Sulfanyltriazole/tetrazoles: A Promising Class of HIV-1 NNRTIs

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Abstract: There is an urgent need for the design and development of new and safer drugs for the treatment of human immunodeficiency virus (HIV) infection, specifically active against drug-resistant viral strains. Recently, sulfanyltriazole/tetrazole derivatives were reported as potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), with low nanomolar intrinsic activity against RT and submicromolar antiviral activity in HIV infected cells. In this review, the structural modifications, SAR analysis and docking studies of sulfanyltriazole/tetrazoles HIV-1 NNRTIs are discussed, and other interesting NNRTIs with the same or similar pharmacophore as the sulfanyltriazole/tetrazole derivatives are also presented and analyzed for their in SAR.

Key Words: AIDS, HIV-1, reverse transcriptase (RT), sulfanyltriazole/tetrazoles, NNRTIs, SAR, scaffold hopping.

1. INTRODUCTION

The acquired immune deficiency syndrome (AIDS) continues to be a major health problem worldwide with approximately 40 million people infected with the human immunodeficiency virus (HIV). Although the introduction of highly active anti-retroviral therapy (HAART) has dramatically decreased the morbidity and mortality from the infection by HIV, however, the AIDS prevalence has remained one of the world's most serious health problems [1].

In the research of anti-AIDS agents, non-nucleoside reverse transcriptase inhibitors (NNRTIs) have gained a definitive and important place due to their unique antiviral potency, high specificity and low toxicity [2,3]. Currently marketed NNRTIs include nevirapine (**1**), delavirdine (**2**), efavirenz (**3**), and etravirine (**4**) (Fig. **1**) [4]. Efavirenz and nevirapine have good pharmacokinetic profiles and effectively inhibit replication of the wild-type virus, but they are less effective against several commonly observed mutant viruses, such as Y181C, Y188C, K103N, and L100A [5-7]. Etravirine shows improved potency against many NNRTI-resistant viruses [5], but must be administered twice daily and is approved for use only in patients infected with HIV-1 strains resistant to an NNRTI and other antiretroviral agents [4]. Therefore, there remains to be an a urgent need for development of new NNRTIs that are active against virus strains resistant to current NNRTIs and have good pharmacokinetic properties suitable for once daily dosing [6,7].

Since the first report of sulfanyltriazole/tetrazoles as potent HIV-1 NNRTIs, these novel substituted scaffolds have been of interest for the development of novel NNRTIs, because of their high potency and low toxicity against HIV-1 wild-type and resistant strains. This review focuses on the progress in the research of sulfanyltriazole/tetrazoles HIV-1 NNRTIs, form the initial discovery to the subsequent extensively structural modification *via* synthetic efforts, as well as presenting the studied results of SAR analysis and the molecular modeling that could directly help elucidating the mechanism of binding of sulfanyltriazole/tetrazoles with HIV-1 RT. In addition, this review shows other newly designed and discovered HIV-1 NNRTIs that are structurally associated with triazole/tetrazoles HIV-1 NNRTIs, based on SAR analysis and computational studies.

2. LEAD DISCOVERY

Recently, from high-throughput screening (HTS) of the compounds library, several interesting sulfanyltriazole and sulfanyltetrazole-derived compounds (**5-8**) were identified as novel inhibitors of HIV-1 RT, which have a simple, yet distinctively different chemical structure than other HIV-1 NNRTIs reported in the literature (Fig. **2**) [8-12].

Sulfanyltriazole (**5**) was identified as an inhibitor with low micromolar inhibitory activity. Analog (**6**) showed moderate activity against viruses carrying wild-type or K103N/Y181C HIV-1 RT, it was also active in an enzymatic assay against the purified WT HIV-1 RT [8,9]. Two sulfanyltetrazole derivatives (**7** and **8**) were identified as potent inhibitors of HIV-1 RT at low nanomolar ranges, and as potent HIV-1 NNRTIs in cell assays at submicromolar ranges against the wild-type and K103N mutant strains [10-12].

3. STRUCTURAL MODIFICATIONS

Based on the molecular characters of the lead compounds (4-8), new series of sulfanyltriazole and sulfanyltetrazole derivatives (Fig. **3**) were synthesized and tested against several NNRTI-resistant HIV-1 isolates [13-18]. Most of these compounds exhibited potent antiviral activities against efavirenz- and nevirapine-resistant viruses, including the K103N and/or Y181C mutations or Y188L mutation.

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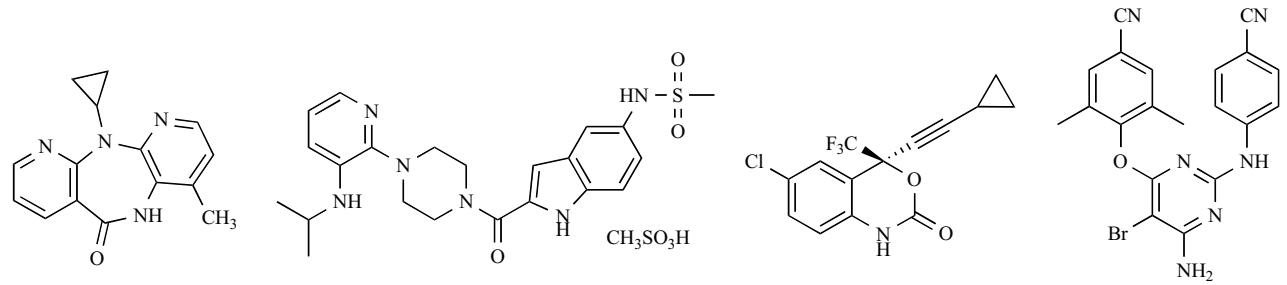
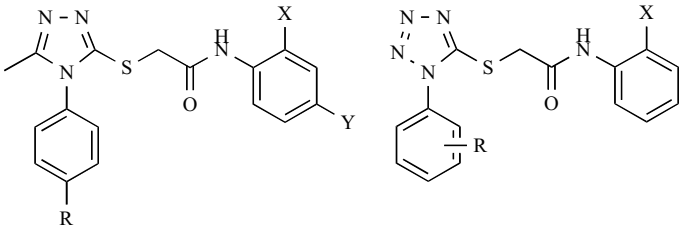


Nevirapine (1) **Delavirdine (2)** **Efavirenz (3)** **Etravirine (4)**

BI-RG-587 **BHAP U-90152** **DMP-266(L-743,726)** **TMC-125**

1996 **1999** **1998** **2008**

Fig. (1). Chemical structures of NNRTIs with the year of their approval by the FDA for HIV-1 treatment.



5. R=CH_3, X=Y=H,
EC_{50}= 2.053 μM(WT)
6. R=H, X=Br, Y=CH_3
EC_{50}= 0.1 μM(WT)
EC_{50}= 1.3 μM(K103N/Y181C)

7. R=2,4,6-TriMe, X=Cl
IC_{50}= 5 nM (WT)
8. R-Ph=1-naphthalene, X=NO_2
IC_{50} = 9.5 nM(WT)
IC_{50} = 766 nM(K103N/Y181C)

Fig. (2). Sulfanyltriazole and sulfanyltetrazole lead compounds [8-12].

A number of improved compounds derived from this triazole/tetrazole scaffold are currently being considered for clinical evaluation. Especially, VRX-480773 (**9**) inhibits viruses from efavirenz-resistant molecular clones and most NNRTI-resistant HIV-1 isolates clinically tested, and also has an excellent pharmacokinetic character, warranting further clinical development for the treatment of HIV infection in both NNRTI-naive and -experienced patients [19].

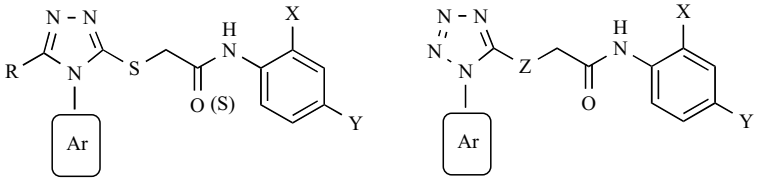
4. MOLECULAR MODELING AND STRUCTURE–ACTIVITY RELATIONSHIP (SAR) STUDIES

Modeling studies were carried out to understand how sulfanyltriazole/tetrazoles interact with the NNRTIs binding pocket (NNIBP) (Fig. **4**) [8,11,12].

Notable features of molecular modeling (Fig. **4**) and SAR features (Fig. **5**) include:

(**1**) The inhibitor's amide carbonyl forms a key hydrogen bond with the backbone N–H of K103, which is consistent with the good activity of these compounds against the K103 mutants (Fig. **5**) [8,11,12]. This hydrogen bond interaction with the residue main chain is unlikely to be disrupted by side chain mutations and contribute substantially to the free energy of binding for inhibitors, and to improve their resistance profiles [20].

(**2**) The aryl linked to the triazole/tetrazole core fits into the important hydrophobic pocket, where many key resistant mutations take place, which include Y188L, Y181C, F227C,



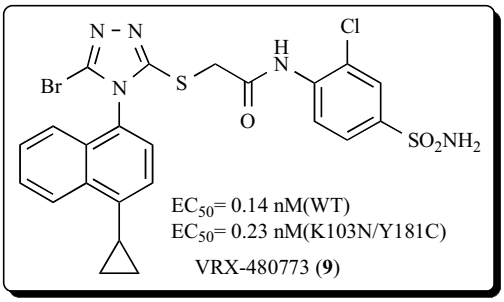
R=-Me, -CF_3, Br, etc
Ar=substitued benzene, naphthalene,quinoline,etc
X= -Cl,-Br,-I,-NO_2,-CH_3
Y= -H,-CH_3,-COOMe, -CN,-SO_2NH_2,etc

Sulfanyltriazole derivatives

Ar=substitued benzene, naphthalene
X= -Cl,-Br,-I,-NO_2,-CH_3
Y= -NO_2,-Cl,-SO_2NH_2,-$CONH_2$, -$O(CH_2)_3N(CH_3)_2$, -$CONH(CH_2)_3N(CH_3)_2$,etc
Z= S,-CH_2-,O

Sulfanyltetrazole derivatives

Fig. (3). Structural modifications of sulfanyltriazole/tetrazoles NNRTIs.



and L100I (Figs. **4**,**5**) [11,12]. Detailed analysis of the binding mode shows that the aryl linked to the triazole/tetrazole core (compounds **9-11**) is parallel to Y188, and an interesting CH–π interaction in which the 4-substituent (*tert*-butyl or cyclopropane) of the phenyl-tetrazole in compound **10** or **11** points directly at, and perpendicular to, the indole side chain of the highly conserved residue W229 (Fig. **4b**,**4c**) [11,12]. The highly conserved amino acid residues in the NNIBP are essential for viral replication, and improved binding at these amino acids could result in the development of novel NNRTIs not sensitive to the common RT mutations, which mainly occur at residues Y181, Y188, and K103 [21-26]. Among the conserved residues, W229 is a priority candidate for targeted design of NNRTIs mainly because it is feasible to target W229 with NNRTIs for its physical participation in creating the characteristic NNIBP [21-23]. Therefore, the aryl linked to the tetrazole/triazole core provides useful information for the rational design of new arylazolylthioacetanilides to improve virus-drug resistance.

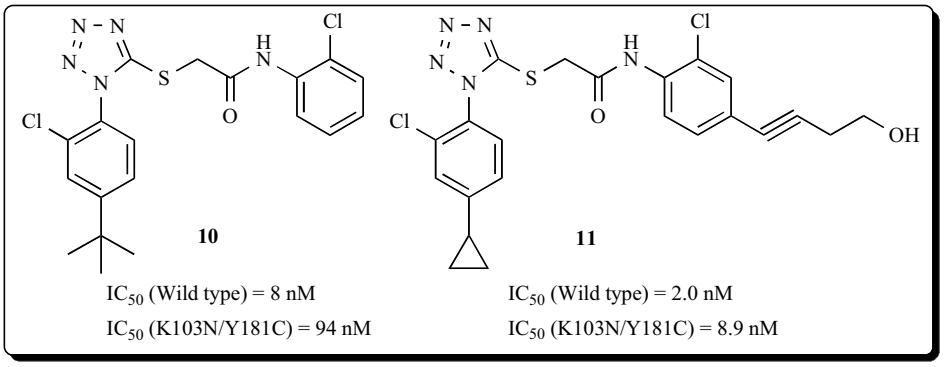
(**3**) In Fig. (**4b**) and Fig. (**4c**), the chlorophenyl moiety of compound **10** or **11** sits between P236 and V106, and points toward the solvent exposed region. Interestingly, the 4-position alkynyl group of the anilide phenyl ring (compound **11**) points directly toward a channel which is lined by P236 and exposes its terminus to the solvent [11,12].

The NNIBP is greatly affected by the movement of the P236 "hairpin loop" and the repositioning of β10 strand (residues 232-234) and β11 strand (residues 239-241) [27]. On binding of larger NNRTIs, the P236 "hairpin loop" is closer to the *apo* conformation, forming a more open pocket. Consequently, it seems possible to exploit the plasticity of this part of the pocket to gain specific protein-inhibitor interactions or, alternatively, to accommodate substantial modifications of the inhibitor molecule to improve the pharmacokinetic properties of the arylazolylthioacetanilides without a significant loss of binding affinity [28]. Indeed, SAR studies of arylazolylthioacetanilides demonstrated that the introduction of substituents at the para position of the anilide leads to substantial improvement in potency [11,12].

In addition, SAR studies at the anilide moiety revealed that 2-substitution is the only allowed monosubstitution, nitro and halogen being the preferred substituents (Fig. **5**) [8-12].

(**4**) The sulfanyltriazole/tetrazole binds in a 'kinked' conformation which involves a rotation about the "S–CH_2–CO–NH" dihedral angle from 180° in the fully extended free-state conformation to almost 0° in the bound state. This brings the two substituted phenyl rings into close proximity and results in the amide N–H pointing toward the sulfur atom (probably forming intramolecular hydrogen bond) [11,12].

Many typical examples reported in recent literature suggested that the conformational and positional adaptability of



an NNRTI can help the drug retain potency against a variety of resistant HIV-1 strains [29,30]. The relative flexibility of the "S–CH_2–CO–NH" linker might allow sulfanyltriazole/tetrazoles to adapt to a mutated drug pocket more readily than, for example, the rigid fused ring structure of the first generation NNRTI nevirapine. Therefore, maintenance of the flexibility of "S–CH_2–CO–NH" linker was considered as a powerful element of novel arylazolylthioacetanilide design.

(**5**) Interestingly, no discernible interaction was apparent for the sulfanyltriazole/tetrazole motif which was vital for potency. As illustrated in Fig. (**4c**), the tetrazole is orthogonal to the cyclopropyl- chlorophenyl, whereas the amide is in a *trans* conformation, bringing the two chlorine atoms of both aryl groups in close proximity. These data suggested that the triazole/tetrazole portion of these inhibitors could simply be acting as a scaffold which orients the pharmacophores into the proper geometry for binding [11,12]. Further structural modifications indicate that other five-membered azoles are also acceptable isosteric replacements for the triazole/tetra-zole moiety in the lead compounds (see **Section 6**) [13,14, 17,18,31-33].

(**6**) Lastly, SAR revealed the importance of the sulfur atom in the tetrazole series. Simply substituting the sulfur with either oxygen, or carbon, leads to 10-and 27-fold

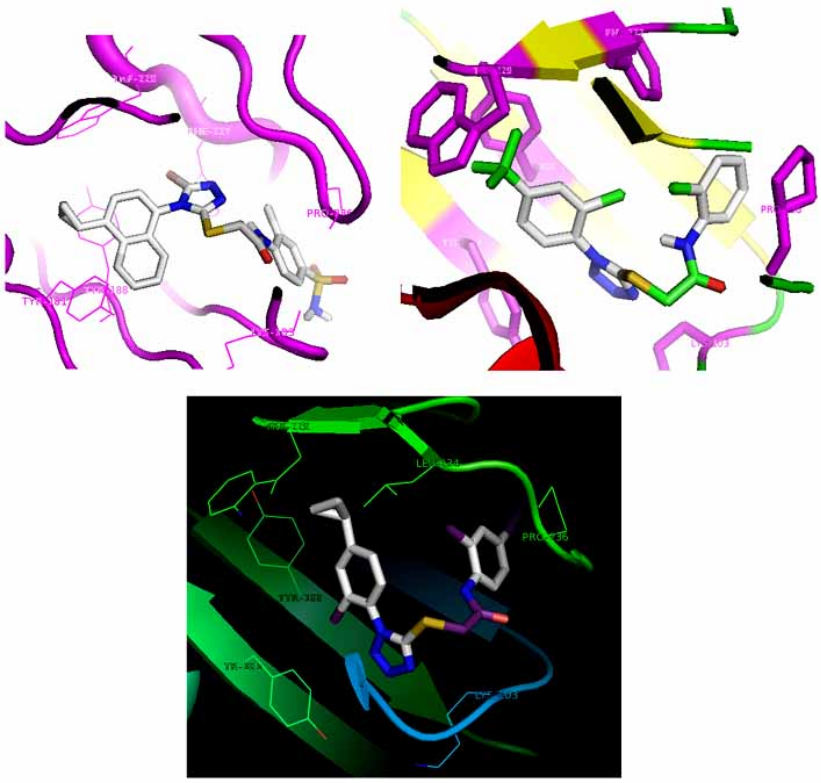


Fig. (4). Model of sulfanyltriazole **9** (**a**), sulfanyltetrazoles **10** (**b**) and **11** (**c**) docked into the NNRTI binding pocket (PDB code: 3DLG; Docking simulations were performed with the program AutoDock Vina 1.0: http://vina.scripps.edu).

decrease in intrinsic anti-wild-type virus potency, respectively [11].

5. STABILITY OF SULFANYLTRIAZOLE/TETRAZOLES

Till now, the stability study only in tetrazole series has been reported. The tetrazole lead compounds suffer from poor stability in the presence of human liver microsomes (HLM) which is predictive of rapid clearance in humans [11]. It was discovered that anilides substituted in the 4-position with sulfonamide, carboxamide, or aliphatic chains bearing a tertiary amine, were stable in rat plasma. By introducing chlorine or methyl in the 2-position, the stability can be obtained in rat plasma. No improvements in HLM stability were observed by substituting the sulfur with either oxygen or carbon [11]. These conclusions proved to be ex-

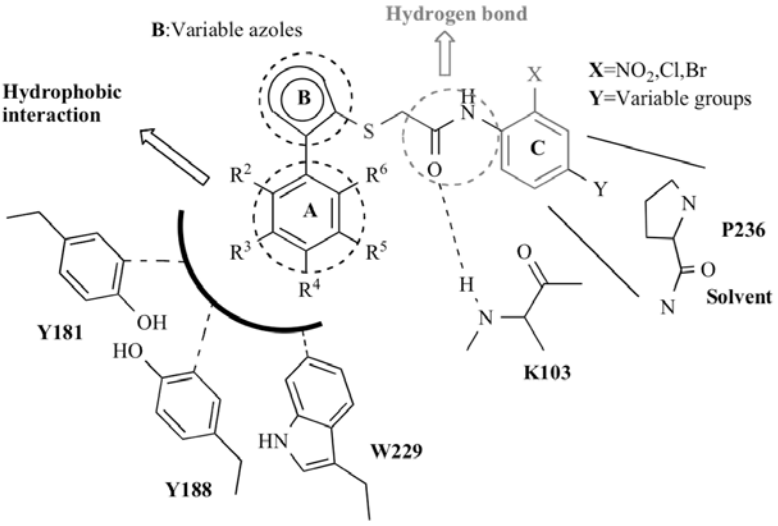


Fig. (5). Schematic SAR and proposed binding mode for arylazolylthioacetanilides to NNIBP.

tremely valuable when designing next generation arylazolylthioacetanilides NNRTIs.

6. OTHER NNRTIS ASSOCIATED WITH SULFANYLTRIAZOLE/ TETRAZOLES

As mentioned in Section 4, molecular modeling indicated that the triazole/tetrazole moiety stays in the middle of the binding pocket, anchoring the substituents on the ring into the optimal space for interactions with NNIBP, which are in agreement with the present insights of SAR and provide valuable avenues for the future development of novel analogs as promising candidates for the treatment of AIDS [31].

Based on these analysis, alternate and potentially more stable scaffolds have been designed and synthesized in several laboratories, independently. Interestingly, the replacement of the triazole/tetrazole by a pyrazolyl group led to reversal of selectivity, providing inhibitors (such as compounds **12** and **13**) with excellent potency against the K103N/Y181C double mutant RT, but with a complete loss of activity against the wild type RT [33]. Modeling studies suggested important interactions between the heterocycles and residue 103, providing a rationale for the potency observed against both RTs [33].

A novel series of 1,2,3-thiadiazole thioacetanilide (TTA) derivatives have been evaluated for their anti-HIV activities in MT-4 cells in our laboratory. Some derivatives proved to be highly effective in inhibiting HIV-1 replication at nanomolar concentrations. Especially, 2-[4-(2,4-dichlorophenyl)-1,2,3-thiadiazol-5-ylthio]-*N*-(2- nitrophenyl)acetamide **14** was identified as the most promising compound (EC_{50} = 0.059 ± 0.02 μM, CC_{50} > 283.25 μM, SI > 4883) [31,34].

The SAR of these novel structural congeners indicated that the antiviral potency of the 1,2,3-thiadiazole thioacetanilides is closely related to the electronic or spatial characteristics of the aryl linked to the 1,2,3-thiadiazole core. Substitution at the phenyl ring of the anilide moiety revealed that nitro or halogen at the *ortho* position were the preferred substituents, but the introduction of a fluorine atom in this position caused a substantial decrease in potency. However, substituents at the *para* position of the anilide almost did not influence the antiviral potency in the same series [31,49]. Bioactivity screening of other newly designed scaffolds is in progress, and further results will be reported in due course.

The scaffold hopping [35,36] from triazole/tetrazoles to tertiary amides, carbamates, and thiocarbamates was achieved *via* through understanding of the binding mode of the sulfanyltriazole/tetrazoles based inhibitors. These compounds (19-23) represent a novel, potent class of HIV-1 NNRTIs with a broad spectrum of antiviral activity, although they did not provide the desired improvement in metabolic stability (Table **1**) [11,18].

It has been suggested that triazole/tetrazole-based compounds shares the similar pharmacophore and bond conformation with pyrrolidinone- [37] and benzophenone -typed NNRTIs (Figs. **6**,**7**) [38-42], which are highly potent against wild-type and drug-resistant HIV-1 (containing Y181C-, K103N-, and Y181C/K103N-based double mutations).

The SAR analysis, crystallography, and molecular modeling of tetrazole and benzophenone-based NNRTIs permitted the scaffold hop to a novel series of diaryl ether NNRTIs which have excellent potency *versus* wild-type and key mutant viruses [43] (Fig. **8**). Further systematic

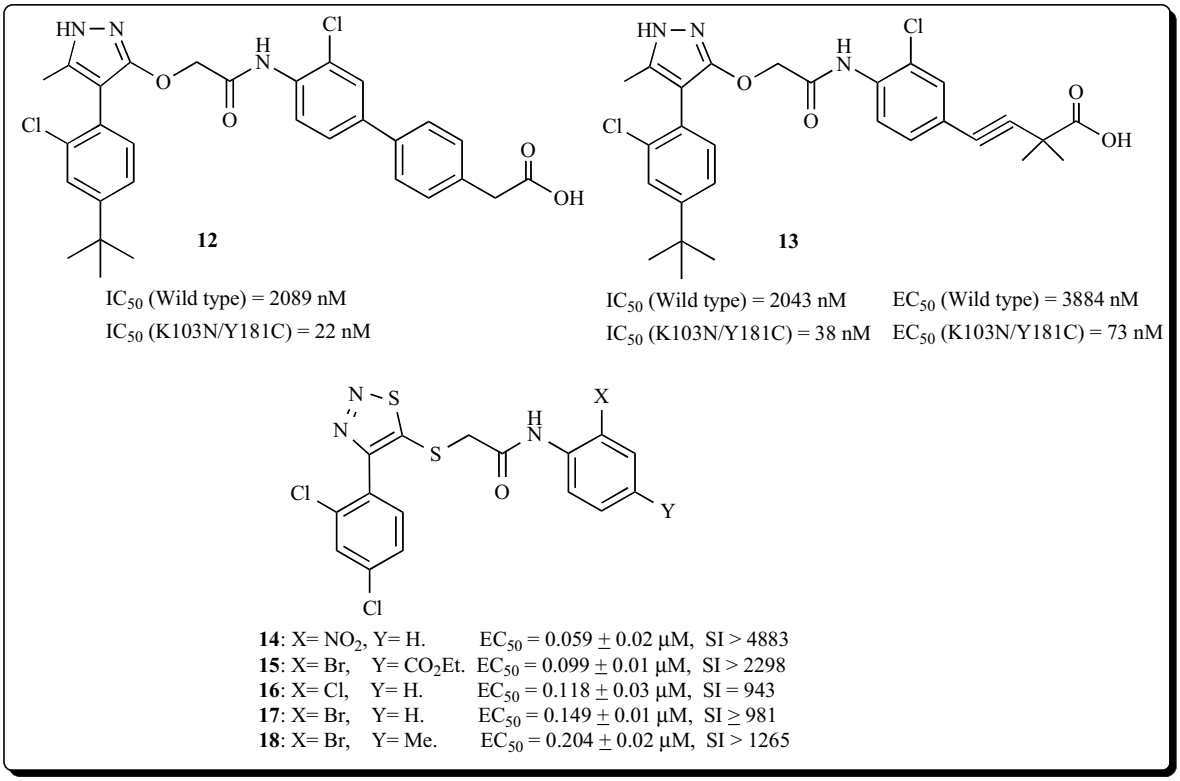
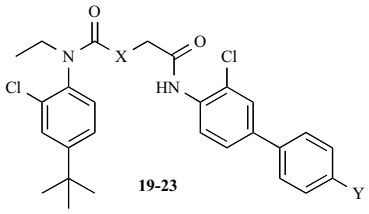


Table 1. The Bioactivities and Metabolic Stability of Tertiary Amides, Carbamates, and Thiocarbamates



Compounds	X	Y	IC_{50}(nM)		$t_{1/2}$ HLM(min)
			WT	K103N/Y181C	
8			<20	849	3
19	CH_2	OCH_2COOH	340	207	6
20	CH_2	CH_2COOH	829	305	3
21	O	CH_2COOH	109	98	9
22	NH	CH_2COOH	1530	414	23
23	S	CH_2COOH	34	35	4

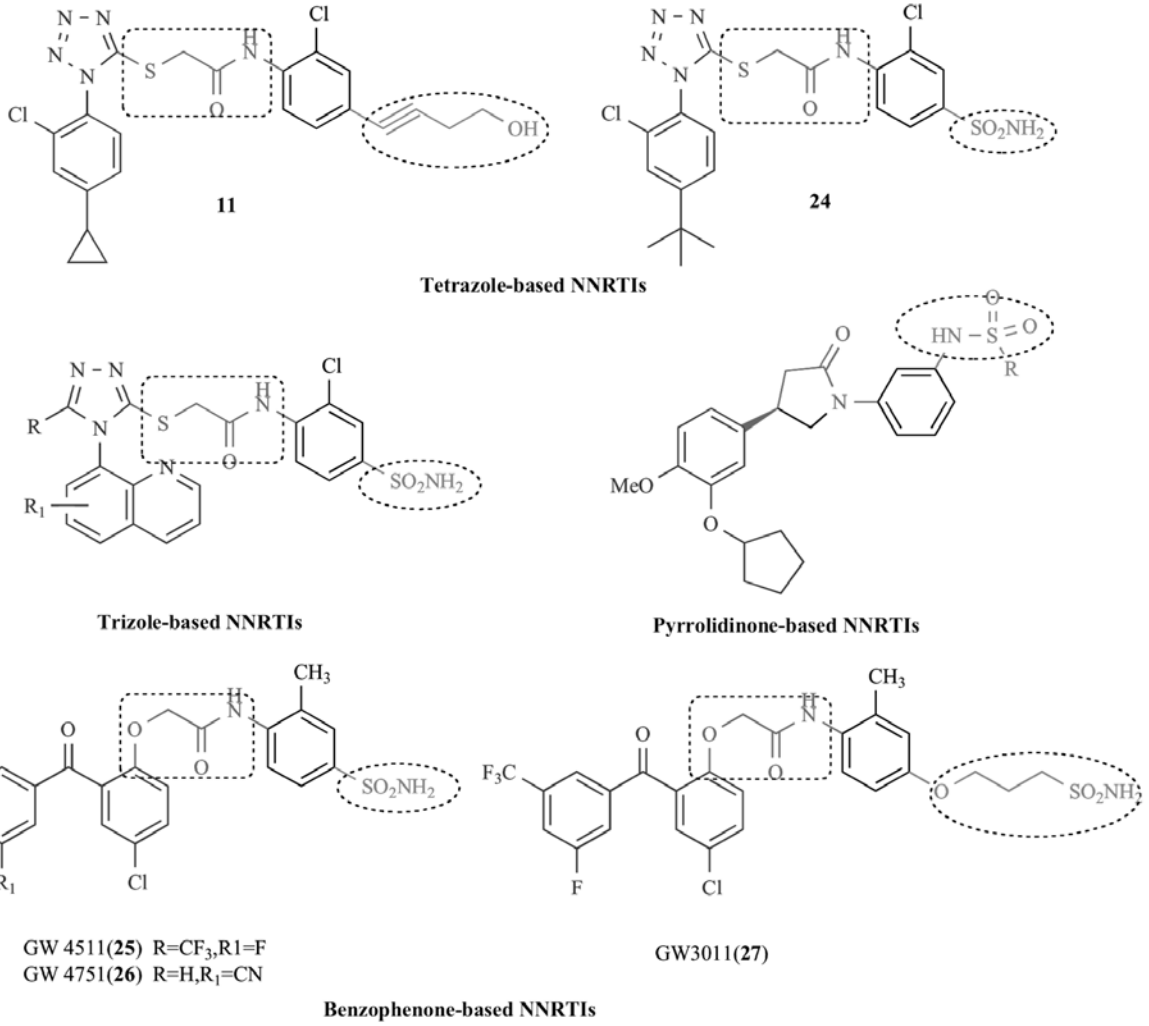


Fig. (6). Other NNRTIs sharing a similar pharmacophore as sulfanyltriazole/tetrazoles [37,38].

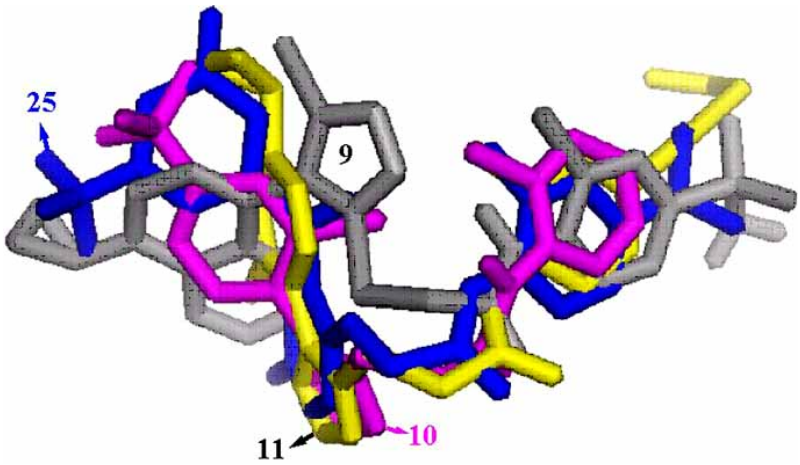


Fig. (7). Stereo diagram showing the superposition of sulfanyltriazole **9** (gray), sulfanyltetrazoles **10** (magenta), **11** (yellow) and benzophenone **25** (blue, the original ligand in crystal structures) in the NNRTI binding site (PDB code: 3DLG; Docking simulations were performed with the program AutoDock Vina 1.0: http://vina.scripps.edu).

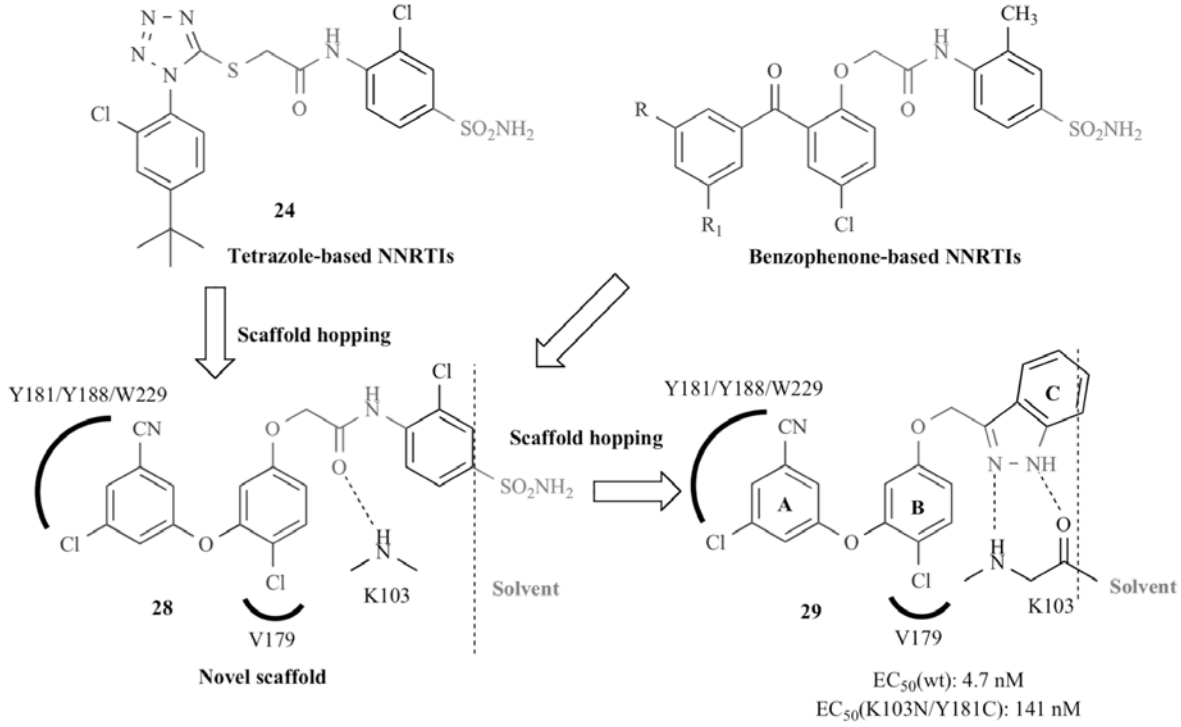


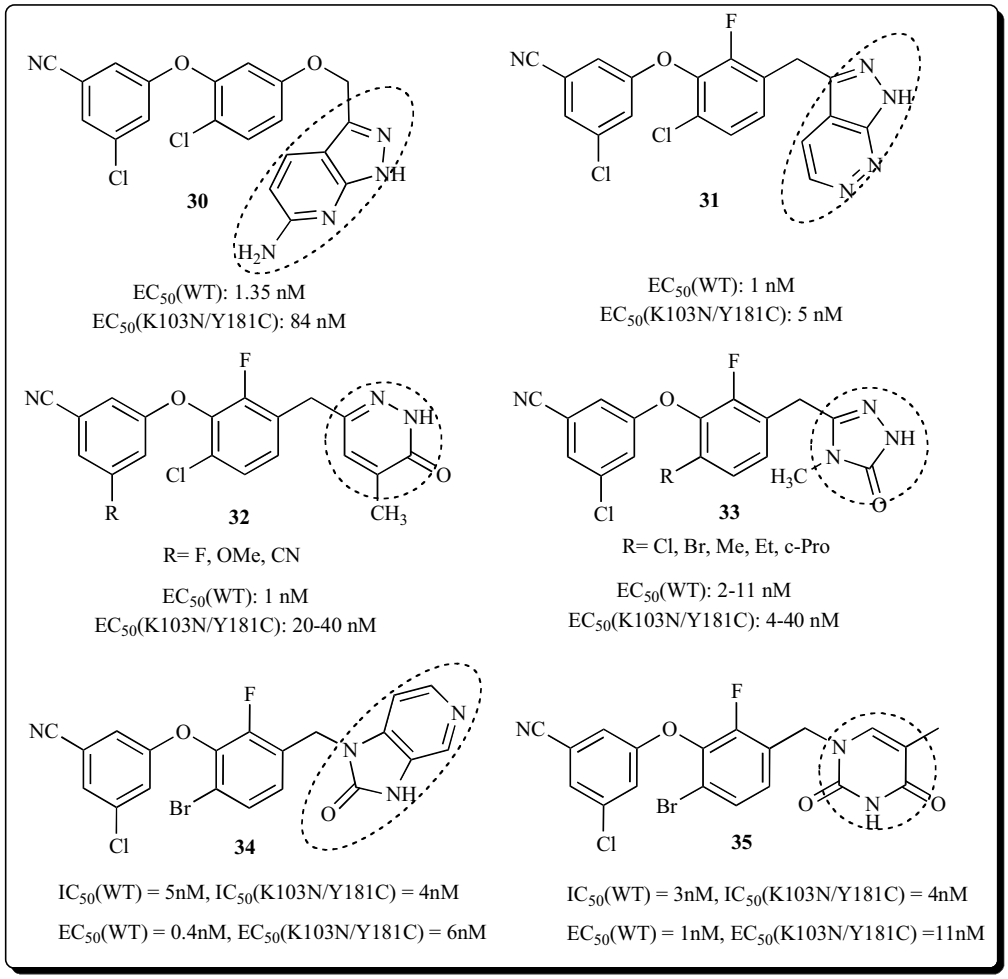
Fig. (8). Design paradigm for novel diaryl ether lead structures and proposed binding mode for compounds **28** and **29** [44].

manipulation of the lead structure **28** resulted in the discovery of compound **29**, which has become the prototype of a potent and novel NNRTI platform. In Fig. **8**, the 4-position "SO_2NH_2" of the anilide phenyl ring in compound **28** and the indazole phenyl ring in compound **29** point directly toward a channel that is lined by P236 and leads into the solvent [44].

Taking advantage of the solvent exposed region of these molecules as a means to incorporate solubilizing groups and to further optimize physical properties and pharmacokinetics has resulted in the identification of novel diaryl ether derivatives, such as pyrazolopyridine **30** (MK-4965)[45], pyrazolopyridazine **31** [46], pyridazinone **32** [47], triazolinone **33** [48], imidazopyridinone **34** and pyrimidone **35** [49], which have high levels of potency against wild-type and key mutant viruses, excellent oral bioavailability and favorable pharmacokinetics.

7. PERSPECTIVES

It has been demonstrated that sulfanyltriazole/tetrazoles typed NNRTIs are novel scaffolds with great potential for further development. With a suitable combination of substitution patterns on the aryl linked to the triazole/tetrazole core, the anilide aryl and the five-membered moiety, it is possible to identify compounds which maintain the same



intrinsic activity on the wild-type HIV-1 RT and the clinically relevant mutants.

In summary, understanding the SAR conclusion and notable features of binding mode underlying the maintenance of high potency of sulfanyltriazole/tetrazole-based NNRTIs is potentially of wider importance for the design of further NNRTIs with novel chemical series. Such efforts are of vital importance for the development of novel drugs for use in the continued treatment of HIV and AIDS.

ACKNOWLEDGMENTS

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