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# 3,3a-Dihydropyrano[4,3,2-*de*]quinazolin-2(1*H*)-ones are Potent Non-Nucleoside Reverse Transcriptase Inhibitors

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**Abstract**—A series of unique 3,3a-dihydropyrano[4,3,2-*de*]quinazolin-2(1*H*)-ones and a 2a,5-dihydro-2*H*-thieno[4,3,2-*de*]quinazoline-4(3*H*)-thione were found to be HIV-1 non-nucleoside reverse transcriptase inhibitors. One of these compounds, as the racemate, possessed an $IC_{90} = 4.6$ nM against wild-type virus in a whole cell antiviral assay and had an $IC_{90} = 76$ and 897 nM against the clinically significant K103N and K103N/L100I mutant viruses, respectively. 

Human immunodeficiency virus type-1 (HIV-1) is a retrovirus and is the causative agent in the development and transmission of HIV.[1] It is estimated that the infectivity rate in the United States has leveled off at an alarming 40,000 new infections per year.[2] Current treatments for HIV infection are designed to interfere with the ability of the virus to replicate by either inhibiting HIV protease or HIV reverse transcriptase (RT). There are two types of drugs available for inhibiting HIV-1 RT: nucleoside reverse transcriptase inhibitors (NRTIs) and non-nucleoside reverse transcriptase inhibitors (NNRTIs).[3] The NRTIs are competitive inhibitors of the nucleoside triphosphate binding site on RT and act as substrate decoys and chain terminators, while the NNRTIs bind at an allosteric site that regulates enzyme activity and are noncompetitive with the NTP binding site.[4]

One of the difficulties encountered clinically during antiviral therapy has been the emergence of resistant mutant viral forms. This was particularly true when agents were used alone or in two drug combination therapy. This led to the use of triple combination therapy such as two NRTIs plus an NNRTI or a protease inhibitor.[5] With such regimens, high rates of virological control can be achieved[3a] but there remains a subset of patients who do not show durable response for reasons of poor compliance, partial pre-existing resistance or poor bioavailability. Frequently outgrowth or de novo generation of resistant viral strains occurs in these virologic failures. This situation is compounded by the selection of some resistance mutations which confer cross-class resistance such as the Q151M mutation for the NRTIs or the K103N single mutation (or the K103N/L100I double mutation) for the NNRTIs. Our continuing efforts to identify NNRTIs that possess a broad spectrum of activity against mutant viral forms of RT has resulted in the selection of a series of quinazolinones for further development, two of which are DPC083 and DPC961 (Fig. 1).[6,7] This paper describes a series of novel tricyclic quinazolinones that were found during these investigations to possess noteworthy biological activity.

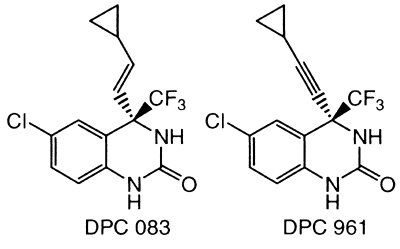


**Figure 1.** Structures of DPC083 and DPC961.

During the preparation of quinazolinthiones,[8] an interesting cyclization occurred to afford a unique tricyclic structure. When 5,6-difluoro-3-pyridyl-ethynyl analogue **3**, prepared by generating 3-pyridyl acetylide in situ from **2** and adding it to PMB-protected ketimine **1**,[9] was heated

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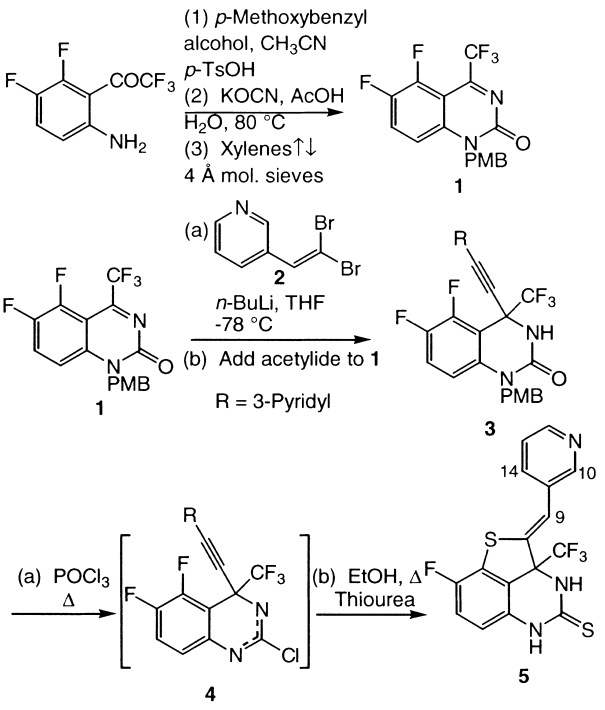



**Scheme 1.** Preparation of thiourea **5**.

with hot phosphorus oxychloride ($POCl_3$), a mixture of imidoyl chlorides **4** were obtained after concentration (Scheme 1).[10] Heating the crude imidoyl chloride mixture **4** in a solution of thiourea in ethanol afforded (2*Z*)-8-fluoro-2-(3-pyridinylmethylene)-2a-(trifluoromethyl)-2a,5-dihydro-2*H*-thieno[4,3,2-*de*]-quinazoline-4(3*H*)-thione (**5**). The structure of **5** was determined by single crystal X-ray analysis[11] and by long range $^{1}H$–$^{13}C$ coupling between H-9 and C-10 and C-14. The olefin stereochemistry was spectroscopically confirmed by an NOE from the $CF_3$ to H-9. The ability to confirm the structure through NMR techniques became important when analyzing other tricyclic analogues (i.e., compounds **14**–**16** in Scheme 3). Thiourea **5** possessed good activity in the antiviral assays, exhibiting an $IC_{90} = 7$ and 84 nM against wild-type and the K103N mutant, respectively.[12]

We postulated that **5** represented a constrained olefin mimic, and it was already apparent from the quinazolinone SAR that olefin analogues possessed good potency against wild-type and mutant virus forms.[6,7] Based upon the potency of **5**, the effect on the resistance profile by confining olefins such as DPC083 (Fig. 1) to a defined region of space needed further exploration.

We were intrigued by the possibility of substituting the alkyne moiety present in the quinazolinones with a nucleophile via an intramolecular cyclization process as depicted in Figure 2. We are unaware of any reports in the literature describing an intramolecular 6-*endo*-dig ring closure of a phenol onto an alkyne, while two reports exist describing the 5-*exo*-dig closure.[13]

The approach used to synthesize these molecules is shown in Schemes 2 and 3. Commercially available 2-chloro-5-nitroanisole (**6**) was reduced with tin chloride

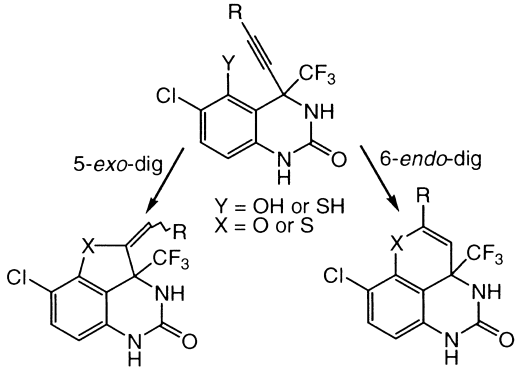
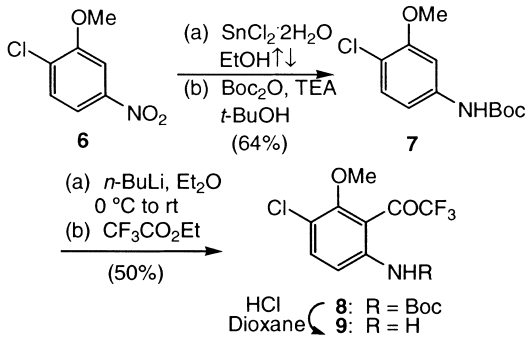



**Figure 2.** Intramolecular cyclization pathways.

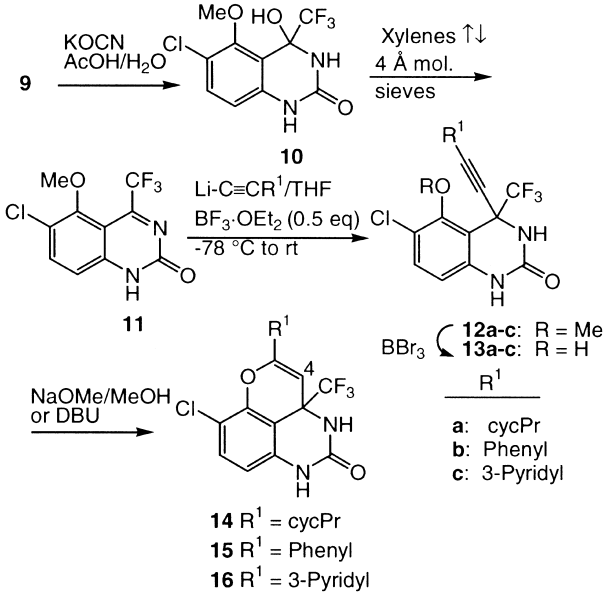
and the resulting aniline protected as the Boc carbamate to afford **7** (Scheme 2). Metallation of **7** using *n*-BuLi followed by quenching the anion with ethyl trifluoroacetate gave the desired trifluoromethyl ketone **8**. The protecting group was removed under standard conditions to yield **9**.




**Scheme 2.** Preparation of keto-aniline **9**.

The tetrasubstituted trifluoromethyl ketone **9** was treated with potassium cyanate to yield aminol **10**, which was subsequently dehydrated in xylenes at reflux containing 4 Å molecular sieves to give ketimine **11** (Scheme 3). Alkylation of the ketimine was achieved using lithium acetylides in THF in the presence of $BF_3{\cdot}OEt_2$ to afford **12a**–**c**. Treating **12a**–**c** with boron tribromide in $CH_2Cl_2$ delivered phenols **13a**,**b**. The facility with which the intermediate phenol **13c** underwent cyclization under the reaction conditions to afford the 3,3a-dihydropyrano-[4,3,2-*de*]quinazolin-2(1*H*)-one **16** precluded its isolation and characterization. The phenols **13a**,**b** were cyclized onto the alkyne using either sodium methoxide in methanol or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to afford **14** and **15**. All of the cyclization processes afforded exclusively the 6-*endo*-dig products.

The structural assignments were confirmed by NMR analysis. For example, long range three bond $^{1}H$–$^{13}C$ coupling was observed between H-4 and carbon atoms on the pendant phenyl ring of **15**. Also, the ability to compare the $^{19}F$ and $^{1}H$ NMR and NOE difference spectra of the 5-*exo*-dig product **5** with the 6-*endo*-dig product **15** assisted in the structural assignment of the products. In particular, a strong NOE was observed between the $CF_3$ and H-9 in **5** which could not occur in




**Scheme 3.** Synthesis of tricyclic quinazolinones.

**15**. The structural assignment of **14** and **16** was also confirmed through extensive NMR experiments. Structural assignments could also be determined by the distinctive chemical shift of the olefinic protons in **5** and **14–16**: the chemical shift of the olefinic proton in **5** was 7.82 ppm, while in **14–16** the olefinic signal was between 5.2 and 6.2 ppm.

Interestingly, methyl ether **12a** had an excellent resistance profile: $IC_{90} = 7.5$ nM and 377 nM against the K103N and K103N/L100I mutants, respectively (Table 1).[12] The most potent quinazolinones previously identified had an $IC_{90} = 15$ nM against K103N mutant[14] and 550 nM for the pure enantiomer (DPC082) against the K103N/L100I double mutant.[6] The activity of phenols **13a**,**b** against wild-type virus remained in the low nanomolar range. However, the resistance profile of phenol **13a** is not as impressive as the corresponding methyl ether **12a**: $IC_{90} = 28$ nM and 3024 nM against the K103N and K103N/L100I mutants, respectively.

The 3,3a-dihydropyrano[4,3,2-*de*]quinazolin-2(1*H*)-ones **14–16** also had $IC_{90}$ values in the low nanomolar range against wild-type virus. The activity of these compounds against the K103N mutant was generally poorer than the second generation NNRTIs DPC083 and DPC961, but better than efavirenz. For example, **15** had an $IC_{90} = 46$ nM against the K103N mutant while DPC083, DPC961 and efavirenz had $IC_{90}$s of 27, 10, and 64 nM, respectively.

Previous SAR on the quinazolinones had shown that when large $R^1$ groups (i.e., compounds related to **12** in Scheme 3) were incorporated into the alkyne, the resistance profile became substantially worse.[7] In contrast to this observation, the larger $R^1$ is in the tricyclics **14–16**, the better the resistance profile is. For instance, the 3-pyridyl derivative **16** is marginally better against K103N and K103N/L100I when compared to **12c** and DPC961, respectively. It is also interesting to note the decrease in activity against the K103N/L100I double mutant for compound **14**, which has $R^1$ = cyclopropyl: methyl ether **12a** had an $IC_{90} = 367$ nM, while the tricycle **14** had an $IC_{90} = 15{,}000$ nM.

A possible explanation for the divergence in the SAR between the quinazolinones and the 3,3a-dihydropyrano[4,3,2-*de*]quinazolin-2(1*H*)-ones in their ability to inhibit the K103N/L100I double mutant form of HIV-1 RT can be posited through an examination of Figure 3. In this figure, the aromatic ring of DPC961[15] was oriented using MacroModel with the aromatic ring of the energy minimized structure of **15**.[16] It is evident that the phenyl group (in yellow) would be expected to extend further into the NNRTI binding pocket than the cyclopropyl acetylene (in red), but not as far as a phenylacetylene group would. Therefore, the assumption is that the larger alkynes in the quinazolinones[17] interact adversely with amino acid residue(s) present in the NNRTI binding pocket of the K103N/L100I mutant form of RT, while the phenyl and 3-pyridyl $R^1$ groups in compounds **15** and **16** do not. Hence, the mutated viral forms appear better able to accommodate the larger $R^1$ groups in compounds **15** and **16**.

It remains unclear why the cyclopropyl $R^1$ group present in **14** suffered such a dramatic loss in activity toward the K103N/L100I RT mutant when compared to **12a**. A possible explanation is that the smaller cyclopropyl group of **14** is unable to form critical nonbonding interactions with residue(s) in the mutated RT binding pocket.

**Table 1.** Biological data for compounds **12a–c**, **13a**,**b**, and **14–16**[12]

| Compounds | RNA $IC_{90}$ (nM) | Enzyme $IC_{50}$ (nM)[a] | K103N $IC_{90}$ (nM) | K103N/L100I $IC_{90}$ (nM) |
|---|---|---|---|---|
| **DPC083** | 2.1 (±0.8)[a] | | 27 (±11)[a] | 1690 (±160)[a] |
| **DPC961** | 2.0 (±0.7)[a] | 31 (±8) | 10 (±3.2)[a] | 1100 (±160)[a] |
| **Efavirenz** | 1.7 (±0.5)[a] | 47 (±25) | 64 (±24)[a] | 7300 (±5000)[a] |
| **12a** | 3.5 | 70 (±39) | 7.5 | 377 |
| **12b** | 7.9 | 144 (±60) | 113 | 5515 |
| **12c** | 7.1 | 139 (±23) | 147 | 2541 |
| **13a** | 3.6 | 54 (±8) | 28 | 3024 |
| **13b** | 6.8 | 174 (±78) | 30 | 1936 |
| **14** | 3.6 | 90 (±14) | 76 | 15000 |
| **15** | 8.2 | 244 (±109) | 46 | 1663 |
| **16** | 4.6 | 122 (±15) | 76 | 897 |

[a]Values are means of three experiments, standard deviation is given in parentheses.

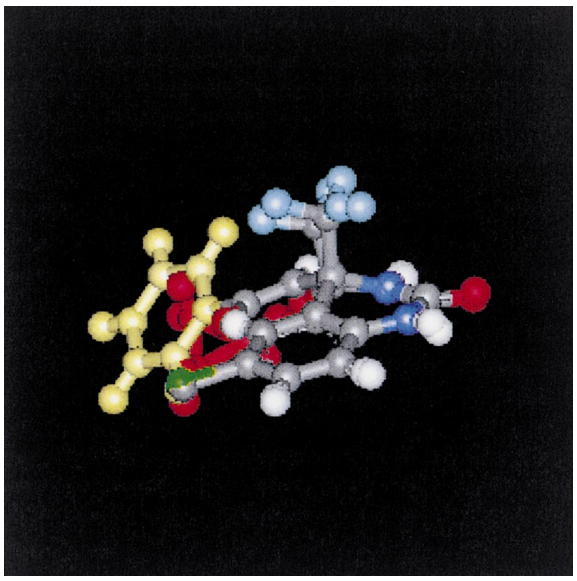


**Figure 3.** Overlay of DPC961 (red highlights) crystal structure and minimized structures of **15** (yellow highlights).

In summary, several compounds were identified which have (or would be expected to have as the single enantiomer) a better K103N/L100I $IC_{90}$ than either DPC083, DPC961 or efavirenz. A unique SAR was also identified for the 3,3a-dihydropyrano[4,3,2-*de*]quinazolin-2(1*H*)-ones which differs from that previously reported for the quinazolinones. Future studies will explore the SAR of this unique series of compounds.


## Acknowledgements

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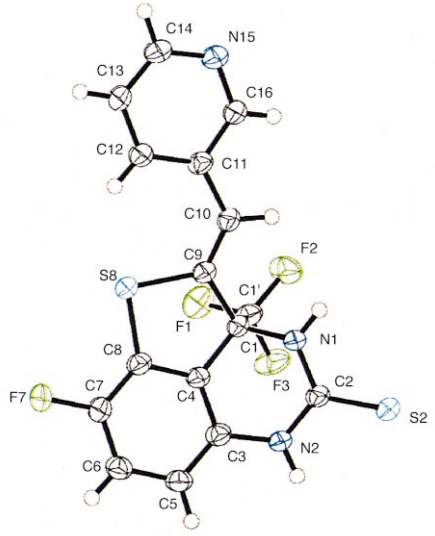
9. Compound **1** was prepared by minor modification of a procedure given in ref 7. Namely, formation of the intermediate aminol required warming to 80 °C.
10. The PMB-group was presumably cleaved by adventitious acid generated during the formation of the iminoyl chlorides.
11. Data for single crystal X-ray of **5**: $T=-100$ °C, space group P21/n, unit cell: $a=9.956(1)$ Å, $b=10.953(1)$ Å, $c=13.882(1)$ Å, $\beta=96.88(1)°$, volume $=1502.9$ Å$^3$, $Z=4$, 1714 unique reflections collected with $I\geq 3.0\sigma(I)$.



12. The biological assays were performed as described in ref 6.
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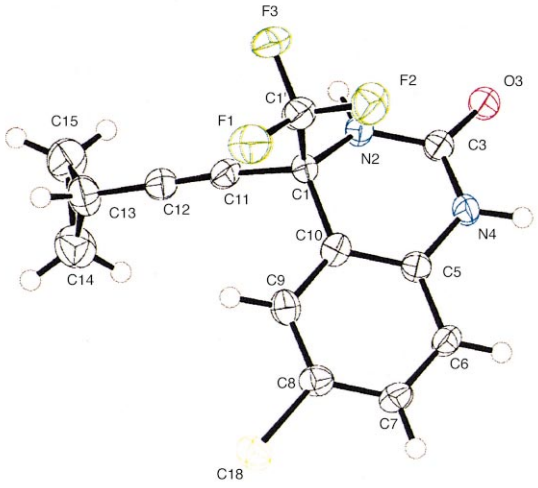
14. 5-Chloro-3,4-dihydro-6-fluoro-4-(3-methylbutyn-1-yl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone, compound **22**, from ref 7.
15. The structure of DPC961 was obtained from a single crystal X-ray: $T=-100$ °C, space group $P2_12_12_1$, unit cell: $a=13.851(1)$ Å, $b=26.283(2)$ Å, $c=8.850(1)$ Å, volume $=3221.8$ Å$^3$, $Z=8$, 3786 unique reflections collected with $I\geq 3.0\sigma(I)$.



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17. For example, 6-chloro-3,4-dihydro-4-(phenyl-ethynyl)-4-(trifluoromethyl)-2(1*H*)-quinazolinone, compound **34** from ref 7, has an $IC_{90}=7$ nM and 250 nM against the wild-type and K103N viruses, respectively.