Pergamon

Bioorganic & Medicinal Chemistry Letters, Vol. 7, No. 14, pp. 1887-1890, 1997

0960-894X/97 $17.00 + 0.00

PII: S0960-894X(97)00320-X

SYNTHESIS AND ANTI-HIV ACTIVITY OF SOME NEW AMINOADAMANTANE HETEROCYCLES

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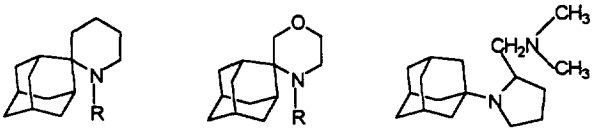
Abstract: A new class of aminoadamantane heterocycles has been synthesized and examined for anti-HIV activity. Three compounds proved to be active against the replication of HIV-1 in MT-4 cells with an EC_{50} ranging from 3.6 to 75.2 μM. No activity was noted with any of the compounds against HIV-2.

In the past the interesting antiviral properties of adamantane derivatives have been demonstrated.[1] During our program to explore new structure-antiviral activity relationships of aminoadamantanes[2,3] we found that spiroheterocycles **1, 2** and diaminoderivative **3** exhibited borderline anti-HIV-1 activity (Figure 1).[3]

Figure 1



1 **2** **3**

This observation prompted us to synthesize the novel 2-(1-adamantyl)piperidine heterocycles **7, 9a-d, 12a, b** and **13a, b** with relevant structural features as regards compounds **1, 2** and **3**. In this new series, the piperidine is allowed to rotate freely with respect to the adamantane nucleus, while the nitrogen atom is substituted by an alkyl, dialkylaminoethyl or carbamoyl group.

The synthetic route followed for the preparation of the new compounds is illustrated in Scheme 1. Tertiary alcohol **5** was synthesized from ester **4** and 1,4-bis(bromomagnesium)butane.[4] The reaction of the tertiary alcohol **5** with conc. sulfuric acid and sodium azide led to the tetrahydropyridine **6**,[5] the formation of which was accomplished by cyclopentane ring expansion of the intermediate alkylazide via nitrenium ion.[6]

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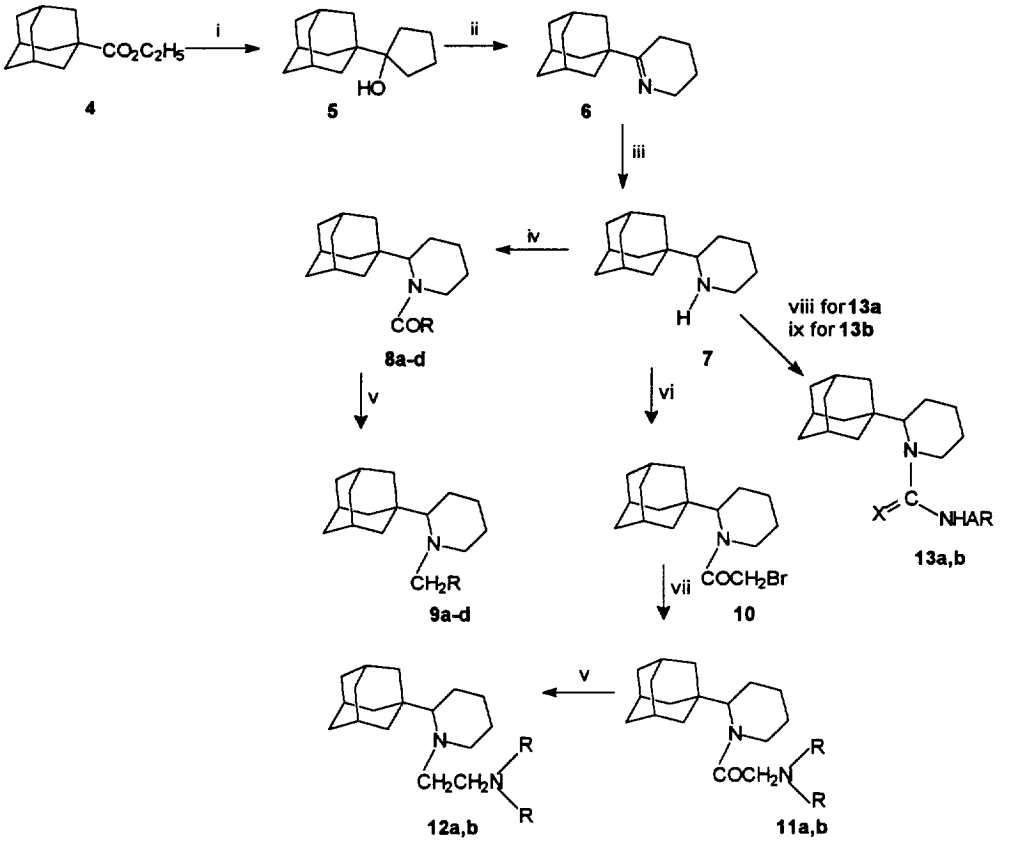
Scheme 1

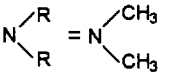


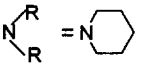
8a: R = OEt, **9a:** R = H

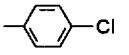
8b, 9b: R = CH_3

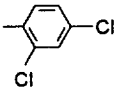
8c, 9c: R = cyclopropyl

8d, 9d: R = C_6H_5

11a, 12a: 

11b, 12b: 

13a: X = O, Ar = 

13b: X = S, Ar = 

Reagents: (i) $BrMg(CH_2)_4MgBr$/THF and then NH_4Cl, H_2O, 67%; (ii) NaN_3/conc.H_2SO_4/$CHCl_3$, 0°C, 1.5h, 73%; (iii) $NaBH_4$/CH_3OH, 0°C, and then RT for 20h, 92%; (iv) RCOCl, Et_3N, Et_2O or THF, 0°C, and then RT for 24h (66-91%); (v) $LiAlH_4$/THF, 15h reflux (70-89%); (vi) $BrCH_2COCl/K_2CO_3/CHCl_3/H_2O$, 0°C, and then RT for 2.5h, 52%; (vii) R_2NH, benzene, 0°C, and then RT for 24h (76-86%); (viii) 4-chlorophenyl isocyanate, Et_2O, 20min reflux, 70%; (ix) 2,4-dichlorophenyl isothiocyanate, acetone, 10min reflux, 53%.

Reduction of imine **6** with $NaBH_4$ gave 2-(1-adamantyl)piperidine **7**. The latter was suitably *N*-acylated to afford the amides **8a-d** which were converted to the piperidines **9a-d** by reduction with $LiAlH_4$. *N*-bromoacetylation of the parent piperidine **7** resulted in bromoacetamide **10**, which after treatment with the appropriate secondary amines gave the dialkylaminoacetamides **11a, b**. These compounds were converted to the corresponding diamines **12a, b** by means of $LiAlH_4$. The preparation of ureas **13a, b** was achieved by treatment of the piperidine **7** with the suitable isocyanate or isothiocyanate.

The new aminoadamantane heterocycles[7] **7, 9a-d, 12a, b** and **13a, b** were examined for activity against the replication of human immunodeficiency virus type 1 (HIV-1) and type 2 (HIV-2) (Table 1). Cytotoxicity of the compounds was monitored in parallel with anti-HIV activity. Both activity and cytotoxicity were determined by the MTT method.[8]

Table 1. Anti-HIV-1 and anti-HIV-2 activity and cytotoxicity of the new aminoadamantane heterocycles in MT-4 cells [a]

Compound	EC_{50} [b] (μM)		CC_{50} [c] (μM)
	HIV-1 (IIIB/LAI)	HIV-2 (ROD)	
7	>403	>403	403
9a	>415	>415	413.2
9b	>419	>419	417.4
9c	75.2	>265	263.0
9d	>64	>64	62.7
12a	40.8	>276	274.5
12b	3.6	>54	52.6
13a	>13	>13	12.6
13b	>19	>19	17.7

[a]MT-4 represents a human T-4 lymphocytic cell line. [b]50% Effective concentration, or concentration required to protect MT-4 cells against the cytopathogenicity of HIV by 50%. [c]50% Cytotoxic concentration, or concentration required to reduce the viability of MT-4 cells by 50%. All data represent mean values for at least two separate experiments.

From the EC_{50} and CC_{50} values (Table 1) compounds **9c** and **12a, b** appeared to be active against HIV-1 at non-toxic concentrations. Interestingly, no activity was noted with any of the compounds against HIV-2.

The unsubstituted, *N*-methyl, *N*-ethyl, and N-benzyl derivatives **7, 9a, b, d**, proved to be inactive against HIV-1, whereas the *N*-cyclopropylmethyl derivative **9c** showed an EC_{50} of 75.2 μM. *N*-substitution by a dialkylaminoethyl group further improved the activity. Indeed, compounds **12a** and **12b** showed an EC_{50} of

40.8 and 3.6 μM respectively. Interestingly, replacement of the dimethylamino moiety in **12a** by a piperidino, **12b**, led to a substantial increase in potency.

Aminoadamantane derivatives have not primarily been pursued as inhibitors of HIV replication. This fact makes the activity of **9c** and **12a, b** againt HIV-1 even more important. Analogous to the mechanism of anti-influenza virus activity exhibited by adamantanamines,[1] the new compounds may be postulated to interact with an early step (i.e. fusion/uncoating) of the HIV replicative cycle.

Since the presence of the second amino group through *N*-substitution of the parent heterocycle **7** enhances the anti-HIV-1 potency, studies are currently underway to obtain further insight in the structure-activity relationship of this series of compounds.

Acknowledgment: These investigations were partially supported by a research grant from the Ministry of Industry, Energy and Technology of Greece (Programme from the Promotion of Research Scientists), and by the Biomedical Research Programme of the European Commission.

References and Notes

1. (a) In *Burger's Medicinal Chemistry*; Wolff, M. E., Ed.; John Wiley & Sons: New York, **1981**; Part II, pp 557-560. (b) Hay, A. J. *Semin. Virol.* **1992**, *3*, 21.
2. Kolocouris, N.; Foscolos, G. B.; Kolocouris A.; Marakos, P.; Pouli, N.; Fytas, G.; Ikeda, S.; De Clercq, E. *J. Med. Chem.* **1994**, *37*, 2896.
3. Kolocouris, N.; Kolocouris A.; Foscolos G. B.; Fytas, G.; Neyts, J.; Padalko, E.; Balzarini, J.; Snoeck, R.; Andrei, G.; De Clercq, E. *J. Med. Chem.* **1996**, *39*, 3307.
4. Fytas, G.; Kolocouris, N.; Foscolos, G. B.; Vamvakides, A. *Eur. J. Med. Chem.* **1991**, *26*, 563.
5. The spectroscopic characteristics of 2-(1-adamantyl)-3,4,5,6-tetrahydropyridine **6** are as follows: IR (Nujol) v (C=N) 1651 cm^{-1}; ^1H NMR ($CDCl_3$, 200 MHz) δ 1.44-1.70 (m, 16H, 2,4,6,8,9-adamantane H, 4,5-piperidine H), 1.96 (s, 3H, 3,5,7-adamantane H), 2.06-2.12 (t, 2H, 3-piperidine H), 3.50-3.60 (m, 2H, 6-piperidine H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ 19.6 (4-piperidine C), 21.9 (5-piperidine C), 23.5 (3-piperidine C), 28.4 (3,5,7-adamantane C), 36.8 (4,6,10-adamantane C), 39.6 (2,8,9-adamantane C), 41.3 (1-adamantane C), 49.1 (6-piperidine C), 177.0 (2-piperidine C).
6. Astier, A.; Plat, M. *Tetrahedron Lett.* **1978**, 2051.
7. Satisfactory analytical results were obtained for all new compounds. The spectral properties were in accord with the assigned structures.
8. Pauwels, R.; Balzarini, J.; Baba, M.; Snoeck, R.; Schols, D.; Herdewyn, P.; Desmyter, J.; De Clercq, E. *J. Virol. Methods* **1988**, *20*, 309.

(*Received in Belgium* 1 *April* 1997; *accepted* 16 *June* 1997)