Pergamon

Tetrahedron Letters 42 (2001) 8189–8192

TETRAHEDRON LETTERS

HIV-1 replication inhibitors of the styrylquinoline class: incorporation of a masked diketo acid pharmacophore

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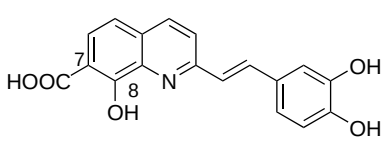
Received 24 July 2001; revised 18 September 2001; accepted 19 September 2001

Abstract—A novel variant of HIV-1 replication inhibitors of the styrylquinoline class, bearing an α-keto acid appendage at C-7, has been synthesized. Though completely inactive in in vitro experiments against HIV-1 integrase, this compound exhibited a significant antiviral activity ($IC_{50}=10$ μM). © 2001 Elsevier Science Ltd. All rights reserved.

AIDS is essentially a viral disease and should be treated with antiretroviral agents. Although the advent of combination therapy with reverse transcriptase and protease inhibitors has made it possible to suppress the replication of HIV-1 in infected individuals, the virus persists in reservoirs such as peripheral blood mononuclear cells or resting T-lymphocytes. Moreover, the capability of HIV to evolve drug resistance and the cytotoxicity of present regimens make the third enzyme, the integrase (IN), a legitimate new drug target.[1]

We have recently reported that polyhydroxylated styrylquinolines, exemplified by **1**, are potent HIV-1 IN inhibitors in in vitro experiments, block the replication of HIV-1 in cell culture, and are devoid of cytotoxicity.[2] Although the exact mechanism by which drug **1** and analogs exert their inhibitory potency remains unknown, their salicylic acid part has been identified as a possible pharmacophore which binds Mg^{2+}, a cation which is essential to the catalytic activity of HIV-1 IN.[3] In addition to styrylquinolines, two other families of



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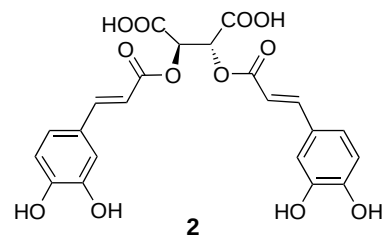

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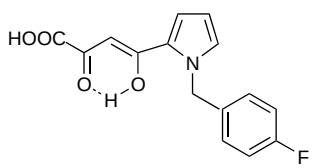

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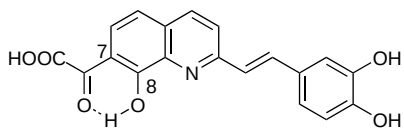

Figure 1.

Keywords: antivirals; enzyme inhibitors; keto acids and derivatives; quinolines; thioacetals.
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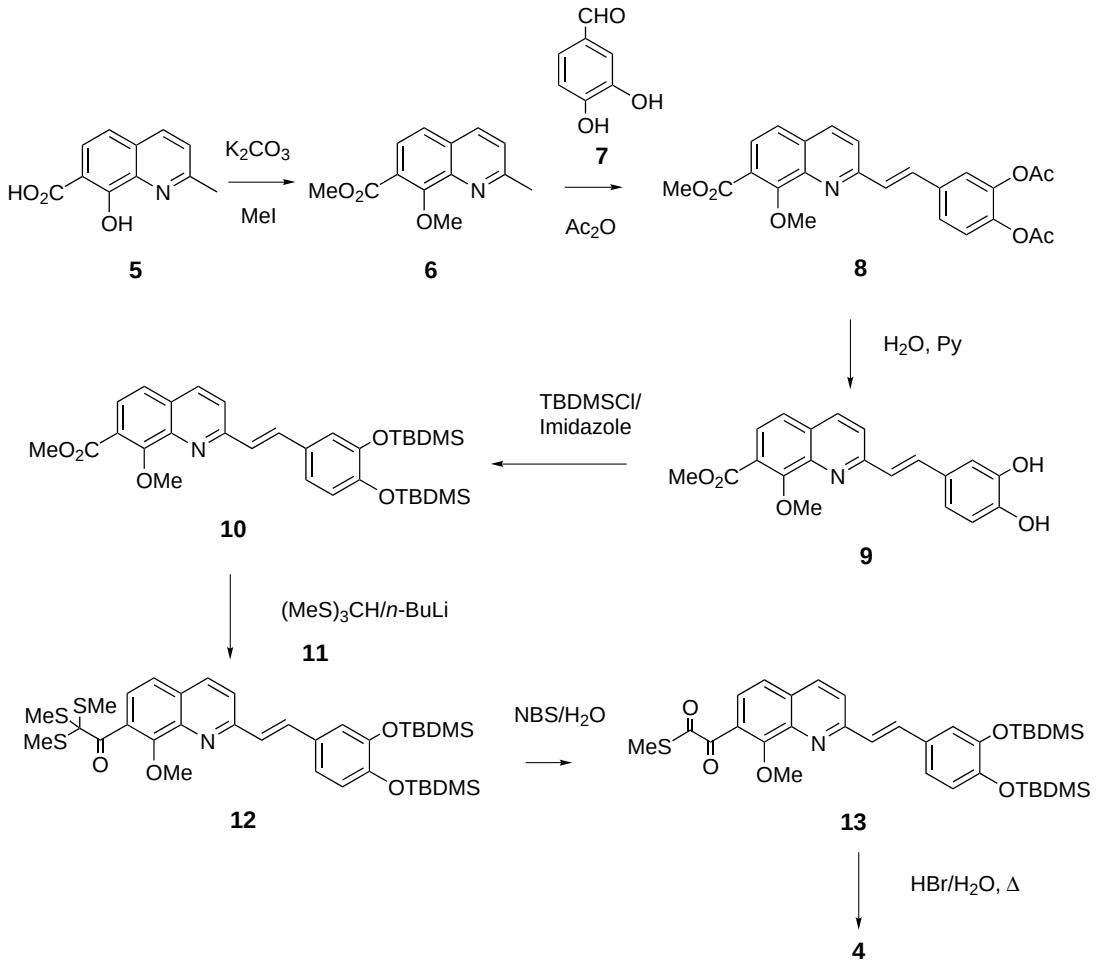
PII: S0040-4039(01)01767-1

HIV-1 IN inhibitors have shown anti-HIV-1 activity in cell culture, namely L-chicoric acid (**2**) and analogs,[4] and various α,γ-diketo acids (exemplified by L 731,988, **3**).[5]

In the course of our ongoing research on HIV-1 replication inhibitors of the styrylquinoline class, we recently envisioned to elaborate the new structural variant **4**, bearing an α-keto acid appendage at C-7. The factor that has stimulated our interest in synthesizing styrylquinoline **4** has been the structural analogy between its HOOC-CO-C=C(OH)- system and the enol form of the α,γ-diketo acid pharmacophore found in inhibitor **3** (Fig. 1). On the other hand, a docking protocol using the program MORCAD has recently been designed to study the interaction between the catalytic core of HIV-1 IN and molecules **1** and **4**.[6] This computer simulation revealed that the two styrylquinolines bind in a similar fashion to the protein. Since drug **1** was proved to be a strong inhibitor of HIV-1 IN,[2] a significant in vitro HIV-1 IN inhibitory activity was therefore expected for compound **4**.

Here, we report the synthesis and the evaluation of the biological activity of styrylquinoline **4**. Structurally, compound **4** only differs from lead inhibitor **1** in the presence of an additional keto group at C-7. Two strategies have evolved for the introduction of this critical moiety. The keto group could be present at the outset of the synthesis on a quinoline ring, or incorporated at an advanced stage, via the displacement of the ester function of a styrylquinoline (e.g. **10**) with an appropriate nucleophile. The second approach, which has been more successful thus far, has taken advantage of the one-carbon elongation of esters developed by Degani and Fochi, using the anion of tris-(methylthio)methane (**11**).[7]

The first stage of the synthesis was the methylation of known hydroxy acid **5**[8] to produce the dimethylated derivative **6**[9] (MeI–K_2CO_3, DMF–acetone, 12 h at 50°C, 81% yield). Perkin-type condensation of quinaldine **6** with 3,4-dihydroxybenzaldehyde (**7**) then afforded styrylquinoline **8** (Ac_2O, 12 h at 140°C, 79% yield).[2] Replacement of the two labile acetoxy groups of compound **8** by more robust *tert*-butyldimethylsilyl ethers (OTBDMS) was next accomplished, employing the following two-step procedure. Hydrolysis of **8** (pyridine–H_2O, 3 h at 100°C) gave with a 74% yield catechol **9**,[10] which was converted into bis-silylated derivative **10** (TBDMSCl, imidazole, DMF, 12 h at 20°C, 84% yield). At this juncture, we stood ready to introduce the crucial keto group at C-7. In the event, condensation of ester **10** with tris(methylthio)methyllithium[7] (i: **11**, *n*-BuLi, THF, 2 h at −95°C; ii: **10**, 30 min at −95°C; iii: H_2O/CH_2Cl_2 at −95°C)



Scheme 1.

Table 1. Biological data of compounds **1**, **3** and **4**

Compound	HIV-1 integrase inhibitory potency (strand transfer process) IC_{50} (μM)	Anti-HIV-1 activity IC_{50} (μM)
1	1	1
3	0.1	1
4	100	10

delivered with a 57% yield the α-oxo trithioorthoester **12**,[11] which, upon treatment with *N*-bromosuccinimide (NBS, THF–H_2O, 2 h at 20°C),[12] gave the α-oxo thiol ester **13**[13] (52% yield). The next issue of the synthesis was the conversion of the thiol ester group of **13** into a carboxylic acid. A variety of operating conditions were considered (1N NaOH, MeOH, 20°C; or 0.1N NaOH, *t*-BuOOH, 20°C; or $AgNO_3$, CH_3CN, H_2O, 20°C), but they all proved to be inappropriate for the purpose. Finally, after extensive experiments, it was discovered that subjection of **13** to harsh hydrolytic conditions (40% aqueous HBr, AcOH, 12 h at 80°C), not only achieved the task, but also resulted in the removal of the aromatic OMe and OTBDMS protecting groups, providing our goal **4**[14] in 47% yield (Scheme 1).

Keto acid **4** was evaluated in vitro for its inhibitory activity against HIV-1 IN, and ex vivo for its antiviral activity against HIV-1 replication in CEM cells.[2] The results, together with those obtained with lead inhibitors **1** and **3**, are listed in Table 1. A moderate antiviral activity was gained with styrylquinoline **4** ($IC_{50}=10$ μM). However, in contrast with parent compound **1**, this keto acid exhibited a complete lack of in vitro inhibitory potency ($IC_{50}>100$ μM). Therefore, in contradiction with the aforementioned docking studies,[6] the ultimate target of drug **4** in the ex vivo experiments *is not* HIV-1 IN. Work directed toward the identification of this viral target is in progress.

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9. Compound **6**: Colorless crystals; mp 33–34°C; IR (neat, cm^{-1}) *v*: 1709, 1610, 1556, 1505; ^1H NMR (DMSO-d_6, 200 MHz) δ: 7.90 (d, $J=8.4$ Hz, 1H), 7.66 (d, $J=8.5$ Hz, 1H), 7.39 (d, $J=8.5$ Hz, 1H), 7.21 (d, $J=8.4$ Hz, 1H), 4.18 (s, 3H), 3.90 (s, 3H), 2.65 (s, 3H); ^{13}C NMR ($CDCl_3$, 50 MHz), δ: 166.6 (C), 158.6 (C), 156.2 (C), 142.3 (C), 135.7 (CH), 129.5 (C), 125.4 (CH), 123.2 (C), 123.1 (CH), 122.2 (CH), 63.1 (CH_3), 51.8 (CH_3), 25.1 (CH_3).
10. Compound **9**: Yellow solid; mp 180–185°C (dec.); IR (neat, cm^{-1}) *v*: 3340, 2946, 1722, 1631, 1600, 1508; ^1H NMR (DMSO-d_6, 200 MHz) δ: 9.20 (broad s, 2H), 8.30 (d, $J=9.1$ Hz, 1H), 7.86 (d, $J=9.1$ Hz, 1H), 7.75–7.55 (m, 3H), 7.16 (d, $J=16.8$ Hz, 1H), 7.10 (s, 1H), 7.00 (d, $J=7.9$ Hz, 1H), 6.78 (d, $J=7.9$ Hz, 1H), 4.20 (s, 3H), 3.98 (s, 3H); ^{13}C NMR (DMSO-d_6, 50 MHz) δ: 166.6 (C), 156.0 (C), 155.5 (C), 147.0 (C), 145.7 (C), 142.3 (C), 136.6 (CH), 135.4 (CH), 130.1 (C), 127.8 (C), 125.2 (2CH), 124.0 (C), 122.9 (CH), 121.3 (CH), 120.1 (CH), 116.0 (CH), 114.1 (CH), 63.0 (CH_3), 52.3 (CH_3).
11. Compound **12**: Orange solid; mp 158–160°C; IR (neat, cm^{-1}) *v*: 2930, 2857, 1688, 1505, 1286, 1250; ^1H NMR ($CDCl_3$, 200 MHz) δ: 8.09 (d, $J=8.4$ Hz, 1H), 7.93 (d, $J=8.2$ Hz, 1H), 7.65 (d, $J=8.4$ Hz, 1H), 7.60 (d, $J=16.2$ Hz, 1H), 7.46 (d, $J=8.2$ Hz, 1H), 7.21 (d, $J=16.2$ Hz, 1H), 7.15–7.05 (m, 2H), 6.84 (d, $J=8.6$ Hz, 1H), 4.20 (s, 3H), 2.12 (s, 9H), 0.95 (s, 9H), 0.92 (s, 9H), 0.19 (s, 6H), 0.18 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 193.5 (C), 155.7 (C), 154.2 (C), 147.9 (C), 147.0 (C), 142.3 (C), 136.2 (CH), 134.6 (CH), 132.0 (C), 130.1 (C), 129.3 (C), 126.9 (CH), 125.3 (CH), 121.8 (CH), 121.1 (2CH), 120.2 (CH), 119.7 (CH), 76.8 (C), 64.0 (CH_3), 25.8 ($6CH_3$), 18.4 (2C) 14.0 ($3CH_3$), –4.1 ($4CH_3$).
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13. Compound **13**: Yellow solid; mp 129–130°C; IR (neat, cm^{-1}) *v*: 2930, 2856, 1672, 1662, 1594, 1506, 1303, 1249; ^1H NMR ($CDCl_3$, 200 MHz) δ: 8.10 (d, $J=8.7$ Hz, 1H), 7.72 (d, $J=8.4$ Hz, 1H), 7.69 (d, $J=8.7$ Hz, 1H), 7.63 (d, $J=16.2$ Hz, 1H), 7.53 (d, $J=8.4$ Hz, 1H), 7.16 (d, $J=16.2$ Hz, 1H), 7.12–7.02 (m, 2H), 6.85 (d, $J=8.8$ Hz, 1H), 4.35 (s, 3H), 2.54 (s, 3H), 1.03 (s, 9H), 1.00 (s, 9H), 0.25 (s, 6H) 0.24 (s, 6H); ^{13}C NMR ($CDCl_3$, 50 MHz) δ: 193.3, 190.2, 158.7, 155.7, 148.8, 147.1, 142.1, 136.5, 135.1, 132.3, 130.0, 126.4, 125.5, 124.9, 123.1, 121.9, 121.2 (2C), 119.9, 63.9, 26.0 (6C), 18.4, 11.0 (2C), –4.0 (4C).

14. Compound **4**: Brick red solid; mp 250°C (dec.); IR (neat, cm^{-1}) v: 3600–2500, 1740, 1580, 1522, 1442, 1290, 1240; ^1H NMR (DMSO-d_6, 400 MHz) δ: 9.50–8.50 (broad s, 4H), 8.36 (d, $J=8.8$ Hz, 1H), 8.12 (d, $J=15.8$ Hz, 1H), 7.89 (d, $J=8.8$ Hz, 1H), 7.70 (d, $J=8.8$ Hz, 1H), 7.42 (d, $J=8.8$ Hz, 1H), 7.23 (d, $J=15.8$ Hz, 1H), 7.10 (d, $J=1.2$ Hz, 1H), 7.00 (dd, $J=8.2$, 1.2 Hz, 1H), 6.80 (d, $J=8.2$ Hz, 1H); ^{13}C NMR (DMSO-d_6, 100 MHz) δ: 186.6 (C), 167.2 (C), 157.2 (C), 155.0 (C), 147.1 (C), 145.6 (C), 138.2 (C), 137.8 (CH), 137.2 (CH), 135.6 (CH), 130.6 (C), 127.8 (C), 124.0 (CH), 123.3 (CH), 120.3 (CH), 118.1 (CH), 116.1 (CH), 115.8 (C), 114.5 (CH); MS (ESI, −70.0 V) m/z (rel. intensity): 352 (M+1, 2), 351 (M, 20), 350 (M−1, 100), 322 (2), 306 (M−1−CO_2, 2), 278 (1).