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

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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<sup>TM</sup>)  $1^2$  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,<sup>3</sup> 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,<sup>3a</sup> N-methylated lactams,<sup>3a</sup> and analogs with fused 5-membered heterocycles in place of the lactam<sup>4</sup> 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.



0960-894X/98/\$ - see front matter © 1998 Elsevier Science Ltd. All rights reserved. *PII*: S0960-894X(98)00369-2 The synthesis of 2 and 3 proceeded as shown in Scheme 1. We used 2-fluoropyridines, rather than 2chloropyridines as in the case of nevirapine, to minimize the likelihood of undesired cross-coupling at the 2position. 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<sub>3</sub>P)<sub>2</sub>Cl<sub>2</sub> and CuI in Et<sub>3</sub>N and THF (Sonogashira conditions)<sup>6</sup> 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 2fluoro-3-trimethylsilylethynylpyridine 7 was isolated in 95% yield. Conversion of the trimethylsilylacetylene to the tributylstannylacetylene 8 was performed according to Buchwald's protocol,<sup>7</sup> with 0.5 equivalent of (Bu<sub>3</sub>Sn)<sub>2</sub>O, 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.<sup>8</sup> 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 pmethoxybenzyl 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<sup>9</sup> 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 <sub>50</sub> (μM) Wild Type	IC <sub>50</sub> (μM) Y181C	IC <sub>50</sub> (μM) P236L	IC <sub>50</sub> (μM) K103N	IC <sub>50</sub> (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<sup>a</sup>

<sup>a</sup> All compounds were characterized by NMR (recorded in CDCl<sub>3</sub>) 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, <sup>1</sup>H NMR  $\delta$  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); <sup>13</sup>C NMR  $\delta$  159.26, 148.53, 137.62, 131.56, 127.32, 119.11, 42.90, 14.18: **3**, yellow crystals, mp 184–5 °C, <sup>1</sup>H NMR  $\delta$  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); <sup>13</sup>C NMR  $\delta$  160.09, 148.66, 137.45, 131.30, 126.66, 119.33, 30.84, 9.55: **6**, colorless oil, <sup>1</sup>H NMR  $\delta$  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, <sup>1</sup>H NMR  $\delta$  8.11 (m, 2H), 7.51 (m, 2H), 7.02 (m, 2H), 6.77 (s, 2H): **11**, yellow oil, <sup>1</sup>H NMR  $\delta$  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), 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, <sup>1</sup>H NMR  $\delta$  7.80 (m, 2H), 6.58 (m, 2H), 6.58 (m, 2H), 5.77 (s, 2H); <sup>13</sup>C NMR  $\delta$  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.<sup>10</sup> 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.<sup>10</sup> In light of the hydrophobic environment of the lactam, it is not unexpected that the modification shown above is effective.

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