_{19}N_5O$: C, 61.52; H, 7.01; N, 25.62. Found: C, 61.50; H, 7.01; N, 25.42.
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