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# Novel Cyclopropyl-Indole Derivatives as HIV Non-Nucleoside Reverse Transcriptase Inhibitors

Mohammad Hassam,[†] Adriaan E. Basson,[‡] Dennis C. Liotta,[§] Lynn Morris,[‡] Willem A. L. van Otterlo,[†] and Stephen C. Pelly*,[†]

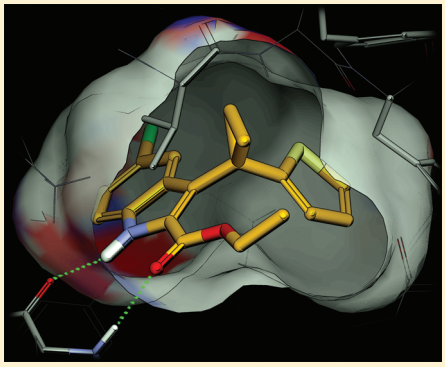
[†]Department of Chemistry and Polymer Science, Stellenbosch University, Western Cape, South Africa

[‡]National Institute for Communicable Diseases, Johannesburg, South Africa

[§]Department of Chemistry, Emory University, Atlanta, Georgia, United States

Supporting Information

**ABSTRACT:** The HIV pandemic represents one of the most serious diseases to face mankind in both a social and economic context, with many developing nations being the worst afflicted. Due to ongoing resistance issues associated with the disease, the design and synthesis of anti-HIV agents presents a constant challenge for medicinal chemists. Utilizing molecular modeling, we have designed a series of novel cyclopropyl indole derivatives as HIV non-nucleoside reverse transcriptase inhibitors and carried out their preparation. These compounds facilitate a double hydrogen bonding interaction to Lys101 and efficiently occupy the hydrophobic pockets in the regions of Tyr181/188 and Val179. Several of these compounds inhibited HIV replication as effectively as nevirapine when tested in a phenotypic assay.



**KEYWORDS:** *NNRTI, indole, HIV, cyclopropyl, rational design*

With more than thirty years of the acquired immunodeficiency syndrome (AIDS) plaguing the human race, a cure for the disease continues to remain elusive. Currently it is estimated that over 33 million people are living with HIV,[1] the majority of which are in sub-Saharan Africa.[2] Fortunately, significant progress has been made in developing therapeutic agents to control viral replication within HIV infected individuals, resulting in delaying the onset of AIDS. However, the high mutation rate of the virus and the resulting emergence of resistance means that researchers are running a never ending marathon to keep developing new drugs to control the viral levels in HIV sufferers.

Currently there are six therapeutic targets utilized for anti-HIV treatment, and within this group, the enzyme reverse transcriptase (RT), which is crucial for the conversion of single stranded viral RNA into double stranded DNA, provides two opportunities for therapeutic intervention. The first of these is at the actual catalytic site utilizing DNA base mimics which act as chain terminators, and in fact the very first drug to be used in the treatment of HIV (AZT) operates in this manner.[3] However, located just 10 Å from the catalytic site is a hydrophobic and relatively small cleft known as the non-nucleoside binding pocket, and the resulting allosteric effect of specific compounds binding in this pocket significantly inhibits the normal functioning of the enzyme. These non-nucleoside reverse transcriptase inhibitors (NNRTIs), being small and somewhat nonpolar molecules, are the only anti-HIV drugs which are suitable candidates to cross the blood brain barrier (BBB).[4] This is particularly important to tackle viral reservoirs located across the BBB, not only to reduce viral levels overall but importantly to prevent complications such as the onset of AIDS dementia complex.[5] Furthermore, unlike the drugs in the other therapeutic categories, the structural variance in known NNRTIs is quite remarkable. Currently there are five licensed NNRTIs (Figure 1), as well as many compounds which have been developed as inhibitors for HIV RT.[1−3,6−9] This structural variation presents a wonderful opportunity in creative exploration for the development of new NNRTIs.

In light of the need for new anti-HIV agents and the benefits described above of the NNRTIs specifically, we embarked upon a study to examine the receptor−ligand crystal structures of the licensed NNRTIs to better understand their binding in the allosteric pocket.[10−13] Not surprisingly, given the general hydrophobic nature of this binding pocket, very few electrostatic interactions were observed between the ligand and the receptor. Nevirapine, for instance, makes no direct electrostatic interactions with the protein, although there is a hydrogen bonding interaction between the amide carbonyl and Leu234 via a bridging water molecule. In the case of efavirenz, however, of particular interest to us was the double hydrogen bond interaction made between the amide portion of the carbamate and Lys101.

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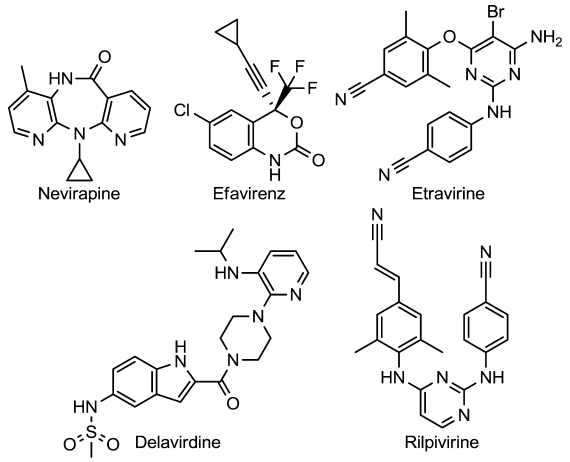


**Figure 1.** Currently licensed NNRTIs.

We envisaged that an indole-2-carboxamide based structure would also facilitate the same interactions as efavirenz, and indeed, a survey of the literature revealed that we were not the first to consider this scaffold. In 1993 Williams et al. reported that phenylsulfinyl-indole **1** showed potent activity against HIV RT (Figure 2).[14] Following this, several other groups became

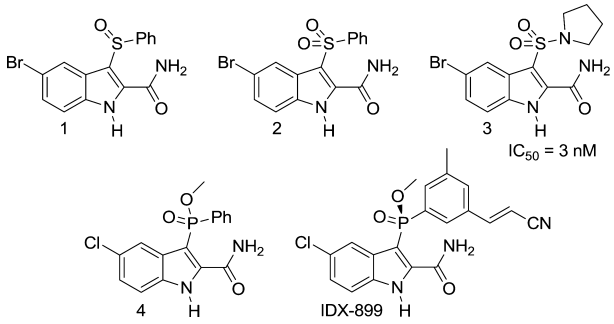


**Figure 2.** Indole based NNRTIs.

interested in this class of indole-based NNRTIs, and the molecules evolved from sulfinyls **1** to sulfonyls **2** and eventually to sulfonamide compounds **3**, which were very potent inhibitors of HIV RT.[15−18] Work in this area continues, and recently another group has published a variant on these molecules containing phosphorus instead of sulfur **4**.[19] In fact, the phosphoindole derivative IDX-899 is currently under clinical trial evaluation.[20,21]

In light of the fact that these indole derivatives exhibited excellent potency against HIV RT, we wished to retain this structural scaffold and investigate novel functional groups decorating the 2, 3, and 5 positions of the indole. Of particular importance to us was to retain the hydrogen bonding interactions to Lys101 facilitated by the indole NH (as donor) and a suitable hydrogen bond acceptor moiety at the 2-position of the indole. A study of the X-ray crystal structure of **3** bound within HIV RT revealed that although the sulfonamide group adequately filled the Val179 binding pocket,[22] no electrostatic interactions were observed with the receptor residues. We envisaged that a cyclopropyl group may be well accommodated in this position and indeed could be more suitable given the hydrophobic nature of the pocket. Initial docking studies on cyclopropyl derivative **5** (Figure 3A) revealed that it adopted a pose very similar to that of **3** and that

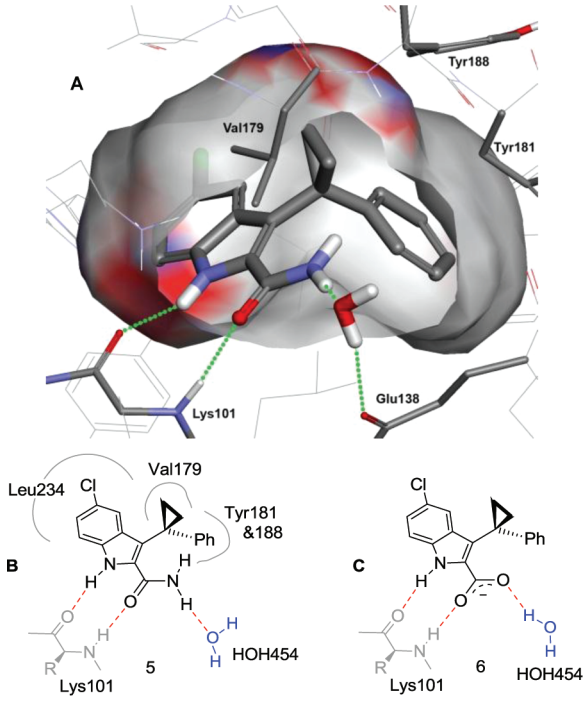


**Figure 3.** Our envisaged indole-cyclopropyl NNRTI **5** docked within the NNRTI allosteric site (A), and its corresponding schematic representation (B), as well as that of the carboxylate **6** (C).

the cyclopropyl moiety snugly occupied the small hydrophobic pocket in the region of Val179. Furthermore, the two important hydrogen bonding interactions between the ligand and Lys101 were maintained as well as additional favorable interactions in the form of $\pi$ stacking between the phenyl ring and Tyr181, as well as a $\sigma-\pi$ interaction between the para-phenyl proton and the indole side chain of Trp229. The amide $-NH_2$ group was directed out toward the entrance of the site hydrogen bonding to HOH454, which facilitated a bridging connection to Glu138 (Figure 3B). Our concern, however, was that although the nonpolar cyclopropyl moiety was well suited to the Val179 pocket, overall the compound may prove to be too hydrophobic, resulting in poor efficacy in our assays. Therefore, we decided to initially synthesize the corresponding carboxylate **6** (Figure 3C) as a proof of concept compound, as the carboxylate group could facilitate the same hydrogen bond acceptor connection to Lys101 while maintaining the electrostatic connections to the water molecules at the site entrance.

At this point we returned to the issue of the cyclopropyl group as a replacement moiety for the sulfonamide. Indeed, although this group clearly fulfilled its role in terms of spatial characteristics, we sought to find more conclusive evidence that its positioning would be effective in binding to RT. Of the five licensed NNRTIs used in HIV therapy, two structures contain a cyclopropyl group, and fortuitously, crystal structures exist for both compounds bound within HIV RT.[12,13] Therefore, an alignment and superimposition of the two structures bound within their respective receptors was performed with our docked structure in 2RF2, and the positioning of the cyclopropyl ring was examined for each ligand. In the case of efavirenz, the ring was found to occupy the Tyr181/188 binding pocket, bearing no resemblance to our envisaged positioning. However, in the case of nevirapine, the cyclopropyl ring was found to occupy a nearly identical position in the region of the small Val179 pocket (Figure 4).


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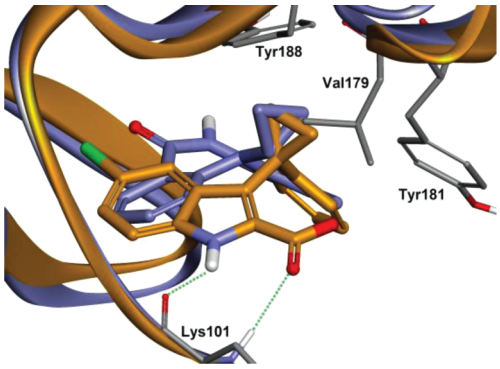
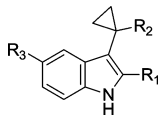



**Figure 4.** Overlay of nevirapine (purple) cocrystallized in HIV RT (PDB 1VRT) and our docked indole derivative **6** (orange) showing the similar placement of the cyclopropyl moiety.

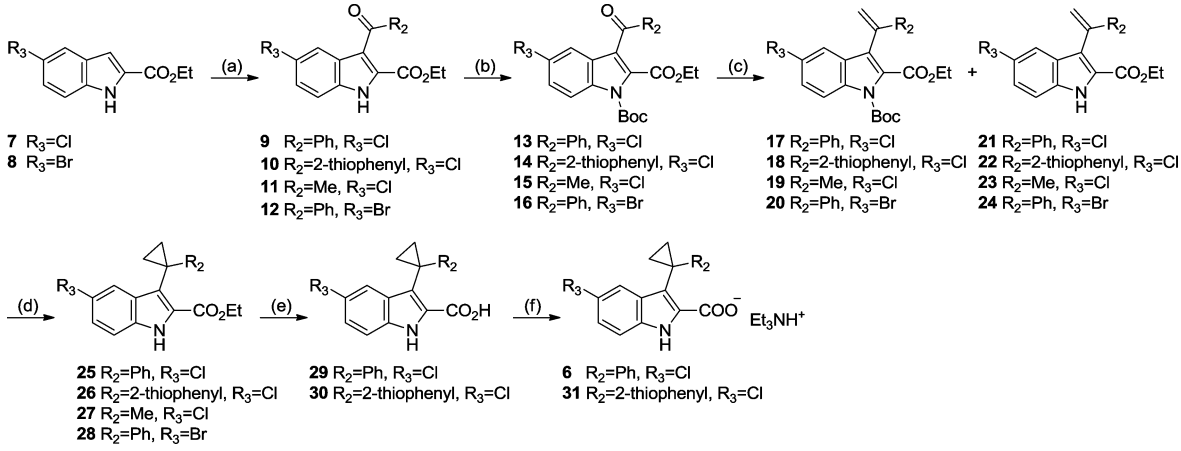
With a promising candidate in mind, we set about the synthesis of **6**, starting from commercially available ethyl 5-chloroindole-2-carboxylate **7** (Scheme 1). Installation of the required phenyl functionality was readily achieved by Friedel–Crafts acylation using benzoyl chloride to furnish **9**. The indole –NH was then protected as the Boc carbamate **13** in preparation for the Wittig reaction to follow. To this end, **13** was subjected to typical Wittig conditions employing the methyl triphenylphosponium ylide, which converted the ketone to the desired alkene **17** yet also resulted in loss of the Boc protecting group to some extent, thereby additionally producing **21**. This unplanned event turned out to be inconsequential, as either compound could be converted directly to the desired cyclopropyl indole derivative **25** in the presence of diethyl zinc, diiodomethane, and trifluoroacetic acid.[23] We also attempted to shorten the synthesis by completely avoiding the installation of the Boc group, but unfortunately in our hands, this led to very poor yields being obtained in the Wittig step. Finally, to complete our synthesis, the ethyl ester **25** was hydrolyzed to the corresponding carboxylic acid **29** and after purification, the carboxylate was recrystallized as the triethyl ammonium salt **6**. With the proof of concept compound **6** in hand, we were finally in a position to test its efficacy as an anti-HIV agent. To this end, we utilized an *in vitro* single-cycle, nonreplicative phenotypic assay employing an HIV-1 retroviral vector system for the production of virus-like particles (VLPs). Compounds were incubated with 293T cells and VLP for 48 h, after which the inhibition of HIV was quantified by luminescence measurement.[24,25] Disappointingly, in this assay **6** proved to be a rather poor inhibitor with an $IC_{50}$ value of 28.5 $\mu$M, significantly less effective than nevirapine, which had an $IC_{50}$ value of 0.087 $\mu$M under these conditions (Table 1). After some consideration it was surmised that, in light of the fact that our evaluation method is a whole cell assay, the paltry potency may indeed not be as a result of the

**Table 1. Phenotypic Assay Values ($IC_{50}/\mu M$) of Cyclopropyl Indole Derivatives Evaluated against Wild Type HIV as Well as the Corresponding Toxicity Values ($CC_{50}/\mu M$)**




| *Cmpd* | *R1* | *R2* | *R3* | *IC50* | *CC50* |
|---|---|---|---|---|---|
| **5** | $CONH_2$ | Ph | Cl | 0.096 | 14.2 |
| **6** | $CO_2^-$ | Ph | Cl | 28.5 | 92.3 |
| **25** | $CO_2Et$ | Ph | Cl | **0.085** | 30.3 |
| **26** | $CO_2Et$ |  | Cl | **0.065** | 67.1 |
| **27** | $CO_2Et$ | Me | Cl | 2.25 | 44.3 |
| **28** | $CO_2Et$ | Ph | Br | **0.066** | 24.5 |
| **31** | $CO_2^-$ |  | Cl | 48.2 | 140 |
| **32** | $CONH_2$ |  | Cl | 0.121 | 25.6 |
| **33** | $CH_2OH$ | Ph | Cl | 8.25 | 34.1 |
| **34** | $CH_2OH$ |  | Cl | 14.4 | 36.6 |

**Scheme 1. Synthesis of Cyclopropyl Indoles**[a]




[a]Reagents and conditions: (a) benzoyl chloride, 2-thiophenecarbonyl chloride, or acetyl chloride, $AlCl_3$, DCE; (b) $Boc_2O$, DMAP, THF; (c) $MePPh_3Br$, *n*-BuLi, THF; (d) $Et_2Zn$, $CH_2I_2$, TFA, DCM; (e) KOH, EtOH, then HCl; (f) $Et_3N$, $Et_2O$.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compound ineffectively binding to the HIV NNRTI binding pocket but may simply be as a result of poor membrane permeability given that **6** contains the negatively charged carboxylate group, which would remain ionized at physiological pH. To investigate this possibility, the preceding ester **25** was subjected to the same phenotypic assay and confirmed our suspicions, as it inhibited HIV replication as effectively as nevirapine, with an $IC_{50}$ value of 0.085 $\mu$M and comparatively low cytotoxicity ($CC_{50}$).[26] Modeling studies indicate that the ester analogue **25** could be well accommodated within the binding site, with the ethyl group directed out the site opening (Figure 5). Work is ongoing in this area, and we are in the process of synthesizing several ester analogues with hydrophilic end groups which we hope will exhibit improved potency.

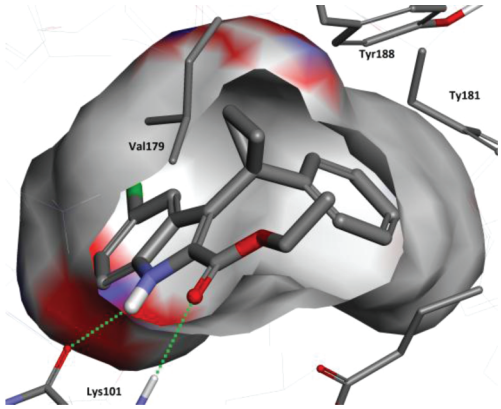


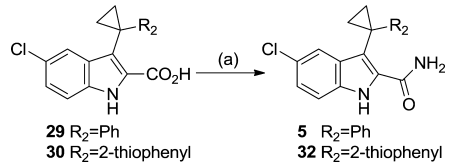

**Figure 5.** Ester derivative **25** docked into the allosteric site of HIV RT (PDB 2RF2) showing that it is well accommodated, with the ethyl ester pointing out the opening of the site (nonpolar hydrogens have been omitted for clarity).

Having obtained proof of concept for our indole-cyclopropyl HIV NNRTIs, we set about investigating smaller groups to occupy the Tyr181/188 pocket. Thiophene derivative **26** (Table 1), obtained from a Friedel–Crafts acylation with 2-thiophenecarbonyl chloride (Scheme 1), showed a similar $IC_{50}$ value to that of **25**. Interestingly, we also synthesized the methyl derivative **27**, as modeling studies indicated that this compound would bind significantly less effectively as a result of inadequately filling the Tyr181/188 pocket. The $IC_{50}$ result of 2.25 $\mu$M for this compound is consistent with our modeling results. Moreover, analogous to our previous finding that the carboxylate structure **6** performed poorly in the phenotypic assay, the thiophene containing carboxylate **31** was also found to be poorly effective against HIV in the phenotypic assay.

With the phenyl and thiophene esters (**25** and **26**) in hand, we then decided to investigate several modifications to the critical H-bond acceptor moiety at $R_1$ (Table 1). To this end, both compounds were converted to the corresponding amides. In fact, direct conversion of the esters to the corresponding amides in methanol saturated with ammonia did not proceed even at reflux. Therefore, the esters were hydrolyzed to the corresponding carboxylic acids (**29** and **30**) and installation of the amides was achieved by way of a PyBOP mediated coupling, thereby forming **5** and **32** (Scheme 2).[27] The $IC_{50}$ values for the amides **5** and **32** are similar to those obtained for the corresponding esters, **25** and **26**, respectively (Table 1).

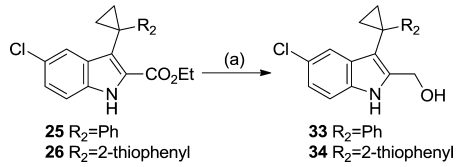
The ester analogues **25** and **26** were also reduced to the corresponding alcohols **33** and **34** (Scheme 3) to determine the

**Scheme 2. Conversion of Indole-2-carboxylates to Amides**[a]




[a]Reagents and conditions: (a) PyBOP, HOBt, $NH_3$, DIPEA.

**Scheme 3. Reduction of the Ethyl Indole-2-carboxylate to the Alcohol**[a]




[a]Reagents and conditions: (a) $LiAlH_4$, $Et_2O$.

effect of replacing the $sp^2$ hybridized carbonyl oxygen hydrogen bond acceptor with an $sp^3$ hybridized alcohol acceptor. In principal, one could envisage that the oxygen could still fulfill its role as an acceptor for the amide proton of Lys101. However, in our docking studies the most favored pose always positioned the oxygen in such a manner that hydrogen bonding could not occur, even in rigorous docking exercises where numerous starting conformations were considered to ensure adequate sampling of the conformational space for these compounds. Interestingly, these modeling results are consistent with our assay results, which show more than an order of magnitude decrease in potency for the $IC_{50}$ values yet the $CC_{50}$ values are similar (Table 1), indicative that cell permeability is not the issue and that these compounds certainly are poorer inhibitors of HIV RT.

To investigate the effect of increasing the size of the halogen at $R_3$, the 5-bromoindole derivative **28** was synthesized. This procedure, which started with ethyl 5-bromoindole-2-carboxylate **8** (Scheme 1), resulted in the synthesis of **28** in five steps and 15% overall yield. Analysis of the effectiveness of this compound in our phenotypic assay showed a similar potency to that of the corresponding 5-chloroindole analogue **25** (Table 1).

The final step in this work involved confirming that the compounds were indeed inhibiting HIV replication by way of binding to the allosteric pocket of HIV RT. To this end, our most potent cyclopropyl-indole derivatives were tested against eight RT single mutant strains of the virus. Of importance, mutations at residues Lys103, Tyr181, and Tyr188, which surround our cyclopropyl-indoles in their predicted binding poses, caused significant changes in the inhibition values for these compounds (Supporting Information Table 2). These residues are also the site of action of current NNRTIs, confirming that our novel compounds are indeed NNRTIs.

In conclusion, we have utilized molecular modeling to design novel indole based HIV-1 non-nucleoside reverse transcriptase inhibitors which are as potent as nevirapine. In addition, cellular toxicity studies indicate promisingly low toxicity. We believe that the compounds can be further optimized by more appropriate substitution at the $R_1$ position (Table 1), and work is currently ongoing in this area.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## ■ ASSOCIATED CONTENT

### Supporting Information

Synthetic procedures, spectral data, and modeling procedures. This material is available free of charge via the Internet at http://pubs.acs.org.

## ■ AUTHOR INFORMATION


### Corresponding Author

*E-mail: scpelly@sun.ac.za. Telephone: +27-21-808-2180. Fax +27-21-808-3360.



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### Notes

The authors declare no competing financial interest.

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