1,3,4-Oxadiazole: A *Privileged Structure* in Antiviral Agents

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Abstract: 1,3,4-oxadiazole, a *privileged structure*, endows its derivatives with broad and potent biological functions, especially in antiviral activities, including anti-HIV, anti-HCV, anti-HBV, anti-HSV activities, etc. Molecular modeling and pharmacokinetic studies have demonstrated that the introduction of 1,3,4-oxadiazole ring to the inhibitors can change their polarity, flexibility as well as metabolic stability, and 1,3,4-oxadiazole scaffold can also act as acceptors of hydrogen bonds formation, which make it possible to be used as a isosteric substituent for amide or ester groups.

This review focuses on the recent advances in the synthesis of 1,3,4-oxadiazole ring and mainly the discovery, biological activities investigations and structural modifications of several distinct classes of 1,3,4-oxadiazoles as potent antiviral agents. In addition, the binding models of some representative 1,3,4-oxadiazoles were also discussed, which provide rational explanation for their interesting antiviral activities, and also pave the way for further optimization of 1,3,4-oxadiazole based antiviral agents.

Keywords: 1,3,4-Oxadiazole, *privileged structure*, solid-phase synthesis, antiviral activity, structural modification, molecule modeling.

1. INTRODUCTION

Privileged structures are defined as molecular frameworks which are able to provide useful ligands for more than one type of receptor or enzyme target by judicious structural modifications [1]. Among all the ubiquitous heterocycles, 1,3,4-oxadiazole is regarded as a *privileged structure* of great practical and theoretical interest. Biological studies have demonstrated that the 1,3,4-oxadiazole class possess broad and potent biological activities, especially in antiviral activities, such as anti-human immunodeficiency virus (HIV), anti-hepatitis C virus (HCV), anti-hepatitis B virus (HBV), anti-influenza virus (IV), anti-herpes simplex virus (HSV), anti-hepatitis-A virus (HAV), anti-varicella-zoster virus (VZV) and anti- human cytomegalovirus (HCMV) activities, etc. [2-4]. Molecular modeling and pharmacokinetic studies suggested that the 1,3,4-oxadiazole pharmacophore is truly a *privileged structure* for the discovery of novel antiviral drugs.

This review focuses on the recent advances in the synthesis of 1,3,4-oxadiazole ring and mainly the discovery, biological activities studies and structural modifications of several distinct classes of 1,3,4-oxadiazoles as potent antiviral agents.

2. SYNTHETIC METHODS OF 1,3,4-OXADIAZOLES

2.1. General Methods for the Synthesis of 1,3,4-Oxadiazoles

Up to now, several protocols have been reported in the literatures for the synthesis of 1,3,4-oxadiazoles (**1**). The majority of these methods are multi-step in nature, and generally involve (i) cyclization of 1,4-disubstituted thiosemicarbazide (**2**) in the presence of either I_2/NaOH [5-10], or dicyclohexylcarbodiimide (DCC) [10] and (ii) condensation of 1,2-diacylhydrazines (**3**) with a variety of reagents including boron trifluoride etherate [11-12], triflic anhydride [13-14], phosphorus pentoxide [15-16], thionyl chloride [17-19], phosphorus oxychloride [20-26], sulfuric acid [27-28] and polyphosphoric acid (PPA) [29-31], usually under harsh reaction conditions. Another general way is the Huisgen route [32], which involves the aroylation of 5-aryltetrazoles (**4**) (Fig. **1**). However, even this reaction was not effective enough to go beyond the first-generation stage.

In order to make the reactions convenient, Kangani *et al.* have reported one-pot direct synthesis of 1,3,4-oxadiazoles from carboxylic acids using the [bis(2-methoxyethyl)amino] sulfur trifluoride (Deoxo-Fluor reagent). The carboxylic acid, benzhydrazide, diisopropylethylamine (DIPEA) and potassium carbonate (K_2CO_3) were dissolved in dichloromethane (DCM), and treated with Deoxo-Fluor reagent for 2 h to furnish the desired products 1,3,4-oxadiazoles in excellent yields [33]. Recently, Rajapakse and teammates [34] investigated a mild and efficient one pot synthesis of 1,3,4-oxadiazoles from carboxylic acids and acyl hydrazides. Acid activation with carbonyl-diimidazole (CDI), followed by coupling with the desired acylhydrazide and dehydration in the same pot with Ph_3P and CBr_4 affords the corresponding 1,3,4-oxadiazoles in good yield. Another synthetic route was introduced by the use of the Schiff bases of aryl hydrazides, obtained by the reaction of aryl hydrazides and its corresponding aromatic aldehydes in chloroform with a catalytic amount of acetic acid, on cyclization in the presence of $FeCl_3$ yielded corresponding 1,3,4-oxadiazoles [35].

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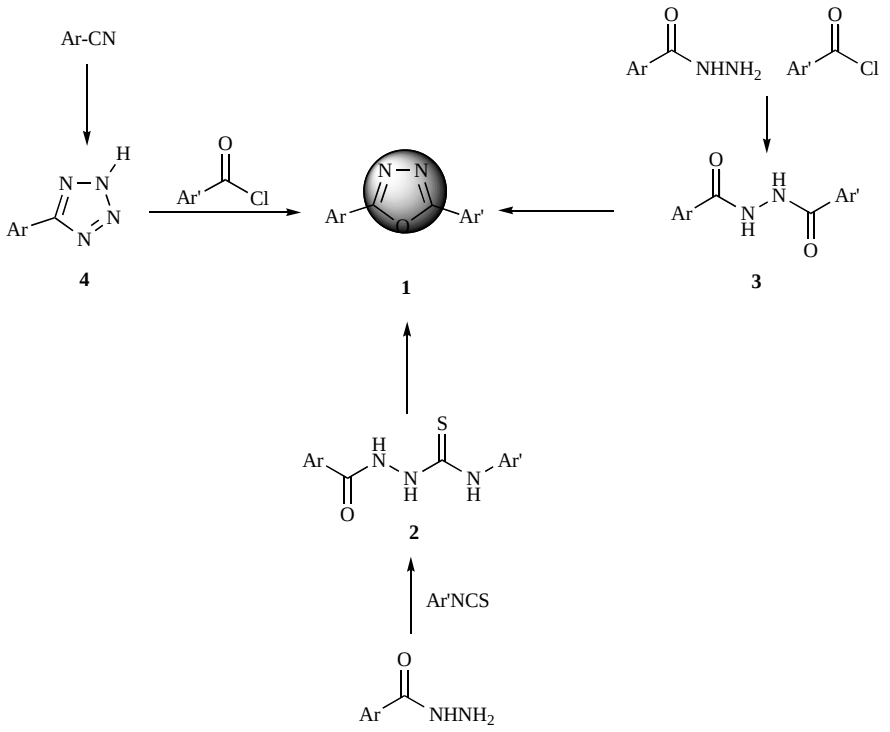


Fig. (1). General synthetic route of 1,3,4-oxadiazole ring.

2.2. Microwave-Assisted and Solid-Phase Supported Synthesis of 1,3,4-Oxadiazoles

Microwave-assisted and solid-phase supported synthesis method have many advantages, such as shortening the reaction time, increasing the yield and high selectivity. Wang *et al.* studied a method of synthesis of 1,3,4-oxadiazoles in the presence of 2 equiv CCl_3CN and 3 equiv of PS-PPh_3 derived from the requisite carboxylic acid and acid hydrazide in acetonitrile under microwave heating at 150˚C for 20 min in one simple step [36]. Another protocol of synthesis of 1,3,4-oxadiazoles was introduced by Coppo and coworkers. Typically, the isothiocyanate was added to a solution of the hydrazide, which was prepared by reaction of the corresponding ester with hydrazine. After mixing overnight at room temperature, PS-Carbodiimide was added to the reaction solution. The vessel was heated for 60 h, then P-Propylamine and PS-bemp were added and the desired product was obtained [37]. Chekler and coworkers [38] have investigated a convenient one-pot method for the preparation of 1,3,4-oxadiazoles. This method is a significant improvement over previously reported syntheses. Reaction of carboxylic acids with thiosemicarbazides afforded the intermediate, which was followed by a cyclization *via* resin-based 1-ethyl-(3-dimethylaminopropyl)carbodiimide (EDCI) reagent to obtain corresponding 1,3,4-oxadiazoles in moderate to good yields.

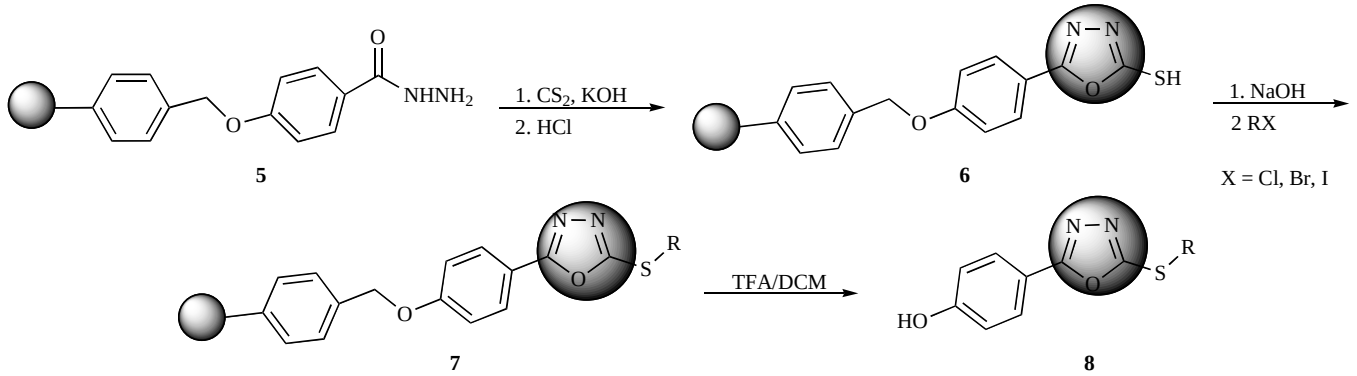
Moreover, an improved solid-phase synthesis of 1,3,4-oxadiazole derivatives from resin-bound acylhydrazines was introduced by Liu and teammates. The acylhydrazine **5** prepared was reacted with CS_2/KOH at reflux to afford the 1,3,4-oxadiazole resin **6**. Further reaction with NaOH and electrophilic reagents (RX) gave the corresponding resin **7**. Release of the final 1,3,4-oxadiazoles **8** was effected after cleavaged by treatment with 10% trifluoroacetic acid (TFA) in dichloromethane (DCM) (Scheme **1**) [39]. Recently, Polshettiwar *et al.* have reported solid-supported synthesis of 1,3,4-oxadiazoles *via* the use of inexpensive Nafion®NR50 and P_4S_{10}/Al_2O_3 as a catalyst and derived from various hydrazides **9** could react efficiently with **10** (triethyl orthoformate, triethyl orthoproponate or triethyl ortho-benzoate) to afford the desired 1,3,4-oxadiazoles **11** in good yields (Scheme **2**) [40].

3. STRUCTURE OPTIMIZATION OF 1,3,4-OXADIAZOLE-BASED ANTIVIRAL AGENTS

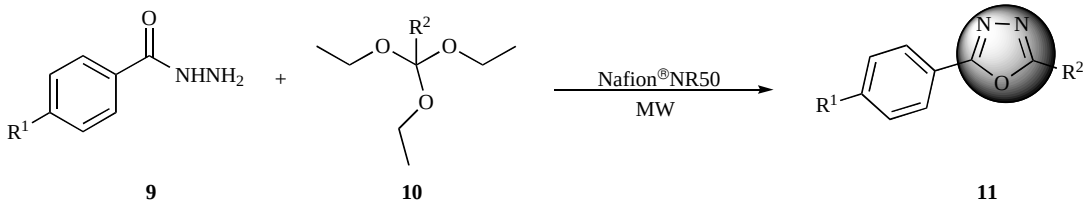
In the 21st century, antiviral chemotherapy is well established for the prevention and treatment of many important virus infections [2]. The emergence of the worldwide virus epidemic fostered much research and great progress in this area, and now more than 40 licensed antiviral drugs are available, most of them for the management of HIV infection, and the rest for the treatment of other viral diseases [3-4]. However, the antiviral drugs currently in clinic have a low genetic barrier to resistance or poor pharmacokinetic properties and, therefore, the need for novel antiviral agents active against drug-resistant mutants selected is of paramount importance. Recently, a number of antiviral agents were reported, which contain 1,3,4-oxadiazole moieties in their molecules. Herein, the structure-activity relationship (SAR) and binding models of these 1,3,4-oxadiazoles are discussed.

3.1. Anti-HIV Activity

As well known, each step of HIV replication cycle can be used as a drug target. Hitherto, there are 25 anti-HIV drugs



Scheme 1.



R^1= H, F, OMe, 2-furyl, 2-thienyl, 4-pyridyl

R^2= H, Et, Ph

Scheme 2.

available, which belong to four main targets (reverse transcriptase, integrase, protease and entry process). Recent literatures showed that 1,3,4-oxadiazole scaffold appeared in several HIV-1 inhibitors, which covered three main targets (reverse transcriptase, integrase and protease) [41-43, 45-46, 48-52]. Therefore, 1,3,4-oxadiazole moiety is really a *privileged structure* for the discovery of novel anti-HIV agents.

3.1.1. NNRTIs

In order to seek novel and potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), virtual screening of the Maybridge library of about 70,000 compounds was performed using a similarity filter, docking, and molecular mechanics-generalized Born/surface area postprocessing. The top-20 ranked compounds were composed of 10 library compounds and 10 known NNRTIs, and six of the top

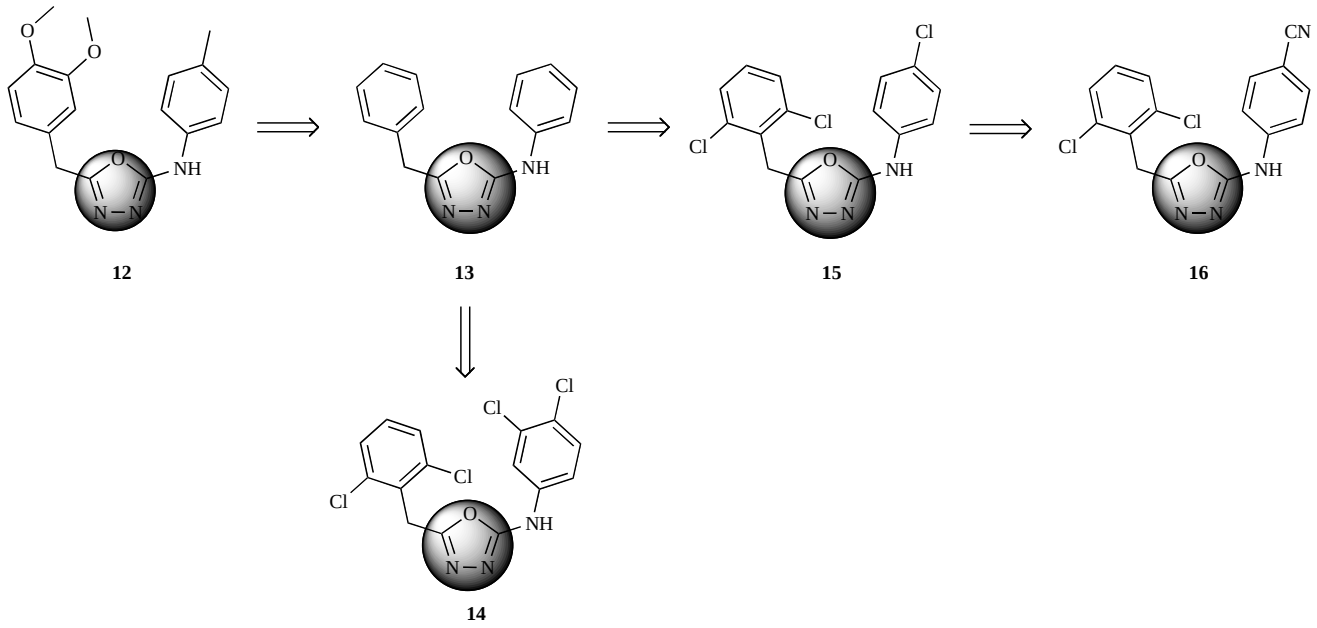


Fig. (2). 1,3,4-Oxadiazole-based HIV-1 NNRTIs.

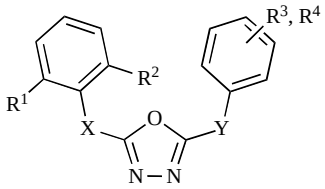
library compounds were purchased and the activities against the HIV-1_{IIIB} strain were determined in MT-2 human T-cells. Unfortunately, the top-ranked library compounds all failed to obtain any potent anti-HIV agents, although known NNRTIs were reverted well [41].

However, the highest-ranked library compound S10087 (**12**), was third overall, seemed to have a potentially viable core and the BOMB program was used to find rational modifications. The substituents were removed to obtain the anilinylbenzyloxadiazole core (**13**) and then a series of substituents was reinserted in place of each hydrogen. Followed by scoring with the BOMB program and the free energy perturbation (FEP) guided optimization, led to subsequent synthesis and assaying of several polychloro analogues with EC_{50} values as low as 310 nM (compound **14**) in an HIV-infected T-cell assay (Fig. **2**). Thus, it was possible to evolve a false positive into a true active with the aid of computational tools [41-42]. Further modification was also guided by FEP calculations to seek potent NNRTIs, which was proposed **15**, optimization of the *C4* substituent to yield **16**, with the EC_{50} value down to 130 nM [43]. The anti-HIV-1 activity of other 1,3,4-oxadiazole analogs are shown in Table **1**. This study dexterously combined with the computer modeling, synthetic organic chemistry, and biological assaying, which provided us a good example for novel inhibitor design.

Oxadiazole **12** was docked into RT pocket using Autodock 4.0 (Fig. **3a**). Results showed that the *p*-tolyl substituent was well accommodated in the large pocket mainly defined by Val106, Leu234, Pro236, and Tyr318, while the 3,4-dimethoxybenzyl moiety was located at another hydrophobic pocket composed of the residues Tyr181, Tyr188, and Trp229 as well as Phe227. In particular, the phenyl ring interacts favorably with the Tyr188 side chain, giving rise to a positive π-stacking interaction. Especially, one *N* atom of oxadiazole and the *NH* moiety between the oxadiazole and *p*-tolyl could form hydrogen bonds with the *NH* moiety and the *C=O* moiety of Lys101, respectively. The same binding model was observed for oxadiazole **16** (see Fig. **3b**).

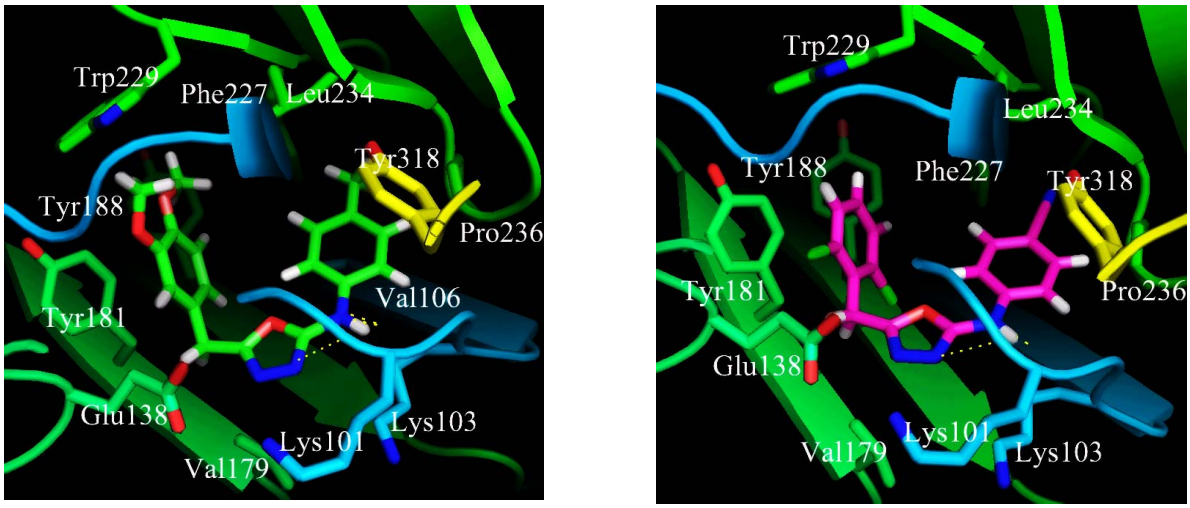
The potential usefulness of the alkenyldiarylmethanes (ADAMs) (lead compound **24**) is limited by the presence of metabolically labile ester moieties that are hydrolyzed by nonspecific esterases present in blood plasma, leading to the formation of inactive carboxylic acid metabolites [45, 46]. Therefore, to discover metabolically stable ADAMs, the replacement of labile esters with some bioisosters, such as thioesters, *N*-methoxy imidoyl halide, and various heterocycles was attempted. Among the newly synthesized analogues, compounds **25** [47], **26** [47] and **27** [48], displayed enhanced metabolic stability in rat plasma along with the improved antiviral activity against HIV-1_{IIIB}. The common feature of these compounds is the presence of an 1,3,4-oxadiazole system (Fig. **4**). Additionally, the methyl ester (**24**) and oxadiazole (**27**) moieties on the end of its alkenyl arm show similar stacking interactions

Table 1. Anti-HIV-1 Activity of 1,3,4-oxadiazoles



Compound	R^1	R^2	R^3	R^4	X	Y	EC_{50}(μM)[a]	CC_{50}(μM)[b]
14	Cl	Cl	3-Cl	4-Cl	CH_2	NH	0.31	>100
15	Cl	Cl	H	4-Cl	CH_2	NH	0.82	20
16	Cl	Cl	H	4-CN	CH_2	NH	0.13	40
17	Cl	Cl	H	3-Cl	CH_2	NH	4.3	71
18	Cl	Cl	3-Me	4-Cl	CH_2	NH	1.3	>100
19	F	F	H	4-CN	CH_2	NH	0.23	90
20	Cl	Cl	H	4-CN	NH	NH	9.8	>100
21	Cl	Cl	H	4-CN	NMe	NH	0.27	>100
22	Cl	Cl	H	4-CN	CHMe	NH	1.20	54
23	Cl	Cl	H	4-CN	CHMe	NH	0.13	8.5
nevirapine							0.11	>10
efavirenz							0.002	>0.1

[a]For 50% protection in MT-2 cells; antiviral curves used triplicate samples at each concentration.
[b]For 50% inhibition of MT-2 cell growth; toxicity curves also used triplicate samples.



(**a**) (**b**)

Fig. (3). Oxadiazole **12** (**a**) and **16** (**b**) were docked into RT pocket (PDB ID: 1RT4) using autodock 4.0 [http://autodock.scripps.edu] and the interaction of residues and the ligand was showed by PyMoL 0.99 [http://www.pymol.org/]. The ligand is positioned as expected from known structures such as for **TMC125** [44].

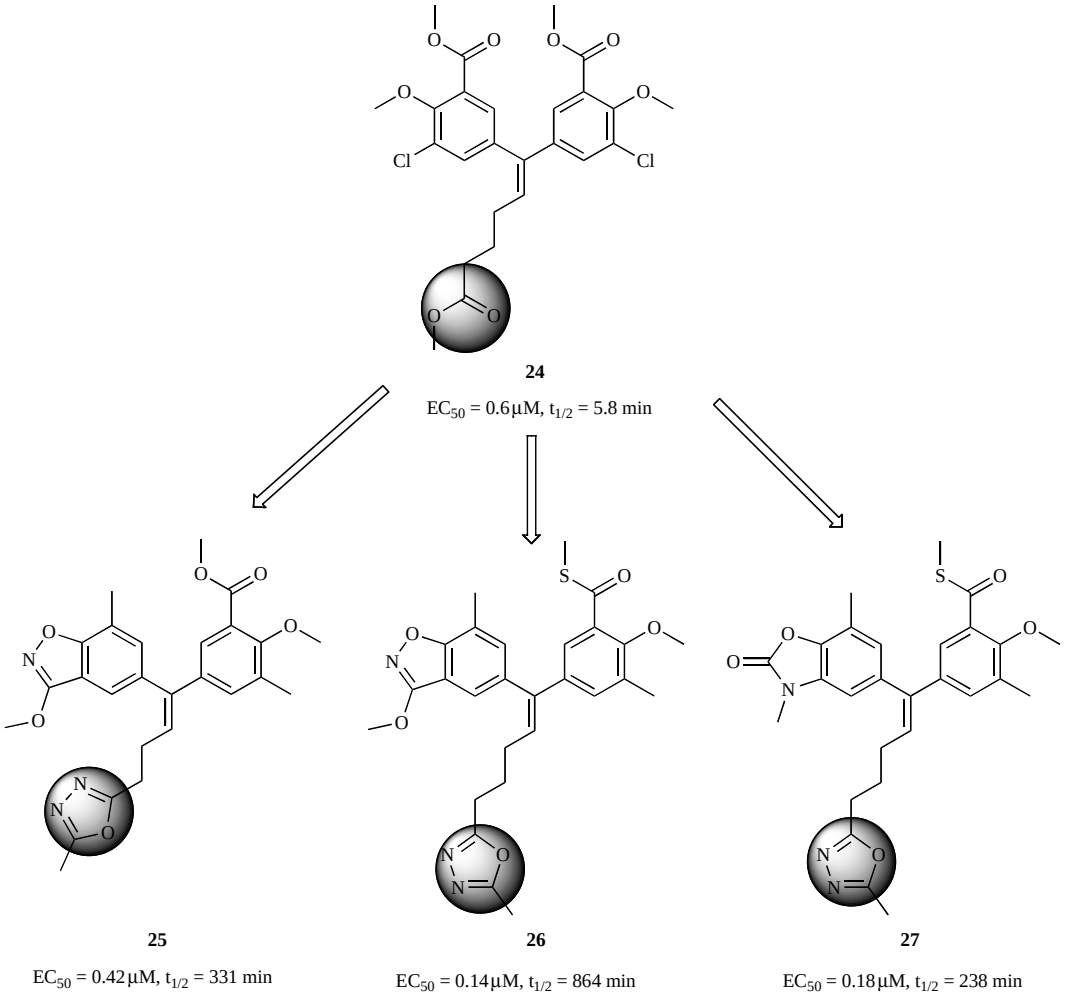


Fig. (4). 1,3,4-Oxadiazole-containing ADAMs NNRTIs with improved antiviral potency and metabolic stability.

with the aromatic side chain of Tyr181. Replacement of the methyl ester group in **24** by the 1,3,4-oxadiazole in **27** may contribute to the rigidity of the atoms in the proper planar orientation for π-π stacking interactions with Tyr181 (Fig. **5**). This may be one hypothesis for the increased potency of **27** [48].

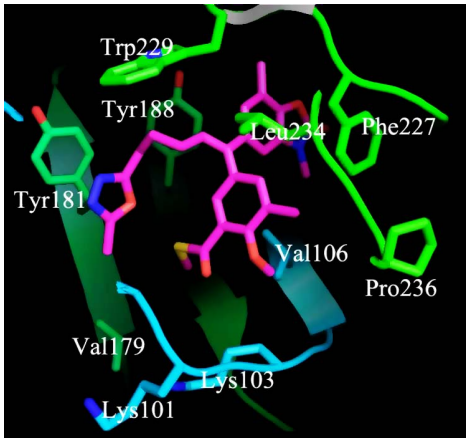


Fig. (5). Picture of the NNIBP obtained from the RT/ADAM **27** crystal structure (3IRX) [48]. (The figure is shown by PyMOL 0.99).

Besides, compound **28** containing a 1,3,4-oxadiazole ring and a diphenyl ether represent a new set of NNRTIs that was recently reported (Fig. **6**) to have favorable pharmacokinetic profiles and excellent antiviral potency against wild-type HIV and key NNRTI-resistant strains [49].

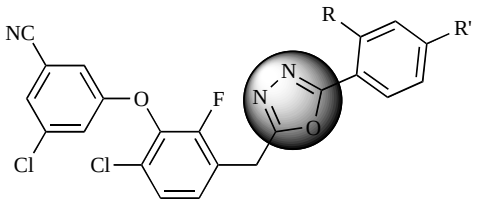
3.1.2. HIV-1 Integrase Inhibitors

Naphthyridine carboxamide derivative L870,810 (**29**), a second generation HIV-1 integrase inhibitor, entered clinical trials due to its remarkable activity against multidrug-resistant viral strains. However, liver and kidney toxicities were exposed after long-term treatment in dogs, resulting in a premature end of the drug's clinical progress [50-51]. Thus, further modification of the clinical candidate L-870,810 was emergent. In order to achieve the co-planarity required for the chelation of the requisite magnesium ions, several five-membered heterocycles triazole, oxazole, isoxazole and oxadiazole were tried as amide isosteres, and their six-membered ring counterparts were not considered due to the sterical factor (Fig. **7**). Finally, 1,3,4-oxadiazole **30** was proved to be the most potent derivative and had potency approaching that of L-870,810 (**29**, IC_{50} = 22.8 nM) [52], with an IC_{50} value of 2 nM [53].

The following structure modifications of the *C5* position of oxadiazole **30** by various amido, urea, carbamate, sulfonyl urea, sulfonamide and aryl substitutents were carried out, which led to several potent HIV-1 integrase inhibitors (Table **2**) [54]. This work showed that the heterocycle, especially 1,3,4-oxadiazole, was a viable bioisostere for the amido group.

3.1.3. HIV-1 Protease Inhibitors

Recently, a series of HIV-1 protease inhibitors (PIs) bearing 1,3,4-oxadiazole were reported. The introduction of 1,3,4-oxadiazole scaffold to the inhibitors can change their polarity and flexibility (Fig. **8**). The P1' modified 1,3,4-oxadiazoles PIs generally displayed superior potency against both native and PI-resistant HIV-1 (Table **3**) [55]. The arylheterocycle P3 substituents were studied previously by the Kim's team and showed to significantly improve the activity of indinavir against both wild-type and PI-resistant HIV-1 [56-57]. The SAR studies demonstrated that compounds with the same P3 substituent displayed similar activities against wild-type HIV-1 protease. In the cell-based assay, their ability to inhibit the spread of wild-type virus change greatly [55]. Oppositely, oxadiazoles exhibit a wider spectrum of activity against V-18 mutant than native enzyme, but their ability to inhibit the spread of PI-resistant



28

EC_{50}< 10 nM (WT, K103N, V106A,Y181C)

R = H, Cl, Me

R' =

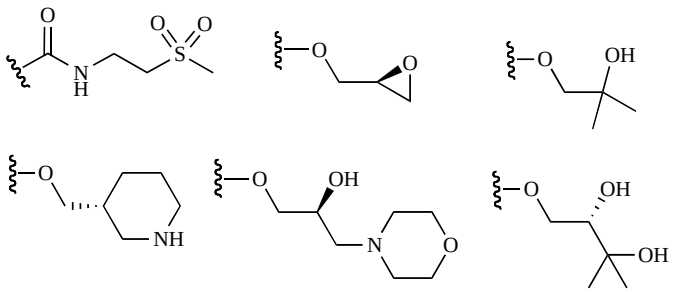
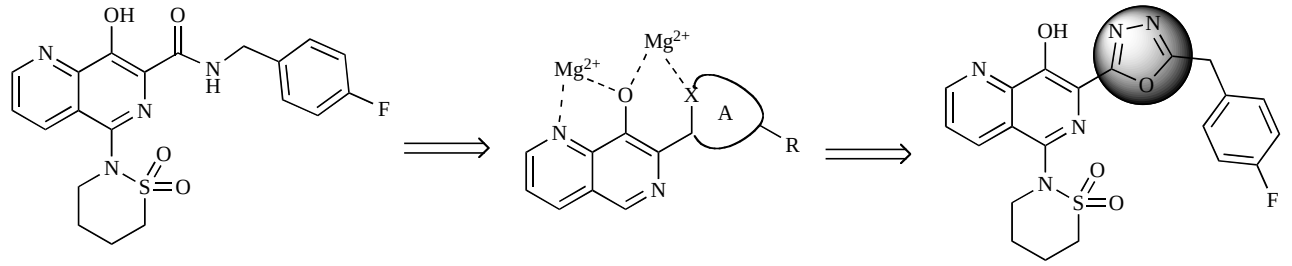


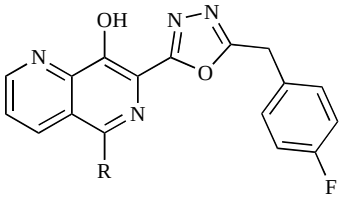
Fig. (6). NNRTIs containing a 1,3,4-oxadiazole ring and a diphenyl ether.

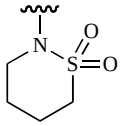
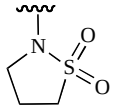
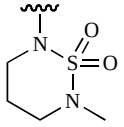
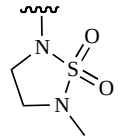
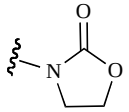
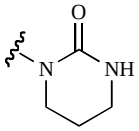
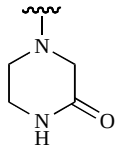


29. L-870,810 **30**

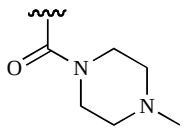
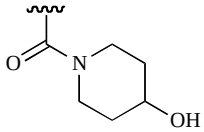
Fig. (7). Structure modification of 1,3,4-oxadiazole-based HIV-1 integrase inhibitors.

Table 2. The Activity of 1,3,4-oxadiazole-based HIV-1 Integrase Inhibitors



Compound	R	$IC_{50}(\mu M)^c$	$EC_{50}(\mu M)^d$	T.I. [e]
30		0.002	0.013	198
31		0.008	0.11	>129
32		0.006	0.031	294
33		0.004	0.063	137
34		0.013	0.021	>666
35		0.011	0.056	>250
36		0.007	0.017	844
37	3-C_6H_4–NHAc	0.080	0.010	1400

(Table 2). Contd…..

Compound	R	$IC_{50}(\mu M)^c$	$EC_{50}(\mu M)^d$	T.I.[e]
38	4- C_6H_4–$CONH_2$	0.006	0.010	1220
39	4-C_6H_4–$NHSO_2Me$	0.003	0.009	915
40	2-Pyrazolyl	0.004	0.016	546
41	3- C_6H_4–NH_2	0.015	0.015	546
42	2-C_6H_4–SO_2NMe_2	0.004	0.029	67
43	–$CONH(CH_2)_3OH$	0.071	0.47	>30
44		0.044	0.097	>144
45		0.027	0.22	>65
29 (L-870,810)		0.0228	0.0036	-

[c]Recombinant HIV-1 integrase strand transfer assay.
[d]Pseudo-type HIV assay (PHIV).
[e]Therapeutic index (CC_{50}/EC_{50}).

strains is less conspicuous than against wild-type virus. In addition, compounds were more potent while inhibiting the spread of a boodle of PI-resistant HIV-1 variants and native HIV-1. The different responses of the 1,3,4-oxadiazoles against wild-type and PI-resistant HIV-1 strains revealed that the P1' position of the inhibitors was very important for developing novel HIV-1 PIs with wide range and high potency [55]. This example showed that 1,3,4-oxadiazole ring in place of phenyl group yielded several HIV protease inhibitors with better potency. It is speculated that the 1,3,4-oxadiazole ring in this series of inhibitors may act as acceptors for the formation of hydrogen bonds.

3.1.4. Other 1,3,4-oxadiazole–based HIV-1 Inhibitors

Emam *et al.* have studied some 5-aryl-1,3,4-oxadiazole-2-thione derivatives for antiviral activity [58]. The anti-HIV-1 activities of these compounds were evaluated using the XTT assay [59]. The result showed that compound 63 produced 100%, 43%, and 37% reduction of viral replication at 50, 10, and 2 μg/mL concentrations, respectively (Fig. **9**) [58]. In addition, some other synthesized 1,3,4-oxadiazoles have also been screened *in vitro* for their anti-HIV activities (Table **4**) [60].

3.2. Anti-HCV Activity

Recently, a novel class of potent HCV NS3/4A protease macrocyclic inhibitors was reported, e.g. compound **68** (Fig. **10**) [61]. The further modification was carried out to identify a structurally diverse series of P2-P4 macrocyclic inhibitors with remarkable potency and liver exposure. Based on the classic bioisostere principle, Francesco *et al.* replaced the carbamate group with the 1,3,4-oxadiazole moiety and other

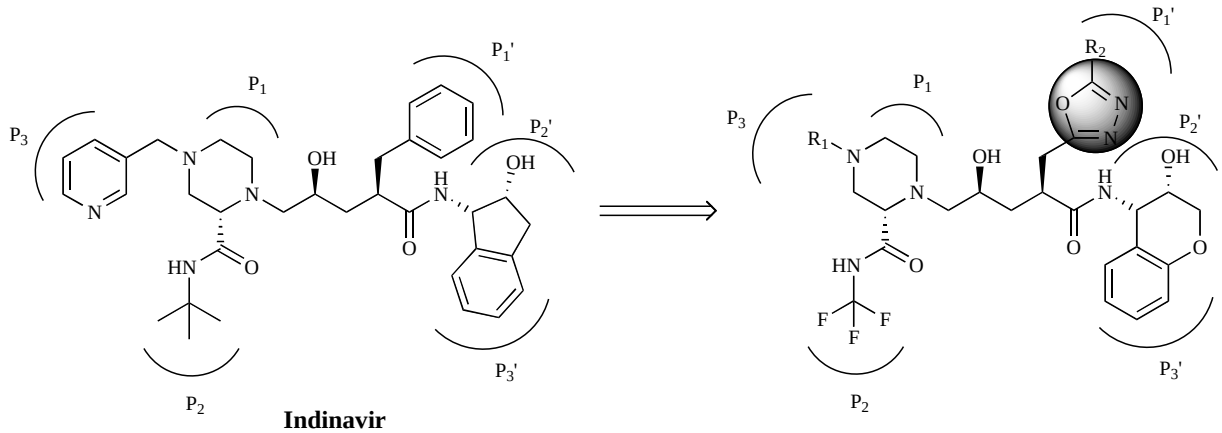
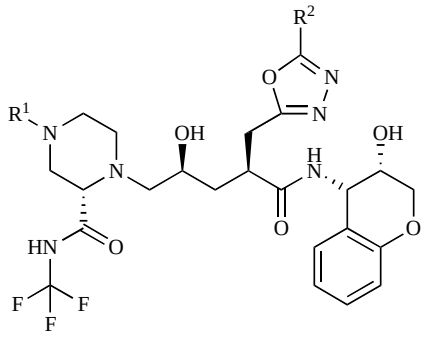
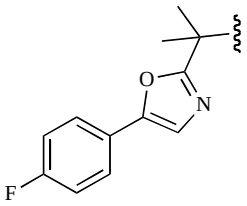
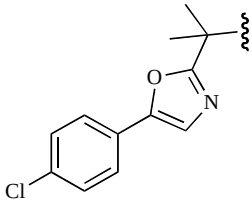
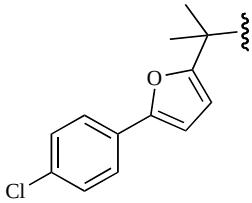
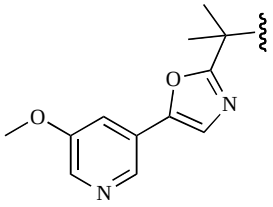


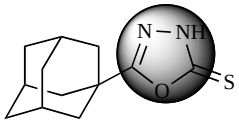
Fig. (8). Structure modification of 1,3,4-oxadiazole-based HIV-1 protease inhibitors.

Table 3. Enzyme Inhibition and Antiviral Activities of 1,3,4-oxadiazole-based HIV Protease Inhibitors



Compound	R^1	R^2	HIV-1 protease IC_{50}(nM)		Viral spread CI_{95}(nM)[f]				
			NL4-3	V-18	NL4-3	V-18	4X	K-60	Q-60
46	Indinavir		0.60	61	50	>1000	400	>1000	>1000
47		H	0.024	0.065	125	125	31	125	31
48		Me	0.027	0.19	125	63	31	125	31
49		Pr	0.016	0.19	16	63	16	16	≤8
50		Ph	0.020		≤8	63	16	≤8	16
51		H	<0.015	0.043	125	63	31	63	31
52		Me	0.016	0.060	250	63	16	31	≤8
53		Pr	<0.015	0.12	≤8	63	≤8	16	≤8
54		Ph	<0.015	0.18	≤8	125	16	≤8	16
55		H	0.015	0.099	63	125	31	63	31
56		Me	<0.015		63	63	31	31	31
57		Pr	<0.015		≤8	125	31	≤8	16
58		Ph	0.019		15.6	250	125	≤8	63
59		H	0.24	7.4					
60		Me	0.40	15	>1000	>1000	>1000	>1000	>1000
61		Pr	0.32		500	>1000	500	500	500
62		Ph	0.48		125	>1000	250	250	500

[f]The < and > values denote the lower and upper concentrations tested in the assays.



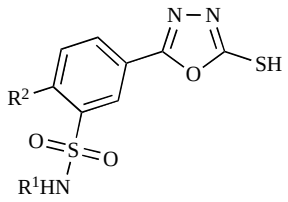
63

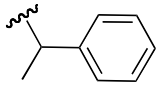
Fig. (9). Structure of other 1,3,4-oxadiazole–based HIV-1 inhibitors.

aminoheterocycles. The introduction of 1,3,4-oxadiazole scaffold could limit the flexibility of the macrocyclic backbone of the inhibitors, and therefore have an expedient effect on their *in vivo* profile while maintaining high activities against NS3/4A [62].

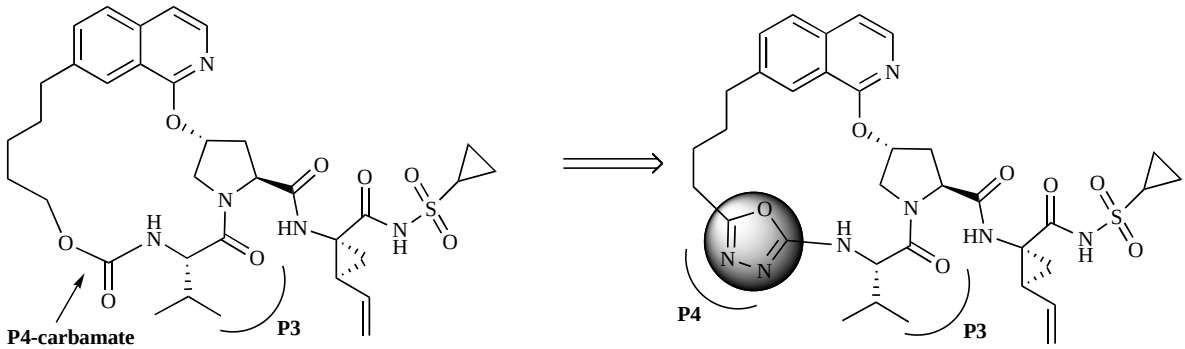
In order to identify the idea, compound **68** was docked into the full length NS3 structure and superimposed it with analogue **69**, containing an 1,3,4-oxadiazole ring [62]. The

Table 4. The Anti-HIV Activities and Cytotoxicities of Some Synthesized 1,3,4-oxadiazoles



Compound	R^1	R^2	% Reduction of HIV-1 [g]			CD_{50} [h] (μg/mL)
			50 μg/mL	25 μg/mL	5 μg/mL	
64	H	H	11	5	0	>100
65	H	OMe	23	7	0	>100
66	H	Cl	27	9	5	>100
67		Cl	62	21	14	67
63	-	-	100	43	37	68

[g]Percentage inhibition of virus replication at each of the indicated concentrations.
[h]The cytotoxic dose (the dose which gives 50% inhibition of growth of uninfected cells).



68 **69**

Fig. (10). Structure modification of 1,3,4-oxadiazole-based HCV inhibitors.

modeling result showed that the oxadiazole **69** could commendably overlap with the corresponding compound **68**. Notably, despite the replacement of the P4-carbamate with 1,3,4-oxadiazole ring, it has no effect on the formation of key hydrogen bonds between the carbonyl and amino groups of the residue Ala 157 at the P3 position (Fig. **11**) [62]. Additionally, the oxadiazole ring did not show to generate an unfavorable steric clash with residue His528, which was reported to be important in specific helicase-inhibitor interactions [62].

The activity experiment results demonstrated that oxadiazole **69** showed to be a potent enzyme inhibitor (K_i = 0.9 nM), and had submicromolar activity in the replication with 10% FBS (EC_{50} = 80 nM). In addition, inhibitor **69** maintained an excellent cellular activity in presence of 50% NHS (EC_{50} = 180nM), a four-fold drop compared with the pioneer **68** (EC_{50} = 46 nM). Moreover, the levels of plasma exposure were detected following oral administration of oxadiazole **69** at 5 mg/kg in Sprague-Dawley rat, which were still lower than inhibitor **68** (AUC = 0.1 μM·h and AUC = 0.27 μM·h for **69** and **68**, respectively). The liver exposure was also reduced significantly by oxadiazole **69** (liver levels at 4 h = 0.03 and 13.4 μM for 65 and 64, respectively) [62]. From this job we know that 1,3,4-oxadiazole was also a usable bioisoster for the ester group.

3.3. Others 1,3,4-oxadiazole-based antiviral agents

Besides, other antiviral activities of 1,3,4-oxadiazoles were also revealed (Fig. **12**). For instance, 1,3,4-oxadiazole derivative **70** was identified as a potent anti-HBV agent, which inhibited the expression of HBsAg and HBeAg antigens in a concentration-dependent manner with no cytotoxicity and effects on the expression of HBV transcripts. The inhibition of virion production of oxadiazole **70** was comparable to that of lamivudine (3TC), with EC_{50}

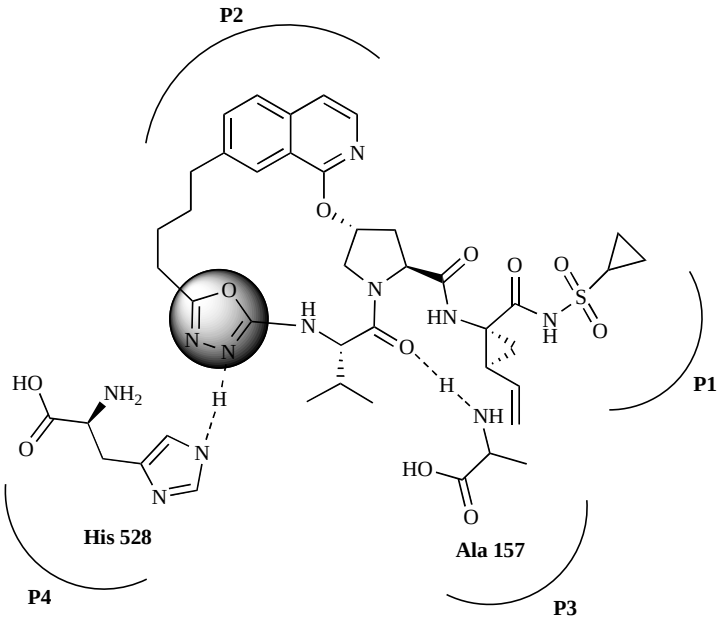


Fig. (11). The key contacts between the oxadiazole **69** and the residues of NS3-4A at the active site.

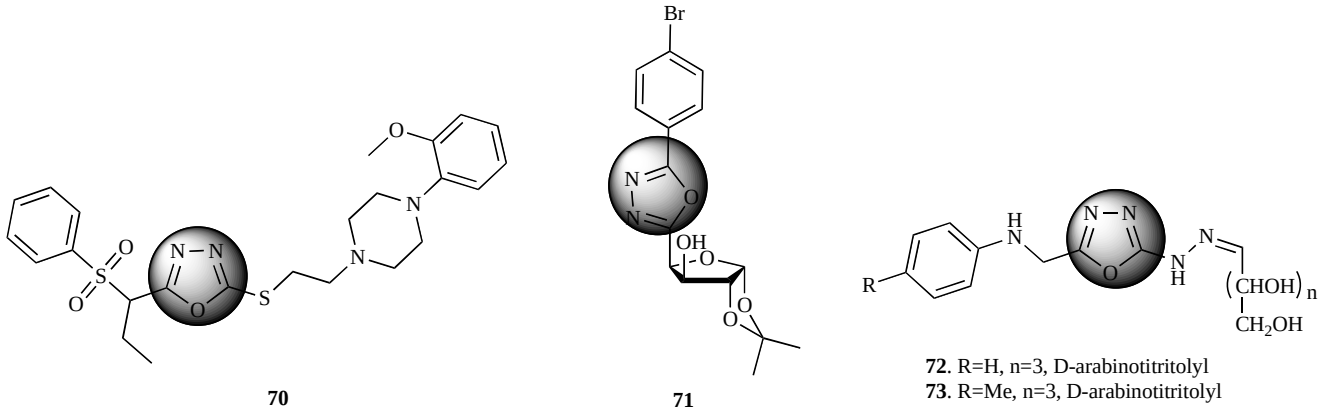


Fig. (12). Structures of other 1,3,4-oxadiazole-based antiviral agents.

values of 1.63×10^{-3} and 2.96×10^{-3} mM for compound **70** and 3TC, respectively [63].

The oxadiazole **71** exhibited antiviral action against dengue virus type 2 (DENV-2) and Junin virus (JUNV) with an EC_{50} value of 64.6 and above 100 μM, respectively [64].

Recently, a plaque infectivity assay was carried out to test a number of new *N*-arylaminomethyl-1,3,4-oxadiazole derivatives for their antiviral activity against HSV-1 and hepatitis-A virus (HAV, MBBcell culture-adapted strain). The results revealed that the 1,3,4-oxadiazoles **72** and **73** showed higher antiviral activity at concentration 2×10^{-4} μg and 1×10^{-4} μg against both HSV-1 and HAV compared to the other 1,3,4-oxadiazole derivatives [65].

4. CONCLUSION

This paper has reviewed the synthetic methods and antiviral activities of 1,3,4-oxadiazole derivatives. Meanwhile, the binding models of some representative 1,3,4-oxadiazole containing antiviral agents were discussed in detail, which provide rational explanation for their interesting antiviral activities. 1,3,4-Oxadiazole in the field of antiviral drug research may offer the following advantages: It can serve as versatile building block to introduce a new functional group, (i) as a scaffold to anchor these groups into the optimal space for interactions with the target, (ii) as a basic pharmacophore element to make hydrogen bonds or hydrophobic interaction for facilitating the spatial filling at the binding site, (iii) as ester surrogate to improve metabolic stability, or (iv) as pharmacophoric motif of metal coordination to coordinate metal ions (i.e. magnesium) within the active site of target (i.e. HIV-1 integrase) [66]. In addition, the synthetic methods expounded above were simple, maneuverable and versatile, which offer the chemical researchers a broader view for the recent information of this field.

To sum up, 1,3,4-oxadiazole pharmacophore is regarded as a *privileged structure* in drug discovery, because it can endow its derivatives with wide range of antiviral activities as well as other biological activities. Besides, the different

structural modifications can promote selective and potent inhibitors to be developed. Hence, *privileged structure* is a new concept of understanding bioactive molecular diversity, and it can also be used for the identification of new structural units that contribute as pharmacophores for different pharmacologic activities.

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