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Trifluoromethyl-Containing 3-Alkoxymethyl- and 3-Aryloxymethyl-2-pyridinones Are Potent Inhibitors of HIV-1 Non-Nucleoside Reverse Transcriptase

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Abstract—3-Alkoxymethyl- and 3-aryloxymethyl-2-pyridinones were synthesized and evaluated for activity as non-nucleoside reverse transcriptase inhibitors (NNRTIs) of HIV-1. It was found that several compounds were potent inhibitors of HIV-1 with the most potent compound **24** exhibiting an $IC_{90} = 32$ nM. Compound **24** also possessed a potent resistance profile as demonstrated by submicromolar IC_{90}s against several clinically meaningful mutant virus strains.

The emergence of mutant forms of HIV-1 in both treatment-experienced and increasingly in treatment-naïve patients underscores the necessity to continue to develop effective, well-tolerated treatments for this disease. Previous work has shown 3-aminoalkyl- and 3-alkyl-2-pyridinones to be active inhibitors of HIV-1 RT.[1,2] Unfortunately, resistant strains of HIV-1 rapidly developed in vivo when 3-aminoalkyl-2-pyridinones were advanced into clinical trials and administered as either monotherapy or in combination with zidovudine.[3,4] As part of a continuing effort in these labs to develop NNRTIs that have a virologic profile sufficient to inhibit wild-type and mutant viral types and possess pharmacokinetics consistent with once-daily dosing, the hybrid 2-pyridinones containing trifluoromethyl and cyclopropyl alkynyl groups were investigated (Fig. 1).[5–7] The incorporation of these functional groups has improved resistance profiles in quinazolinones, as demonstrated by DPC961 and DPC083, and are incorporated in the marketed NNRTI SUSTIVA ™ (efavirenz).[5]

The synthesis of the target pyridinones in Figure 1 required the preparation of the trifluoromethyl ketones shown in Scheme 1. 2-Methoxypyridine (**1**) was metallated with mesityl lithium followed by quenching the anion with ethyl trifluoroacetate to cleanly afford trifluoromethyl ketone **2**.[8] It proved critical to use the hindered mesityl lithium base when metallating **1** to eliminate the production of alkylated side products. Employing the mesityl lithium metallation procedure to 2-methoxyquinoline (**3**) resulted in the isolation of hemiketal **4**, with no ketone being present. Compound **4** was used as is in subsequent alkylation reactions. 5-Ethyl-3-formyl-6-methyl-2-methoxypyridine **5** was prepared as

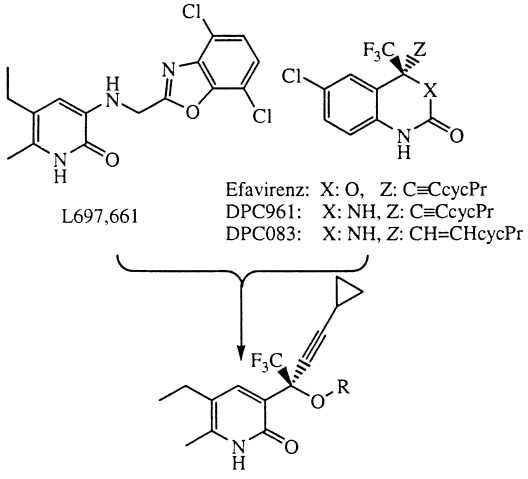

Figure 1. Design of trifluoromethyl-containing pyridinones.

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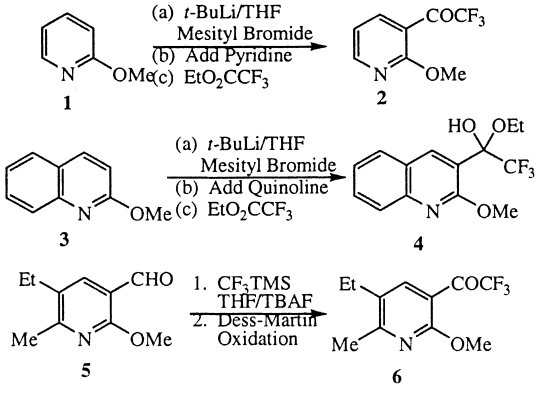
previously described in the literature.[1c] To **5** was added trimethyl(trifluoromethyl)silane and tetrabutylammonium fluoride (TBAF) to give the secondary alcohol which was subsequently oxidized with the Dess–Martin periodinane reagent to afford ketone **6**.[9]

Treating **2**, **4**, and **6** with an excess of lithiated alkynes in THF afforded tertiary alcohols **7a–c** as shown in Scheme 2 (see Table 1 for definitions of R^3 and R^4). The alcohols were then alkylated with various alkyl halides to yield ethers **8a–c**. When sodium methiolate was used to deprotect **8a**, the only material isolated was **9** in which the pyridinone oxygen cyclized onto the alkyne. The best conditions found for removal of the methyl ether from **8a–c** utilized trimethylsilyl iodide (TMSI) in methylene chloride at reflux.

Other attempts were made to prepare pyridinones wherein R^4 was either a benzimidazole or benzoxazole (Scheme 3). In the event, treating **7c** with 2-(bromomethyl)benzimidazole[10] or (2-bromo-methyl)benzoxazole[11] afforded the desired ethers **10a**,**b**. Unfortunately, all attempts to deprotect **10a**,**b** using TMSI led to the exclusive formation of the pyrano[2,3-*b*]pyridines **11a**,**b**. The structure of **11a** was confirmed through a single crystal X-ray structure. It remains unclear why compounds possessing the benzimidazole or benzoxazole groups undergo an intramolecular cyclization while a benzyl group in the same position does not induce a similar reaction. Attempts at preparing alternately protected pyridines were pursued without success. Compounds **9** and **11a**,**b** were found to not possess any activity in the enzyme and antiviral whole cell assays.

To explore the steric environment surrounding the alkynyl group, two alkynes **7a** (R^3 = cyclopropyl or phenyl) were reduced with lithium aluminum hydride to afford *trans*-olefins **12** (Scheme 4). Alkylation of the tertiary alcohol with benzyl bromide and removal of the methyl ether with TMSI delivered olefins **13** and **14**, respectively. All of the compounds prepared via Schemes 2 and 4 for which biological data were obtained are listed in Table 1.[12]

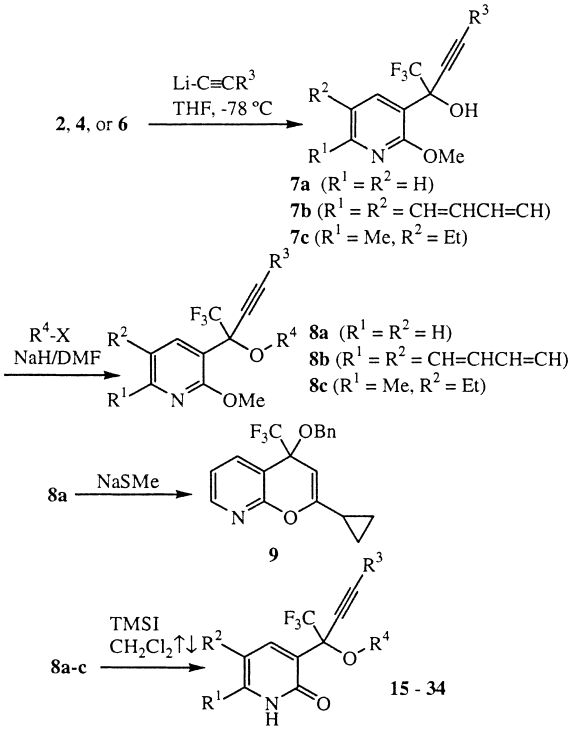
The importance of the R^1 and R^2 substituents became evident when pyridinone **27** was compared to pyridinone **15**, which lacks the methyl and ethyl groups: **27** was 9 times more active in the enzyme assay and 4 times more active in the whole cell assay (Table 1). It was also found that the size of the R^4 group is critical for activity. In comparing **22–27**, a trend becomes apparent wherein compounds with a hydrophobic R^4 group of at least three carbons are the most active compounds. Replacing the methyl and ethyl groups with an aromatic ring afforded quinolinone **21**, which was approximately 10 times less active in the whole cell assay than pyridinone **27**. Also, the compound that had a phenyl group at R^3 (**20**) was less potent than the corresponding analogue with a cyclopropyl group (**15**).



Scheme 1. Synthesis of 2-methoxypyridyl and 2-methoxyquinoline trifluoromethyl ketones.

The incorporation of a *trans*-olefin into quinazolinones DPC961 and DPC963 led to compounds that exhibited unique virologic and pharmacokinetic properties.[5] However in the trifluoromethyl-containing pyridinones, an unexpected decrease in the biological activity, as demonstrated in the whole cell assay, was observed. For instance, *trans*-olefin **13** and the corresponding alkyne **15** had enzyme IC_{50}s of >1400 nM and 182 nM, respectively. The divergence in the SAR between the pyridinones and the quinazolinones implies that at least the olefin containing pyridinones are binding in a different orientation than the olefin-containing quinazolinones DPC082 and DPC083.[5]

The K103N mutation has been designated as a 'pan-class' mutation since it is frequently observed in patients failing an NNRTI-containing therapy.[7] Following the appearance of the K103N mutation, double mutant viruses containing the K103N mutation occur with the K103N/P225H and K103N/V108I mutations more common than the K103N/L100I mutation. Since a series of compounds predicted to provide inhibition of the



Scheme 2. Synthesis of trifluoromethyl-containing pyridinones.

K103N, K103N/P225H, and K103N/V108I mutants were selected for further development,[5,7] our attention focused upon identifying agents capable of inhibiting the K103N/L100I mutant while maintaining activity against other single and double mutant viral forms. Therefore, compounds **24** and **27** were evaluated for activity against clinically important mutant strains of HIV-1 (Table 2).[12]

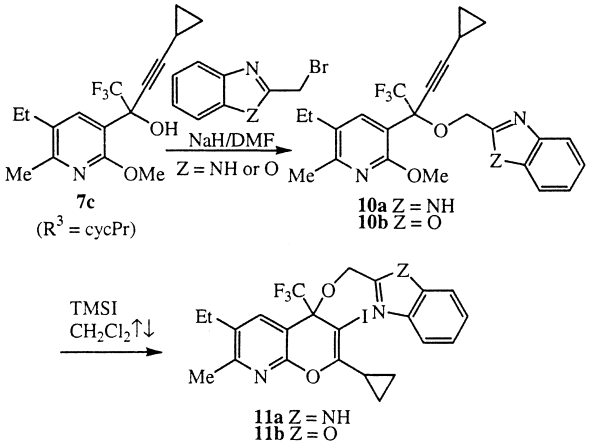
The quinazolinones DPC961 and DPC083 were more potent than **24**, **27** and efavirenz at inhibiting the K103N single mutant virus than Table 2. Since the values in Table 2 for **24** and **27** are for the racemates, and the single enantiomers are typically twice as active as the racemates, one would anticipate that enantiomeric **24** and **27** would be as active against K103N as efavirenz.[5,6] Pyridinones **24** and **27** were also significantly more potent against the K103N mutant than L697,661.[13] Pyridinone **27** suffered a significant loss in activity against the K103N/V108I mutant and was less potent against this mutant when compared to the quinazolinones and efavirenz. However, **27** possessed significant activity against virus containing the K103N/P225H mutation: **27** was at least as potent as efavirenz and possibly DPC083. Finally, **27** was significantly more potent than efavirenz and marginally better than the quinazolinones DPC961 and DPC083 at inhibiting the K103N/L100I double mutant virus.

In summary, a series of potent trifluoromethyl-containing pyridinone NNRTIs was discovered that possess nanomolar activity toward wild-type virus and, more importantly, had a good resistance profile toward the K103N/L100I and K103N/P225H double mutants. In fact, **27** was more potent against the K103N/L100I double mutant than DPC961, DPC083 and efavirenz.

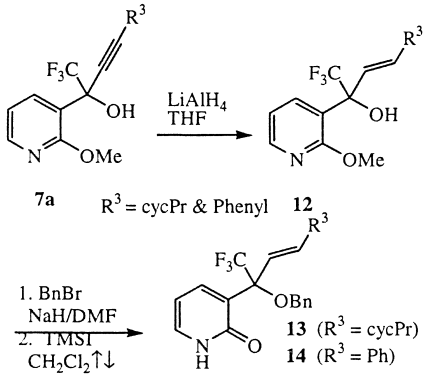
Table 1. Structure and biological activity of compounds.[12] See Schemes 2 and 4 for generic structures containing R^1, R^2, R^3, and R^4

Compound	R^1	R^2	R^3	R^4	Alkyne/olefin	Enzyme assay IC_{50} (nM)	Whole cell assay IC_{90} (nM)
Efavirenz						47 (±25)	1.7 (±0.5)
DPC961						31 (±8)	2.0 (±0.7)
L697,661						19 (±4)[a]	50–100[b]
13	H	H	cycPr	Benzyl	Olefin	16,676	>1400
14	H	H	Phenyl	Benzyl	Olefin	43,894	>1300
15	H	H	cycPr	Benzyl	Alkyne	11,824	182
16	H	H	cycPr	2-Pyridylmethyl	Alkyne	25,999	1006
17	H	H	cycPr	3-Pyridylmethyl	Alkyne	25,564	>1435
18	H	H	cycPr	4-Pyridylmethyl	Alkyne	8115	431
19	H	H	cycPr	Ph-3-(OPhenyl)	Alkyne	24,338	>1140
20	H	H	Phenyl	Benzyl	Alkyne	11,691	>1300
21	CH=CHCH=CH		cycPr	Benzyl	Alkyne	36,008	579
22	Methyl	Ethyl	cycPr	Methyl	Alkyne	770	201
23	Methyl	Ethyl	cycPr	Ethyl	Alkyne	183 (±71)	95
24	Methyl	Ethyl	cycPr	Propyl	Alkyne	105 (±38)	32
25	Methyl	Ethyl	cycPr	CH_2cycPr	Alkyne	188 (±34)	37
26	Methyl	Ethyl	cycPr	Butyl	Alkyne	129 (±38)	42
27	Methyl	Ethyl	cycPr	Benzyl	Alkyne	1348 (±271)	46
28	Methyl	Ethyl	cycPr	2,6-diF-benzyl	Alkyne	613 (±270)	49
29	Methyl	Ethyl	cycPr	2-Cl, 6-F-benzyl	Alkyne	6093	61
30	Methyl	Ethyl	cycPr	2,6-diCl-benzyl	Alkyne	41,102	157
31	Methyl	Ethyl	cycPr	2-F, 6-MeOBenzyl	Alkyne	1951 (±457)	160
32	Methyl	Ethyl	cycPr	2,4-diCl-Benzyl	Alkyne	2696 (±2111)	190
33	Methyl	Ethyl	cycPr	3,5-diMeO	Alkyne	3843 (±2014)	579
34	Methyl	Ethyl	cycPr	CH_2CN	Alkyne	1842	1400

[a]The assay conditions used to determine the enzyme IC_{50} for L697,661 reported in ref 1d are different from the conditions used in our enzyme assay.
[b]The value reported in ref 1g is the CIC_{95}, not the IC_{90}.



Scheme 3. Formation of 4*H*-pyrano[2,3-*b*]pyridines.



Scheme 4. Preparation of olefins **13** and **14**.

Table 2. Resistance profile of pyridinones **24** and **27**

	Efavirenz	DPC961	DPC083	L697661	**24**	**27**
K103N IC_{90} (nM)	64 (±24)[a]	10 (±3.2)[a]	27 (±11)[a]	800[b]	144	113
K103N/V108I IC_{90} (nM)	240 (±68)[a]	38 (±4)[a]	90 (±6.6)[a]	nd	nd	1207
K103N/P225H IC_{90} (nM)	310 (±130)[a]	73 (±18)[a]	140 (±92)[a]	nd	nd	283
K103N/L100I IC_{90} (nM)	7300 (±5000)[a]	1100 (±160)[a]	1690 (±160)[a]	nd	nd	668

[a]Values are means of three experiments, standard deviation is given in parentheses.
[b]The value reported is the CIC_{95} from ref 13. No data = nd.

Compounds **24** and **27** were also more potent against the K103N single mutant than previously reported pyridinones, including L697,661.[13] Efforts to expand on the SAR of this new series of NNRTIs will be reported in due course.

References and Notes

1. (a) Saari, W. S.; Hoffman, J. M.; Wai, J. S.; Fisher, T. E.; Rooney, C. S.; Smith, A. M.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Stern, A. M.; Anderson, P. S. *J. Med. Chem.* **1991**, *34*, 2922. (b) Goldman, M. E.; Nunberg, J. H.; O'Brien, J. A.; Quintero, J. C.; Schleif, W. A.; Freund, K. F.; Gaul, S. L.; Saari, W. S.; Wai, J. S.; Hoffman, J. M.; Anderson, P. S.; Hupe, D. J.; Emini, E. A.; Stern, A. M. *Proc. Natl. Acad. Sci. U.S.A.* **1991**, *88*, 6863. (c) Hoffman, J. M.; Wai, J. S.; Thomas, C. M.; Levin, R. B.; O'Brien, J. A.; Goldman, M. E. *J. Med. Chem.* **1992**, *35*, 3784. (d) Sarri, W. S.; Wai, J. S.; Fishe, T. E.; Thomas, C. M.; Hoffman, J. M.; Rooney, C. S.; Smith, A. M.; Jones, J. H.; Bamberger, D. L.; Goldman, M. E.; O'Brien, J. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. A. *J. Med. Chem.* **1992**, *35*, 3792. (e) Carrol, S. S.; Olsen, D. B.; Bennett, C. D.; Gotlib, L.; Graham, D. J.; Condra, J. H.; Stern, A. M.; Shafer, J. A.; Kuo, L. C. *J. Biol. Chem.* **1993**, *268*, 276. (f) Wai, J. S.; Williams, T. M.; Bamberger, D. L.; Fisher, T. E.; Hoffman, J. M.; Hudcosky, R. J.; MacTough, S. C.; Rooney, C. S.; Saari, W. S.; Thomas, C. M.; Goldman, M. E.; O'Brien, J. A.; Emini, E. A.; Nunberg, J. H.; Quintero, J. C.; Schleif, W. A.; Anderson, P. S. *J. Med. Chem.* **1993**, *36*, 249. (g) Hoffman, J. M.; Smith, A. M.; Rooney, C. S.; Fisher, T. E.; Wai, J. S.; Thomas, C. M.; Bamberger, D. L.; Barnes, J. L.; Williams, T. M.; Jones, J. H.; Olson, B. D.; O'Brien, J. A.; Goldman, M. E.; Quintero, J. C.; Schleif, W. A.; Emini, E. A.; Anderson, P. A. *J. Med. Chem.* **1993**, *36*, 953.

2. Goldman, M. E. In *The Search For Antiviral Drugs—Case Histories From Concept To Clinic*; Adams, J., Merluzzi, V. J., Eds.; Birkhäuser: Boston, 1993; pp 105–127.

3. Artico, M. *Il Farmaco* **1996**, *51*, 305.

4. Staszewski, S.; Massari, F. E.; Kober, A.; Gohler, R.; Durr, S.; Anderson, K. W.; Schneider, C. L.; Waterbury, J. A.; Bakshi, K. K.; Taylor, V. I.; Hildebrand, C. S.; Kreisl, C.; Hoffstedt, B.; Schleif, W. A.; von Briesen, H.; Rübsamen-Waigmann, H.; Calandra, G. B.; Ryan, J. L.; Stille, W.; Emini, E. A.; Byrnes, V. W. *J. Infect. Diseases* **1995**, *171*, 1159.

5. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Jeffrey, S.; Bacheler, L. T.; Klabe, R. M.; Diamond, S.; Lai, C.-M.; Rabel, S. R.; Saye, J. A.; Adams, S. P.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *Antimicrob. Agents Chemother.* **1999**, *43*, 2893.

6. Corbett, J. W.; Gearhart, L. A.; Ko, S. S.; Rodgers, J. D.; Cordova, B. C.; Klabe, R. M.; Erickson-Viitanen, S. K. *Bioorg. Med. Chem. Lett.* **2000**, *10*, 193.

7. Corbett, J. W.; Ko, S. S.; Rodgers, J. D.; Gearhart, L. A.; Magnus, N. A.; Bacheler, L. T.; Diamond, S.; Jeffrey, S.; Klabe, R. M.; Cordova, B. C.; Garber, S.; Trainor, G. L.; Anderson, P. S.; Erickson-Viitanen, S. K. *J. Med. Chem.* **2000**, *43*, 2019.

8. Comins, D. L.; Killpack, M. O. *J. Org. Chem.* **1990**, *55*, 69.

9. The Dess–Martin reagent was purchased from Lancaster Chemicals.

10. Mylari, B. L.; Beyer, T. A.; Scott, P. J.; Aldinger, C. E.; Dee, M. F.; Siegel, T. W.; Zembrowski, W. J. *J. Med. Chem.* **1992**, *35*, 457.

11. Uno, H.; Kurokawa, M.; Masuda, Y. *Chem. Pharm. Bull.* **1981**, *29*, 2359.

12. The biological assays were performed as described in ref 5.

13. Byrnes, V. W.; Sardana, V. V.; Schleif, W. A.; Condra, J. H.; Waterbury, J. A.; Wolfgang, J. A.; Long, W. J.; Schneider, C. L.; Schlabach, A. J.; Wolanski, B. S.; Graham, D. J.; Gotlib, L.; Rhodes, A.; Titus, D. L.; Roth, E.; Blahy, O. M.; Quintero, J. C.; Staszewski, S.; Emini, E. A. *Antimicrob. Agents Chemother.* **1993**, *37*, 1576.