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Strategies for the Design of HIV-1 Non-Nucleoside Reverse Transcriptase Inhibitors: Lessons from the Development of Seven Representative Paradigms

Dongyue Li,[†] Peng Zhan,[†] Erik De Clercq,[‡] and Xinyong Liu*[,†]

[†]Department of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University, 44, West Culture Road, 250012, Jinan, Shandong, P. R. China

[‡]Rega Institute for Medical Research, K.U. Leuven, Minderbroedersstraat 10, B-3000 Leuven, Belgium

1. INTRODUCTION

According to the latest data released by Joint United Nations Programme on HIV/AIDS (UNAIDS) and World Health Organization (WHO), there are 2.6 million people newly infected with human immunodeficiency virus type 1 (HIV-1) in 2009 compared to 2.5 million people newly infected in 2007.[1] Therefore, acquired immune deficiency syndrome (AIDS) caused by HIV-1 is still a prevalent disease. The most efficient and standard treatment regimen for HIV-1 infection, namely, as highly active antiretroviral therapy (HAART), commonly involves two nucleoside reverse transcriptase inhibitors (NRTIs) and a ritonavir-boosted protease inhibitor (PI) or a non-nucleoside reverse transcriptase inhibitor (NNRTI). As a key component of HAART, NNRTIs present higher specificity and lower toxicity than NRTIs and PIs.[2,3]

Currently, five NNRTIs have been approved by U.S. Food and Drug Administration (U.S. FDA) for the clinical treatment of AIDS, i.e., nevirapine, delavirdine, efavirenz, etravirine, and rilpivirine (Figure 1). However, for the first-generation NNRTIs

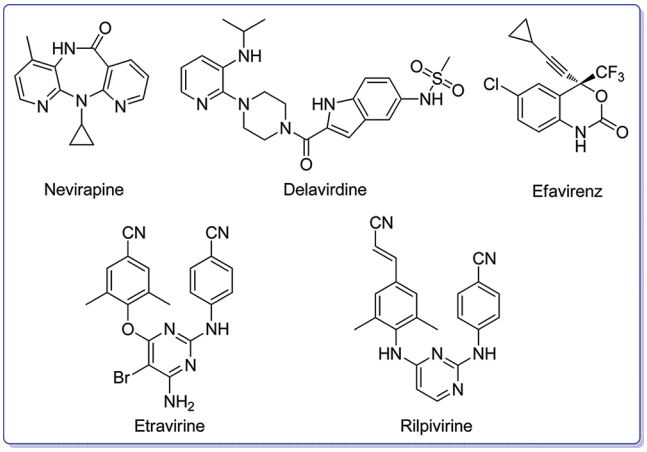

Figure 1. Structures of currently approved NNRTIs.

(nevirapine, delavirdine, and efavirenz), the rapid emergency of drug resistance (such as L100I, K103N, Y181C, Y188L, V106A, G190A, L100I/K103N, and K103N/Y181C mutations) dramatically reduced their potency, thus compromising the patient's clinical compliance. Alternatively, the second-generation NNRTI (etravirine and rilpivirine) possesses a high genetic barrier to resist various clinically relevant mutations, attributing to its structurally intrinsic flexibility, and readily adapted conformations to adjust to the NNRTI binding pocket (NNIBP) rearrangements caused by drug-resistant mutants.[4] Nonetheless, in 2009, clinical cases with Stevens–Johnson syndrome, hypersensitivity reactions, or other adverse effects were found in postmarketing surveillance reports.[5] In addition, more drug resistance occurred when patients failed therapy with rilpivirine compared to efavirenz.[6] Therefore, there is still an urgent need for novel NNRTIs possessing high potency while overcoming drug resistance, lesser toxicity, good patient adherence, and better pharmacokinetic properties.

NNRTIs are targeted at a hydrophobic binding site (namely, NNIBP), which is located at a short distance of 10 Å from the catalytic site.[7] The NNIBP has high flexibility, as it does not exist until binding with NNRTI, the formation of which is related to torsional rotations of the flexible side chains of some important amino acids.[8,9] In addition, mutations can be observed frequently in and around the NNIBP.[9] Although the three-dimensional structure of HIV reverse transcriptase (RT) has been elucidated, the inherent flexibility and mutability of NNIBP still limit the structure-based NNRTI design. Currently, with the continued efforts in the development of computational tools and increased structural information on the RT, coordinated multidisciplinary efforts involving medicinal chemistry (bioisosterism, molecular hybridization, scaffold hopping, and fragment-based drug discovery), structural biology (crystallography), and computational chemistry (molecular modeling) have proven to be powerful strategies for handling the flexibility and mutability of the NNIBP for identifying new generation of NNRTIs.

As a result of coordinated multidisciplinary efforts, great achievements have been made in the discovery of new generation of NNRTIs. In past 5 years, seven NNRTI representatives have been marketed or are undergoing clinical trials, i.e., etravirine, rilpivirine (Figure 1), **1** (UK-453061),[10] **2** (RDEA806),[11] **3** (IDX-899),[12] **4** (MK-4965),[13] and a discontinued drug candidate **5** (BILR 355)[14] (Figure 2). Their development processes are representative and full of revelations. In this review, we will successively describe (1) the pharmacophoric similarities[15] of NNRTIs and elaborate a typical pharmacophore model, (2) the convoluted development processes of seven representative candidates and drugs of NNRTIs, (3) the common structural characteristics of seven NNRTIs, and (4) the fragment-based drug discovery, with implications of halogenated aryls and nitrile groups.

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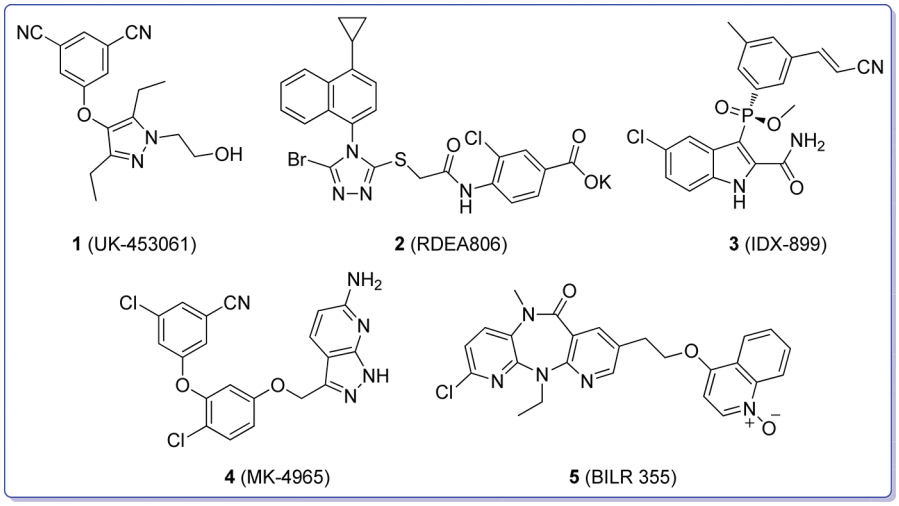

Figure 2. Chemical structures of five representatives for HIV-1 NNRTI candidates.

2. PHARMACOPHORIC SIMILARITIES OF NNRTIS: ELABORATION OF A PHARMACOPHORE MODEL

Although the NNRTIs possess structurally diverse scaffolds, they share nearly the same pharmacophoric features, namely, well-known "butterfly-like" or "horseshoe" conformation.[16] The first generation NNRTIs possess rigid structures, such as nevirapine, which adopts a "butterfly-like" conformation. The second generation of NNRTIs encompasses flexible structures, such as etravirine and rilpivirine, which adopt a horseshoe conformation. There are important differences in the conformations of these two models and specific positioning within the NNIBP. For instance, the "horseshoe" model could better adapt to the plasticity and changes of the NNIBP, which appears to be critical for potency against wild-type (WT) and a wide range of drug-resistant mutant HIV-1 RTs.

According to the known binding information of the seven NNRTIs (two drugs and five candidates), an elaborate pharmacophore model is summarized as follows (Figure 3A).

(1) F and B represent hydrophobic/π-electron containing parts that interact with the side chains of residues Y181, Y188, W229, F227, V106, P236, L100, L234, and Y318.
(2) D is the most tolerant region, mainly responsible for conformational adaptability. A wide range of substructures involving aryl or alkyl, benzene or heterocyclics, single ring or double rings, phosphonate or sulfonyl, electron-rich or electron-deficient groups are available for modification.
(3) C represents motifs that are able to form hydrogen bonding interactions with the main chains of residues K101, K103, and P236.
(4) A represents a polar part that interacts with the solvent interface to improve pharmacokinetic profiles.
(5) To a certain extent, the linker parts between B and F (i.e., C and E) are responsible for the whole molecular conformational flexibility.
(6) Substituents R_1 and R_2, respectively at D and F moieties, have delicate influence on the activity in both HIV-1 WT and mutant strains (Table 1). R_1 and R_2 are commonly halogen atoms, nitrile groups, or methyl groups.

It is noteworthy that the absence of some moieties of this model is allowed, as long as broad spectrum antiviral activity and pharmacokinetic properties are warranted. According to the pharmacophore model, the corresponding pharmacophoric parts of the seven NNRTIs (drugs and candidates) are marked with a dashed circle in Figure 3B.

The pharmacophoric similarities of NNRTIs allow medicinal chemists to use many analogue-based or "follow-on"-based drug discovery strategies[19] such as bioisosterism principle, molecular hybridization, and scaffold hopping in the design of novel NNRTIs. Some fragments such as halogenated aryl and nitrile exist extensively in NNRTIs, thus playing significant roles in fragment-based ligand discovery strategy. In addition, the "pharmacokinetic similarity", i.e., the existence of enzyme/water interface, provides an effective way to improve pharmacokinetic properties. These strategies in drug design will be exemplified by description of the development processes in the seven representative NNRTIs.

3. DEVELOPMENT PROCESSES OF SEVEN REPRESENTATIVE NNRTIS

The different development processes of the seven representatives provide researchers plenty of inspiration on the design of novel NNRTIs. Concretely, the discovery of diarylpyrimidine (DAPY) derivatives etravirine and rilpivirine is a comprehensive result of the coordinated multidisciplinary effort lasting for more than 20 years of research on NNRTIs, full of tenacity and persistence. Pyrazole derivative **1** was identified by extensive structural modifications on metabolic vulnerable sites of an abandoned clinical candidate. The discovery of aryltriazolylthioacetanilide **2** is a representative of the modified hits from high-throughput screening (HTS), with the aid of crystallographic structural information. 3-Phosphoindole **3** represents a new scaffold that was discovered by molecular hybridization and bioisosterism principles. On the basis of structural similarity of NNRTIs, scaffold hopping strategy has been successfully applied to identify a novel potent diaryl ether derivative **4**. Optimization on an already marketed non-nucleoside drug nevirapine resulted in a brand new candidate **5**. In the following sections, the different development processes of these representatives will be respectively described in detail.

3.1. From TIBO to Etravirine and Rilpivirine: Application Paradigm of Multidisciplinary Coordination. As early as 1987, Janssen Pharmaceutica in collaboration with the Rega Institute started with an MT-4 cell-based anti-HIV random

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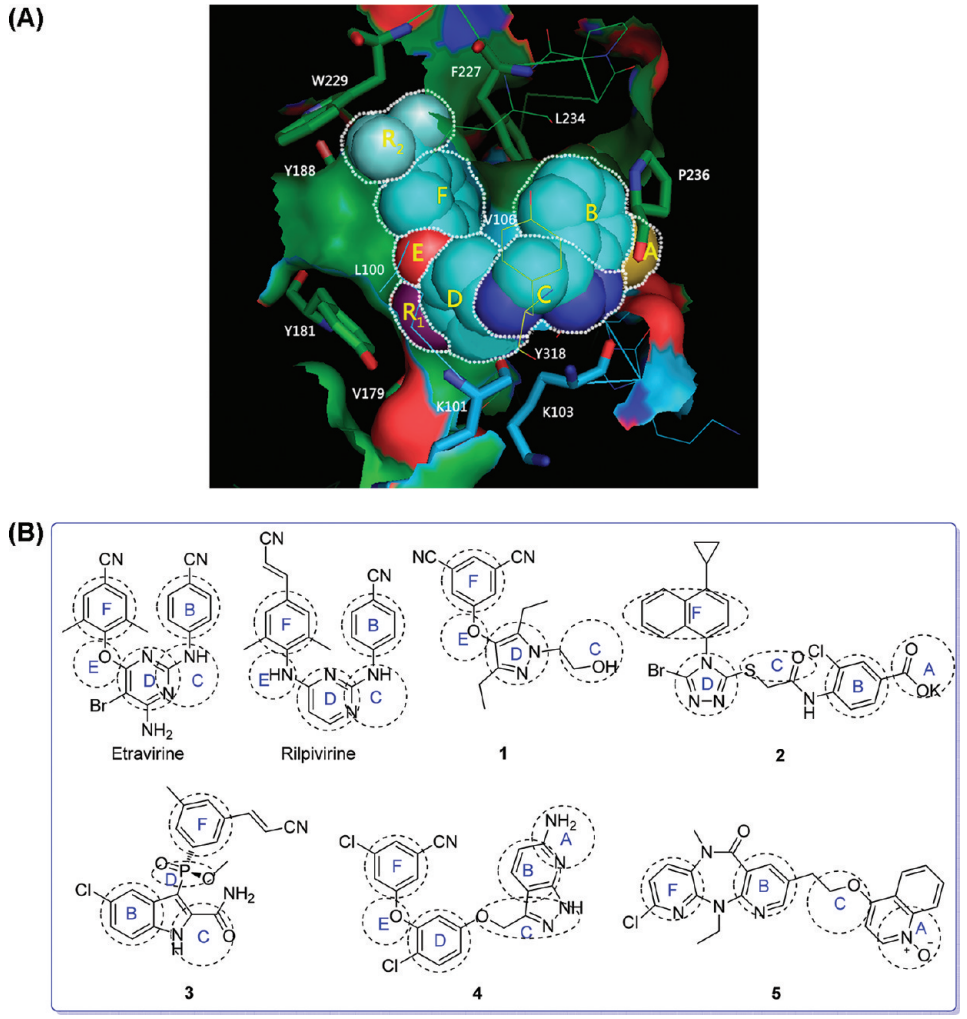

Figure 3. (A) Elaborate pharmacophore model for NNRTIs. The irregular spheres are divided into A, B, C, D, E, F, R1 (substituents at D), and R2 (substituents at F) pharmacophoric moieties present in all NNRTIs, which are surrounded by the relevant crucial amino acids in NNIBP. (B) Corresponding pharmacophoric parts in the seven representatives of NNRTIs.

screening program consisting of 600 compounds that belonged to different chemical series and displayed no unrelated pharmacological activity. Among these molecules, 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*][1,4]benzodiazepin-2(1*H*)-one **6** (TIBO, R14458, Figure 4)[20] was found to possess moderate but specific potency against HIV-1 replication. Subsequently, structure−activity relationship (SAR) studies led to the discovery of **11** (Figure 5), which inhibited HIV-1 strains HTLV-IIIB in MT-4 cells with an IC_{50} of 28 nM and a selectivity index (SI) of 31071 compared to AZT with an IC_{50} of 1.5 nM and a SI of 6200. The resulting compound was then submitted to preliminary clinical evaluation.

Crystallographic studies have been involved in the early stages of the rilpivirine development process. With the development of structural biology, the visual three-dimensional allosteric NNIBP adjacent to the polymerase catalytic site was unveiled by X-ray crystal structure of HIV-1 RT complexed with nevirapine (Figure 6A), which opened up a new era in structure-based NNRTI design.[7] Crystallographic structure of HIV-1 RT/TIBO derivative **12** (Figure 5) was also revealed, as shown in Figure 6B. The dimethylallyl functional group made hydrophobic π-interactions with Y181, Y188, and W229. The chlorophenyl group made hydrophobic interactions with L100, K101, and Y318, and the NH group of **12** could form hydrogen bond interactions with the main chain of K101.

The HTS method allows a researcher to quickly conduct millions of biochemical tests and can rapidly identify active compounds. When TIBO derivative **11** was under clinical assessment, an extensive program of high-capacity screening from a chemical library comprising 2000 entities led to a new class of NNRTIs, namely, the α-anilinophenylacetamide (α-APA) series. Through further lead optimization, **7** (loviride)[22] with an IC_{50} of 13 nM was finally developed for further clinical evaluation. Unfortunately, its development was halted, as it did not provide sufficient superiority over the two marketed NNRTIs nevirapine and delavirdine.[23]

The subsequent search for more potent compounds began with the SAR studies of the α-APA series. In contrast to the SAR of compound **13**, when the imide moiety was replaced with thiourea (**14**), para substituents on the A ring were favored instead of ortho substituents (Figure 7). This resulted in an imidoylthiourea (ITU) derivative **15**, which exhibited excellent anti-HIV-1 activity superior to that of its predecessors. However, the lability of the imidoylthiourea moiety became a major issue (Figure 8).[23]

In order to solve the unstable issue of ITU derivatives, based on the bioisosterism principle,[24] a well-known cyanoguanidine

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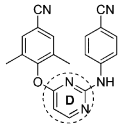
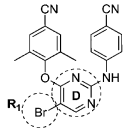
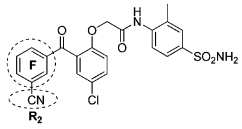
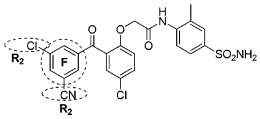
Table 1. Influence of Substituents R_1 and R_2 at D and F Moieties[17,18]

Compd	IC_{50} (nM)							
	WT	100I	103N	181C	106A	188L	100I+103N	103N+181C
	1.1	73	2.7	37		19	798	94
	1.4	6.6	1.4	22		5.9	49	25
	0.7		1.5	1.5	30			
	0.5		1.0	0.7	3.4			

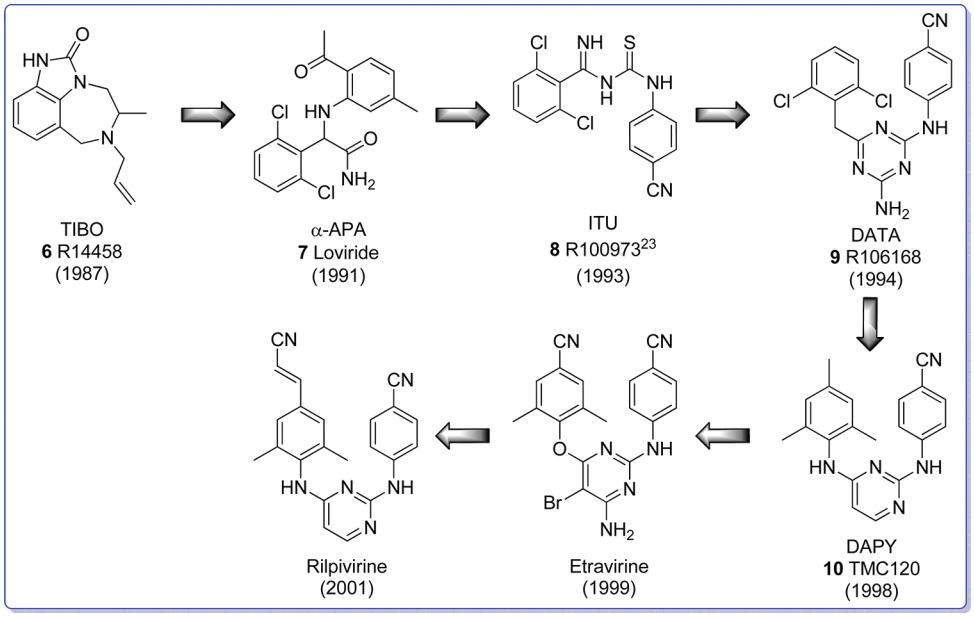


Figure 4. Development process from TIBO to etravirine and rilpivirine.

bioisostere was brought in to replace the unstable imidoylthiourea functional group. Surprisingly, the synthesis of desired ITU **17** with the cyanoguanidine bioisostere resulted in an unexpected but impressively stable diaryltriazine (DATA) derivative **9** (R106108)[26] (Figure 8), showing nearly the same antiviral activity as ITU **15**.

SAR studies of DATA derivatives were guided by X-ray crystallography and molecular modeling. The molecular modeling suggested that the C-4 position of the triazine ring was oriented to the opening region of NNIBP while the left ring of DATA derivative **18** interacted with Y181, Y188, and W229 (Figure 9). So the following modifications mostly focused on the C-4 position and the left ring. From systematic optimization, several compounds were found to possess adequate potency against a variety of prevalent RT mutants. In particular, the G190A mutant, which caused resistance through steric conflict, could be effectively inhibited by DATA derivatives, as the central triazine ring was spatially far away from the 190 residue according to the structural analysis of the DATA derivative **18**/RT complex (Figure 9). However, the potency against the L100I/K103N double mutant was not satisfactory.[26] Hence, a new modification project was started with the goal of improving solubility, bioavailability, pharmacokinetics, and potency against HIV-1 double mutations, eventually leading to the identification of diarylpyrimidine (DAPY) analogues.

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Excellent activity against HIV-1 WT was maintained as the central triazine ring was replaced by a bioisostere pyrimidine ring. When a bromine atom was introduced at the 5-position of the pyrimidine ring (Figure 10), DAPY NNRTIs showed greatly improved activity against common mutations, e.g., L100I, K103N, V106A, Y181C, Y188L, L100I/K103N, and K103N/Y181C, compared to DATA NNRTIs.[17] High-resolution crystal structure of RT/etravirine was difficult to obtain because of its intrinsic flexibility. As a result of their conformational flexibility, highly potent DAPY NNRTIs could easily adapt themselves to the steric interference caused by L100I and V106A mutations.[27] The much fewer interactions between DAPY NNRTIs and RT 181 and 188 residues resulted in remarkable potency against Y181C and Y188L mutations.[27] A crystallographic structure of unliganded mutant RT K103N indicated that a hydrogen bond could be formed between Y188 and N103 residues. The disruption to the N103−Y188 hydrogen bond by the cyano substituent on the aniline ring of DAPY NNRTIs,[28] as well as the interaction of DAPY NNRTIs with the main chain atoms of 100−103 residues,[25] may be attributed to their high potency against the K103N mutant.

In summary, this long-term optimization project from TIBO to DAPY series resulted in several promising clinical candidates including **10** (TMC120),[29] etravirine, and rilpivirine. **10** showed excellent potency against most single mutants. It had satisfactory profiles of safety and pharmacokinetics in a phase I/II study, but the antiviral activity against double mutants such as L100I/K103N and K103N/Y181C is modest. It was licensed by Tibotec to the international society for microbicide (IPM) to be developed as a vaginal microbicide.[30]

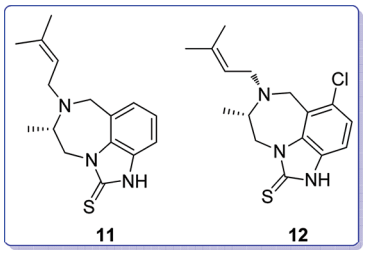

Figure 5. Chemical structures of TIBOs **11** and **12**.

Etravirine, under the trade name of Intelence, was approved in 2008 for the treatment of NNRTI-experienced patients. It has proven to be highly potent against both WT HIV-1 and many clinically prevalent mutants with IC_{50} below 10 nM. The IC_{50} values against double mutants including K103N/Y181C and L100I/K103N were 4.3 and 19 nM, respectively.[31] Data from phase I clinical trials showed that etravirine had a plasmatic half-life of 30−40 h and was mainly metabolized by cytochrome P450 (CYP)3A4. In phase IIb trials, the viral load decrease with etravirine was 1 log_{10} at week 24. In phase III trials, the viral load decrease was 2.3 log_{10} at week 24 when etravirine was coadministered with darunavir/ritonavir.[32]

Rilpivirine is more active than other NNRTIs partly because the extended cyanovinyl group could make strong interaction with the highly conserved W229.[33] It had an IC_{50} below 5 nM against both WT and many clinically prevalent mutants. Data from phase IIa clinical trials showed that rilpivirine had a half-life of 2 days, and the viral load decay was 1.199 log_{10} at day 8.[34] In phase IIb trials, more than 70% of patients receiving the 25, 75, or 150 mg dose of rilpivirine achieved an undetectable viral load (<50 copies/mL).[35] Phase III studies demonstrated that rilpivirine had the same efficacy as efavirenz but with fewer side effects. Rilpivirine has been recently approved by the U.S. FDA in May 2011 and awaits approval in the EU by EMEA. For a novel antiviral drug, it almost meets all requirements proposed by Dr. Paul Janssen (vide infra) and possesses satisfactory pharmacokinetic profiles.

Modifications on DAPY compounds led to the identification of several new NNRTI families, such as pyrazinone,[36]

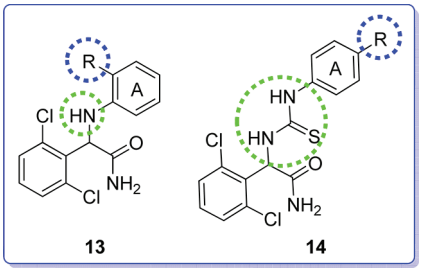

Figure 7. Exceptional SAR results caused by the replacement of the imide with thiourea.

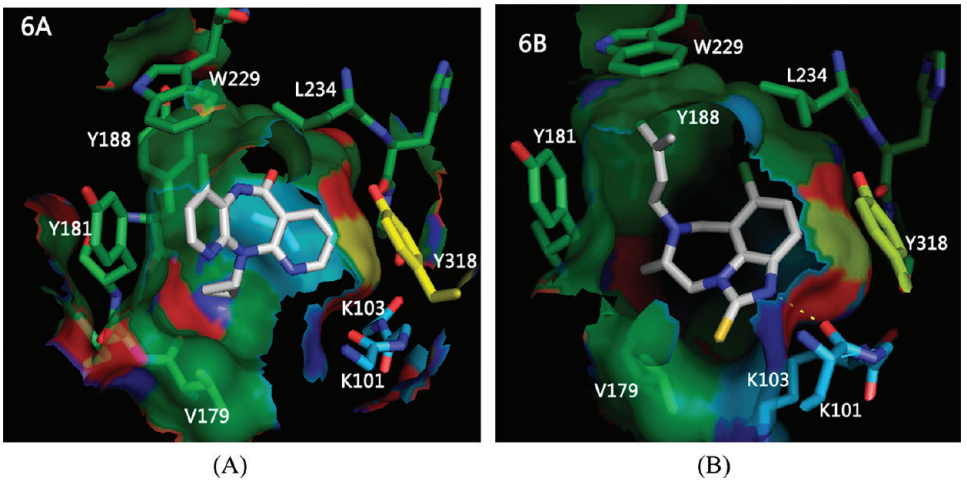

Figure 6. (A) X-ray crystallographic structure of RT/nevirapine complex (PDB entry 1VRT), shown by use of PyMOL 0.99. (B) X-ray crystallographic structure of RT/TIBO **12** complex (PDB entry 1HNV),[21] shown by use of PyMOL 0.99.

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diarylpyridine,[37] diarylaniline,[38] piperidin-4-ylaminopyrimidine,[39−41] diarylbenzopyrimidine,[42] and others,[43−46] as shown in Figure 11. Obviously, DAPY analogues will continue to be a hot research focus.

3.2. Pyrazole NNRTI. 1: Application Paradigm of Ligand-Lipophilicity Efficiency (LLE). **1** was identified by modification of a failed candidate **28** (capravirine) that was discovered by Shionogi & Co Ltd. and then licensed to Pfizer for further evaluation. **28** displayed a high antiviral potency against WT and mutant HIV variants, which may be attributed to the three hydrogen bond interactions with the main chain of residues 101, 103, and 236 (Figure 13) and its sufficient flexibility.[47] The existence of hydrogen bond interacting between **28** and the backbone of P236 caused the 3,5-dichlorophenyl ring to be adjacent to W229 based on the cluster analysis of many crystal structures. Actually, targeting at the highly conserved residue W229 was an efficient option to compensate the lost activity induced by many common RT mutants. However, clinical development of **28** was discontinued because in phase II studies there was no statistically significant difference between the gold standard triple drug regimens and the same therapy with **28** for the treatment of HIV-1 infection, which may be ascribed to a low drug exposure with a megadose regimen of 1400 mg b.i.d. given orally.[48,49] On the basis of preclinical and clinical results, **28** was thought to be feasible for further modification. It was hoped that further development would yield a novel template with retained antiretroviral potency while improving the metabolic stability associated with large pill burden.

Several groups such as 4-pyridyl, sulfur atom, primary carbamate, and imidazole nucleus were confirmed to have negative impact on pharmacokinetic profiles (e.g., oral absorption, metabolic stability) and thus were replaced with other functional groups (Figure 14). On the basis of the above molecular modification, a novel lead **29** was generated with an IC_{50} of 1.9 μM against WT of RT after previous optimization. Encouragingly, there were no significant side effects and drug−drug interactions. Subsequently, different biaryl linkers such as oxygen atom, ketone, and methoxymethylene were explored and ultimately produced compound **30** with improved oxidative stability. However, the hydroxylethyl moiety went through rapid glucuronidation in the isolated perfused rat liver preparation, replacement of which resulted in loss of potency. In order to solve this issue researchers focused on reducing lipophilicity (lead **29** with clogP = 4.2, log D > 4.0) in a comprehensive modification program.[50]

Lipophilicity, a very important druglike property, is related to nonspecific toxicity, poor solubility, and metabolic clearance. Drug candidates with high lipophilicity may hold increased risk for clinical failure. A new terminology named ligand-lipophilicity efficiency (LLE = pIC_{50}/K_i −log P/D) is described as a marker for the selection of a clinical drug candidate. Increasing LLE to >5 (i.e., potency of <10 nM, clogP < 3) is recommended.[51,52]

3,5-Diethylpyrazole derivative was the most potent compound that retained activity against mutant HIV-1 strains. Efforts of modification on 3,5-substituents of pyrazole nucleus in order to lower the lipophilicity (clogP = 4.2 of compound **29**) did not yield improved ligand-lipophilicity efficiency (LLE).

A large group of phenyl-substituted compounds were synthesized, as the 3,5-dichlorophenyl group was deemed to

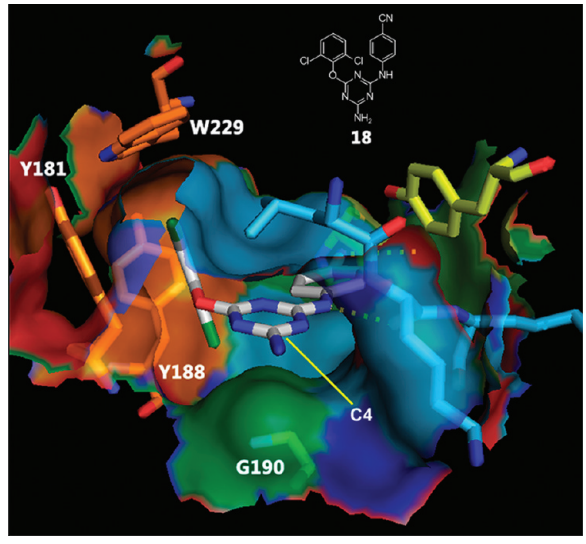

Figure 9. X-ray crystallographic structure of RT/**18** complex (PDB entry 1S9E),[25] shown by use of PyMOL 0.99.

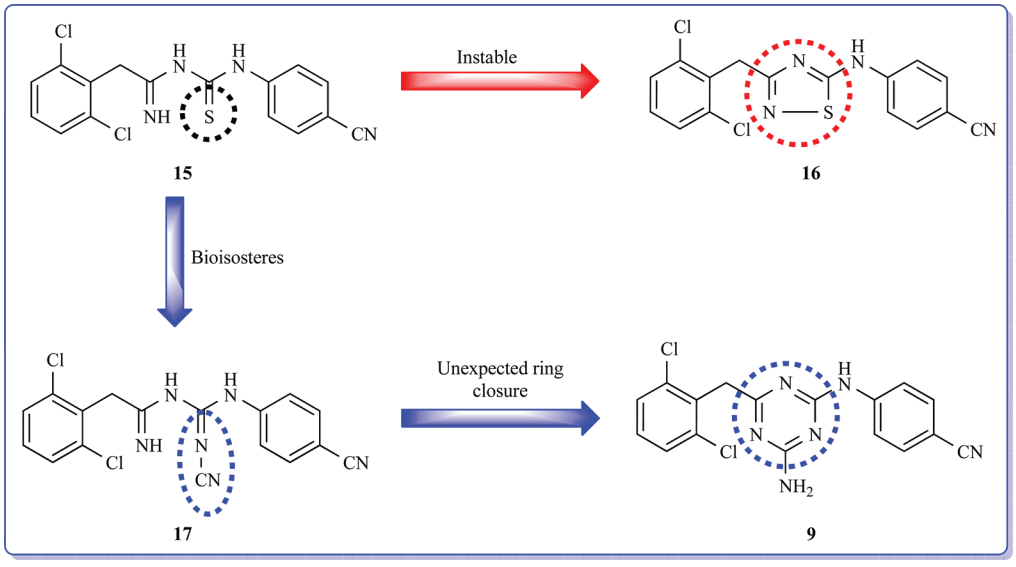

Figure 8. Oxidative unstable product **16** and the unexpected ring cyclization of ITU **17** to DATA **9**.

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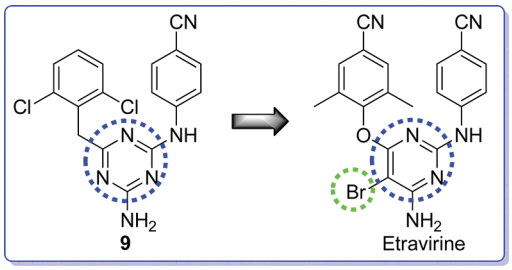

Figure 10. Bioisosteric replacement of triazine with pyrimidine ring and the introduction of 5-Br.

be crucial to the overall lipophilicity. Excitingly, the 3-nitrile compound **31** and 3,5-dinitrile compound **1** (Figure 12) exhibited satisfactory clogP and LLE by contrast with compound **30** (Table 2). Actually, the nitrile group that was introduced to improve clog P and LLE appeared in a new generation of NNRTIs such as etravirine, rilpivirine, **3**, and **4**. Through this structure modification, **1** was identified and displayed anticipated improvement in metabolic stability and antiviral potency.

1 possessed moderate anti-HIV-1 activity with IC_{50} values of 119 nM for the WT RT and 215 nM for the K103N RT while showing an excellent absorption profile. The F227C, L234I, V106A/F227L, and Y181I/Y188L mutations caused a decrease of the activity of **1**.[10] It showed synergistic interactions with NRTIs and integrase inhibitors. Clinical results demonstrated that after administration of 500 or 750 mg once daily, **1** decreased the viral load by 1.9 and 2.0 $\log_{10}$ at day 8, respectively.[54] With advantages of good pharmacokinetics, aqueous solubility, safety, and antiviral activity profiles, **1** has now proceeded to clinical trials at phase IIb.

Taking into account the existence of unsatisfactory pharmacokinetic and toxicity issues of NNRTIs, it has great significance for molecular modification by increasing the LLE value.

3.3. Aryltriazolylthioacetanilide NNRTI. 2: Paradigm of Using Crystallographic Structural Information To Modify the HTS Leads. Compound **32** (Figure 15) with moderate activity against both WT and K103N/Y181C mutation of RT was discovered in 2006 from a cellular-based screening of a library of 87 000 compounds. From further SAR studies, analogue **33** was disclosed to have excellent activity against WT and several mutant viruses but with the exception of Y188L mutant. Subsequent molecular modifications were guided by the crystallographic structure of the RT/**33** complex.

On the basis of the crystallographic study, the binding mode of **33** (Figure 16) indicates the following:[11]

(1) The phenyl ring at N-4 makes a $\pi-\pi$ stacking interaction with Y181 and Y188, while the methyl on the phenyl ring is oriented toward W229.
(2) The chlorophenyl group makes lipophilic interactions with the side chains of F227, P236, and V106.
(3) The carboxamide group make a direct hydrogen bonding interaction with the backbone NH of K103.
(4) The 4-position of the chlorophenyl moiety lies adjacent to the solvent opening and appears to be amenable to hydrophilic functional groups.

The following optimization strategies are outlined on the basis of the results of crystallographic studies:

(1) Exchanging the phenyl ring at N-4 with a naphthalene ring affords closer interaction with Y181, which showed increased activity against almost all mutant HIV-1 strains and extraordinary activity against Y188L mutation. This improvement could be ascribed to the fact that strong interaction with Y181 offsets the reduced potency caused by the Y188L mutation.
(2) Replacing the methyl of the left phenyl ring with a larger cyclopropyl group provides closer interaction with the conserved W229.
(3) Introducing a polar sulfonamide group at C-4 position of chlorophenyl ring that was adjacent to the enzyme/water interface improved aqueous solubility and antiviral activity. The sulfonamide group was then replaced with a carboxylic acid group because the latter was easier to prepare.

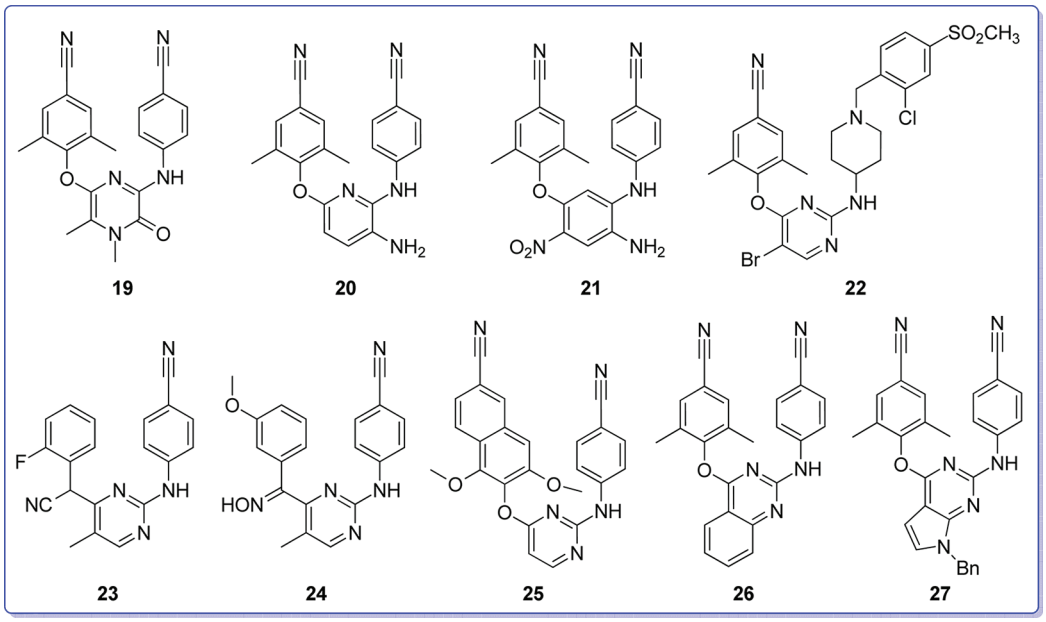

Figure 11. Chemical structures of DAPY analogues.

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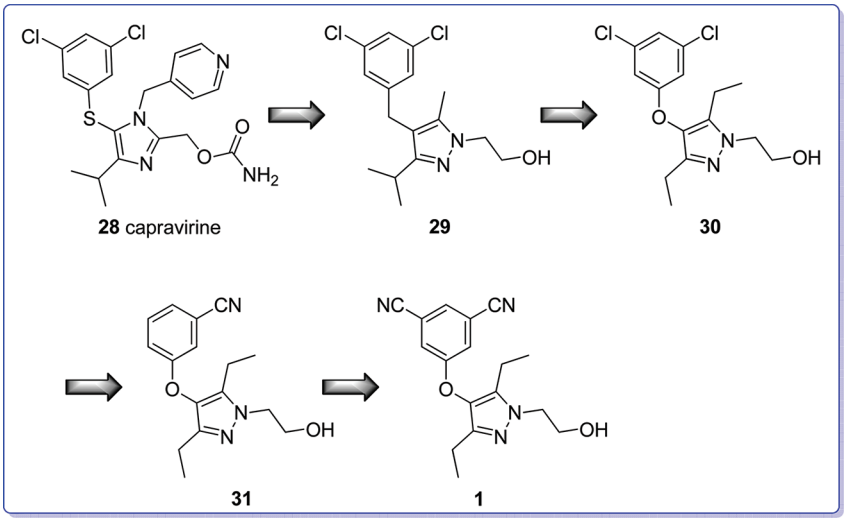

Figure 12. Development process from **28** to **1**.

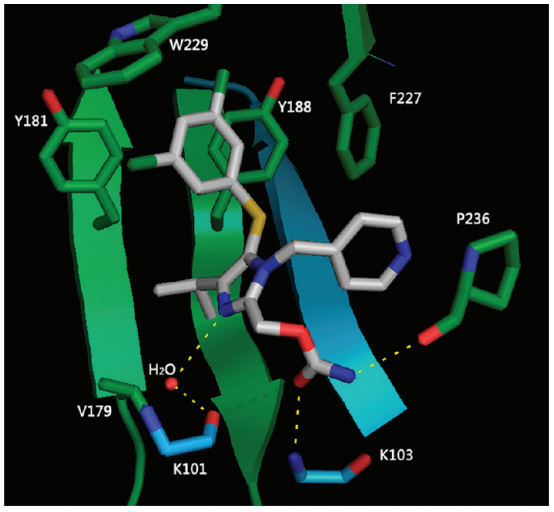

Figure 13. Three hydrogen bond interactions of **28** with NNIBP (PDB entry 1EP4), shown by use of PyMOL 0.99.

(4) Attempts to replace naphthalene ring by other bicyclic ring systems or replace central carboxamide group by its bioisosteres were not successful.

These modifications led to the identification of **34** (VRX-480773)[55] and **2**. Compound **34**, as the prodrug of **2**, inhibited WT and K103N/Y181C double mutant HIV-1 strains with EC_{50} values of 0.14 and 0.23 nM, respectively. Moreover, **34** was active (<2.5-fold change) against 49% NNRTI-resistant isolates in the Stanford database in contrast with 10.6% and 8.6% for efavirenz and nevirapine, respectively. Data from phase I trials indicated that **2** had excellent solubility in water and a half-life of 11 h.[56] The viral load decrease on day 9 was 1.95 and 1.70 $\log_{10}$ when **2** was dosed at 400 mg twice a day or 1000 mg once a day, respectively.[57] These results from phase I and IIa trials warranted **2** to undergo phase IIb clinical trials in treatment-naive subjects.

3.4. Drug Candidate. 3: Application Paradigm of Molecular Hybridization. 3-Phosphoindole NNRTI **3** proved to be extremely potent against both WT and clinically relevant single and double mutant strains of HIV-1 with nanomolar to subnanomolar activity. Resistance selection to **3** was developed by the E138K/Y181/M230L mutation. In phase IIa clinical trials, **3** decreased the viral load by 2.1 $\log_{10}$ on day 8 when dosed at 800 mg once a day. **3** is now the subject of phase IIb clinical evaluation.

Obviously, 3-phosphoindole NNRTIs possess significant similarities with the indolylarylsulfone (IAS) family. The original IAS derivative **35** (L-737126)[58] that emerges from a HTS effort at Merck represents a novel scaffold for further optimization. In particular, the extremely high broad spectrum antiviral potency of rilpivirine is related to its extensive interaction of cyanovinyl group with NNIBP, which afforded valuable inspiration for the scaffold evolution of the IAS family.[59] By combination of the superior aspects of these two NNRTIs, **3** was structurally constructed using the molecular hybridization method and bioisosterism principle (Figure 17).[15]

Currently, molecular hybridization has been a useful tool to design new drug prototypes.[60] It has been successfully applied in the design of other anti-HIV agents possessing excellent metabolic stability and mutant resilience, such as indazole NNRTIs (Figure 18).[61] Similar to the wide use of the molecular hybridization approach in the search for new NNRTI scaffolds, the synthesis of new drugs with improved overall efficiency will facilitate further developments.[61]

3.5. Diaryl Ether NNRTI. 4: Application Paradigm of Scaffold Hopping. HTS has been widely applied to identify active compounds as mentioned above in the NNRTI lead discovery, by which the benzophenone derivative **36** (Figure 19) was also obtained as a lead with an IC_{50} of 10 μg/mL.[62] Efforts on molecular modification in this series of compounds led to the identification of a new lead **37** (GW4511)[63] with an IC_{50} of 0.5 nM in MT-4 cell lines. Subsequently, with the guidance of systematic SAR studies and crystallographic analysis, **38** (GW678248)[64] was identified as an excellent antiviral agent against both WT and clinical relevant mutant strains (i.e., K103N, Y181C, and V106A) with nanomolar to subnanomolar activity but with unsatisfactory solubility and bioavailability. According to the previously described "pharmacokinetic similarity", the structural modification in the enzyme/water interface would provide an effective way to improve the pharmacokinetic properties. From the crystal structure of **38**/RT, it is clearly indicated that the sulfamide part is located in the enzyme/water interface (Figure 20). As structure modification

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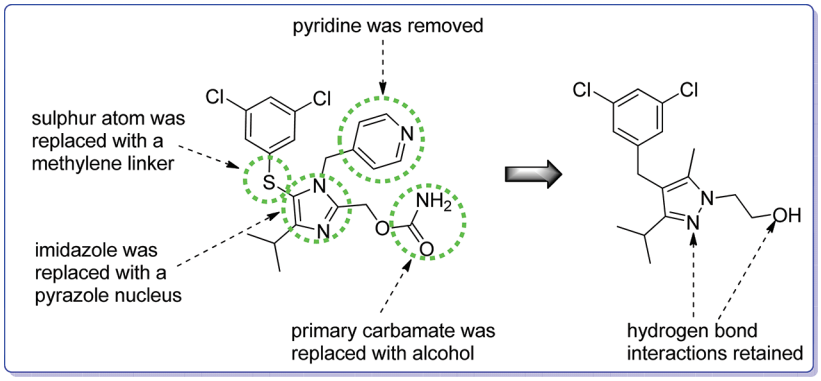

Figure 14. Available sites of **28** for structure modification.

Table 2. Changes of LLE with Addition of One or Two Nitrile Groups[10,53]

compd	clogP	RT $IC_{50}(\mu M)$	LLE
30	4.7	0.12	2.23
31	2.7	0.35	3.76
1	2.1	0.119	4.92

based on the prodrug principle, a propionyl group was introduced to the sulfamide group for adjustment of the lipid/water balance, generating **39** (GW695634)[64] with excellent pharmacokinetic profile and high antiviral potency. The crystal structure of **39**/RT showed that the protected sulfamide moiety was oriented to the solvent opening without affecting the binding with RT (Figure 20). Finally, **39** was selected for clinical development, but unfortunately it was halted in phase III clinical trials because of inferior antiviral efficacy compared with other NNRTIs.[65]

As previously mentioned, the scaffold hopping strategy is used in novel NNRTIs design on the basis of pharmacophoric similarities of NNRTIs. The term scaffold hopping has drawn increasing interest in lead generation.[66] Zhao[67] described that "scaffold hopping is a computational technique that identifies compounds containing a topologically different scaffold from the parent compound but with similar or improved activity". Structural diversity and pharmacophore similarity of NNRTIs provide more opportunities to construct novel inhibitors by implementing the scaffold hopping technique.

By comparison of lead **36** with tetrazole thioacetanilides NNRTI **38** (through HTS) by molecular modeling, scaffold hopping led to the identification of diaryl ether NNRTIs **39** and **40** (Figure 21),[15,68] in which a new flexible diaryl structure was introduced and the metabolic unstable anilide was replaced by an indazole substructure. The crystal structure of the **40**/RT complex (Figure 22) demonstrated that (1) the diaryl part interacted with the lipophilic pocket formed by Y181, Y188, and W229, (2) a bidentate hydrogen-bonding interaction was present between two nitrogen atoms of the indazole ring (superseding the amide carbonyl of **36**) and the K103 amide backbone, and (3) the indazole ring interacted with the solvent interface.[68]

Although compound **42** had promising antiviral activity, pharmacokinetic studies showed that it had poor oral bioavailability due to the low solubility. The phenyl ring of the indazole was replaced by a polar pyridine ring with the nitrogen atom at the 7-position that pointed to the enzyme/water interface (Figure 22). A novel compound **43** (MK-1107)[64] was developed as a drug candidate. Disappointingly, low solubility of compound **43** made it difficult to formulate in a proper dosage form. Information from crystallographic structure and molecular modeling analysis recommended that addition of an

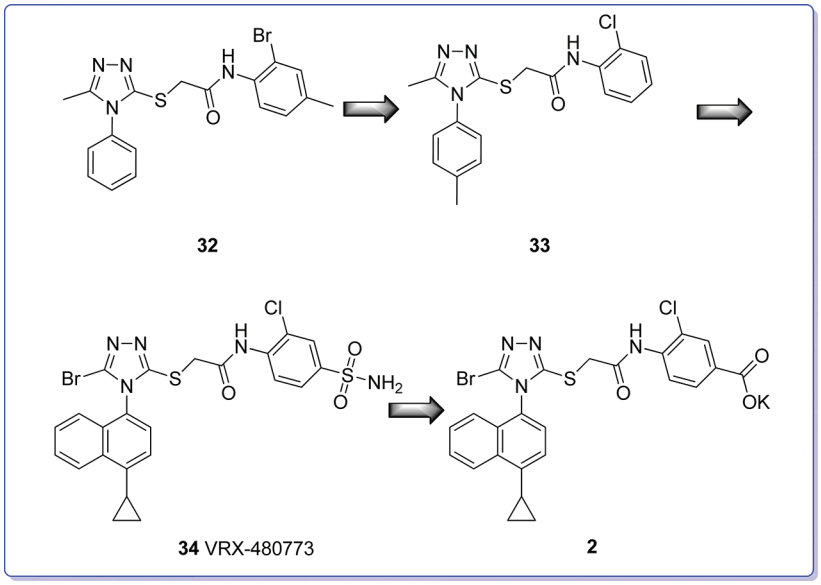

Figure 15. Discovery pathway of drug candidate **2**.

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amino group in the 6-position of pyridine would be beneficial. Excitingly, this amino substituted NNRTI displayed good oral bioavailability allowing once-daily dosing. Compound **4** has low solubility at pH 7, which may affect the gastrointestinal absorption. Antiviral potency of **4** against various clinically prevalent mutant viruses ranged from single digit nM to double digit nM but with the exception of Y188L mutation. As shown clearly in Figure 22, the phenyl ring of analogue **42** makes direct π-stacking interaction with the phenyl ring of the Y188, which is annihilated when Y188 is mutated to L188, but Y188L mutation is considered to rarely happen. To date, **4** undergoes phase I clinical trials.[13]

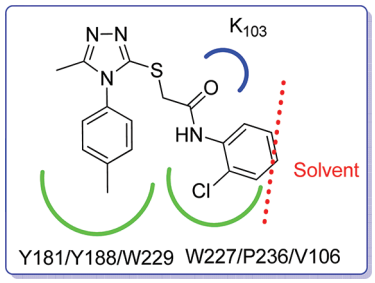

Figure 16. Binding mode of **33** with RT.

3.6. NNRTI. 5: Modification of an Old Drug by Involving Additional Interactions with RT Binding Site. The pharmacologist and Nobel laureate James Black once said that "the most fruitful basis for the discovery of a new drug is to start with an old drug".[69] As existing candidates and drugs have advantages of excellent pharmacodynamic, pharmacokinetic, or toxicological profiles, utilizing old drugs as a new template for modification may be of value in new drug discovery, avoiding costly and time-consuming work. The "follow-on" approaches involve molecular operation of altering or modifying the scaffold

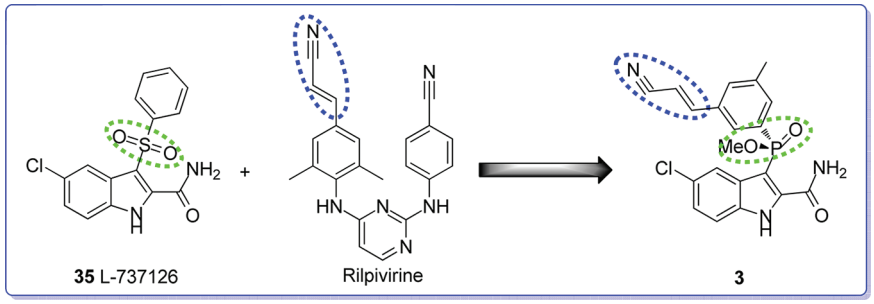

Figure 17. Identification of **3** using molecular hybridization and bioisosterism principle.

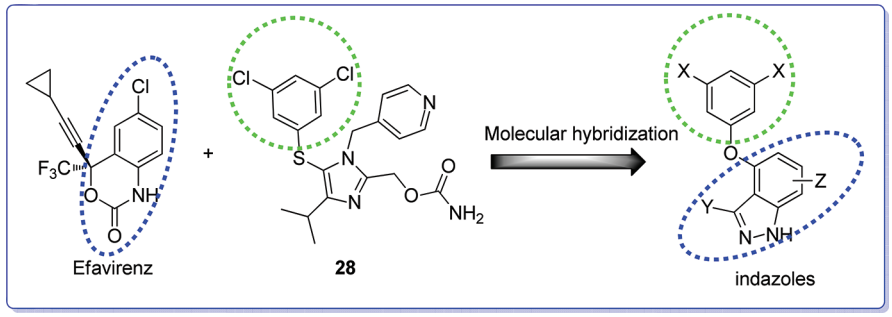

Figure 18. Identification of indazole NNRTIs through molecular hybridization.

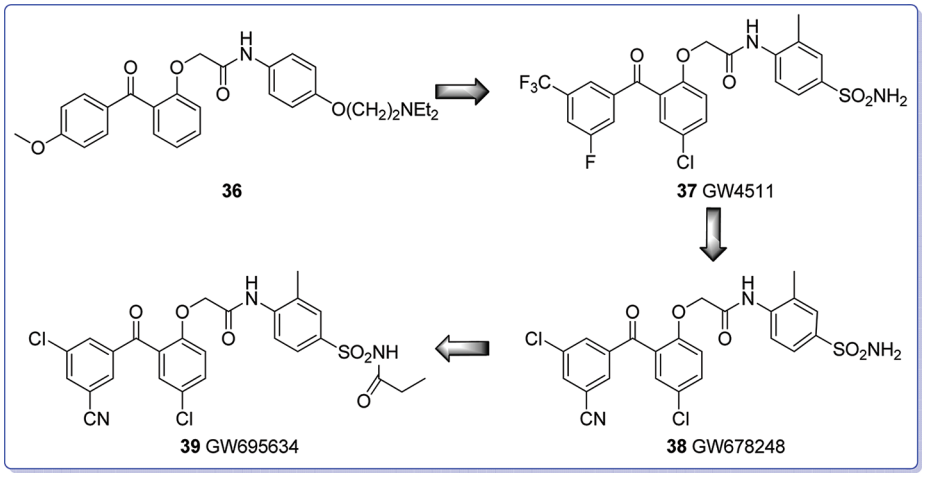

Figure 19. Discovery of compounds **38** and **39**.

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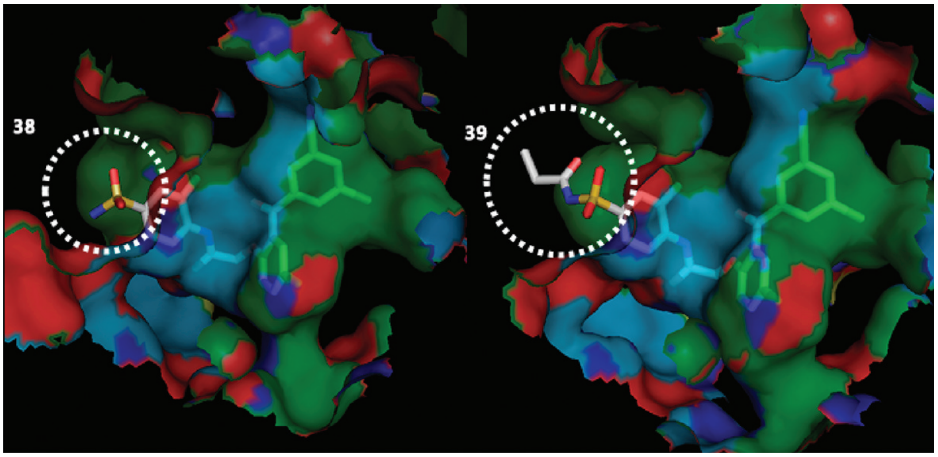

Figure 20. Modification of solvent opening region for improving pharmacokinetic properties (PDB entries 3DOK and 3DOL), shown by use of PyMOL 0.99.

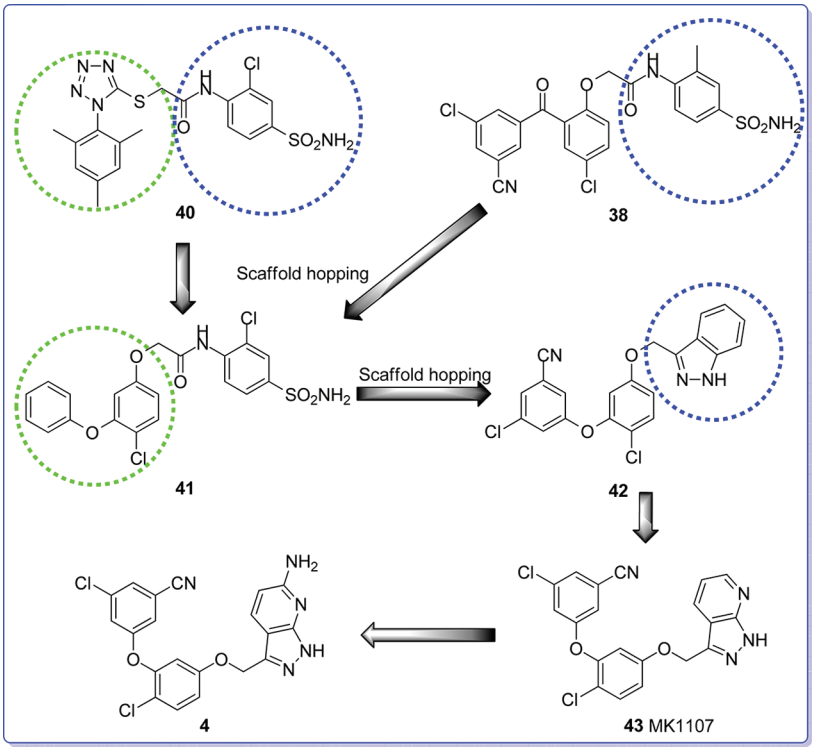

Figure 21. Scaffold hopping paradigm from compounds **38** and **40** to NNRTI **4**.

of existing agents but maintaining the pharmacophore.[19] The validated targets, definite SAR, and pharmacophoric features of the known NNRTIs make the follow-on approach straightforward with low risk.

Nevirapine is the first marketed NNRTI developed by Boehringer Ingelheim as a component of HAART for the treatment of HIV infection. However, the clinical use of nevirapine is greatly hindered by the presence of mutations, especially of the Y181C and K103N mutants. In search of a novel anti-HIV drug bearing broad spectrum antiviral activity, Boehringer Ingelheim carried out an extensive SAR analysis program to get information on what position of nevirapine was amenable to modifications (Figure 23). Extensive studies on molecular modification and biological assay demonstrated that the 8-position for substituents was the main modification site that could bring remarkable activity across strains carrying common mutations. Other positions that could be envisaged for modification are also illustrated in Figure 24.[14]

On the basis of the main modification site being the 8-position, **5** was identified as a potent NNRTI with an EC_{50} of 0.26 ng/mL, with a more than 10-fold improved potency of nevirapine against several clinical NNRTI-resistant isolates. **5** was recommended for coadministration with a booster ritonavir because it was a P-glycoprotein substrate and mainly metabolized by cytochrome P450 (CYP)3A4. **5** was terminated after a clinical trial, owing to the unsatisfactory clinical data obtained in the phase II study.[69]

It has been proposed that the maximal volume of NNRTI occupied in NNIBP may result in improved potency.[70] To a

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large extent, the potency of nevirapine relied on π-stacking interactions with Y181 and Y188. The occurrence of mutations at these residues led to a drastic decrease in nevirapine binding.[71] **5** exemplified the conjecture by extending the substitution at the 8-position to make additional interactions with the backbone of P236 and K103, being endowed with excellent antiretroviral profile against both HIV-1 WT and NNRTI-resistant mutants. Compared to the compact structure of nevirapine, additional interactions in other promising NNRTI candidates (i.e., rilpivirine, **1**, and **2**) were also fully exploited (i.e., strong interactions with conserved amino acid W229 of rilpivirine, **5** and extra hydrogen bond interaction with P236 of **1**), providing an efficient pathway to improve the potency of other novel NNRTIs.

4. COMMON CHARACTERISTICS OF SEVEN REPRESENTATIVE NNRTIS

Although the development routes of these seven NNRTI representatives are widely diverse, they hold common characteristics during lead discovery, structural modification, and pharmacodynamic and pharmacokinetic optimization processes.

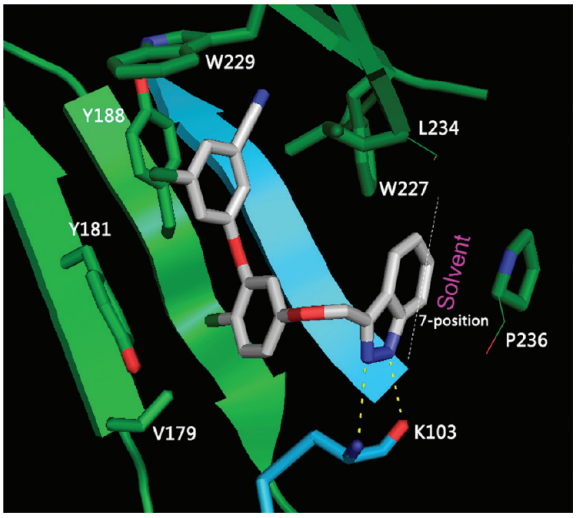

Figure 22. Crystal structure of **42**/RT complex (PDB: entry 3C6U), shown by use of PyMOL 0.99.

4.1. HTS Hits, Old Active Molecules, or Marketed Drugs as Lead Compounds. HTS has become the major paradigm for lead discovery for pharmaceuticals. NNRTI leads such as sulfanyltriazole (**32**),[72] benzophenone (**36**),[62] and sulfanyltetrazole (**40**)[73] are all from traditional HTS. Utilizing old molecules or marketed drugs (exemplified by **28** to **1**, **39** to **4**, and nevirapine to **5**) as the starting point is still worth exploring partly because of the favorable profiles of old drugs as previously mentioned and partly because of the difficulties in searching for new leads through NNIBP-based de novo drug design. The unique properties of NNIBP being deficient in structure-based NNRTIs design refer in particular to the following: (1) NNIBP does not exist until binding a substrate; (2) NNIBP is inherently flexible; (3) NNIBP is extremely mutable.

4.2. Multidisciplinary Coordination in the Process of Structure Modification. Multidisciplinary coordination involving structural biology, computational chemistry, and traditional medicinal chemistry is applied in the structure modification of the seven NNRTIs. Throughout the modification process, SAR analysis, crystallography, and molecular modeling are used to determine structural requirements and to guide further synthesis. Traditional medicinal chemistry approaches ("follow-on"-based drug discovery) such as bioisosterism principle, molecular hybridization, and scaffold hopping are still highlighted in novel NNRTI design.

4.3. Optimization Strategies on Pharmacodynamics. The first generation NNRTIs exhibit excellent antiviral activity

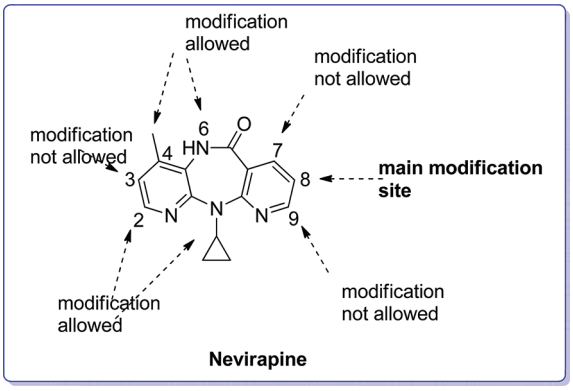

Figure 24. Sites that are amenable to modifications of nevirapine.

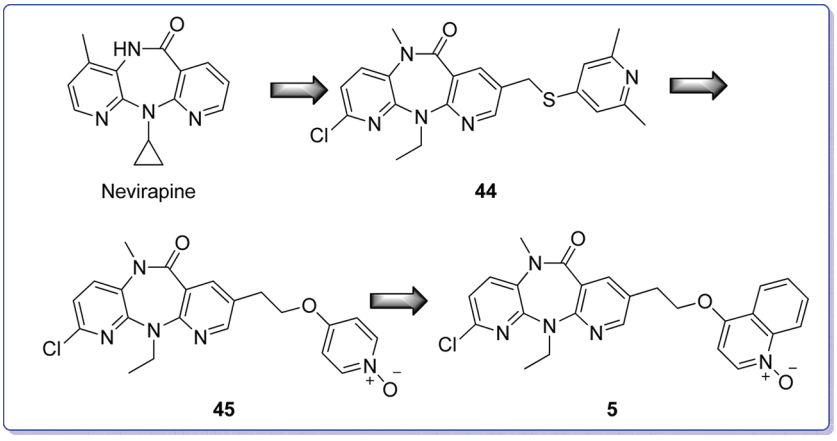

Figure 23. Discovery route of NNRTI **5**.

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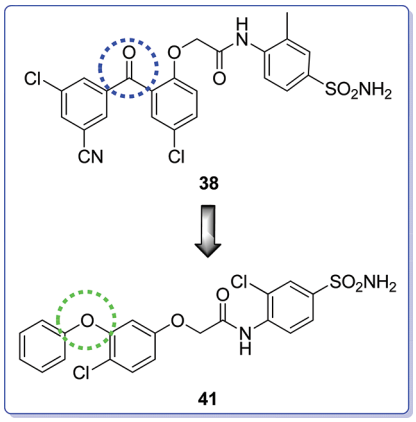

Figure 25. Replacement of carbonyl with a more flexible oxygen atom.

against WT HIV-1 virus but lose their ability to inhibit single or double mutant HIV-1 viruses. Consequently, remedying drug resistance is at the leading edge of current NNRTI research and development. There are four primary ways to overcome anti-AIDS drug resistance:

(1) Improving NNRTI conformational flexibility and positional adaptability. For example, the existence of O and NH linkers between two aromatic rings allows etravirine to adopt multiple conformations to accommodate the flexible and mutable NNIBP.[25] Also, in the development process of **4**, the benzophenone scaffold was replaced with a more flexible diaryl substructure (Figure 25).

(2) Forming extensive hydrogen bonds with NNIBP main chains. Hydrogen bond interaction in NNIBP is easily influenced by the mutations of amino acid residues. One or more hydrogen bonds with the main chain has been taken into account to design the next generation NNRTIs. As depicted in Figure 26, etravirine, rilpivirine, **1**, **2**, **3**, and **4** structurally set good examples in forming extensive hydrogen bonds with the main chains of HIV-1 NNIBP.

(3) Targeting highly conserved residue W229 (Figure 26). Strong interaction between molecules and highly conserved W229 is an important strategy for designing new NNRTIs overcoming HIV mutation.[74] For instance, the cyanovinyl group of rilpivirine in the RT/rilpivirine complex extends deeply into a hydrophobic tunnel formed by residues Y188, F227, W229, and L234, which is related to the movement of the prime grip of the RT. This fact was used to explain why rilpivirine is more active than other NNRTIs.[59] The cyclopropyl of **2** and the cyanovinyl of **3** play the same role as the cyanovinyl of rilpivirine, to bind to the conserved residue W229. A unique hydrogen bond interaction exists between **1** and the backbone of P236, indirectly causing the 3,5-dicyanophenyl ring to be adjacent to W229. Hence, elongated substituents, hydrogen bond interaction with the backbone of P236, or other potential factors that can form close contact with W229 are particularly beneficial for improving antiviral potency vs WT and mutant strains of HIV-1.

(4) Involving additional interactions. The maximal volume of NNRTIs occupied in NNIBP results in improved potency, which has been exemplified in the development route of **5**.

4.4. Optimization Strategies on Pharmacokinetics. NNRTIs are quite potent in vitro, but they may have poor exposure in vivo because of unsatisfactory pharmacokinetic properties including absorption, distribution, metabolism, and excretion. The way to improve pharmacokinetic profiles is to replace metabolic unstable sites (exemplified by the development route from **28** to **1**) or to modify the sites that point to the solvent accessible region without affecting the antiviral potency (exemplified by drug candidates **2**, **4**, and **5**). Increasing LLE is also a helpful indicator in improving pharmacokinetic properties.

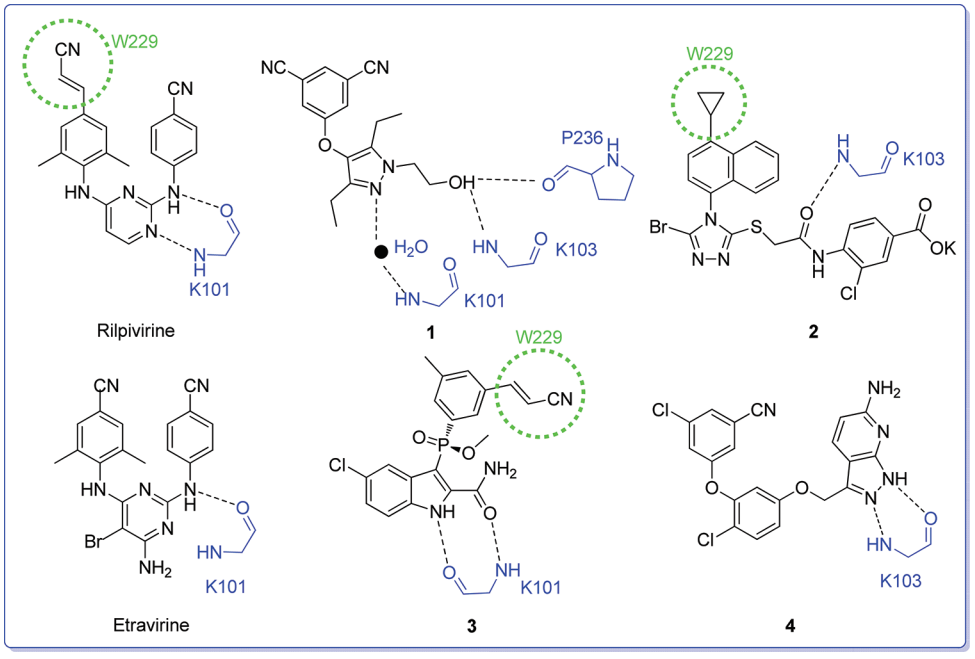

Figure 26. Main chain hydrogen bond of NNRTIs with NNIBP and extensive interaction with the conserved W229.

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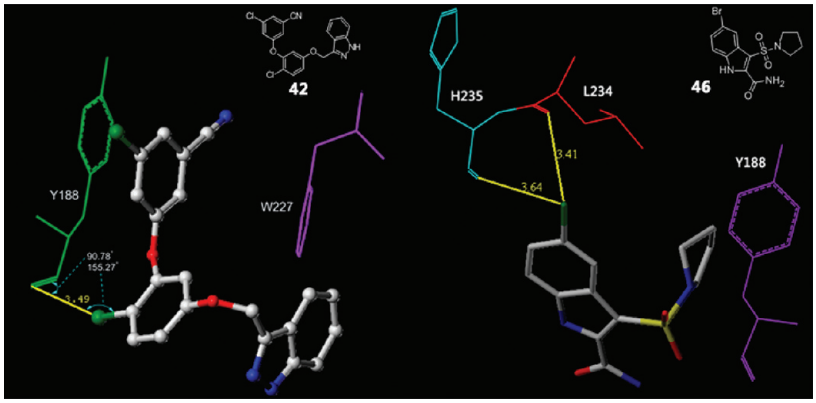
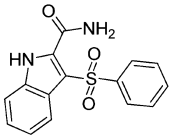
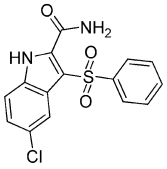


Figure 27. Existence of halogen bonds in two NNRTIs **42** and **46** (PDB entries 3C6U and 2RF2), shown by use of the program SYBYL-X.

Table 3. Influence of Halogen on the Antiviral Activity in IAS Derivatives

Compd	EC_{50} (μM)
	0.18
	0.001

5. FRAGMENT BASED DRUG DISCOVERY: IMPLICATIONS OF HALOGENATED ARYLS AND A NITRILE GROUP

As described above, although NNRTIs belong to different chemical families, they have pronounced pharmacophoric similarities. Ubiquitous fragments such as halogenated aryls and a nitrile group exist extensively in NNRTIs, especially in the new generation NNRTI candidates. They make unique interactions with functionally important amino acid residues in NNIBP, thus playing a significant role in the antiviral potency against both HIV-1 WT and NNRTI-resistant mutants.

5.1. Roles of Halogen Atom: To Form Halogen Bonds. The halogenated aryl is present in several NNRTI representatives such as etravirine, **2**, **3**, **4**, and **5**. The functional roles of halogen atom in drug design have been studied and reported in many cases.[75,76] Noncovalent interaction can be formed with halogens C—X···O—Y, where X is Cl, Br, or I; O is oxygen (most frequent), N, S, or NH; and Y is C═O, OH, charged carboxylate, or a phosphate group.[75] As depicted in Figure 27, the X-ray crystallographic structure of the **42**/RT complex appears to show halogen bonds between chlorine atom and main chain carbonyl oxygen of Y188. Dihedral angles of C—X···O and X···O—Y are 155.27° and 90.78°, respectively, just as Auffinger et al. described.[75] Only the X···O distance (3.49 Å) is slightly larger than their van der Waals radii (3.27 Å). During the discovery course of **3**, halogen on the sulfone indolyl ring was regarded to be crucial for antiviral activity (Table 3). In Figure 27, the X-ray crystallographic structure of a sulfone indolyl congener **46**/RT complex showed a X···O distance of 3.41 and 3.64 Å (van der Waals radii of Br···O is 3.37 Å). The big difference in antiviral potency between the two sulfone indolyl congeners in Table 3 may be attributed to these halogen bonds.

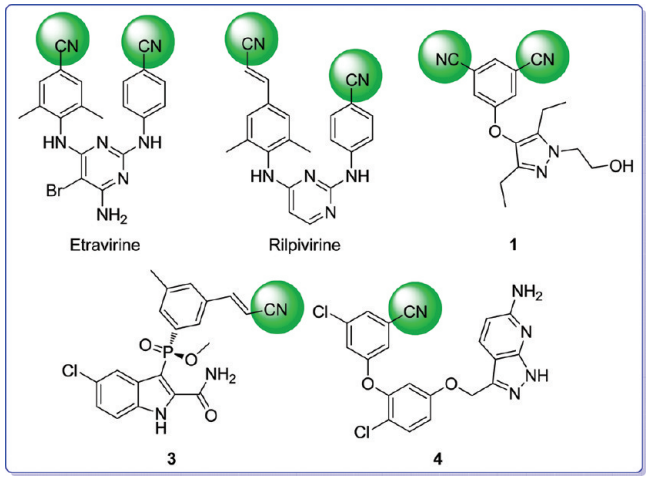


Figure 28. Nitrile groups in etravirine, rilpivirine, **1**, **3**, and **4**.

Therefore, halogen bonds, to some extent behaving as electrostatic-type interactions, are strong enough in competition with hydrogen bonds and should be taken into account in modern drug design.[77]

5.2. Role of a Nitrile Group. A nitrile group is also present in several NNRTIs, i.e., etravirine, rilpivirine, **1**, **3**, and **4** (Figure 28), which is considered to play several roles in non-nucleoside molecules, for instance, as bioisosteres of carbonyl and halogen and making polar or hydrogen bond interactions with the target.[78] On account of the hydrophobic character of NNIBP, NNRTIs are somewhat lipophilic, which is related to low bioavailability and rapid clearance. The overall lipophilicity can be compromised by a polar nitrile group, thus affording a high LLE as previously discussed in the optimization of **1**.

The halogenated aryls and nitrile motifs, as "privileged fragments" in NNRTIs, are very similar with the concept of "privileged scaffolds", showing significance in fragment-based ligand discovery strategy. These "privileged fragments" can be applied to build fragment libraries to identify biologically active compounds. It is also possible to build new molecules using these "privileged fragments" as a starting point. For example, the $\pi-\pi$ interactions with conserved aromatic residue Y318, van der Waals contacts with the conserved hydrophobic L234 subpocket, and hydrogen bond interaction with the residue K101 are thought to be efficient in overcoming mutant resilience.[79] These three

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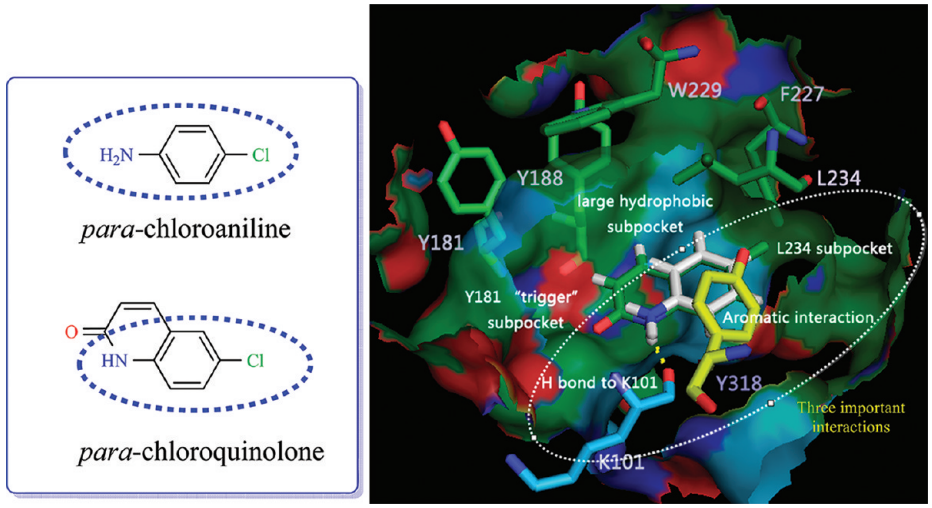

Figure 29. Interactions of the *p*-chloroaniline and *p*-chloroquinolone motifs with Y318, K101, and L234 subpocket in NNIBP. *p*-Chloroaniline is shown by white sticks, and *p*-chloroquinolone is shown by green sticks. The figure is shown by use of PyMOL 0.99.[79]

interactions can be assemblied to form a *p*-chloroaniline motif (Figure 29). Considering the NNRTI structural requirement and synthetic accessibility, together with the above three interactions, the *p*-chloroaniline motif was replaced with *p*-chloroquinolone, generating novel quinolone NNRTIs with nearly the same binding mode and improved drug resistance properties (Figure 29).[79] A number of clinical candidates for the treatment of other disease have also emerged from fragment-based drug discovery strategy, and the approach is anticipated to be increasingly applied as an additional route for discovering novel active NNRTIs.[80]

6. CONCLUSION

Great achievements in NNRTIs research have been made in the past 2 decades. Nevirapine, delavirdine, and efavirenz had been approved by U.S. FDA for the treatment of HIV infection in the 1990s. However, the advantages offered by these NNRTIs are often compromised by the rapid emergence of drug-resistant strains of HIV and potentially serious toxicities, to hamper their clinical use. Therefore, identification of novel NNRTIs has become the most important serious issue, which impelled scientists in the past decade to focus their efforts on designing novel NNRTIs with improved potency against both HIV wild-type and mutant strains. Ultimately, etravirine and rilpivirine with a high genetic barrier to resistance were successfully launched on the market in 2008 and 2011 under coordinated multidisciplinary efforts, respectively. But this is not the end point in the development of NNRTIs because of the natural high genetic HIV heterogeneity and the imperfection existing in the second-generation NNRTIs. For instance, etravirine was reported in 2009 to have adverse effects of Stevens–Johnson syndrome and hypersensitivity reactions and rilpivirine led to virologic failure with resistance to one or more NNRTIs, so it is still necessary to involve modern drug design strategies as efficient tools to design and discover new generation NNRTIs to overcome drug resistance and toxicity profiles.

By this review of the development processes of seven representative NNRTIs, different drug design strategies emerged clearly for the researchers to identify novel NNRTIs with improved pharmacodynamic, pharmacokinetic, and toxicity profiles. HTS-derived compounds, old molecules, or marketed drugs are often used as the lead compounds in the NNRTI modification process. In particular, multidisciplinary coordination has proved to be a powerful way to handle the flexibility and mutability of the NNIBP, from which novel NNRTs could be designed to get around the resistance mechanisms.

In consideration of the difficulty in structure-based NNRTI design, an elaborate pharmacophore model from these seven stories could be established, which may be helpful for designing the next generation of NNRTIs. Besides, the ubiquitous halogenated aryl and nitrile fragments can serve as "privileged scaffolds" in fragment-based ligand discovery, being an additional route for discovering new active NNRTIs.

As the classical and modern drug design approaches are widely used, the next generation of NNRTIs with (1) high antiviral activity against WT and mutant viruses, (2) high oral bioavailability, allowing once-daily administration, (3) minimal adverse effects to satisfy patient compliance and tolerance, and (4) ease of synthesis and formulation, as Dr. Paul Janssen described,[30] may continue to emerge in the near future.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +86-531-88380270. Fax: +86-531-88382731. E-mail: xinyongl@sdu.edu.cn.

Notes

The authors declare no competing financial interest.

Biographies

Dongyue Li graduated from the School of Pharmaceutical Sciences in Shandong University, P. R. China, in 2007. He is currently studying for the Master degree in the Department of Medicinal Chemistry of the School of Pharmaceutical Sciences in Shandong University.

Peng Zhan obtained his B.S. degree from Shandong University, China, in 2005. Then he earned his M.S. and Ph.D. degrees in Medicinal Chemistry from Shandong University, P. R. China, under the supervision of Prof. Xinyong Liu in 2008 and 2010, respectively. He is now working as a young researcher in the laboratory of Prof. Xinyong Liu. His research area involves design and synthesis of novel non-nucleoside reverse transcriptase HIV-1 inhibitors.

Erik De Clercq has M.D. and Ph.D. degrees and has taught courses in Cell Biology, Biochemistry, and Microbiology at Katholieke

Universiteit Leuven (and Kortrijk) Medical School, Belgium, and was Chairman of the Department of Microbiology and Immunology until September 2006. He is currently Emeritus Professor of K.U. Leuven—Leuven University, Member of the Belgian (Flemish) Royal Academy of Medicine and the Academia Europaea, and Fellow of the American Association for the Advancement of Science. In 2008, he was elected European Inventor of the Year (Lifetime Achievement Award), and in 2010 he, together with Dr. A. S. Fauci, was Laureate of the Dr. Paul Janssen Award for Biomedical Research. He is the (co)inventor of a number of antiviral drugs (valaciclovir, brivudin, cidofovir, adefovir dipivoxil, and tenofovir disoproxil fumarate).

Xinyong Liu received his M.S. and Ph.D. degrees from School of Pharmaceutical Sciences, Shandong University, P. R. China, in 1991 and 2004, respectively. From 1997 to 1999 he worked at the Instituto de Quimica Medica (CSIC) in Spain as a Senior Visiting Scholar. He is currently a Distinguished Professor, Director of the Institute of Medicinal Chemistry, School of Pharmaceutical Sciences, Shandong University. His research interests are mainly focused on the design and synthesis of anti-HIV agents based on the mechanism of a drug's action and computer-assisted drug design. His second ongoing program is total synthesis and structural modifications of some natural products from Chinese Traditional Medicine that are active in cerebro- and cardiovascular biology. He has contributed to about 150 scientific publications and patents as well as many monographs.

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■ ABBREVIATIONS USED

UNAIDS, Joint United Nations Programme on HIV/AIDS; WHO, World Health Organization; HIV-1, human immunodeficiency virus type 1; AIDS, acquired immune deficiency syndrome; HAART, highly active antiretroviral therapy; NRTI, nucleoside reverse transcriptase inhibitor; PI, protease inhibitor; NNRTI, non-nucleoside reverse transcriptase inhibitor; U.S. FDA, U.S. Food and Drug Administration; NNIBP, non-nucleoside reverse transcriptase inhibitor binding pocket; RT, reverse transcriptase; WT, wild-type; DAPY, diarylpyrimidine; HTS, high-throughput screening; SI, selectivity index; LLE, ligand-lipophilicity efficiency; TIBO, 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-*jk*](1,4)benzodiazepin-2(1*H*)-one; ITU, imidoylthiourea; α-APA, α-anilinophenylacetamide; DATA, diaryltriazine; LLE, ligand-lipophilicity efficiency; IAS, indolylarylsulfone; SAR, structure−activity relationship

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