Pergamon

Bioorganic & Medicinal Chemistry Letters 8 (1998) 2169–2172

BIOORGANIC &
MEDICINAL CHEMISTRY
LETTERS

A DIPYRIDO [2,3-b:3',2'-f]AZEPINE ANALOG OF THE HIV-1 REVERSE TRANSCRIPTASE INHIBITOR NEVIRAPINE

Alexey B. Dyatkin,[a,*,1] Janice R.Brickwood,[b] and John R. Proudfoot.[b,*]

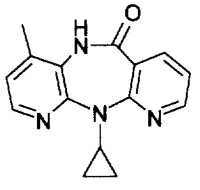
Departments of [a]Chemical Development and [b]Inflammatory Diseases,
Boehringer Ingelheim Pharmaceuticals, Inc.,
900 Ridgebury Road, PO Box 368, Ridgefield, CT 06877, U.S.A.

Received 6 March 1998; accepted 13 July 1998

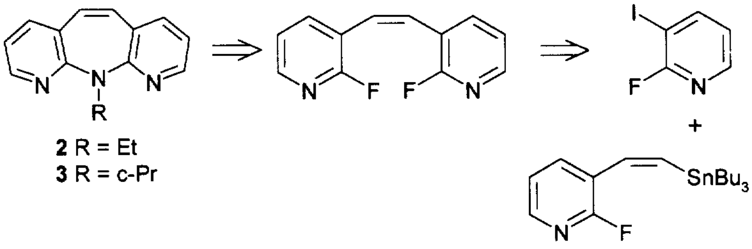
Abstract: The syntheses of 11-ethyl and 11-cyclopropyldipyrido[2,3-*b*:3',2'-*f*]azepines, analogs of the HIV-1 reverse transcriptase inhibitor nevirapine **1**, are described. These compounds exhibit potency equivalent to nevirapine in the inhibition of wild-type and some mutant RT enzymes. © 1998 Elsevier Science Ltd. All rights reserved.

Nevirapine (Viramune^{TM}) **1**[2] is a potent and selective non-nucleoside inhibitor of HIV-1 reverse transcriptase (RT), and has been approved for use in the treatment of AIDS. Here we extend the SAR studies on the dipyridodiazepinone system,[3] and show that dipyrido[2,3-*b*:3',2'-*f*]azepines **2** and **3** are as potent as **1** against wild-type and some mutant HIV-1 RT enzymes. Earlier studies demonstrated that thioamides,[3a] N-methylated lactams,[3a] and analogs with fused 5-membered heterocycles in place of the lactam[4] are good RT inhibitors. Based on the tolerance for these structural variations, we wondered whether an olefin replacement for the lactam, incapable of forming hydrogen bonds and unable to partake in polar interactions, would be effective.

In contrast to nevirapine **1**, for **2** and **3** no disconnection leading to convenient available pyridine precursors was evident. However, we envisioned that coupling of the vinylstannane and iodopyridine below would produce the Z-dipyridoethylene, which on subsequent amination and ring closure would give **2** or **3**.



1



2 R = Et
3 R = c-Pr

PII: S0960-894X(98)00369-2

The synthesis of **2** and **3** proceeded as shown in Scheme 1. We used 2-fluoropyridines, rather than 2-chloropyridines as in the case of nevirapine, to minimize the likelihood of undesired cross-coupling at the 2-position. Lithiation of commercially available 2-fluoropyridine **4**, and reverse addition to a solution of iodine in THF at –70 °C gave 2-fluoro-3-iodopyridine **5**[5] (75%). Coupling of **5** with trimethylsilyl acetylene catalyzed by $Pd(Ph_3P)_2Cl_2$ and CuI in Et_3N and THF (Sonogashira conditions)[6] gave the acetylene **7**. After workup, purification of **7** was accomplished by distillation (90–95 °C/2 Torr) followed by precipitation at –5 °C of the solid 1,4-bis(trimethylsilyl)butadiyne impurity formed by coupling of excess trimethylsilyl acetylene. The 2-fluoro-3-trimethylsilylethynylpyridine **7** was isolated in 95% yield. Conversion of the trimethylsilylacetylene to the tributylstannylacetylene **8** was performed according to Buchwald's protocol,[7] with 0.5 equivalent of $(Bu_3Sn)_2O$, and TBAF as catalyst, in THF.

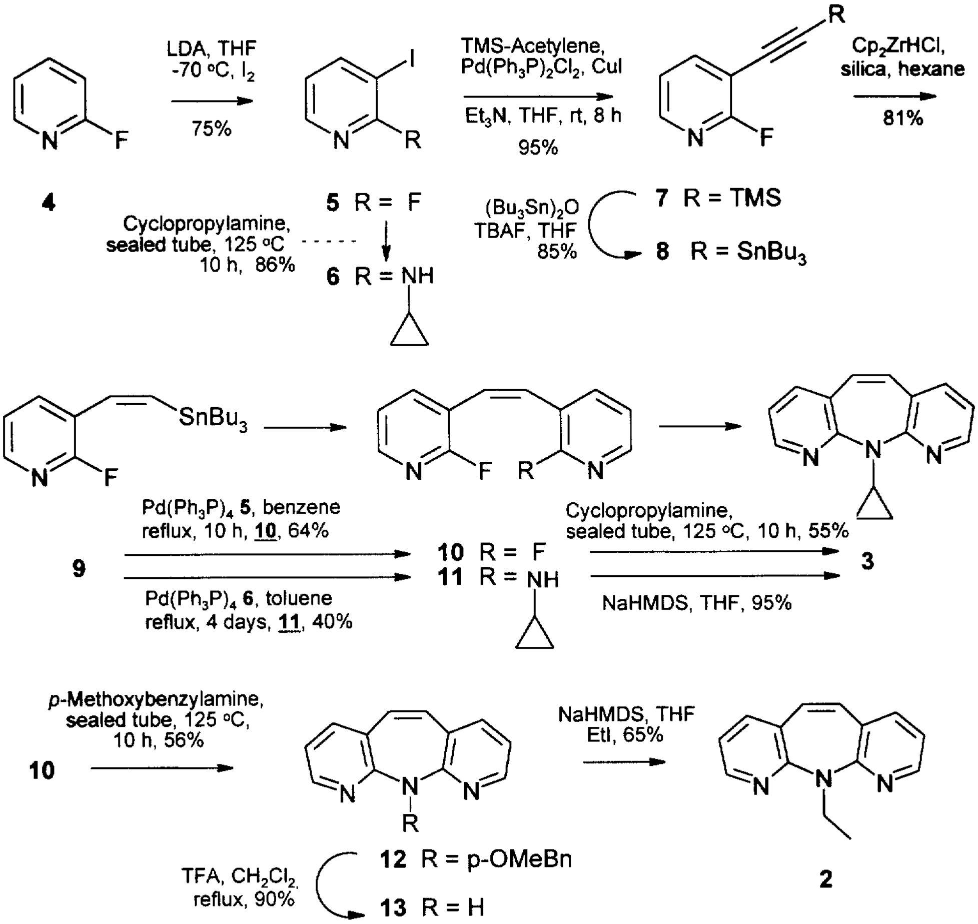
Reduction of the acetylenic stannane **8** to the Z-vinylstannane **9** (81%) was accomplished by hydrozirconation with Schwartz's reagent, followed by hydrolysis of the vinylzirconium intermediate.[8] Stille coupling of **9** with 2-fluoro-3-iodopyridine **5** in refluxing benzene provided Z-olefin **10** (64%). Treatment of **10** with excess cyclopropylamine in a sealed tube at 125 °C effected both amination and ring closure, and gave the dipyrido[2,3-*b*:3',2'-*f*]azepine **3** in 55% yield. We also explored a modified route to **3**. Stille coupling of the Z-vinylstannane **9** with 2-cyclopropylamino-3-iodopyridine **6** gave **11**, although this reaction is much slower than the corresponding reaction of **9** with **5**. Cyclization of **11** with NaHMDS in THF efficiently provided **3**.

For the synthesis of the N-ethyl compound **2**, we proceeded via the N-*p*-methoxybenzyl derivative **12**. Reaction **10** with ethylamine might also give **2** directly; however, we felt that the greater volatility of ethylamine would result in a lower conversion, and we chose to follow the two-step procedure shown. The *p*-methoxybenzyl group was removed with TFA/methylene chloride under reflux, and alkylation with NaHMDS and EtI in THF gave **2** in 65% yield.

Compounds **2** and **3** were tested against the wild type RT enzyme, and also against other mutant enzymes[9] which arise in response to treatment with nevirapine and other non-nucleoside RT inhibitors. Although **2** and **3** are slightly more potent against the wild type and mutant enzymes than nevirapine, they did not confer a sufficiently significant advantage with respect to the Y181C RT to warrant further investigation.

Compound	**IC_{50} (μM) Wild Type**	**IC_{50} (μM) Y181C**	**IC_{50} (μM) P236L**	**IC_{50} (μM) K103N**	**IC_{50} (μM) L100I**
1	0.06	3.2	0.18	1.3	0.17
2	0.04	2.5	0.01	1.5	0.23
3	0.02	0.96	0.01	0.63	0.15

Scheme 1[a]



[a] All compounds were characterized by NMR (recorded in $CDCl_3$) and mass spectra. In addition, elemental analyses for compounds **2**, **3**, **10**, **12**, and **13** are in accord with the calculated values. Selected data for these and other compounds are as follows: **2**, yellow crystals, mp 94–5 °C, ^{1}H NMR δ 8.29 (dd, *J* = 5, 2, 2H), 7.29 (dd, *J* = 7, 2, 2H), 6.90 (dd, *J* = 7, 5, 2H), 6.60 (s, 2H), 4.12 (q, *J* = 7, 2H), 1.17 (t, *J* = 7, 3H); ^{13}C NMR δ 159.26, 148.53, 137.62, 131.56, 127.32, 119.11, 42.90, 14.18: **3**, yellow crystals, mp 184–5 °C, ^{1}H NMR δ 8.35 (dd, *J* = 5, 2, 2H), 7.27 (dd, *J* = 8, 2, 2H), 6.91 (dd, *J* = 8, 5, 2H), 6.50 (s, 2H), 3.76 (m, 1H), 0.91 (m, 2H), 0.37 (m, 2H); ^{13}C NMR δ 160.09, 148.66, 137.45, 131.30, 126.66, 119.33, 30.84, 9.55: **6**, colorless oil, ^{1}H NMR δ 8.14 (dd, *J* = 5, 1, 2H), 7.77 (dd, *J* = 8, 1, 2H), 6.33 (dd, *J* = 8, 5, 2H), 5.14 (broad s, 1H), 2.76 (m, 1H), 0.86–0.79 (m, 2H), 0.55–0.50 (m, 2H): **10**, colorless crystals, mp 93–5 °C, ^{1}H NMR δ 8.11 (m, 2H), 7.51 (m, 2H), 7.02 (m, 2H), 6.77 (s, 2H): **11**, yellow oil, ^{1}H NMR δ 8.17 (m, 1H), 8.04 (m, 1H), 7.45 (m, 1H), 7.17 (m, 1H), 6.93 (m, 1H), 6.71 (d, *J* = 12, 1H), 6.58–6.51 (m, 2H), 4.64 (s, 1H), 2.74 (m, 1H), 0.78/0.72 (m, 2H), 0.32–0.27 (m, 2H): **12**, yellow crystals, mp 124–7 °C, ^{1}H NMR δ 8.22 (m, 2H), 7.40 (d, *J* = 9, 2H), 7.28 (m, 2H), 6.84 (m, 2H), 6.72 (d, *J* = 9, 2H), 6.61 (s, 2H), 5.27 (s, 2H), 3.71 (s, 3H): **13**, dark red crystals, mp 126–9 °C, ^{1}H NMR δ 7.80 (m, 2H), 6.88 (m, 2H), 6.58 (m, 2H), 5.77 (s, 2H); ^{13}C NMR δ 158.45, 149.38, 139.82, 131.40, 123.88, 119.48.

The published crystal structures of dipyridodiazepinones in complex with HIV-1 RT show that the lactam portion of **1** interacts with hydrophobic side-chains of Y188, V106 and F227 in the non-nucleoside inhibitor binding pocket.[10] No hydrogen bonding interactions between the lactam and the protein are apparent, although the carbonyl group of **1** is seen to interact with a bound water molecule.[10] In light of the hydrophobic environment of the lactam, it is not unexpected that the modification shown above is effective.

Acknowledgment

We thank Dr. Carl Busacca for many helpful suggestions during the course of this work.

References and Notes

1. Current address: The R.W. Johnson Pharmaceutical Research Institute, Welsh and McKean Roads, Spring House, PA 19477-0776.
2. Merluzzi, V. J.; Hargrave, K. D.; Labadia, M.; Grozinger, K.; Skoog, M.; Wu, J. C.; Shih, C.-K.; Eckner, K.; Hattox, S.; Adams, J.; Rosenthal, A. S.; Faanes, R.; Eckner, R. J.; Koup, R. A.; Sullivan, J. L. *Science* **1990**, *250*, 1411.
3. (a) Hargrave, K. D.; Proudfoot, J. R.; Grozinger, K. G.; Cullen, E.; Kapadia, S. R.; Patel, U. R.; Fuchs, V. U.; Mauldin, S. C.; Vitous, J.; Behnke, M. L.; Klunder, J. M.; Pal, K.; Skiles, J. W.; McNeil, D. W.; Rose, J. M.; Chow, G. C.; Skoog, M. T.; Wu, J. C.; Schmidt, G.; Engel, W. W.; Eberlein, W. G.; Saboe, T. D.; Campbell, S. J.; Rosenthal, A. S.; Adams, J. *J. Med. Chem.* **1991**, *34*, 2231. (b) Proudfoot, J. R.; Patel, U. R.; Campbell, S. J. *J. Org. Chem.* **1993**, *58*, 6996. (c) Proudfoot, J. R.; Patel, U. R.; Kapadia, S. R.; Hargrave, K. D. *J. Med. Chem.* **1995**, *38*, 1406. (d) Proudfoot, J. R. *Bioorg. Med. Chem. Lett.* **1995**, *5*, 163. (e) Klunder, J. M.; Hargrave, K. D.; West, M.; Cullen, E.; Pal, K.; Behnke, M. L.; Kapadia, S. R.; McNeil, D. W.; Wu, J. C.; Chow, G. C.; Adams, J. *J. Med. Chem.* **1992**, *35*, 1887. (f) Bellarosa, D.; Antonelli, G.; Bambacioni, F.; Gianotti, D.; Viti, G.; Nannicini, R.; Giachetti, A.; Dianzani, F.; Witvrouw, M.; Pauwels, R.; Desmyter, J.; De Clercq, E. *Antiviral Research*, **1996**, *30*, 109.
4. Terret, N. K.; Bojanic, D.; Merson, J. R.; Stephenson, P. T.; *Bioorg. Med. Chem. Lett.* **1992**, *2*, 1745.
5. Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740.
6. (a) Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467. (b) Sakamoto, T.; Shiraiwa, M.; Kondo, Y.; Yamanaka, H. *Synthesis*, **1983**, 312.
7. Warner, B. P.; Buchwald, S. L. *J. Org. Chem.* **1994**, *59*, 5822.
8. Lipshutz, B. H.; Keil, R.; Barton, J. C. *Tetrahedron Lett.* **1992**, *33*, 5861.
9. For details of the enzyme assay see ref 3a.
10. Ren, J.; Esnouf, R.; Garman, E.; Somers, D.; Ross, C.; Kirby, I.; Keeling, J.; Darby, G.; Jones, Y.; Stuart, D.; Stammers, D. *Structural Biology* **1995**, *2*, 293.