Inhibition of Clinically Relevant Mutant Variants of HIV-1 by Quinazolinone Non-Nucleoside Reverse Transcriptase Inhibitors

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A series of 4-alkenyl and 4-alkynyl-3,4-dihydro-4-(trifluoromethyl)-2-(1*H*)-quinazolinones were found to be potent non-nucleoside reverse transcriptase inhibitors (NNRTIs) of human immunodeficiency virus type-1 (HIV-1). The 4-alkenyl-3,4-dihydro-4-(trifluoromethyl)-2-(1*H*)-quinazolinones DPC 082 and DPC 083 and the 4-alkynyl-3,4-dihydro-4-(trifluoromethyl)-2-(1*H*)-quinazolinones DPC 961 and DPC 963 were found to exhibit low nanomolar potency toward wild-type RF virus (IC_{90} = 2.0, 2.1, 2.0, and 1.3 nM, respectively) and various single and many multiple amino acid substituted HIV-1 mutant viruses. The increased potency is combined with favorable plasma serum protein binding as demonstrated by improvements in the percent free drug in human plasma when compared to efavirenz: 3.0%, 2.0%, 1.5%, 2.8%, and 0.2−0.5% for DPC 082, DPC 083, DPC 961, DPC 963, and efavirenz, respectively.

Introduction

The fact that human immunodeficiency virus (HIV) infection is a global health problem is apparent from the estimated emergence of 16 000 new cases daily.[1−3] There is substantial evidence to suggest that immediate therapy be considered for persons with acute HIV infection to effectively inhibit the replication of HIV virus.[4] Unfortunately, mutant virus forms appear in clinical situations where there is continued replication of HIV virus in the presence of suboptimal levels of drug(s) and through acute HIV infection with drug resistant strains.[5] These phenomena require the development of new therapeutics capable of suppressing the viral replication of these mutant virus forms.

One therapeutic target in the treatment of AIDS is the inhibition of HIV reverse transcriptase (RT), the enzyme responsible for the formation of proviral DNA from viral RNA.[6] The inhibition of HIV RT results in DNA chain termination, a decrease in viral replication, and a concomitant decrease in viremia. The first generation of therapeutics designed to inhibit viral RT were nucleoside substrate analogues, which bind to the ATP-binding pocket and act as substrate decoys and chain terminators. Clinical evidence has demonstrated limited long-term efficacy for these agents in certain combinations, due to the appearance of drug-resistant mutant viruses and because of hematological toxicities frequent with this class of drug.

A second class of RT inhibitors are the non-nucleoside reverse transcriptase inhibitors (NNRTIs), which bind to an allosteric site in the HIV-1 RT enzyme.[7] Three NNRTIs have been approved for the treatment of HIV-1 infection: nevirapine, delavirdine, and, most recently, efavirenz (Figure 1).

In clinical trials with NNRTIs as monotherapy,[8] and in in vitro selection experiments,[9] rapid emergence of resistant virus with greatly decreased susceptibility to the particular NNRTI has been observed. Although specific mutations unique to individual NNRTIs (e.g., P236L for delavirdine, Y181C for nevirapine or delavirdine) have been documented in vitro or in genotyping data, the RT mutation at amino acid lysine 103 to asparagine is frequently observed in patients failing therapy, either alone or in combination with additional mutations.[10] This has led to the designation of K103N as a "pan-class resistance mutation".

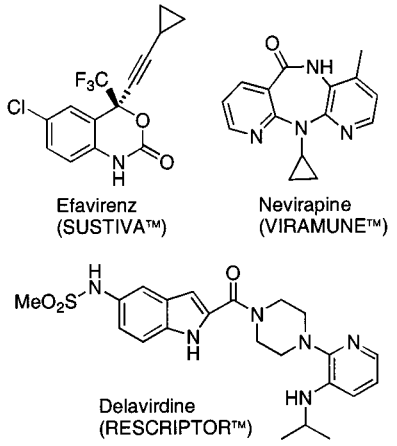

Figure 1. Structures of marketed non-nucleoside reverse transcriptase inhibitors.

Efavirenz is an NNRTI with nanomolar potency, substantial plasma protein binding, and pharmacokinetics allowing once-daily dosing which has demonstrated significant clinical activity, both in combination with protease inhibitors or in a protease-sparing regimen consisting of efavirenz plus two nucleoside RT inhibitors.[11] In clinical trials in which efavirenz is combined with other highly active antiretroviral agents, viral load response is at least as significant and durable as any other HIV compound tested to date.[11,12] Although the majority of patients on efavirenz-containing regi-

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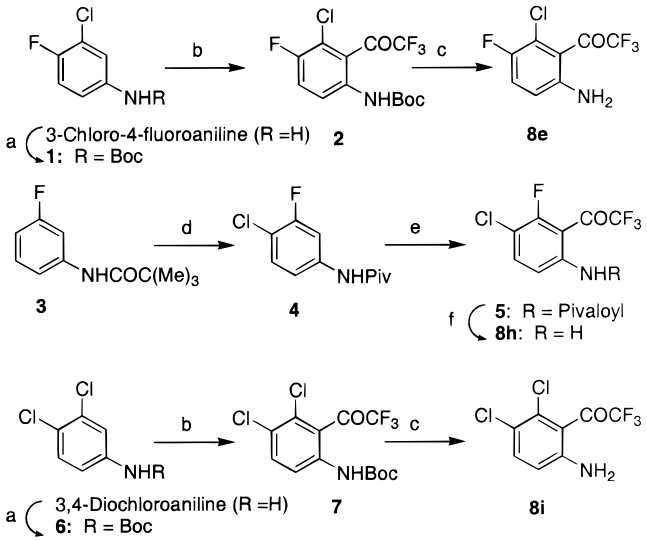
Scheme 1. Synthesis of **8e**, **8h**, and **8i**[a]



[a] (a) NaHMDS, Boc_2O, THF; (b) (i) *t*-BuLi, TMEDA, THF, (ii) CF_3CO_2Et; (c) 4 N HCl in dioxane; (d) NCS, DMF, 80 °C; (e) (i) *n*-BuLi, THF, (ii) CF_3CO_2Et; (f) 6 N HCl, DME, reflux.

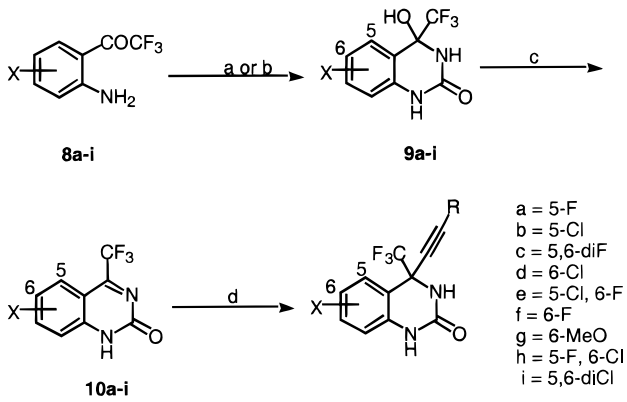
mens have shown a sustained antiviral response, patients whose viral load levels have rebounded after an initial response to drug have the K103N mutation in over 90% of sequences examined.[12] Following the appearance of virus with the K103N mutation, viruses with multiple mutations arise more slowly. For instance, the double mutations K103N+V108I or K103N+P225H are observed in a large number of samples approximately 4 months after initial viral load rebound.[12] The highly resistant virus with the double mutation K103N+L100I is much less prevalent. Considering the significant antiviral benefit apparent from ongoing clinical trials with efavirenz, development of additional NNRTIs which retain similar ease of administration and safety profiles, but with superior overall profiles against mutant viruses such as K103N, K103N+V108I, and K103N+P225H, should provide even more powerful drugs to serve as cornerstones of combination regimens and as components of salvage therapy when other treatment modalities have failed.

The structure−activity relationship leading to the identification of four new NNRTI analogues is described wherein we simultaneously considered intrinsic potency, plasma protein binding, and pharmacokinetics during the iterative synthesis process. We have identified a cohort of four related analogues that combine improved potency against mutant HIV variants with substantial oral bioavailability, long plasma half-life, and moderate plasma protein binding.

Chemistry and Biological Results

Amino ketones **8a**−**h** (Scheme 2) were prepared as previously reported,[13,14] with the exception of **8e**, **8h**, and **8i**, which were prepared as described in Scheme 1. N-Boc-protected 3-chloro-4-fluoro aniline **1**, prepared via Kelly's procedure using sodium hexamethyldisilazide (NaHMDS),[15] was metalated under conditions previously described in the literature[16] and quenched with ethyl trifluoroacetate to give **2**. Removal of the N-Boc protecting group delivered amino ketone **8e**. Pivaloylated 3-fluoroaniline **3**[17] was chlorinated using N-

Scheme 2. Synthesis of 4-Alkynyl-3,4-dihydro-4-trifluoromethylquinazolin-2(1*H*)-ones[a]



[a] (a) (i) TMSNCO, THF, (ii) TBAF/THF; (b) KOCN, AcOH/H_2O; (c) toluene or xylenes, reflux, 4 Å molecular sieves; (d) Li≡R, BF_3·OEt_2, THF.

chlorosuccinimide in hot DMF to give the 5-fluoro-6-chloro derivatized aniline **4**. Metalation of **4** with *n*-butyllithium at −78 °C followed by quenching the anion with ethyl trifluoroacetate gave **5**. Hydrolysis of the pivaloyl group afforded the desired aniline **8h**. Similar to the synthesis of **8e**, 3,4-dichloroaniline was functionalized as the N-Boc derivative **6** and metalated using a mixture of *tert*-butyllithium and N, N, N′, N′-tetramethylethylenediamine (TMEDA) in tetrahydrofuran (THF) at −78 °C, and the resultant anion was quenched with ethyl trifluoroacetate to afford **7**. Removal of the Boc group from **7** gave aniline **8i**.

Treatment of amino ketones **8a**−**i** with either trimethylsilylisocyanate[18] followed by tetrabutylammonium fluoride (TBAF) or potassium cyanate in aqueous acetic acid delivered aminols **9a**−**i** (Scheme 2). Heating **9a**−**i** with 4 Å molecular sieves in either toluene or xylenes at reflux effected the desired dehydration to afford the trifluoromethyl ketimines **10a**−**i**. Aminols containing a 5-halogen substituent required higher temperatures to effect dehydration and were therefore dehydrated using xylenes as the solvent. Ketimines **10a**−**i** were alkylated with a THF solution of lithiated alkynes in the presence of a catalytic amount of boron trifluoride etherate (BF_3·OEt_2) to give the desired quinazolinones. It was found necessary to use a Lewis acid since the rate of lithium acetylide addition to ketimine **10** in the absence of BF_3·OEt_2 was sluggish, while use of greater than 0.5 equiv of BF_3·OEt_2 resulted in reduced yields of the desired products.

The ability of the racemic quinazolinones to inhibit HIV-1 RT in an in vitro enzyme assay (IC_{50} data)[3] and to inhibit wild-type RF strain of HIV-1[19] (IC_{90} data) is represented in Table 1. To get an estimate of the extent of protein binding, and its subsequent impact on antiviral potency, a rapid assay to determine the effects of plasma protein binding was devised. The addition of heat inactivated human serum at concentrations in excess of about 25% is cytotoxic, precluding a direct assessment. However, since albumin and acid glycoprotein comprise the major proteins of serum, the impact of these two components was examined at concentrations found in human serum. In the "protein binding shift assay", the antiviral potency is determined by measurement of viral RNA in standard tissue culture

Table 1. In Vitro Biological Activity of 4-Alkynyl, 4-Trifluoromethyl-3,4-dihydro-2(1*H*)-quinazolinones

				IC_{90} (nM)		
compd	X	R	enzyme IC_{50} (nM)[3]	antiviral activity[19]	PB adj wild-type IC_{90} (nM)	PB fold shift
25	5,6-F_2	ethyl	74 ± 27	1.5	10	6.9
11	5-F	cyclopropyl	62 ± 13	1.4	14	10
22	5-Cl,6-F	isopropyl	78 ± 25	3.0	15	5
12	5-Cl	cyclopropyl	72 ± 15	2.5	18	7
13	5,6-F_2	cyclopropyl	74 ± 35	2.1	19	9
20	5,6-F_2	isopropyl	91 ± 13	2.1 ± 1.4	21	9.8
16	6-F	cyclopropyl	50 ± 4	2.0	24	12
28	5,6-F_2	2-pyridyl	68 ± 17	2.0	24	12
27	6-F	ethyl	54 ± 9	2.5	25	10
15	5-Cl,6-F	cyclopropyl	59 ± 12	2.7	27	10
efavirenz		see Figure 1	47 ± 25	1.7 ± 0.5	28	16.5
17	6-MeO	cyclopropyl	124 ± 90	2.9	29	10
31	6-F	2-pyridyl	126 ± 30	5	33	7
18	5-F,6-Cl	cyclopropyl	102 ± 67	4.8	40	8.4
30	5-Cl,6-F	2-pyridyl	80 ± 15	2.3	41	18
14	6-Cl	cyclopropyl	111 ± 34	2.7 ± 0.6	41	15
24	6-MeO	isopropyl	401 ± 182	3.8	42	11
36	6-MeO	phenyl	219 ± 34	3.2	42	13
33	5,6-F_2	phenyl	181 ± 83	6.2	43	7
35	6-F	phenyl	143 ± 30	6.6	66	10
29	6-Cl	2-pyridyl	129 ± 36	3.4	79	23
26	6-Cl	ethyl	110 ± 61	3.3	83	25
34	6-Cl	phenyl	277 ± 94	7.1	86	12
23	6-F	isopropyl	39 ± 8	2.6	86	33
19	5,6-Cl_2	cyclopropyl	166 ± 38	8.0	88	11
21	6-Cl	isopropyl	281 ± 105	3.0 ± 0.2	90	30
nevirapine		see Figure 1	4848 ± 1739	50 ± 10	100	2
32	6-MeO	2-pyridyl	237 ± 99	8.1	138	17
delavirdine		see Figure 1	422 ± 92	37 ± 9	1406	38

medium or in tissue culture medium to which 45 mg/mL human serum albumin and 1 mg/mL alpha-1 acid glycoprotein have been added. The ratio of the measured 90% inhibitory concentrations were then expressed as a fold increase in measured IC_{90} (PB fold shift).

As seen in Table 1, except for **32**, all compounds tested were more potent inhibitors of wild-type HIV-1 than either nevirapine or delavirdine and most analogues had wild-type antiviral potency similar to that of efavirenz, with compounds **11** and **25** appearing potentially more potent (racemates contain only 50% of the active enantiomer). Taking into account the estimated effect of human plasma protein binding by multiplying the observed IC_{90} value by the PB fold shift gave the protein binding adjusted (PB Adj) IC_{90} data. When this was done, it became evident that several analogues appeared more potent than efavirenz. It was also apparent that incorporation of a 5-halo substitituent, either in the presence or the absence of a 6-halo substituent, conferred beneficial activity as exemplified by the six most active compounds in Table 1. Small groups on the alkyne, such as the ethyl analogue **25**, appear to be favored over larger groups, such as phenyl analogue **33**.[20] Two 2-pyridyl containing compounds, **28** and **31**, are also very potent, but less so than their corresponding cyclopropylalkynyl (**13** and **16**, respectively) and butynyl (**25** and **27**, respectively) analogues. Comparing similar pairs of analogues, 5,6-difluoro substituents confer improvements in potency compared to 6-chloro analogues.

The ability of racemic quinazolinones to inhibit replication of mutant viruses possessing the amino acid substitution K103N or L100I is listed in Table 2. The clinically significant HIV single mutant K103N is the most prevalent mutation observed in vivo in patients who have failed efavirenz-containing regimens and is frequently observed alone, or in combination with other mutations in nevirapine and delavirdine failures.[10,12] The L100I mutation was selected by efavirenz through in vitro selection experiments.[19] The compounds in Table 2 are ranked by their potency against the K103N mutant virus, adjusting for the effects of protein binding using the PB shift assay. The potency of some of the new analogues against the K103N mutant virus was significantly increased compared to that of efavirenz. When the estimated effects of protein binding were taken into account, the superior potency of the new analogues became even more evident. It was found that compounds having a 5-halogen substitution, with or without a halogen in the 6-position, showed the most potent activity against the K103N mutant. In particular, the racemate **22** exhibited exceptional activity toward inhibiting the K103N containing virus, as exhibited by its 74 nM protein binding adjusted IC_{90}. The improvement of racemic **22** toward the protein binding adjusted K103N IC_{90} value over delavirdine, nevirapine, and efavirenz is striking: 510-, 140-, and 14-fold improvement, respectively.

Prior to the discovery of **22**, several of the best quinazolinones, **13**, **14**, and **20**, were synthesized on gram scale and the enantiomers separated by chiral HPLC. The active isomers of these compounds are DPC 961, DPC 963, and **37** (Figure 2). The absolute stereochemistry of DPC 961 was determined from a single-crystal X-ray, while the absolute stereochemistry of DPC 963 and **37** was inferred from the data obtained in the enzyme and whole cell assays, with the undesired enantiomers exhibiting virtually no activity (Table 3).

Upon oral dosage of a mixture of **37**, DPC 961, and DPC 963 in rhesus monkeys, only DPC 961 and DPC 963 were found to be present in micromolar concentrations, whereas **37** was undetectable in plasma. Studies

Table 2. Resistance Profiles of 4-Alkynyl, 4-Trifluoromethyl-3,4-dihydro-2(1*H*)-quinazolinones

			IC_{90} (nM)		
compd	X	R	antiviral activity K103N	antiviral activity L100I	PB adj antiviral activity toward K103N
22	5-Cl,6-F	isopropyl	15	13	74
25	5,6-F_2 e	ethyl	14	18	93
13	5,6-F_2	cyclopropyl	13	12	119
20	5,6-F_2	isopropyl	14	10	139
18	5-F,6-Cl	cyclopropyl	18	ND[a]	151
15	5-Cl,6-F	cyclopropyl	18	16	178
19	5,6-Cl_2	cyclopropyl	18	ND	196
14	6-Cl	cyclopropyl	22	18	336
17	6-MeO	cyclopropyl	40	46	396
12	5-Cl	cyclopropyl	63	70	441
16	6-F	cyclopropyl	48	29	566
24	6-MeO	isopropyl	56	28	599
21	6-Cl	isopropyl	22	28	653
27	6-F	ethyl	71	74	710
26	6-Cl	ethyl	26	ND	826
23	6-F	isopropyl	27	17	891
11	5-F	cyclopropyl	89	108	917
efavirenz			64 ± 24	77 ± 26	1056
30	5-Cl,6-F	2-pyridyl	73	44	1307
28	5,6-F_2	2-pyridyl	109	37	1308
33	5,6-F_2	phenyl	191	256	1337
34	6-Cl	phenyl	250	365	3000
31	6-F	2-pyridyl	483	255	3140
35	6-F	phenyl	322	677	3220
36	6-MeO	phenyl	283	462	3594
29	6-Cl	2-pyridyl	160	64	3728
32	6-MeO	2-pyridyl	338	98	5881
nevirapine			5100 ± 830	ND	10200
delavirdine			1000 ± 270	ND	38000

[a] ND = not determined.

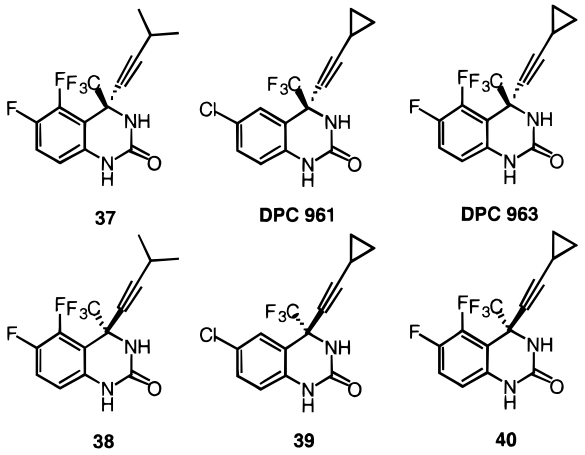


Figure 2. Absolute stereochemistry of **37**, DPC 961, and DPC 963.

Table 3. Activity of Resolved Quinazolinones

	IC_{90} (nM)		
compd	antiviral activity K103N	antiviral activity wild-type	enzyme IC_{50} (nM)
37	9	1.6	15 ± 8
38	ND[a]	229	1519 ± 49
DPC 961	10 ± 3.2	2.0 ± 0.7	31 ± 8
39	ND	34000	267
DPC 963	11 ± 4.8	1.3 ± 0.6	18 ± 5
40	ND	101	6600

[a] ND = not determined.

indicated that the 3-methylbutynyl substituent present in **37** was rapidly metabolized by liver homogenate fractions when compared to efavirenz. The metabolic liability found with compound **37** precluded its further evaluation in the other assay systems shown in Tables 4 and 5. Using the same line of reasoning, the chiral resolution of other compounds possessing a metabolically labile iso-propyl substituted alkyne, such as is found in compound **22**, and evaluation of the single enantiomer in the assay systems described in Tables 4 and 5 would not lead to an advancement of our ultimate goal: identifying compounds which possess not only excellent virologic profiles but have physical properties consistent with once-daily dosing in humans.

With the favorable pharmacokinetic results obtained with DPC 961 and DPC 963, we turned our attention to trying to obtain compounds which might possess better overall qualities. It was known from previous SAR for efavirenz that olefin analogues had a slightly improved profile.[20] Therefore, the olefin analogues were prepared by lithium aluminum hydride reduction of DPC 961 and DPC 963 to afford DPC 083 and DPC 082, respectively (Scheme 3). 1,2-Dichlorobenzene was used in order to suppress dehalogenation of the aromatic rings during the reduction.

Table 4 compares the virologic profile and protein binding properties of DPC 961, DPC 963, DPC 082, and DPC 083 to that of efavirenz using laboratory strains and clinical isolates of HIV-1 and detection by several different methods. Like efavirenz, DPC 961, DPC 963, DPC 082, and DPC 083 are potent in the nanomolar range against both laboratory and clinical isolates, maintain that potency against zidovudine resistant isolates, and are inactive against HIV-2. Within the standard deviations of the assays, the four new analogues are equal in measured potency to efavirenz.

Many drugs bind to plasma proteins, and the effect of such binding is to decrease the concentration of free drug available to equilibrate across cell membranes and interact with the target. For AIDS therapeutics, clinical failure has been associated with significant and unex-

Table 4. Antiviral Activity and Protein Binding of Second-Generation NNRTIs

		IC_{90} nM					
virus	cells	assay	DPC 961	DPC 963	DPC 082	DPC 083	efavirenz
RF	MT-2	RNA	2.0 ± 0.7	1.3 ± 0.6	2.0 ± 0.2	2.1 ± 0.8	1.7 ± 0.5
RF	MT-2	yield	2.7 ± 0.4	2.3 ± 0.8	2.7 ± 0.2	1.9 ± 0.9	2.4 ± 0.5
Thai 9466[a]	PBMC	P24	5.0 ± 3.5	1.9 ± 0.1	ND[d]	0.9	8.5
A018C[b]	PBMC	P24	2.5 ± 0.4	1.6 ± 0.1	ND	ND	2.8
E[b]	MT-2	Yield	ND	1.7	2.9	1.3 ± 0.7	2.8
HIV-2	MT-2	Yield	>2800	>950	>2800	>2800	>3000
PB shift	MT-2	RNA	17	6.9	3.5	3.7	17

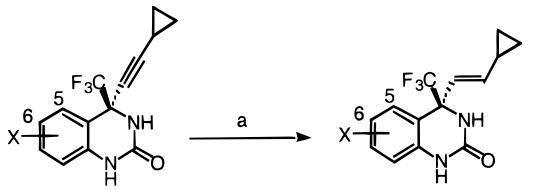
	DPC 961	DPC 963	DAC 082	DPC 083	efavirenz
% free in human serum[c]	1.5%	2.8%	3.0%	2.0%	0.2−0.5%
% free in tissue culture medium	31%	37%	53%	39%	27%
plasma IC_{90} for RF virus	40 nM	18 nM	33 nM	40 nM	92−220 nM

[a] Thai 9466 is a wild-type clinical isolate. [b] A018C and E are zidovudine-resistant clinical isolates. The genotype of A018C is unknown and the genotype of E contains the mutations D67N and K70R. [c] Data from ref 3. [d] ND = Not determined.

Table 5. Potency of Second-Generation NNRTIs against Mutant HIV-1 Variants

parameter	efavirenz	DPC 961	DPC 963	DPC 082	DPC 083
K103N measured IC_{90} (nM)	64 ± 24	10 ± 3.2	11 ± 4.8	21 ± 9.2	27 ± 11
K103N free drug IC_{90} (nM)	17	3.1	4.0	11	11
K103N plasma IC_{90} (nM)	**3400−8100**	**210**	**140**	**370**	**550**
sL100I measured IC_{90} (nM)	120 ± 30	13 ± 7.9	8.0 ± 5.7	5.9 ± 3.8	11 ± 6.8
sL100I free drug IC_{90} (nM)	33	4.0	3.0	3.1	4.3
sL100I plasma IC_{90} (nM)	**6600−15700**	**270**	**110**	**100**	**220**
sV179D/L100I/Y181C measured IC_{90} (nM)	2400 ± 420	190 ± 28	110 ± 44	250 ± 34	320
sV179D/L100I/Y181C free drug IC_{90} (nM)	650	59	41	130	120
sV179D/L100I/Y181C plasma IC_{90} (nM)	**130000−309500**	**3900**	**1460**	**4300**	**6000**

Scheme 3. Synthesis of DPC 082 and DPC 083[a]



DPC 961: X = 6-Cl
DPC 963: X = 5,6-diF

DPC 083: X = 6-Cl
DPC 082: X = 5,6-diF

[a] (a) $LiAlH_4$, 1,2-dichlorobenzene, THF.

pected protein binding. The influence of albumin and acid glycoprotein can be estimated by the increase in the measured IC_{90} in the presence of these purified components in the tissue culture medium. As shown in Table 4, the PB shift assay indicated that all four analogues showed some binding by the albumin in the tissue culture medium, as reflected by an increase in the measured IC_{90}. Importantly, tissue culture medium is supplemented with heat-inactivated calf serum to maintain cell integrity. The shift data suggested that binding to the albumin in the fetal calf serum might likely occur. To accurately assess binding to tissue culture medium and human serum in order to predict drug levels required for adequate inhibition of replication, ultrafiltration was used to determine the free fraction at equilibrium. The percent free drug in tissue culture medium or human serum is shown in Table 4. Note that for efavirenz and the new analogues, the PB shift assay underpredicts the extent of plasma protein binding measured by physical separation and detection.

To maintain suppression of virus replication, the concentration of free drug in the plasma must exceed the free drug concentration required for inhibition of replication. Table 4 shows that the percentage binding of the second-generation NNRTIs by proteins in human plasma is 3−14-fold lower than that of efavirenz, depending on the value used for efavirenz free fraction. We have defined the property plasma IC_{90} as the total drug concentration needed to achieve 90% suppression of HIV replication. The plasma IC_{90} is determined by dividing the concentration of free drug required for inhibition of HIV (calculated by adjusting the measured IC_{90} values by the tissue culture medium binding) by the free fraction present in human serum. The plasma IC_{90} is thus a calculated parameter based on three different measured values. In the case of efavirenz, the high degree of plasma protein binding was characterized by a number of different assays. The data are expressed as a range of free drug values for this inhibitor (Sustiva (efavirenz capsules) Product Information Leaflet). The plasma IC_{90} for the RF form of HIV-1 is shown in Table 4. The plasma IC_{90} for all four analogues is 2−12-fold less than the range determined for efavirenz, an effect driven almost exclusively by improvements in plasma protein binding properties. More importantly, a lower plasma IC_{90} indicates that at comparable total plasma levels, greater inhibition of replication should be observed with the second-generation analogues.

Table 5 shows the measured potency, calculated free drug potency and plasma IC_{90} for the second-generation compounds against mutant HIV-1 variants, including recombinant K103N, and viruses selected for in tissue culture after exposure of infected cells to efavirenz. Such selected viruses are indicated by an "s" prefix and contain the L100I mutation or the triple mutation V179D/L100I/Y181C.[21]

Table 5 indicates that all four second-generation analogues show improved measured potency against K103N, sL100I, and the triple substituted virus selected in tissue culture by exposure to efavirenz. This improvement in measured potency ranges from 2.3-fold (K103N potency for DPC 083 versus efavirenz) to 22-fold (triple

mutant potency for DPC 963 versus efavirenz). Because of decreased binding by human serum proteins, the plasma IC_{90} values are markedly improved for the second-generation compounds. Using the most favorable plasma IC_{90} values for efavirenz, the second-generation compounds show at least 6-, 24-, and 22-fold lower plasma IC_{90} values than efavirenz for the K103N, sL100I, and sV179D/L100I/Y181C triple substituted viruses, respectively. Provided human plasma levels are similar to those observed for efavirenz, where 5.6 μM is the observed trough level at 600 mg qd, any of the four second-generation compounds could provide sufficient drug at trough for at least 90% suppression of wild type and K103N- and L100I-containing single and triple substituted viruses. We have previously reported that chimpanzee pharmacokinetics are consistent with once daily dosing and the attainment of high plasma levels.[3] Chimpanzee trough levels normalized to a single 10 mg/kg dose were 12.7 μM for DPC 961, 6.2 μM for DPC 963, 4.7 μM for DPC 082, and 7.6 μM for DPC 083. For comparison, the trough level for efavirenz in the chimpanzee is 2.7 μM. All four compounds are completing phase I studies in sero-negative volunteers so that we may identify which compound gives the required trough levels to cover the target virus populations.

Conclusions

A series of trifluoromethyl-containing quinazolinones were synthesized and evaluated for their ability to inhibit wild-type and various mutant forms of HIV-1. Quinazolinones were examined since previous work had shown that potency toward HIV-1 reverse transcriptase could be achieved with these compounds, although the previously reported materials had a poor resistance profile.[22] It was felt that an improvement in the overall resistance profile could be achieved by the incorporation of a trifluoromethyl group into the molecule, as found in efavirenz, and by manipulating the alkyne side chain.

We simultaneously considered potency, protein binding, and pharmacokinetic properties when characterizing and ranking new analogues. It was found that the presence of the cyclopropyl acetylene moiety was critical in order to achieve satisfactory blood plasma levels. An increase in the overall resistance profile was observed for compounds possessing a 5,6-dihalogen substitution pattern when compared to the 5- or 6-monohalogen-substituted analogues. The improvement in potency of the 5,6-dihalogen-substituted analogues was due in large part to less protein binding when compared to monohalogenated compounds. The overall profile of DPC 961, DPC 963, DPC 082, and DPC 083 suggests strongly that any of these new analogues could provide superior coverage of wild type and mutant HIV variants relative to efavirenz, provided that the pharmacokinetics in humans are similar to those previously observed for efavirenz. Considering the powerful antiviral benefit apparent from ongoing clinical studies with efavirenz, development of additional NNRTIs that retain similar ease of administration and safety profile, but with superior overall profiles against mutant variants, should provide even more durable drugs to serve as constituents of combination drug regiments and as components of salvage therapy when other treatment modalities have failed.

Experimental Section

Chemical Methods. All procedures were carried out under argon in oven-dried glassware unless otherwise indicated. Proton NMR spectra were obtained on VXR or Unity 300 MHz instruments (Varian Instruments, Palo Alto) with chemical shifts δ in ppm downfield from TMS as an internal reference standard. Melting points were determined on a Büchi 535 melting point apparatus and are uncorrected. Elemental analyses were performed by Quantitative Technologies, Inc., Bound Brook, NJ 08805. Mass spectra were measured with a HP 5988A mass spectrometer with particle beam interface using NH_3 for chemical ionization or a Finnigan MAT 8230 mass spectrometer with NH_3-DCI or VG TRIO 2000 for ESI. High-resolution mass spectra were measured on a VG 70-VSE instrument with NH_3 ionization. Optical rotations were obtained on a Perkin-Elmer 241 polarimeter. Solvents and reagents were obtained from commercial vendors in the appropriate grade and used without further purification unless otherwise indicated.

(3-Chloro-4-fluorophenyl)carbamic Acid *tert*-Butyl Ester (1). To a solution of 3-chloro-4-fluoroaniline (10.0 g, 68.7 mmol) in anhydrous THF (69 mL) was slowly added sodium bis(trimethylsilyl)amide (137 mL of 1.0 M solution in THF). The mixture was stirred at room temperature for 1.5 h before addition of a solution of Boc_2O (15.0 g, 68.7 mmol) in anhydrous THF (5 mL). The mixture was aged at room temperature for 3 h, concentrated under reduced pressure, diluted with EtOAc (200 mL), and washed with 0.5 N HCl (250 mL). The aqueous phase was back-extracted with EtOAc (100 mL). The combined organic extracts were dried over $MgSO_4$, filtered, and concentrated, to give 16.1 g of crude **1** which was used without further purification (95% yield): mp 130−132 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.59 (br s, 1H), 7.80 (dd, J = 6.4, 2.4 Hz, 1H), 7.45−7.39, (m, 1H), 7.22−7.16 (m, 1H), 1.46 (s, 9H).

[3-Chloro-4-fluoro-2-(2,2,2-trifluroethanone)phenyl]carbamic Acid *tert*-Butyl Ester (2). To a solution of anhydrous THF (15 mL) containing TMEDA (2.37 g, 3.08 mL, 20.4 mmol) at −78 °C was added *t*-BuLi (12.0 mL of 1.7 M solution). The mixture was aged at −78 °C for 0.5 h, before addition of a −78 °C solution of **1** (2.50 g, 10.2 mmol) in anhydrous THF (20 mL) via cannula over approximately 10 min. The mixture was aged at −78 °C for 2 h and then ethyl trifluoroacetate (2.90 g, 2.43 mL, 20.4 mmol) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature. The mixture was quenched with saturated aqueous NH_4Cl after 2 h and extracted with EtOAc (150 mL), washed with saturated aqueous $NaHCO_3$ (80 mL) and aqueous NaCl (80 mL), dried over $MgSO_4$, filtered, and concentrated. The concentrate was purified by flash chromatography (15% EtOAc/hexanes) to give 1.03 g of **2** as a yellow solid (30% yield): mp 144 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.83 (dd, J = 8.8, 4.8 Hz, 1H), 7.32−7.25 (m, 1H), 1.68 (s, 9H); ^{19}F NMR (282 MHz, acetone-d_6) δ −77.7 (s, 3F), −117.8 (s, 1F).

2,2-Dimethyl-*N*-(3-fluorophenyl)propanamide (3) was prepared according to a literature procedure:[17b] mp 112.5−113 °C (lit. mp 100−101 °C[17a] and 112−114 °C[17b]).

1-(2-Amino-6-chloro-5-fluorophenyl)-2,2,2-trifluoroethanone (8e). A solution of **2** (1.03 g, 3.01 mmol) in 4 N HCl in dioxane (3 mL) was stirred at room temperature for 1.5 h before addition of water (5 mL). Solid $NaHCO_3$ was added until basic. The mixture was diluted with Et_2O (25 mL) and water (25 mL) and the phases were separated. The aqueous phase was extracted with more Et_2O (15 mL) and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The concentrate was purified by flash chromatography (15% EtOAc/hexanes) to give 245 mg of **8e** (34% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.30 (t, J = 9.2 Hz, 1H), 6.94 (dd, J = 9.2, 4.0 Hz, 1H), 5.58 (br s, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −75.4 (s, 3F), −132.1 (s, 1F).

2,2-Dimethyl-*N*-(4-chloro-3-fluorophenyl)propanamide (4). A solution of **3** (2.00 g, 10.2 mmol) in DMF (20 mL) containing N-chlorosuccinimide (1.50 g, 11.2 mmol) was heated at 80 °C for approximately 20 min before cooling to room

temperature. The mixture was diluted with EtOAc; washed with saturated aqueous $NaHCO_3$, water, and saturated aqueous NaCl; dried over $MgSO_4$; filtered; and concentrated to afford a white solid, which was purified by flash chromatography (10% EtOAc/hexanes) to give 1.48 g of **4** as a white solid (63% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 8.85 (br s, 1H), 7.86 (dd, J = 12, 2.0 Hz, 1H), 7.44−7.34 (m, 2H), 1.25 (s, 9H); ^{19}F NMR (282 MHz, acetone-d_6) δ −116.74 to −116.89 (m, 1F). Anal. ($C_{11}H_{13}ClFNO$) C, H, N.

2,2-Dimethyl-*N*-(4-chloro-3-fluoro-2-trifluoroacetylphenyl)propanamide (5). To a solution of **4** (1.00 g, 4.35 mmol) in anhydrous THF (14.5 mL) at −78 °C was added *n*-BuLi (6.5 mL of 1.6 M solution in hexanes, 10.4 mmol) via an addition funnel over 10 min. The mixture was aged at −78 °C for 1.5 h before the dropwise addition of ethyl trifluoroaceate (1.4 g, 1.2 mL, 10 mmol). The mixture was stirred at −78 °C for 0.5 h and then the reaction was allowed to warm to room temperature. The reaction was quenched by addition of saturated aqueous NH_4Cl and poured into Et_2O (50 mL) and water (50 mL). The organic phase was isolated, washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered and concentrated. The concentrate was purified by flash chromatography to yield 1.20 g of **5** (85% yield): mp 106−108 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.61 (br s, 1H), 7.70 (t, J = 8.4 Hz, 1H), 7.28 (dd, J = 8.8, 1.5 Hz, 1), 1.21 (s, 9H); ^{19}F NMR (282 MHz, acetone-d_6) δ −76.1 to −76.2 (m, 3F), −109.8 to −110.2 (m, 1F). Anal. ($C_{13}H_{12}ClF_4NO_2$) C, H, N.

1-(2-Amino-5-chloro-6-fluorophenyl)-2,2,2-trifluoroethanone (8h). A solution of **5** (5.32 g, 16.3 mmol) in ethylene glycol dimethyl ether (13 mL) and 6 N HCl (65 mL) was heated at reflux for 1.5 h. The mixture was cooled to room temperature, and solid Na_2CO_3 (CO_2 evolution!) was slowly added until the solution was basic. Water (150 mL) was added and the mixture was extract with Et_2O (200 mL). The aqueous phase was back-extract with Et_2O (100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. Baseline material was removed by passage through a plug of silica (10% EtOAc/hexanes) to give 3.45 g of **8h** as a yellow oil which was used without further purification (88% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.48−7.39 (m, 3H), 6.84 (dd, J = 9.2, 1.5 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −76.1 to −76.2 (m, 1F), −76.0 to −76.2 (m, 3F).

(3,4-Dichlorophenyl)carbamic Acid *tert*-Butyl Ester (6). To a solution of 3,4-dichloroaniline (10.0 g, 61.7 mmol) in anhydrous THF (62 mL) was slowly added sodium bis-(trimethylsilyl)amide (123 mL of 1.0 M solution in THF). The reaction was stirred at room temperature for 1.5 h before addition of a solution of Boc_2O (13.5 g, 61.7 mmol) in anhydrous THF (5 mL). The mixture was aged at room temperature for 3 h, concentrated under reduced pressure, diluted with EtOAc (200 mL), and washed with 0.5 N HCl (250 mL). The aqueous phase was back-extracted with EtOAc (100 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated to give 15.4 g of crude **6**, which was used without further purification (95% yield): mp 112−113 °C (lit.[26] mp 114−115 °C); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.70 (br s, 1H), 7.88 (s, 1H), 7.43 (s, 2), 1.46 (s, 9H).

[3,4-Dichloro-2-(2,2,2-trifluroethanone)phenyl]carbamic Acid *tert*-Butyl Ester (7). To a solution of anhydrous THF (14 mL) containing TMEDA (2.22 g, 2.88 mL, 19.1 mmol) at −78 °C was added *t*-BuLi (11.2 mL of 1.7 M solution). The mixture was aged at −78 °C for 0.5 h, before addition of a −78 °C solution of **6** (2.50 g, 9.54 mmol) in anhydrous THF (19 mL) via cannula over approximately 10 min. The mixture was aged at −78 °C for 2 h, and then ethyl trifluoroacetate (2.71 g, 2.27 mL, 19.1 mmol) was added. The cooling bath was removed and the mixture was allowed to warm to room temperature. The reaction was quenched with saturated aqueous NH_4Cl after 2 h and extracted with EtOAc (150 mL), washed with saturated aqueous $NaHCO_3$ (80 mL) and aqueous NaCl (80 mL), dried over $MgSO_4$, filtered, and concentrated. The concentrate was purified by flash chromatography (15% EtOAc/hexanes) to give 0.76 g of **7** as an impure yellow oil which was used without further purification (22% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.72 (d, J = 8.4 Hz. 1H), 7.51 (d, J = 8.4 Hz, 1H), 1.68 (s, 9H); ^{19}F NMR (282 MHz, acetone-d_6) δ −77.4 (s, 3F).

1-(2-Amino-5,6-dichlorophenyl)-2,2,2-trifluoroethanone (8i). A solution of **7** (0.76 g, 2.12 mmol) in 4 N HCl in dioxane (2 mL) was stirred at room temperature for 1.5 h before addition of water. Solid $NaHCO_3$ (CO_2 evolution!) was added until the mixture was basic. The mixture was diluted with Et_2O (25 mL) and water (25 mL), and the phases were separated. The aqueous phase was extracted with more Et_2O (15 mL), and the combined organic extracts were dried over $MgSO_4$, filtered, and concentrated. The concentrate was purified by flash chromatography (15% EtOAc/hexanes) to give 100 mg of **8i** (19% yield); the major byproduct was recovered **6**: ^{1}H NMR (300 MHz, acetone-d_6) δ 7.41 (d, J = 9.2 Hz, 1H), 6.92 (d, J = 9.2 Hz, 1H), 5.69 (br s, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −75.6 (s, 3F).

General Procedure for Aminol Formation. Procedure A. To a solution of ketone **8** in anhydrous THF (0.5 M) were added N,N-(dimethylamino)pyridine (0.1 equiv) and trimethylsilylisocyanate (2.6 equiv). The mixture was stirred at room temperature for 5 h before addition of tetrabutylammoniun fluoride (2 equiv of a 1 M solution in THF). The mixture was stirred at room temperature for an additional 0.5 h; diluted with EtOAc; washed sequentially with 1 N HCl, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl; dried over $MgSO_4$, filtered; and concentrated. The resulting solid was triturated with hexanes and dried.

Procedure B. To a solution of ketone **8** in acetic acid (0.55 M) and water (5.5 M) was added potassium cyanate (2.5 equiv). The resulting mixture was stirred at room temperature overnight, diluted with water (4 mL/mmol of **8**), and stirred for 15 min before collection of the precipitate. The white solid was washed with water and dried under reduced pressure.

3,4-Dihydro-5-fluoro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9a) was prepared as described in procedure A to afford 323 mg of **9a** (85% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 9.08 (br s, 1H), 7.43−7.30 (m, 2H), 6.96 (br s, 1H), 6.85−6.74 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.4 (s, 3F), −111.8 (s, 1F).

5-Chloro-3,4-dihydro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9b) was prepared as described in procedure A to afford 234 mg of **9b** (99% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 9.03 (br s, 1H), 7.33 (t, J = 8.1 Hz, 1H), 7.26 (br s, 1H), 7.07 (d, J = 8.1 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 6.94 (br s, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −85.6 (s, 3F).

5,6-Difluoro-3,4-dihydro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9c) was prepared as described in procedure A to afford 110.9 g of **9c** (92% yield): mp 215 (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.13 (br s, 1H), 7.45−7.32 (m, 2H), 7.18 (br s, 1H), 6.85−6.80 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.6 (d, J = 17.2 Hz, 3F), −137.5 to −137.7 (m, 1F), −148.5 to −148.6 (m, 1F). Anal. ($C_9H_5F_5N_2O_2 \cdot 0.2C_4H_8O_2$) C, H, N.

6-Chloro-3,4-dihydro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9d) was prepared as described in procedure B to afford 2.70 g of **9d** (85% yield): mp 235 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.06 (br s, 1H), 7.48 (s, 1H), 7.40 (br s, 1H), 7.34 (dd, J = 8.8, 2.6 Hz, 1H), 6.97 (d, J = 8.8 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.4 (s, 3F); MS (CI) 266 (MH^+, 100). Anal. ($C_9H_6ClF_3N_2O_2$) C, H, N.

5-Chloro-3,4-dihydro-6-fluoro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9e) was prepared as described in procedure A to afford 2.10 g of **9e** (99% yield): mp 220 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.08 (br s, 1H), 7.39−7.33 (m, 2H), 7.21 (br s, 1H), 7.08−7.03 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −85.5 (s, 3F), −121.9 (s, 1F). Anal. ($C_9H_5ClF_4N_2O_2 \cdot 0.1C_3H_6O$) C, H, N.

3,4-Dihydro-6-fluoro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9f) was prepared as described in procedure A to afford 3.22 g of **9f** (87% yield): mp 202−204 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.02 (br s, 1H), 7.38 (br s, 1H), 7.30 (dd, J = 9.2, 1.8 Hz, 1H), 7.23−7.16 (m, 1H),

7.07−7.00 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.2 (s, 3F), −123.4 (s, 1F); MS (CI) 234 (M−H_2O, 100).

3,4-Dihydro-4-hydroxy-6-methoxy-4-trifluoromethylquinazolin-2(1*H*)-one (9g) was prepared as described in procedure B to afford 244 mg of **9g** (83% yield): mp 195 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 8.81 (br s, 1H), 7.17 (br s, 1H), 7.11 (br s, 1H), 7.00−6.92 (m, 2H), 6.83 (s, 1H), 3.76 (s, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.0 (s, 3F); HRMS calcd for $C_{10}H_9F_3N_2O_2$ [M + H]$^+$ 246.0613, 246.0616 found. Anal. ($C_{10}H_9F_3N_2O_3$) C, H, N.

6-Chloro-3,4-dihydro-5-fluoro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9h) was prepared as described in procedure B to afford 1.93 g of **9h** (79% yield): mp 216 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.27 (br s, 1H), 7.55−7.49 (m, 2H), 6.88 (dd, J = 8.8, 1.54 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −86.5 to −86.6 (m, 3F), −112.8 to −113.0 (m, 1F).

5,6-Dichloro-3,4-dihydro-4-hydroxy-4-trifluoromethylquinazolin-2(1*H*)-one (9i) was prepared as described in procedure A to afford 116 mg of **9i** (99% yield): mp 249−252 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.11 (br s, 1H), 7.57 (d, J = 8.8 Hz, 1H), 7.37 (br s, 1H), 7.04−7.01 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −85.4 (s, 3F).

General Procedure for Ketimine Formation. A solution of aminol **9** in either toluene or xylene containing 4 Å molecular sieves was heated at reflux until the CF_3 signal of **9** was no longer present as determined by ^{19}F NMR. The solution was cooled to room temperature, and the molecular sieves were removed by vacuum filtration and rinsed with acetone. The filtrate was concentrated and triturated with hexanes to afford the desired ketimine **10**.

5-Fluoro-4-trifluoromethylquinazolin-2(1*H*)-one (10a). Prepared according to the general procedure using xylenes to afford 238 mg of **10a** (80% yield): mp >275 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 7.90−7.83 (m, 1H), 7.36 (d, J = 8.4 Hz, 1H), 7.15−7.08 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −70.7 (s, 3F), −108.7 (s, 1F); Anal. ($C_9H_4F_4N_2O$) C, H, N.

5-Chloro-4-trifluoromethylquinazolin-2(1*H*)-one (10b). Prepared according to the general procedure using xylenes to afford 177 mg of **10b** (81% yield): mp 222 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.75 (t, J = 8.1 Hz, 1H), 7.52 (d, J = 8.1 Hz, 1H), 7.43 (d, J = 7.7 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −64.3 (s, 3F); Anal. ($C_9H_4ClF_3N_2O\cdot0.2C_3H_6O$) C, H, N.

5,6-Difluoro-4-trifluoromethylquinazolin-2(1*H*)-one (10c). Prepared according to the general procedure using xylenes to afford 9.91 g of **10c** (97% yield): mp 208 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.92−7.83 (m, 1H), 7.46−7.44 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −70.7 (d, J = 38.7 Hz, 3F), −136.7 (s, 1F), −146.5 to −146.6 (m, 1F); Anal. ($C_{10}H_7F_5N_2O_2$) C, H, N.

6-Chloro-4-trifluoromethylquinazolin-2(1*H*)-one (10d). Prepared according to the general procedure using toluene to afford 2.30 g of **10d** (96% yield): mp 217 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.86−7.82 (m, 2H), 7.61 (d, J = 8.8 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −67.9 (s, 3F).

5-Chloro-6-fluoro-4-trifluoromethylquinazolin-2(1*H*)-one (10e). Prepared according to the general procedure using xylenes to afford 175 mg of **10e** (65% yield): mp 190 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.79 (br s, 1H), 7.64 (br s, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −64.2 (s, 3F), −116.7 (s, 1F).

6-Fluoro-4-trifluoromethylquinazolin-2(1*H*)-one (10f). Prepared according to the general procedure using toluene to afford 6.64 g of **10f** (93% yield): mp 156 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.77−7.71 (m, 1H), 7.64−7.59 (m, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −68.2 (s, 3F), −119.5 (s, 1F).

6-Methoxy-4-trifluoromethylquinazolin-2(1*H*)-one (10 g). Prepared according to the general procedure using toluene to afford 0.50 g of **10g** (93% yield): mp 267 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.52 (br s, 2H), 7.27 (s, 1H), 3.90 (s, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −68.1 (s, 3F).

6-Chloro-5-fluoro-4-trifluoromethylquinazolin-2(1*H*)-one (10h). Prepared according to the general procedure using xylenes to afford 1.39 g of **10h** (79% yield): mp 239 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 7.94−7.88 (m, 1H), 7.43−7.40 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −70.5 to −70.7 (m, 3F), −110.2 to −110.5 (m, 1F).

5,6-Dichloro-4-trifluoromethylquinazolin-2(1*H*)-one (10i). Prepared according to the general procedure using xylenes to afford 75 mg of **10i** (69% yield): ^{1}H NMR (300 MHz, acetone-d_6) δ 7.90 (d, J = 8.1 Hz, 1H), 7.58−7.55 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −63.8 (s, 3F).

General Procedure for Lithium Acetylide Addition to Ketimines 10. A 0 °C solution of lithiated acetylide (4 equiv) in anhydrous THF (0.5 M) was cannulated into a solution of ketimine **10** in anhydrous THF (0.2 M) at − 78 °C. To this was then added $BF_3\cdot OEt_2$ (0.5 equiv), the −78 °C cooling bath was removed, and the mixture was allowed to warm to room temperature. After stirring overnight at room temperature, the reaction was quenched by the addition of 1 M citric acid and diluted with EtOAc, and the phases were separated. The organic solution was sequentially washed with water, saturated aqueous $NaHCO_3$, and saturated aqueous NaCl; dried over $MgSO_4$; filtered; and concentrated. The crude product was purified either by flash chromatography, HPLC, or crystallization.

4-(Cyclopropylethynyl)-3,4-dihydro-5-fluoro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (11). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 64 mg of **11** (59% yield): mp 168 °C (dec); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.20 (br s, 1H), 7.57 (br s, 1H), 7.42−7.35 (m, 1H), 6.84−6.77 (m, 2H), 1.41−1.32 (m, 1H), 0.88−0.81 (m, 2H), 0.72−0.67 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.2 (s, 3F), −110.5 (s, 1F); HRMS calcd for $C_{14}H_{11}F_4N_2O$ [M + H]$^+$ 299.0808, found 299.0799. Anal. ($C_{14}H_{10}F_4N_2O\cdot0.25H_2O$) C, H, N.

5-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (12). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) and crystallized from acetone to afford 25 mg of **12** (20% yield): mp 184 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.98 (br s, 1H), 7.36−7.31 (m, 1H), 7.10 (dd, J = 8.1, 1.1 Hz, 1H), 6.99 (d, J = 8.4 Hz, 1H), 1.42−1.37 (m, 1H), 0.87−0.72 (m, 4H); ^{19}F NMR (282 MHz, acetone-d_6) δ −81.6 (s, 3F); HRMS calcd for $C_{14}H_{11}ClF_3N_2O$ [M + H]$^+$ 315.0512, found 315.0494. Anal. ($C_{14}H_{10}ClF_3N_2O\cdot0.3H_2O$) C, H, N.

4-(Cyclopropylethynyl)-5,6-difluoro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (13). Prepared according to the general procedure and purified by crystallization from acetone to afford 8.16 g of **13** (63% yield): mp 192 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.01 (br s, 1H), 7.46 (br s, 1H), 7.44−7.35 (m, 1H), 6.86−6.81 (m, 1H), 1.41−1.37 (m, 1H), 0.90−0.83 (m, 1H), 0.74−0.69 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (d, J = 12.9 Hz, 3F), −136.0 to −136.2 (m, 1F), −148.1 to −148.3 (m, 1F); HRMS (CI) calcd for $C_{14}H_{10}F_5N_2O$ [M + H]$^+$ 317.0713, found 317.0708. Anal. ($C_{14}H_9H_5N_2O$) C, H, N.

6-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (14). Prepared according to the general procedure and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford 3.85 g of **14** (97% yield): mp 86.6−88 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.95 (br s, 1H), 7.51 (br s, 1H), 7.43 (br s, 1H), 7.40 (dd, J = 8.8, 2.4 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 1.49−1.41 (m, 1H), 0.93−0.82 (m, 1H), 0.77−0.74 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (s, 3F); HRMS calcd for $C_{14}H_{10}ClF_3N_2O$ [M + H]$^+$ 315.0512, found 315.0516. Anal. ($C_{14}H_{10}N_2ClF_3O\cdot0.25H_2O$) C, H, N.

5-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-6-fluoro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (15). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 70 mg of **15** (56% yield): mp 88−90 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.23 (br s, 1H), 7.64 (br s, 1H), 7.37 (t, J = 8.8 Hz, 1H), 7.03 (dd, J = 8.8, 4.4 Hz, 1H), 1.46−1.37 (m, 1H), 0.89−0.73 (m, 4H); ^{19}F NMR (282 MHz,

acetone-d_6) δ −81.6 (m, 3F), −121.0 to −121.0 (m, 1F); HRMS calcd for $C_{14}H_{10}ClF_4N_2O$ [M + H]$^+$ 333.0418, found 333.0417. Anal. ($C_{14}H_9ClF_4N_2O \cdot 0.75C_3H_6O$) C, H, N.

4-(Cyclopropylethynyl)-3,4-dihydro-6-fluoro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (16). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 44 mg of **16** (34% yield): mp 155 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.86 (br s, 1H), 7.36 (br s, 1H), 7.30−7.27 (m, 1H), 7.22−7.15 (m, 1H), 7.04−6.99 (m, 1H), 1.47−1.42 (m, 1H), 0.90−0.87 (m, 2H), 0.76−0.75 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.9 (m, 3F), −123.4 to −123.4 (m, 1F); HRMS calcd for $C_{14}H_{11}F_4N_2O$ [M + H]$^+$ 299.0808, found 299.0800. Anal. ($C_{14}H_{10}F_4N_2O$) C, H, N.

4-(Cyclopropylethynyl)-3,4-dihydro-6-methoxy-4-(trifluoromethyl)-2(1*H*)-quinazolinone (17). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 103 mg of **17** (81% yield): mp 208 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.77 (br s, 1H), 7.29 (br s, 1H), 7.06 (br s, 1H), 6.99−6.90 (m, 2H), 3.77 (s, 3H), 1.46−1.38 (m, 1H), 0.91−0.85 (m, 2H), 0.79−0.72 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.6 (s, 3F); HRMS calcd for $C_{15}H_{14}F_3N_2O_2$ [M + H]$^+$ 311.1007, found 311.1000. Anal. ($C_{15}H_{12}F_3N_2O_2 \cdot 0.5\ C_3H_6O$) C, H, N.

6-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-5-fluoro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (18). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 156 mg of **18** (62% yield): mp 202−203 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.11 (br s, 1H), 7.56−7.50 (m, 2H), 6.88 (dd, J = 8.8, 1.4 Hz, 1H), 1.44−1.36 (m, 1H), 0.90−0.84 (m, 2H), 0.79−0.70 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.2 (s, 3F), −111.7 (s, 1F); HRMS Calc'd for $C_{14}H_{10}ClF_4N_2O$ [M + H]$^+$ 333.0418, found 333.0431. Anal. ($C_{14}H_9ClF_4N_2O \cdot 0.3C_3H_6O$) C, H, N.

4-(Cyclopropylethynyl)-5,6-dichloro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (19). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 20 mg of **19** (16% yield): mp 175−176 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.05 (br s, 1H), 7.60 (d, J = 8.8 Hz, 1H), 7.41 (br s, 1H), 7.04 (d, J = 8.8 Hz, 1H), 1.48−1.42 (m, 1H), 0.86−0.84 (m, 2H), 0.77−0.76 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −81.3 (s, 3F); HRMS calcd for $C_{14}H_{10}Cl_2F_3N_2O$ [M + H]$^+$ 349.0122, found 349.0141; HPLC purity, 96.4%.

5,6-Difluoro-3,4-dihydro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (20). Prepared according to the general procedure and purified by crystallization from acetone to afford 6.77 g of **20** (74% yield): mp 86.5−88.5 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.02 (br s, 1H), 7.50 (br s, 1H), 7.44−7.35 (m, 1H), 6.87−6.82 (m, 1H), 2.69−2.65 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.4 (d, J = 12.9 Hz, 1F), −135.8 to −135.9 (m, 1F), −148.1 to −148.3 (m, 1F); HRMS calcd for $C_{14}H_{12}F_5N_2O$ [M + H]$^+$ 319.0870, found 319.0874. Anal. ($C_{14}H_{11}F_5N_2O$) C, H, N.

6-Chloro-3,4-dihydro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (21). Prepared according to the general procedure and purified by flash chromatography (35% EtOAc/hexanes) to afford 26 mg of **21** (41% yield): mp 180 °C; ^{1}H NMR (300 MHz,) δ 9.08 (br s, 1H), 7.59 (br s, 1H), 7.53 (br s, 1H), 7.40 (dd, J = 8.4, 2.2 Hz, 1H), 7.02 (d, J = 8.8 Hz, 1H), 2.81−2.68 (m, 1H), 1.20 (dd, J = 6.6 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.1 (s, 3F); HRMS calcd for $C_{14}H_{12}ClF_3N_2O$ [M + H]$^+$ 317.0669, found 317.0694. Anal. ($C_{14}H_{12}ClF_3N_2O$) C, H, N.

5-Chloro-3,4-dihydro-6-fluoro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (22). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 28 mg of **22** (22% yield): mp 208 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.19 (br s, 1H), 7.62 (br s, 1H), 7.04 (dd, J = 9.2, 4.8 Hz, 1H), 2.74−2.65 (m, 1H), 1.18 (d, J = 7.0 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −81.6 (s, 3F), −121.0 (s, 1F); HRMS calcd for $C_{14}H_{12}ClF_4N_2O$ [M + H]$^+$ 335.0574, found 355.0570. Anal. ($C_{14}H_{11}ClF_4N_2O$) C, H, N.

3,4-Dihydro-6-fluoro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (23). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 24 mg of **23** (19% yield): mp 158 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.07 (br s, 1H), 7.60 (br s, 1H), 7.32−7.30 (m, 1H), 7.24−7.16 (m, 1H), 7.05−6.99 (m, 1H), 2.77−2.67 (m, 1H), 1.20 (dd, J = 7.0, 2.6 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (s, 3F), −123.4 to −123.5 (s, 1F); HRMS calcd for $C_{14}H_{13}F_4N_2O$ [M + H]$^+$ 301.0964, found 301.0962. Anal. ($C_{14}H_{12}F_4N_2O$) C, H, N.

3,4-Dihydro-6-methoxy-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (24). Prepared according to the general procedure and purified by flash chromatography (3% MeOH/CH_2Cl_2) to afford 30 mg of **24** (24% yield): mp 228−229 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.72 (br s, 1H), 7.27 (br s, 1H), 7.10 (br s, 1H), 7.00−6.91 (m, 2H), 3.77 (s, 3H), 2.73−2.67 (m, 1H), 1.20 (dd, J = 7.0, 1.5 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.7 (s, 3F); HRMS calcd for $C_{15}H_{16}F_3N_2O_2$ [M + H]$^+$ 313.1164, found 313.1159. Anal. ($C_{15}H_{15}F_3N_2O_2$) C, H, N.

4-(1-Butyn-1-yl)-5,6-difluoro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (25). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 69 mg of **25** (57% yield): mp 191−194 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.03 (br s, 1H), 7.50 (br s, 1H), 7.45−7.35 (m, 1H), 6.87−6.82 (m, 1H), 2.34−2.27 (m, 2H), 1.20−1.15 (m, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (d, J = 12.9 Hz, 3F), −135.8 to −136.0 (m, 1F), −148.2 to −148.3 (m, 1F); HRMS calcd for $C_{13}H_{10}F_5N_2O$ [M + H]$^+$ 305.0713, found 305.0711. Anal. ($C_{13}H_9F_5N_2O$) C, H, N.

4-(1-Butyn-1-yl)-6-chloro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (26). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 25 mg of **26** (20% yield): mp 217−219 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.05 (br s, 1H), 7.54 (br s, 2H), 7.41−7.39 (m, 1H), 7.02 (d, J = 8.4 Hz, 1H), 2.36−2.32 (m, 2H), 2.18−1.13 (m, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (s, 3F); HRMS calcd for $C_{13}H_{10}ClF_3N_2O$ [M + H]$^+$ 303.0512, found 303.0519. Anal. ($C_{13}H_{10}ClF_3N_2O$) C, H, N.

4-(1-Butyn-1-yl)-3,4-dihydro-6-fluoro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (27). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 40 mg of **27** (33% yield): mp 190 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.86 (br s, 1H), 7.38 (br s, 1H), 7.34−7.31 (m, 1H), 7.22−7.16 (m, 1H), 7.05−7.00 (m, 1H), 2.04−2.01 (m, 2H), 1.19−1.14 (m, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −75.4 (s, 3F), −123.4 to −123.5 (m, 1F); HRMS calcd for $C_{13}H_{11}F_4N_2O$ [M + H]$^+$ 287.0808, found 287.0807. Anal. ($C_{13}H_{10}F_4N_2O$) C, H, N.

5,6-Difluoro-3,4-dihydro-4-[(2-pyridyl)ethynyl]-4-(trifluoromethyl)-2(1*H*)-quinazolinone (28). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 83 mg of **28** (59% yield): mp 219−220 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.15 (br s, 1H), 8.61 (d, J = 4.4 Hz, 1H), 7.88−7.82 (m, 2H), 7.63 (dd, J = 7.0, 1.1 Hz, 1H), 7.47−7.42 (m, 2H), 6.94−6.88 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.8 (d, J = 12.9 Hz, 3F), −135.8 to −135.9 (m, 1F), −147.9 to −148.0 (m, 1F); HRMS calcd for $C_{16}H_9F_5N_3O$ [M + H]$^+$ 354.0666, found 354.0678. Anal. ($C_{16}H_8F_5N_3O \cdot 0.45C_4H_8O_2$) C, H, N.

6-Chloro-3,4-dihydro-4-[(2-pyridyl)ethynyl]-4-(trifluoromethyl)-2(1*H*)-quinazolinone (29). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 110 mg of **29** (78% yield): mp 105 °C (dec); ^{1}H NMR (300 MHz, acetone-d 6) δ 9.14 (br s, 1H), 8.64−8.61 (m, 1H), 7.89−7.84 (m, 2H), 7.70−7.66 (m, 2H), 7.48−7.43 (m, 2H), 7.09 (d, J = 8.8 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.5 (s, 3F); HRMS calcd for $C_{16}H_{10}ClF_3N_3O$ [M + H]$^+$ 352.0465, found 352.0470. Anal. ($C_{16}H_9ClF_3N_3O \cdot 0.12H_2O$) C, H, N.

5-Chloro-3,4-dihydro-6-fluoro-4-[(2-pyridyl)ethynyl]-4-(trifluoromethyl)-2(1*H*)-quinazolinone (30). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 50 mg of **30** (36% yield): mp 186 °C;

^{1}H NMR (300 MHz, acetone-d_6) δ 9.13 (br s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 7.88−7.83 (m, 1H), 7.65 (d, J = 7.7 Hz, 1H), 7.47−7.41 (m, 1H), 7.11 (dd, J = 9.2 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −81.0 (s, 3F), −121.1 (s, 1F); HRMS calcd for $C_{16}H_9ClF_4N_3O$ [M + H]$^+$ 370.0370, found 370.0355. Anal. ($C_{16}H_8ClF_4N_3O$·0.6CH_4O) C, H, N.

3,4-Dihydro-6-fluoro-4-[(2-pyridyl)ethynyl]-4-(trifluoromethyl)-2(1*H*)-quinazolinone (31). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 65 mg of **31** (45% yield): mp 155 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.02 (br s, 1H), 8.60 (d, J = 4.0 Hz, 1H), 7.87−7.78 (m, 2H), 7.66 (d, J = 7.7 Hz, 1H), 7.45−7.41 (m, 2H), 7.26−7.20 (m, 1H), 7.09−7.05 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.4 (s, 3F), −122.9 to −123.0 (m, 1F); HRMS calcd for $C_{16}H_{10}F_4N_3O$ [M + H]$^+$ 336.0760, found 336.0742. Anal. ($C_{16}H_9F_4N_3O$·0.25H_2O) C, H, N.

3,4-Dihydro-6-methoxy-4-[(2-pyridyl)ethynyl]-4-(trifluoromethyl)-2(1*H*)-quinazolinone (32). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 56 mg of **32** (39% yield): mp 97−98 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.81 (br s, 1H), 8.61 (d, J = 4.8 Hz, 1H), 7.88−7.82 (m, 1H), 7.66 (d, J = 7.7 Hz, 1H), 7.61 (br s, 1H), 7.46−7.42 (m, 1H), 7.23 (br s, 1H), 7.06−6.97 (m, 2H), 3.79 (s, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.1 (s, 3F); HRMS calcd for $C_{17}H_{13}F_3N_3O_2$ [M + H]$^+$ 348.0960, found 348.0956. Anal. ($C_{17}H_{12}F_3N_3O_2$·0.25C_3H_6O) C, H, N.

5,6-Difluoro-3,4-dihydro-4-(phenylethynyl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (33). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 92 mg of **33** (65% yield): mp 215−217 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.14 (br s, 1H), 7.80 (br s, 1H), 7.57−7.54 (m, 2H), 7.49−7.40 (m, 4H), 6.92−6.87 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (d, J = 12.9 Hz, 3F), −136.1 to −136.3 (m, 1F), −147.9 to −148.0 (m, 1F); HRMS calcd for $C_{17}H_{10}F_5N_2O$ [M + H]$^+$ 353.0713, found 353.0717. Anal. ($C_{17}H_9F_5N_2O$) C, H, N.

6-Chloro-3,4-dihydro-4-(phenylethynyl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (34). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 54 mg of **34** (38% yield): mp 104−107 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.07 (br s, 1H), 7.74 (br s, 1H), 7.67 (br s, 1H), 7.62−7.58 (m, 2H), 7.48−7.40 (m, 4H), 7.08 (d, J = 8.4 Hz, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.7 (s, 3F); HRMS calcd for $C_{17}H_{10}F_5N_2O$ [M]$^+$ 353.0713, found 353.0717. Anal. ($C_{17}H_{10}ClF_3N_20$·0.25H_2O) C, H, N.

3,4-Dihydro-6-fluoro-4-(phenylethynyl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (35). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 41 mg of **35** (29% yield): mp 107 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 9.00 (br s, 1H), 7.69 (br s, 1H), 7.63−7.59 (m, 2H), 7.50−7.40 (m, 4H), 7.27−7.20 (m, 1H), 7.10−7.05 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.6 (s, 3F), −123.0 to −123.1 (m, 1F); HRMS calcd for $C_{17}H_{11}F_4N_2O$ [M + H]$^+$ 335.0808, found 335.0821.

3,4-Dihydro-6-methoxy-4-(phenylethynyl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (36). Prepared according to the general procedure and purified by HPLC (2.5% MeOH/CH_2Cl_2) to afford 34 mg of **36** (24% yield): mp 206−207 °C; ^{1}H NMR (300 MHz, acetone-d_6) δ 8.85 (br s, 1H), 7.60−7.57 (m, 3H), 7.49−7.39 (m, 3H), 7.21 (br s, 1H), 7.05−6.96 (m, 2H), 3.79 (s, 3H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.3 (s, 3F); HRMS calcd for $C_{18}H_{14}F_3N_2O_2$ [M + H]$^+$ 347.1007, found 347.1015. Anal. ($C_{18}H_{13}F_3N_2O_2$) C, H, N.

Isolation of Optically Active Compounds. The enantiomers of **20** (**37** and **38**) were separated by HPLC using Chiralpak AD, 5% H_2O in methanol with a flow rate of 0.5 mL/min at ambient temperature. A UV detector set to 250 nm was used, and the first enantiomer to elute was **37**. The ee of **37** was 99% and the ee of **38** was 100%, as determined by chiral HPLC analysis.

(4*S*)-5,6-Difluoro-3,4-dihydro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (37): mp 155 °C; $[\alpha]_D^{20}$ = −2.14° (c = 0.280, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.15 (br s, 1H), 7.62 (br s, 1H), 7.44−7.35 (m, 1H), 6.86−6.81 (m, 1H), 2.72−2.63 (m, 1H), 1.17 (d, J = 6.6 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (s, 3F), −135.7 to −135.9 (m, 1F), −148.0 to −148.1 (m, 1F); HRMS calcd for $C_{14}H_{12}F_5N_2O$ [M + H]$^+$ 319.0870, found 319.0864. Anal. ($C_{14}H_{11}F_5N_2O$) C, H, N.

(4*R*)-5,6-Difluoro-3,4-dihydro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone (38): mp 98 °C; $[\alpha]_D^{20}$ = +4.45° (c = 0.292, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.19 (br s, 1H), 7.66 (br s, 1H), 7.44−7.35 (m, 1H), 6.86−6.81 (m, 1H), 2.74−2.60 (m, 1H), 1.17 (d, J = 7.0 Hz, 6H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (s, 3F), −135.7 to −135.9 (m, 1F), −148.0 to −148.1 (m, 1F); HRMS calcd for $C_{14}H_{12}F_5N_2O$ [M + H]$^+$ 319.0870, found 319.0864. Anal. ($C_{14}H_{11}F_5N_2O$) C, H, N.

The enantiomers of **14** (DPC 961 and **39**) were separated by HPLC using Chiralcel OD, 3% 2-propanol, 5% CH_2Cl_2, and 92% hexanes with a flow rate of 1.0 mL/min at ambient temperature. A UV detector set to 250 nm was used and the first enantiomer to elute was DPC 961. The ee of DPC 961 was 99% and the ee of **39** was 99.4%, as determined by chiral HPLC analysis.

(4*S*)-6-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (DPC 961): mp 180−181 °C; $[\alpha]_D^{20}$ = −60.34° (c = 0.274, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.01 (br s, 1H), 7.51 (br s, 1H), 7.40 (dd, J = 8.4, 2.2 Hz, 1H), 7.01 (d, J = 8.4 Hz, 1H), 1.49−1.41 (m, 1H), 0.93−0.86 (m, 2H), 0.77−0.72 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (s, 3F); HRMS calcd for $C_{14}H_{11}ClF_3N_2O$ [M + H]$^+$ 315.0512, found 315.0525. Anal. ($C_{14}H_{10}ClF_3N_2O$), C, H, N.

(4*R*)-6-Chloro-4-(cyclopropylethynyl)-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (39): mp 105−107 °C; $[\alpha]_D^{20}$ = +58.33° (c = 0.288, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.21 (br s, 1H), 7.69 (br s, 1H), 7.52−7.51 (m, 1H), 7.39 (dd, J = 8.4, 2.6 Hz, 1H), 7.00 (d, J = 8.4 Hz, 1H), 1.49−1.40 (m, 1H), 0.92−0.86 (m, 2H), 0.77−0.72 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.0 (s, 3F); HRMS calcd for $C_{14}H_{11}ClF_3N_2O$ [M + H]$^+$ 315.0512, found 315.0500. Anal. ($C_{14}H_{10}ClF_3N_2O$), C, H, N.

The enantiomers of **13** (DPC 963 and **40**) were separated by HPLC using Chiralpak AD, 5% H_2O in methanol with a flow rate of 0.8 mL/min at ambient temperature. A UV detector set to 250 nm was used, and the first enantiomer to elute was DPC 963. The ee of DPC 963 was 100% and the ee of **40** was 99%, as determined by chiral HPLC analysis.

(4*S*)-4-(Cyclopropylethynyl)-5,6-difluoro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (DPC 963): mp 187 °C; $[\alpha]_D^{20}$ = +1.46° (c = 0.274, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.00 (br s, 1H), 7.45−7.35 (m, 2H), 6.84 (dq, J = 9.2, 4.0 Hz, 1H), 1.42−1.35 (m, 1H), 0.90−0.83 (m, 1H), 0.74−0.69 (m, 1H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (d, J = 12.9 Hz, 3F), −136.0 to −136.2 (m, 1F), −148.1 to −148.3 (m, 1F); HRMS calcd for $C_{14}H_{10}F_5N_2O$ [M + H]$^+$ 317.0713, found 317.0715. Anal. ($C_{14}H_9F_5N_2O$) C, H, N.

(4*R*)-4-(Cyclopropylethyn-1-yl)-5,6-difluoro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (40): mp 188−189 °C; $[\alpha]_D^{20}$ = −1.45° (c = 0.278, MeOH); ^{1}H NMR (300 MHz, acetone-d_6) δ 9.04 (br s, 1H), 7.50 (br s, 1H), 7.44−7.35 (m, 1H), 6.86−6.81 (m, 1H), 1.44−1.35 (m, 1H), 0.90−0.83 (m, 2H), 0.74−0.69 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −83.3 (d, J = 12.9 Hz, 3F), −136.0 to −136.2 (m, 1F), −148.1 to −148.2 (m, 1F); HRMS calcd for $C_{14}H_{10}F_5N_2O$ [M + H]$^+$ 317.0713, found 317.0704. Anal. ($C_{14}H_9F_5N_2O$) C, H, N.

General Procedure for Alkyne Reduction. To a −78 °C solution of either DPC 961 or DPC 963 in anhydrous THF (0.5 M) containing 1,2-dichlorobenzene (2 equiv) was added dropwise via an addition funnel a 1 M solution in THF of lithium aluminum hydride (LAH) (2 mol equiv). Following the addition of the LAH, the cooling bath was removed and the mixture was allowed to reach room temperature. The mixture was stirred at room temperature overnight, and the reaction was monitored for completion by analyzing for the presence of the CF_3 from the starting material, as determined by ^{19}F NMR. If necessary, more LAH (0.4 mol equiv) was added and the

mixture monitored for completion as previously described. Upon completion of the reaction, determined by the absence of the starting material's CF_3 signal in ^{19}F NMR, the mixture was cooled to 0 °C and carefully quenched with 20% aqueous $KHSO_4$. The solids were removed by vacuum filtration and washed with EtOAc. The organic extract was separated from the filtrate. The aqueous phase was back-extracted with EtOAc, and the combined organic extracts were washed with saturated aqueous NaCl, dried over $MgSO_4$, filtered, and concentrated to afford a yellow oil. The material was then purified flash chromatography and/or crystallization.

(4*S*)-4-[(1*E*)-2-Cyclopropylethenyl)-5,6-difluoro-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (DPC 082). Prepared by reduction of DPC 963 according to the general procedure and purified by flash chromatography (30% EtOAc/hexanes) followed by crystallization from hexanes to afford a white solid. This material was dried at 75 °C/0.5 mmHg overnight to give 13.65 g of DPC 082 as a white powder (55% yield): mp 188.7−189.4 °C; $[\alpha]_D^{20} = +72.77°$ ($c = 0.382$, MeOH); ^1H NMR (300 MHz, acetone-d_6) δ 9.03 (br s, 1H), 7.37−7.28 (m, 1H), 6.90 (br s, 1H), 6.90−6.79 (m, 1H), 6.27 (dd, $J = 15$, 7.7 Hz, 1H), 5.67 (dd, $J = 15$, 9.5 Hz, 1H), 1.66−1.54 (m, 1H), 0.82−0.71 (m, 2H), 0.51−0.40 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −82.6 to −82.8 (m, 3F), −135.0 to −135.2 (m, 1F), −148.5 to −148.6 (m, 1F); HRMS calcd for $C_{14}H_{12}F_5N_2O$ $[M + H]^+$ 319.0870, found 319.0878. Anal. ($C_{14}H_{11}F_5N_2O$) C, H, N.

(4*S*)-6-Chloro-4-[(1*E*)-cyclopropylethenyl)-3,4-dihydro-4-(trifluoromethyl)-2(1*H*)-quinazolinone (DPC 083). Prepared by reduction of DPC 961 according to the general procedure and purified by crystallization from EtOAc/hexanes to afford a white solid. This material was dried at 80 °C/0.5 mmHg overnight to give 22.8 g of DPC 083 as a white powder (91% yield): mp 167−168 °C; $[\alpha]_D^{20} = -6.81°$ ($c = 0.382$, MeOH); ^1H NMR (300 MHz, acetone-d_6) δ 8.94 (br s, 1H), 7.40 (s, 1H), 7.32 (dd, $J = 8.4$, 2.2 Hz, 1H), 6.98 (d, $J = 8.4$ Hz, 1H), 6.88 (br s, 1H), 6.25 (d, $J = 15$ Hz, 1H), 5.60 (dd, $J = 15$, 9.5 Hz, 1H), 1.68−1.56 (m, 1H), 0.83−0.71 (m, 2H), 0.53−0.41 (m, 2H); ^{19}F NMR (282 MHz, acetone-d_6) δ −81.7 (s, 3F); HRMS calcd for $C_{14}H_{13}ClF_3N_2O$ $[M + H]^+$ 317.0669, found 317.0659. Anal. ($C_{14}H_{12}ClF_3N_2O$) C, H, N.

Biological Assays. The ability of NNRTI analogues to inhibit the HIV-1 reverse transcriptase was assessed using purified, recombinant, radiolabeled dTTP and a poly r(A)·oligo $d(T)_{12-18}$ template/primer as substrate. The ability of NNRTI analogues to inhibit HIV replication in tissue culture was assessed using several assay systems. The yield of infectious virus produced in 3-day acute infections by laboratory strains or clinical isolates of HIV-1 in MT-2 cells or viruses previously selected for in tissue culture by exposure to efavirenz was measured using a plaque assay of the culture fluid containing progeny virions as previously described.[24] The antiviral activity was also determined by measurement of viral RNA accumulation in HIV-1(RF)-infected MT-2 cells using biotinylated capture and alkaline phosphatase-derivatized reporter oligonucleotides.[19] In a third system, the effects of analogues on the replication of recombinant viruses in the HXB2 or NL4−3 background was determined by measurement of viral p24 antigen from MT-4 infections as previously described.[3] In all assays, the concentration of compound which reduced the measured parameter by 90% was designated the IC_{90}.

To estimate the effect of human plasma protein binding on antiviral efficacy, a functional assay and, in some cases, physical measurement of the extent of binding to serum proteins were used. For the functional assay, in vitro antiviral assays were conducted in the presence or absence of the two major components of human plasma, namely human serum albumin (HSA) and alpha-1-acid glycoprotein (AAG) (antiviral protein binding shift assay). Under the latter condition, the tissue culture medium contained a final concentration of 45 mg/mL HSA and 1 mg/mL AAG, concentrations of serum proteins likely found in the plasma of AIDS patients. The IC_{90} in the presence and absence of these added components were then compared and reported as the fold increase in IC_{90} observed (PB shift).

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