

Antiviral activity of thiadiazoles, oxadiazoles, triazoles and thiazoles

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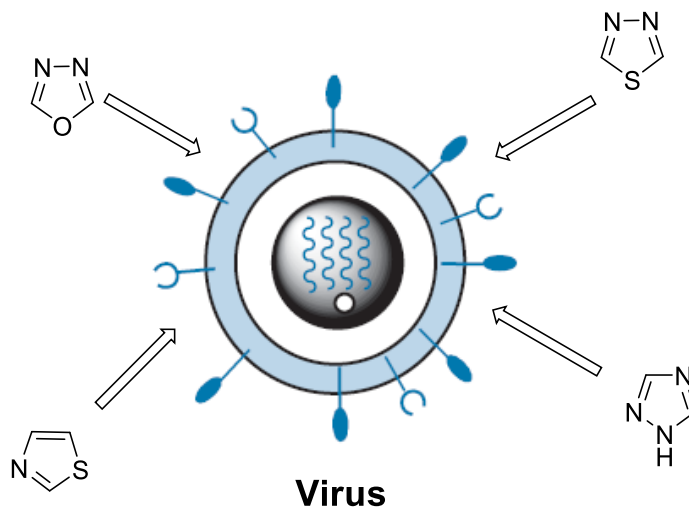
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Abstract

Drugs containing the heterocyclic five-membered thiadiazoles and isosteres possess a wide range of biological activities, including but not limited to, antiviral, antifungal, antihistamine, anticancer. In this study, we list the agents containing thiadiazoles and isosteres which are reported to have antiviral activity. We believe that this compilation will be a useful resource for researchers working in the field of antiviral agents.



Keywords: Antiviral drugs, thiadiazoles, oxadiazoles, triazoles, thiazoles

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1. Introduction

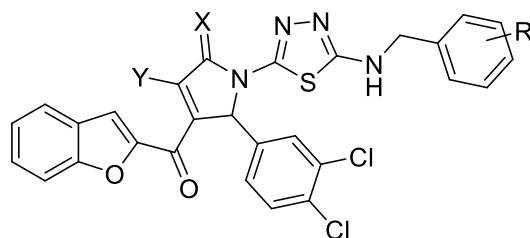
Viruses are non-cellular, infectious organisms that invade a host cell to survive and multiply. There are many different viruses capable of infecting animal, bacterial, or plant cells, with more than 400 known to infect humans. Those capable of being transmitted to humans from insects or animals can be particularly dangerous and belong to a class of diseases defined as zoonoses.¹ The current most dangerous virus disease Coronavirus (COVID-19) is an infectious disease caused by a newly discovered coronavirus (SARS-CoV-2) that is transmitted from animal to human is an example of zoonoses.² Consequently, both human and veterinary medicine play important roles in the control of such diseases. Historically, viral infections were devastating to mankind. It has been suggested that smallpox was the reason for the major epidemics which weakened the Roman Empire during the periods AD 165–180 and AD 251–266.³ Smallpox was a major cause for the high mortality in the indigenous tribes in both North and South America at the time of European colonization.⁴ Various flu epidemics and pandemics have proved devastating. The flu pandemic of 1918–1920 which was called Spanish flu left between 17 and 50 million deaths and 500 million infections worldwide,⁵ far larger than the number killed because of World War I. Finally, 32.7 million [24.8 million–42.2 million] people have died from AIDS-related illnesses since the start of the epidemic in the early 1980s.⁶ Africa has its fair share of lethal viruses, including AIDs, Ebola, and the virus responsible for Lassa fever.⁷ Vaccination is the most effective method to protect against viral infection and has proved extremely successful against fetal childhood diseases such as measles, mumps, and rubella (MMR vaccine)⁸ as well as historically serious infections such as yellow fever⁹ and smallpox which was the first vaccine to be developed, in 1796.¹⁰ Antiviral remedies are useful in tackling viral infections where there is a lack of an effective vaccine or where the infection has already taken place. The antiviral agents may be non-nucleoside analogues: those which are a group of heterogeneous compounds and interact directly with the target,¹¹ or nucleoside analogues: they must be activated intracellularly by phosphorylation to the active triphosphate form.¹² Thiadiazoles and their isosteres, triazoles, oxadiazoles, and thiazoles have shown broad biological activities as mentioned in the next paragraph. Here we will focus on the antiviral activities of the agents containing the specified ring systems thiadiazoles, triazoles, oxadiazoles, and thiazoles.

Five-membered heterocyclic compounds have shown a wide range of biological activities,¹³ namely thiadiazoles, thiazoles, 1,3,4-oxadiazoles, triazoles,¹⁴⁻²⁷ in addition to the benzimidazole ring.²⁸ They have been used as scaffolds for the synthesis of a wide range of agents with versatile activities including antibacterial,^{29,30} antifungal,^{31,32} analgesic, anti-inflammatory,²³ anticancer^{33,34} and antihypertensive activity.³⁵

These five-membered heterocyclic rings have also proved to have very effective antiviral activity against a wide range of viruses, making them of great value in the antiviral research.³⁶⁻⁴¹

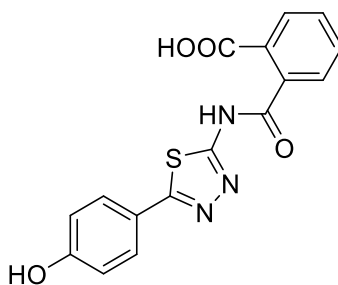
2. Thiadiazole-containing Compounds as Antiviral Agents

Cui *et al.*^{42,43} synthesized a series of pyrrolyl-1,3,4-thiadiazole derivatives of structure **1** which showed antiviral activity against the West Nile virus and Dengue virus.

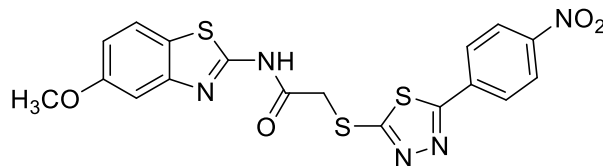
**1**

X = O, S, NH; Y = OH, SH; R = H, OH, CN, halo, alkyl, alkoxy

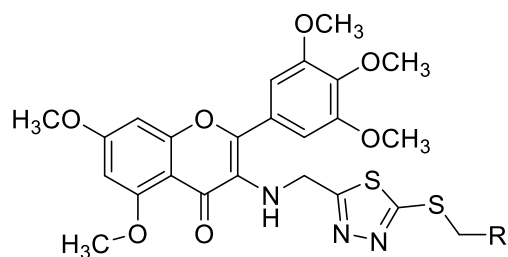
Brai *et al.*⁴⁴ found that compound **2** of the newly synthesized series of 1,3,4-thiadiazole derivatives was the most promising as an anti-HIV-1 agent without *in vitro* signs of cytotoxicity.

**2**

Tang *et al.*⁴⁵ have reported the synthesis of a series of benzothiazole derivatives bearing 1,3,4-thiadiazole moiety. The newly synthesized compounds exhibited good antiviral activity against tobacco mosaic virus, with compound **3** being the most effective.

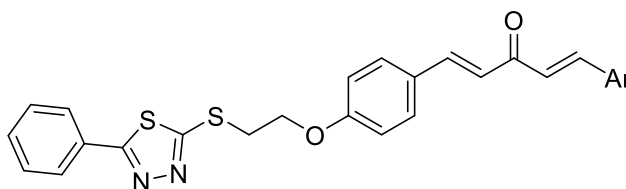
**3**

Zhong *et al.*⁴⁶ synthesized a series of novel myricetin derivatives linked to 1,3,4-thiadiazole species. Their antiviral activity against the tobacco mosaic virus was evaluated. Results showed that some of the compounds exhibited potential antiviral activity. Compounds **4a-d** had the best effect.

**4a-d**

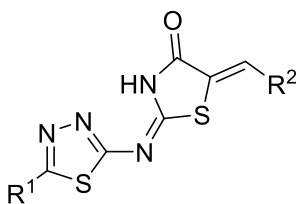
R = 4-chlorophenyl, 2-chlorophenyl, 2,4-dichlorophenyl, 2-chlorothiazol-5-yl)

Yu *et al.*⁴⁷ found that 1,4-pentadien-3-one derived from curcumin proved to have remarkable activity against plant viruses. That is why a series of new derivatives containing a 1,3,4-thiadiazole moiety together with a 1,4-pentadien-3-one unit was synthesized. Most of the synthesized compounds showed good activity against the tobacco mosaic virus and cucumber mosaic virus with compounds **5a-d** showing the best activity.

**5a-d**

Ar = 4-F-Ph, 4-Br-Ph, 2-F-Ph, 3-NO₂-Ph

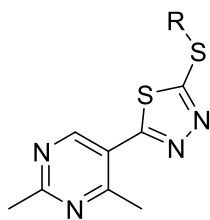
Manvar *et al.*⁴⁸ synthesized a series of thiazolidinone-thiadiazole derivatives, of which compounds **6a,b** had a promising effect against the Dengue virus and can be used as lead compounds.

**6a,b**

6a R¹ = C₆H₄F R² = C₆H₄F

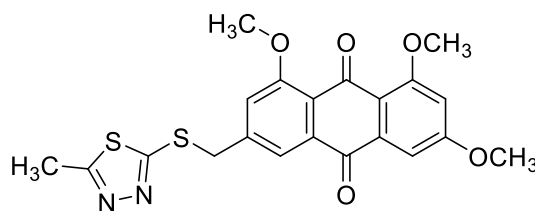
6b R¹ = C₆H₄Cl R² = C₆H₄F

Wu *et al.*⁴⁹ prepared a novel series of 2-substituted methylthio-5-(4-amino-2-methylpyrimidin-5-yl)-1,3,4-thiadiazole derivatives. Bioassay screening showed that compounds **7a-d** exhibited the best activity against the tobacco mosaic virus *in vivo*.

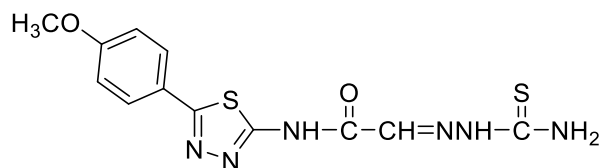
**7a-d**

R = n-Pr, CH₂CH₂CH(OMe)₂, sec-Bu, 4-Cl-C₆H₄-CH₂

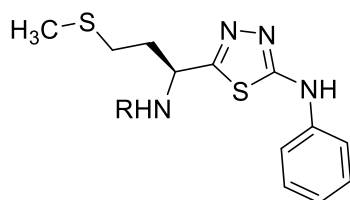
A novel series of thioether derivatives linked to 1,3,4-thiadiazole and emodin moieties were synthesized. The bioassay results showed that the thiadiazole derivative **8** showed excellent activity against the tobacco mosaic virus.⁵⁰

**8**

2-(2-Carbamothioylhydrazono)-N-(5-(4-methoxyphenyl)-1,3,4-thiadiazol-2-yl)acetamide (compound **9**) was synthesized for exploring its antiviral activity; it showed high activity against the cowpea mosaic virus.^{51,52}

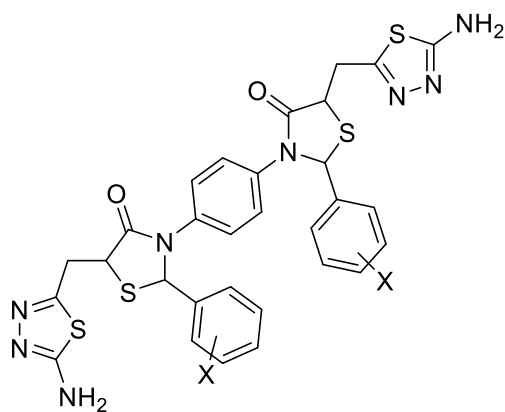
**9**

Tatar *et al.*⁵³ found that at subtoxic concentrations, compounds **10a-c** showed interesting antiviral activity against Herpes simplex-1 virus that can be considered as a lead for further work and research.

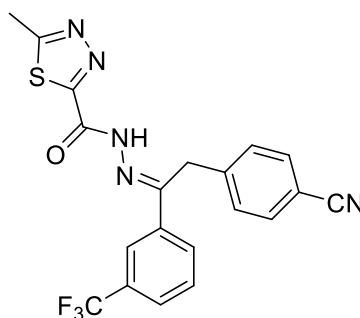
**10a-c**

10a R= H
10b R= CSNHC₆H₄CN
10c R= CSNHC₆H₃(CF₃)₂-Cl

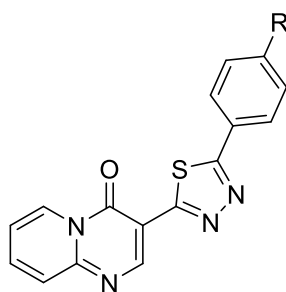
A series of thiazolidinone based heterocycles (compounds **11a-e**) was synthesized and tested for their activity against varicella zoster virus and cytomegalovirus. Most of the produced compounds exhibited good activity⁵⁴.

**11a-e**X = H, 4-Cl, 4-OMe, 3-NO₂, 4-NMe₂

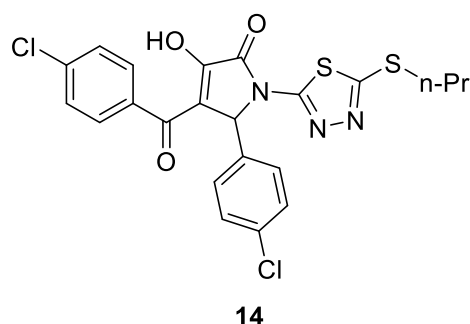
2-(4-Cyanobenzyl)-1-[3-(trifluoromethyl)phenyl]ethanone hydrazone derivatives (**12**) can be utilized in combination with commercial anti-plant virus agents to control diseases and viruses in agriculture, gardening and forestry.⁵⁵

**12**

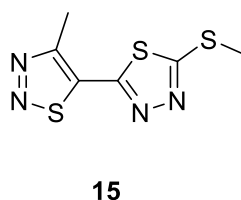
A new series of 4-oxo-4*H*-pyrido[1,2-*a*]pyrimidine derivatives linked to 1,3,4-thiadiazole ring was prepared. All the produced compounds exhibited moderate activity against HIV-1 with **13a,b** showing the best activity.⁵⁶

**13a, b**
R = CH₃, F

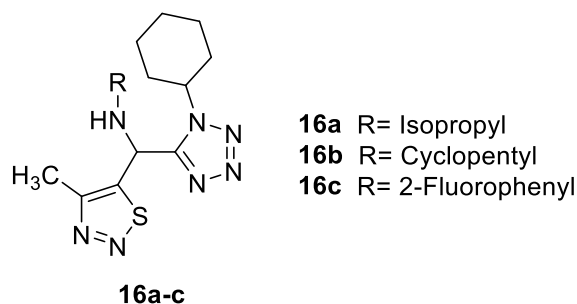
1,3,4,5-Tetrasubstituted 1*H*-pyrrol-2(5*H*)-one can be used as a scaffold for the synthesis of a new series of compounds against the West Nile virus. Of these, compound **14** showed the best activity.⁵⁷



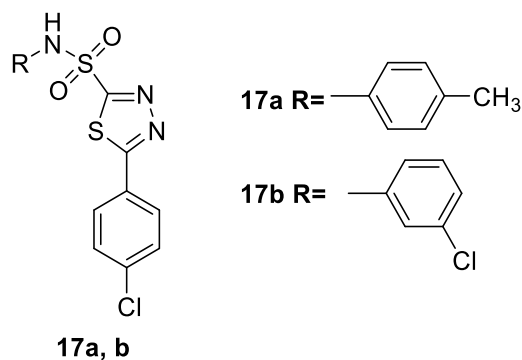
Xu *et al.*⁵⁸ prepared a series of 2-(4-methyl-1,2,3-thiadiazolyl)-5-substituted-1,3,4-thiadiazole derivatives. The prepared compounds were tested for their antiviral activity. It was found that compound **15** exhibited an inhibition of 55% against the tobacco mosaic virus.



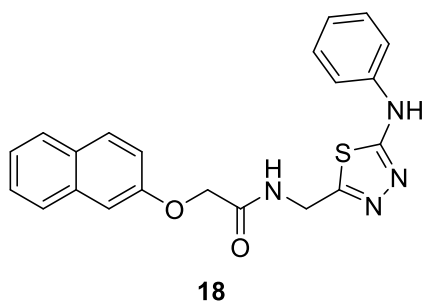
Wang *et al.*⁵⁹ synthesized a series of 1,2,3-thiadiazoles **16a-c** attached to a tetrazole moiety that proved to have a much better effect against the tobacco mosaic virus than that of ribavirin at 100 µg/ml.



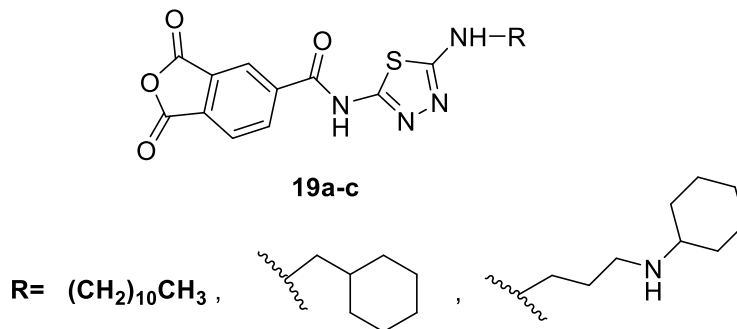
Zhuo Chen *et al.*⁶⁰ described the synthesis of a new series of thiadiazole analogues hybridized with the sulfonamide group. These compounds proved to have moderate antiviral activity against the tobacco mosaic virus, especially compounds **17a,b**.



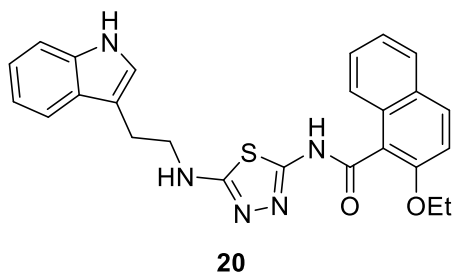
Hamad *et al.*^{61,62} synthesized a series of 2-(naphthalen-2-yloxy)-*N*-[(5-(phenylamino)-1,3,4-thiadiazol-2-yl)methyl] acetamide derivatives and examined them for *in vitro* activity against HIV-1 and anti-HIV-2. Of the synthesized compounds, compound **18** showed the best activity.



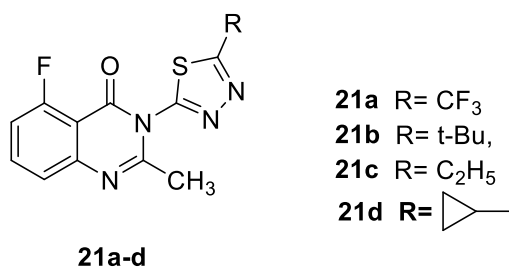
A new series of 1,3-dioxo-1,3-dihydro-2-benzofuran-5-carboxamide derivatives linked to 1,3,4-thiadiazole was synthesized. The new compounds **19a-c** showed 100% inhibition of human cytomegalovirus⁶³.



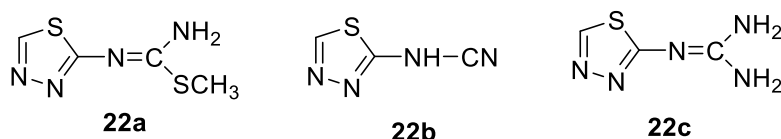
A series of 1,3,4-thiadiazole derivatives was prepared. The prepared compounds were found to have useful antiviral activity against cytomegalovirus (CMV). Most of the new compounds gave *in vitro* inhibition more than 90% of that of CMV polymerase.⁶⁴



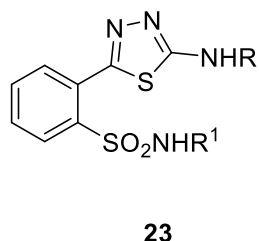
Parkanyi *et al.*⁶⁵ synthesized a group of thiadiazole quinazolinone derivatives **21a-d** for their antiviral investigation, these compounds showed moderate antiviral activity against HSV-1.



Paget *et al.*⁶⁶ found that compounds **22a-c** exhibited useful antiviral activity against measles, vaccinia and HSV type I and II, compound **22a** possessed *in vivo* activity, **22b** had both *in vivo* and *in vitro* activity and compound **22c** proved to be extremely active *in vitro*.

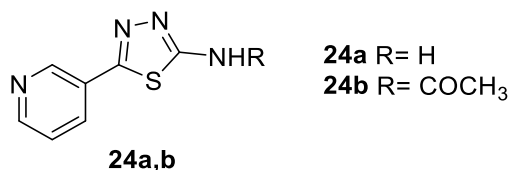


Orzalesi *et al.*⁶⁷ found that a series of virucidal compounds containing 1,3,4-thiadiazole (compound **23**) was active against herpes simplex-2 *in vitro*.



R = H, Me, Et, Me₂CH, Bu, H₂C:CHCH₂; R¹ = H, Me, Et

Jones *et al.*⁶⁸ was able to synthesize a group of thiadiazolyl pyridine derivatives **24a-b** for exploring their antiviral activity against neurovaccinia virus in mice. The results showed that the thiadiazole derivatives have excellent antiviral activity.

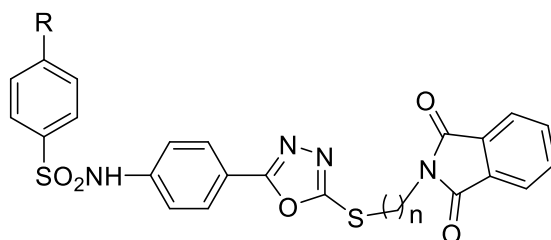


3. Oxadiazole-containing Compounds as Antiviral Agents

The 1,3,4-oxadiazole ring is considered a privileged structure in antiviral chemotherapy,⁶⁹ it is a molecular framework that can provide beneficial ligands for various receptors and enzymes by some modifications in the structure.⁷⁰

This heterocycle has proved to have very potent activity against a wide range of viruses such as human immunodeficiency virus (HIV),^{39,71} influenza virus, hepatitis A virus (HAV),³⁶ hepatitis B virus (HBV),³⁶ hepatitis C virus (HCV),³⁶ herpes simplex virus (HSV), cytomegalovirus (CMV), varicella zoster virus (VZV).^{72,73}

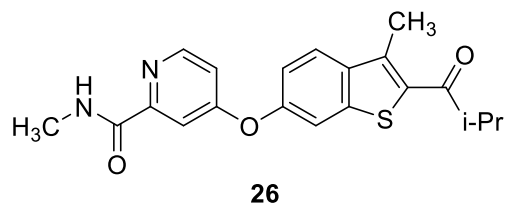
Hamdani *et al.*⁷⁴ linked together two pharmaceutically interesting motifs, 1,3,4-oxadiazole, and benzene sulfonamide in two series to develop novel hybrids. Bioactivity assays showed that **25a,b** are the most potent inhibitors among the synthesized analogs against dengue virus protease.



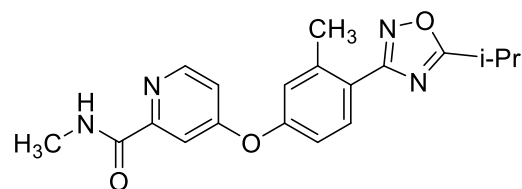
25a R= CF₃, n= 3
25b R= CF₃, n= 4

The human rhinovirus (HRV) is the main cause of common cold that leads to respiratory complications, the high rate of mutations limits the development of anti-HRV drugs, which urges the need for discovery of new lead compounds.

Kim *et al.*⁷⁵ synthesized compound **26** which showed antiviral activity and was further used for the synthesis of a series of compounds which proved to have high efficacy against HRV-A and B. Compound **27** exhibited a high efficacy against HRV-B14, HRV-A21, and HRV-A71H.

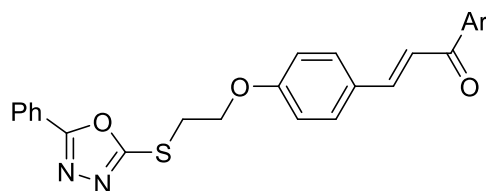


26

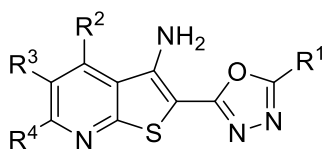


27

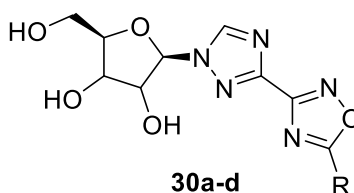
Gan *et al.*⁷⁶ synthesized a series of novel 1,3,4-oxadiazole/thiadiazole–chalcone conjugates, compounds **28a, b** were found to possess remarkable activity against tobacco mosaic virus both *in vitro* and *in vivo*.

**28a,b****28a** Ar= 2,4-diCl-Ph**28b** Ar= thiophen-2-yl

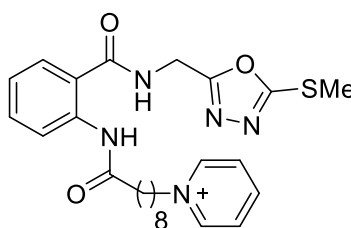
2-(1,3,4-Oxadiazol-2-yl)-3-aminothieno[2,3-*b*]pyridine derivatives (compounds **29**) have been synthesized, and were found useful against hepatitis C, also giving an idea for further development of anti-HIV agents.⁷⁷

**29**

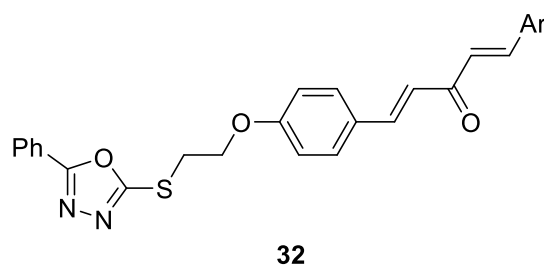
Chudinov *et al.*⁷⁸ prepared new ribofuranosyl oxadiazolyl triazole derivatives (compound **30a-d**) which were tested against herpes simplex, influenza A and hepatitis C viruses showing high efficacy.

**30a-d****30a** R= H**30b** R= CH₃**30c** R= iso-Pr**30d** R= Ph

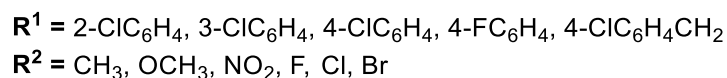
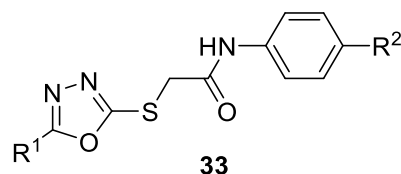
Wang *et al.*⁷⁹ prepared diamide 1,3,4-oxadiazole derivatives, compound **31** showed the best effect against tobacco mosaic virus *in vivo* that it can act as a lead compound.

**31**

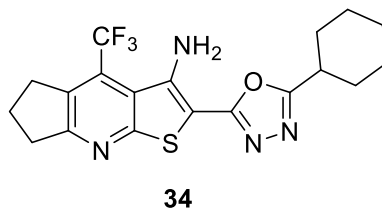
Gan *et al.*⁸⁰ designed a series of 1,4-pentadien-3-one derivatives containing 1,3,4-oxadiazole, of which compound **32** showed excellent activity against the tobacco mosaic virus.



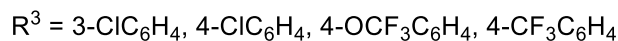
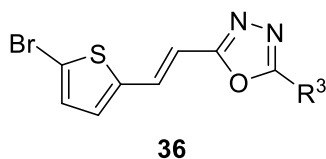
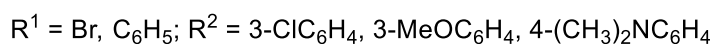
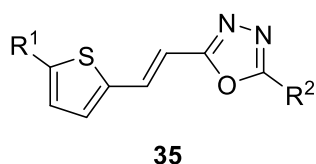
Bioassay screening showed that the 1,3,4-oxadiazole acetamide derivatives (compound **33**) showed remarkable activity against tobacco mosaic virus that it can act as an alternative candidate for other antiviral drugs.⁸¹



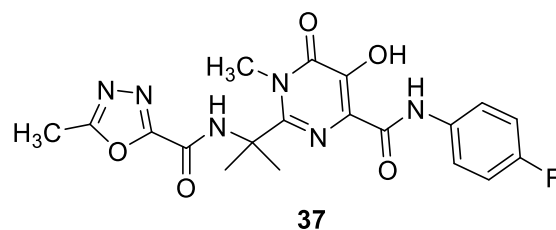
A new series of 2-(thieno[2,3-*b*]pyridin-2-yl)-1,3,4-oxadiazole scaffold was produced for further investigation against HCV, compound **34** was found to be the most potent of the designed compounds.⁸²



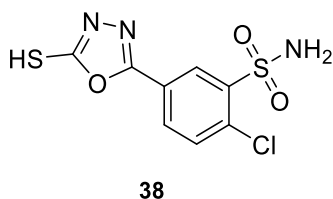
Benmansour *et al.*⁸³ reported the synthesis and antiviral activity of compound **35** and **36** derived from a rapid and easy chemical route. Compounds prepared by this method possessed *in vitro* activity against the polymerase enzyme of the Dengue virus. The following series of oxadiazole derivatives showed a submicro-molar activity against the four dengue virus serotypes.



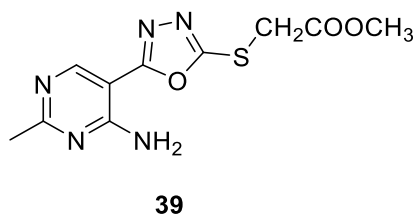
Raltegravir (compound **37**)⁸⁴ marketed as Isentress is an antiretroviral drug produced by Merck and Co., was approved by U. S. Food and Drug Administration (FDA) in 2007 and was approved for infant use in 2011, used for the treatment of HIV infections. This drug contains an oxadiazole ring in its basic skeleton.^{59,60}



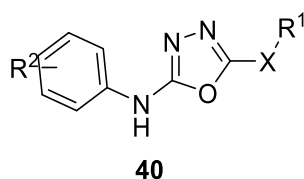
Iqbal *et al.*⁸⁵ studied the antiviral effect of introducing 1,3,4-oxadiazole moiety to benzenesulfonamide, one of the synthesized compounds **38** was found to be the most active against HIV.^{76,77}



Wu Wenneng *et al.*⁸⁶ synthesized a new series of 2-substituted methylthio-5-(4-amino-2-methylpyrimidin-5-yl)-1,3,4-oxadiazole derivatives. Of these, compound **39** exhibited excellent activity against tobacco mosaic virus.



1,3,4-Oxadiazole derivatives (compound **40**) were prepared and found to have an inhibitory effect against tobacco mosaic virus.⁸⁷

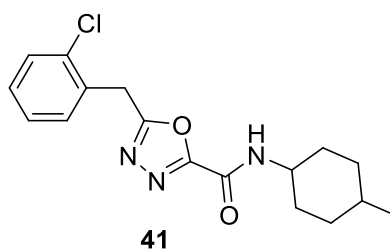


X = S or SO₂

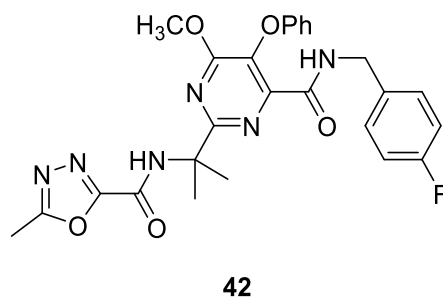
R¹ = Me, Et, or (un)substituted benzyl

R² = halo, alkyl, or alkoxy

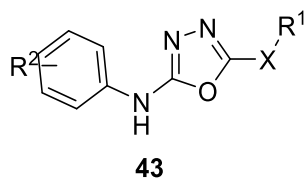
5-Benzyl-N-phenethyl-1,3,4-oxadiazole-2-carboxamide derivatives (compound **41**) were synthesized and tested for their activity against the Flaviviridae family of viruses, such as HCV.⁸⁸



A series of raltegravir derivatives were synthesized and examined for their activity against HIV. The results showed that most of the compounds exhibited good to excellent activity with compound **42** showing the most potent activity.⁸⁹



The 1,2,4-oxadiazole analog is a potent nucleoside inhibitor of Hepatitis C virus (HCV) NS5B polymerase. Compound **43** showed high antiviral potency against HCV replication in replicon cells and efficient conversion to the corresponding NTP *in vivo*, NTP level was very high in rat liver following i.v. and oral administration.⁹⁰

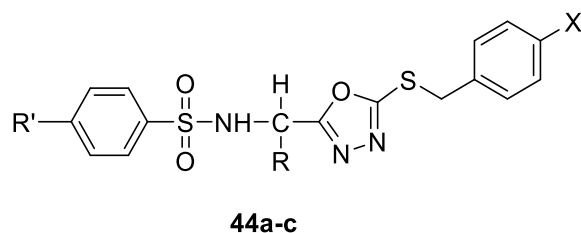


X = S or SO₂

R¹ = Me, Et, or (un)substituted benzyl

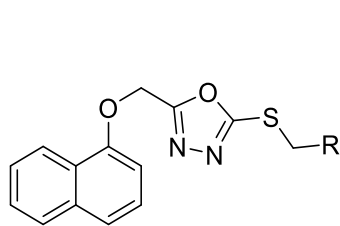
R² = halo, alkyl, or alkoxy

Syed *et al.*⁹¹ synthesized a new series of 5-benzylthio-1,3,4-oxadiazoles **44a-c** for their expected antiviral activity. Their activity was tested against HIV-I and HIV-II and showed high inhibitory activity against both viruses.

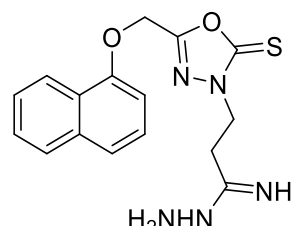
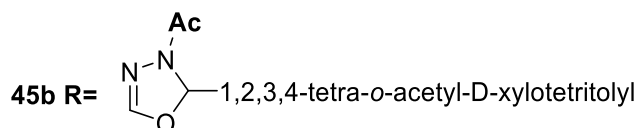


	R	R'	X
44a	CH ₃	Cl	Br
44b	(CH ₂) ₂ SCH ₃	CH ₃	Br
44c	CH ₂ Ph	CH ₃	H

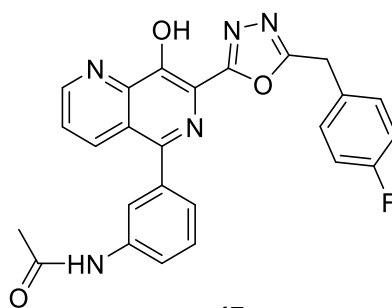
A new series of 2,5-disubstituted 1,3,4-oxadiazole **45a,b** and **46** were synthesized and evaluated against HIV and HCV, the results showed that the activity against HIV was in the order **45a** followed by **45b** and then **46**, while as anti-HCV, compound **46** has the highest activity followed by **45a** then **45b**.⁹²

**45a,b**

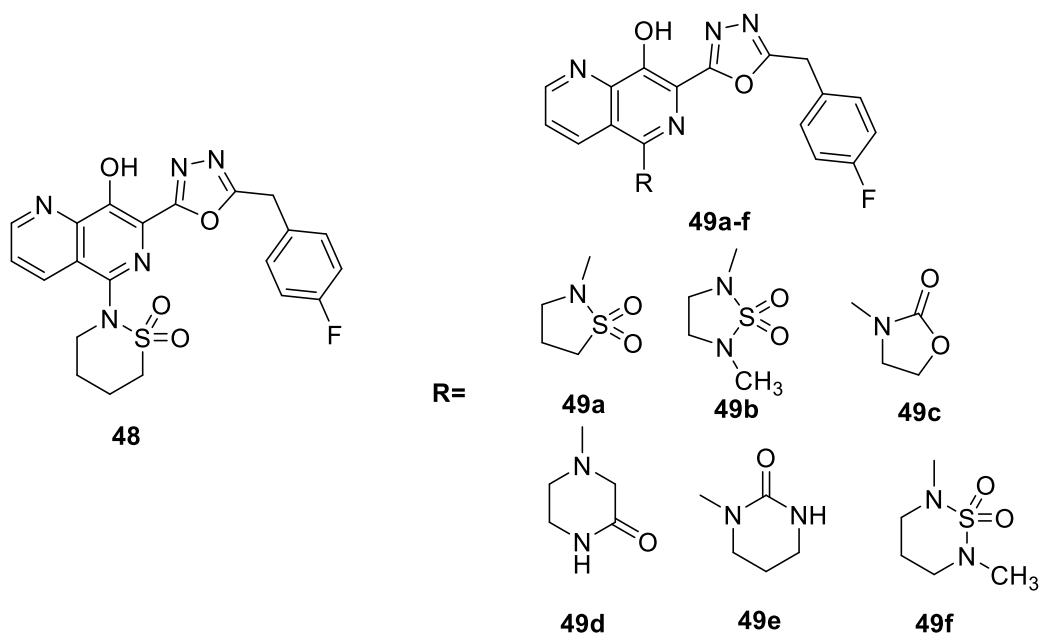
45a R= CONHNCH₂-D-xylotetritolyl

**46**

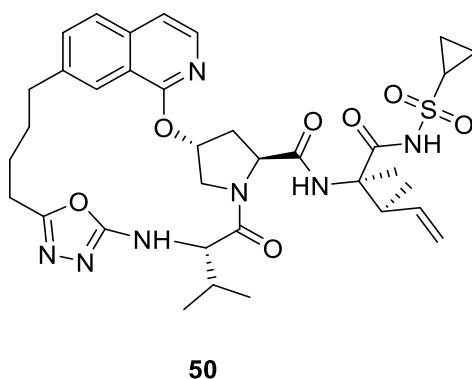
QSAR model was done for studying the inhibition of HIV-1 integrase on recently discovered 1,3,4-oxadiazole substituted naphthyridine derivatives. Amongst them, compound **47** showed the best activity.⁹³

**47**

Johns *et al.*⁹⁴ found that the 1,3,4-oxadiazole derivative (compound **48**) was a very potent HIV-1 integrase inhibitor.³⁷ Modification of substitution at C5 of the naphthyridine ring yielded other oxadiazole derivatives **49a-f** with comparable HIV-1 integrase inhibitory activity.

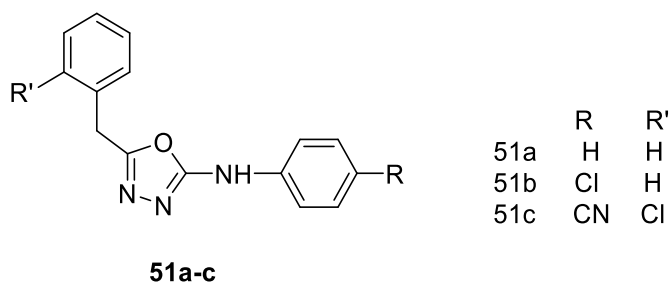


Di Francesco *et al.*⁹⁵ synthesized 1,3,4-oxadiazole derivative (compound **50**) which showed excellent cellular anti-HCV activity.

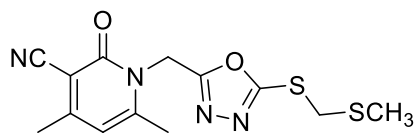


Recent literature showed that 1,3,4-oxadiazole scaffold is present in many HIV-1 inhibitors, acting by different mechanisms, through inhibition of viral reverse transcriptase, protease or integrase.⁹⁶

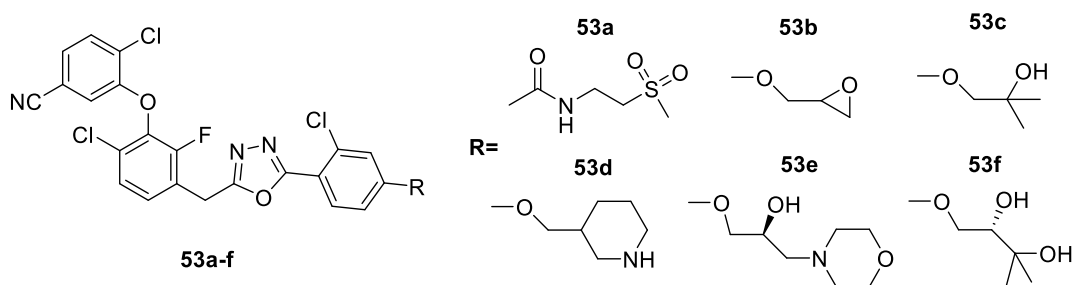
Barreiro *et al.*⁹⁷ prepared a new series of oxadiazole compounds **51a-c** and was tested for the activity as HIV-1 reverse transcriptase inhibitors, these compounds showed potent activity as inhibitors of the viral enzyme.



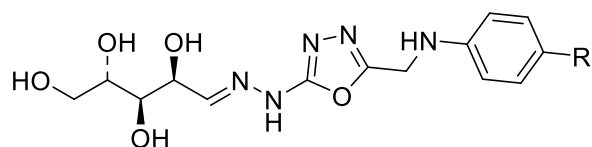
El-Assawy *et al.*⁹⁸ synthesized a series of 1,3,4-oxadiazole derivatives to be tested against HBV. Of the synthesized series, compound **52** showed the best activity with the least cytotoxicity.

**52**

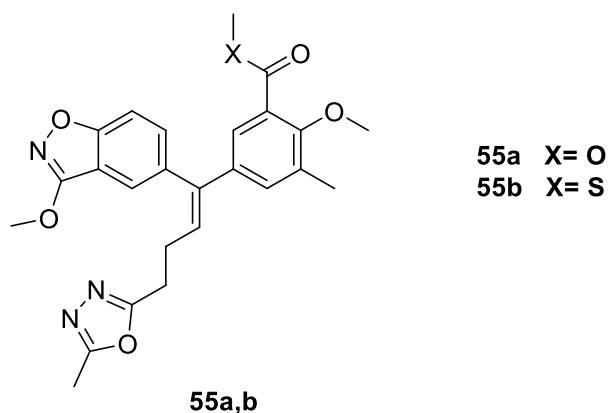
Compounds **53a-f** were synthesized containing 1,3,4-oxadiazole ring. These compounds showed excellent anti-HIV activity against wild types and resistant strains.⁷²



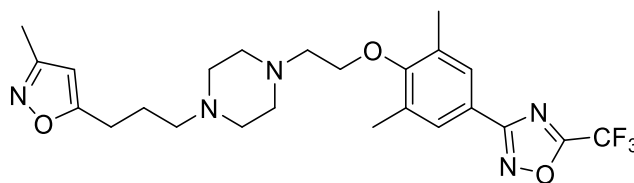
A series of *N*-arylamino-methyl-1,3,4-oxadiazole derivatives was prepared, the synthesized compounds were tested against herpes simplex virus type-1 (HSV-1) and Hepatitis-A virus (HAV). The sugar hydrazones **54 a, b** showed the best antiviral activity of all the synthesized compounds.⁹⁹

**54a,b****54a** R= H**54b** R= CH₃

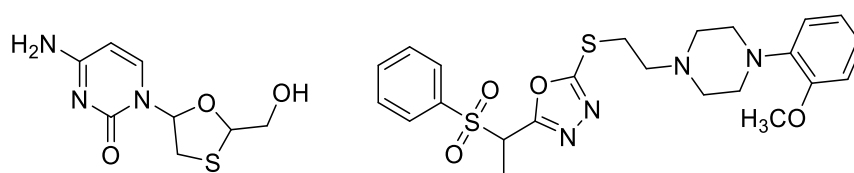
Cullen *et al.*¹⁰⁰ synthesized new 1,3,4-oxadiazole analogues **55a, b** that showed improved anti-HIV activity together with enhanced metabolic stability in rats.

**55a** X= O**55b** X= S**55a,b**

The dihydrochloride salt of the trifluoromethyl-substituted oxadiazole compound **56** showed good anti-picornavirus activity.¹⁰¹

**56**

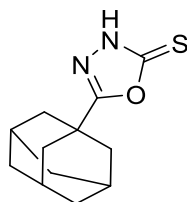
Tan *et al.*¹⁰² were able to synthesize the oxadiazole derivative **57**, this compound showed excellent activity against hepatitis B virus comparable to that of lamivudine.¹⁰³



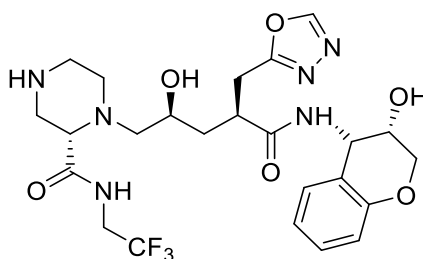
Lamivudine

57

The anti-HIV activity of 5-adamantyl-1,3,4-oxadiazole-2-thione (compound **58**) was studied. It showed excellent activity at different concentrations.⁴⁰

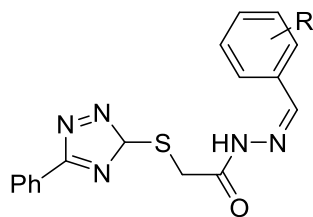
**58**

A new oxadiazole derivative (compound **59**) was synthesized by a novel method through diastereoselective installing of a carboxylic acid and transforming it into the heterocycle. This compound showed excellent HIV-1 protease inhibition.¹⁰⁴

**59**

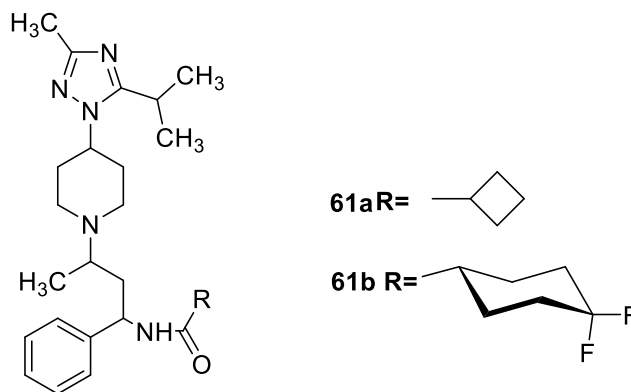
4. Triazole-containing Compounds as Antiviral Agents

Many triazole-based compounds are available in the market as drugs. The triazole derivative **60** was used as a precursor for the synthesis of new antiviral agents that showed remarkable activity against HBV.¹⁰⁵

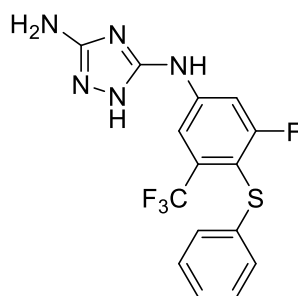
**60**

R = 3,4-(OMe)₂, 3,5-Cl₂, 4-Me₂N, 2,4-(OH)₂, 2-OH-1-naphthyl

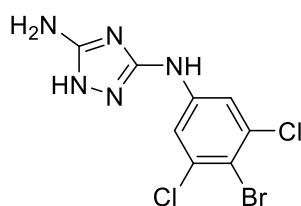
Triazolopiperidines **61a, b** were synthesized and tested for their anti-HIV activity. They were found to be very potent agents.¹⁰⁶

**61a,b**

A series of 1,2,4-triazole derivatives was synthesized and tested for activity against HCV. Compound **62** was found to have the best activity.¹⁰⁷

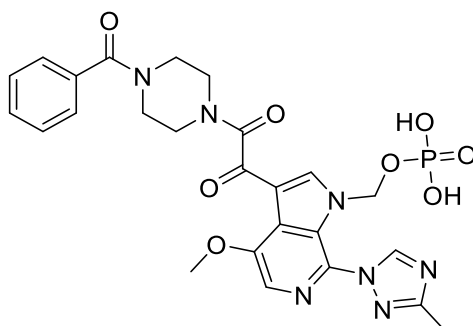
**62**

A new series of triazole derivatives was synthesized and examined for their activity against HCV.¹⁰⁸



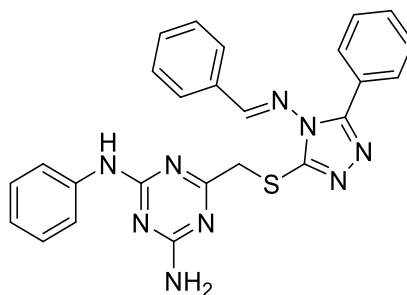
63

Fostemsavir (compound **64**) BMS-663068; experimental HIV-entry inhibitor prodrug, it offers a promise for individuals with HIV-resistant infections.¹⁰⁹



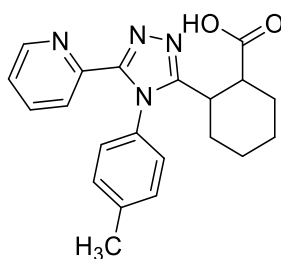
64

A new series of triazolyl-1,3,5-triazines was synthesized. Compound **65** showed high anti-HSV activity.¹¹⁰



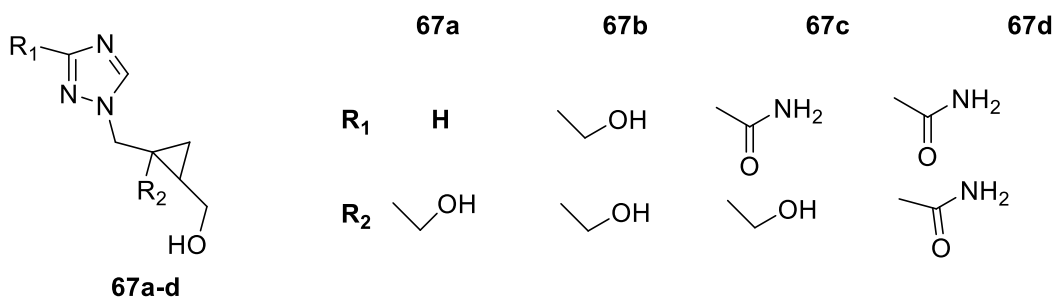
65

A series of new compounds was synthesized through the reaction of N^3 -substituted amidrazones together with cyclohexane dicarboxylic anhydride. Of the newly synthesized compounds, compound **66** showed the best anti-HIV-1 activity.¹¹¹



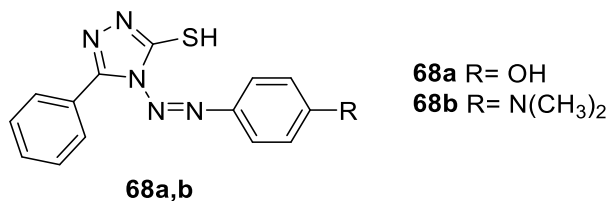
66

Benci *et al.*¹¹² synthesized a series of triazole cyclopropane analogues **67a-d**, these compounds showed moderate antiviral activity against vaccinia and Punta toro viruses that cause an acute febrile illness.¹¹³



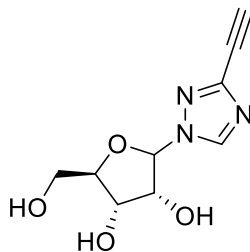
67a-d

The synthesis of diazo-triazoles was reported; compounds **68a, b** showed good activity against HSV-1.¹¹⁴



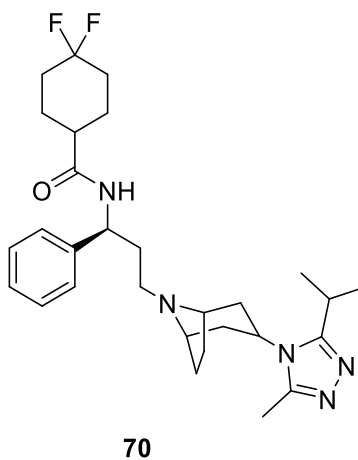
68a,b

1-β-D-ribofuranosyl-3-ethynyl-1,2,4-triazole (ETAR) (compound **69**) significantly reduced the replication of dengue virus. Moreover, it also reduced the replication of five flaviviruses, Langkat virus (a flavivirus that causes encephalitis) and Modoc virus that cause fever or chills, cough, shortness of breath or difficulty breathing. That is why it represents a promising lead compound for treatment of flavivirus infections. It also proved to be active against Hantaan virus (HTNV) and Andes virus that cause fever, headache, nausea, and muscle ache.^{115,116}

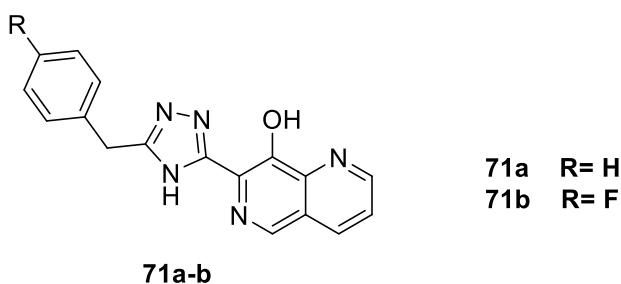


69

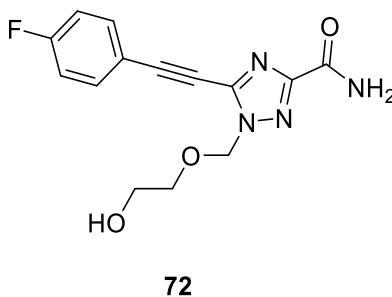
Maraviroc (compound **70**) marketed as Selzentry or Calsentri outside U.S.A., is an antiretroviral agent used for treatment of HIV-1 infections, first developed by Pfizer, and was fully approved in 2007.¹¹⁷



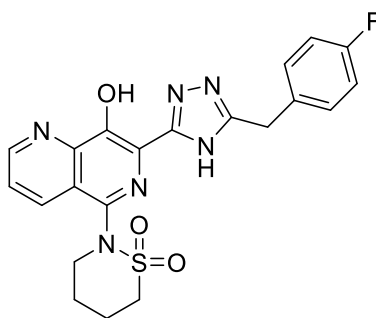
A new pharmacophore named 8-hydroxy-1,6-naphthyridine together with 1,2,4-triazole was identified; the two moieties were selected for the synthesis of the key structural components **71a, b** which showed high anti-HIV-1 activity.³⁷



Zhou *et al.*¹¹⁸ synthesized acyclic nucleoside triazole (compound **72**) which was able to successfully inhibit HIV replication.¹¹⁹

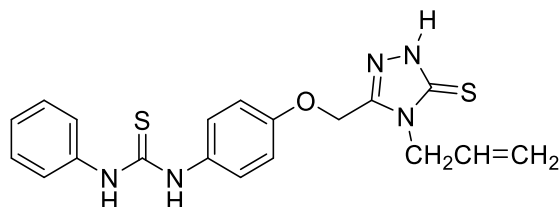


Johns *et al.*¹²⁰ synthesized triazole naphthyridine compound **73** which displayed excellent activity against HIV-1 integrase.



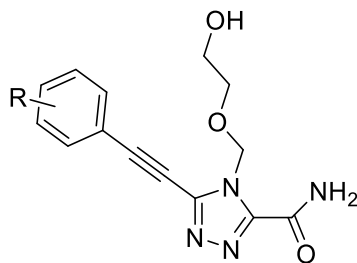
73

Küçükgüzel *et al.*¹²¹ synthesized some new triazole derivatives, 1-{4-[(4-allyl-5-thioxo-4,5-dihydro-1H-1,2,4-triazol-3-yl)methoxy]phenyl}-3-phenyl-thiourea (**74**) proved to have good activity against varicella-zoster virus and Coxsackie virus.



74

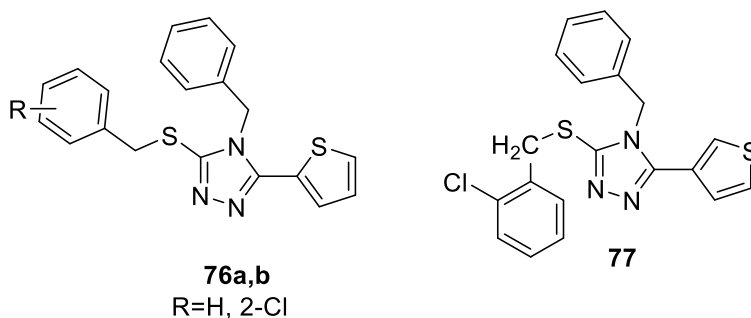
Zhu *et al.*¹²² synthesized a series of new acyclic triazole nucleosides **75a-h** which were tested for their anti-HCV activity. All the new compounds, except **75b**, exhibited good antiviral activity.



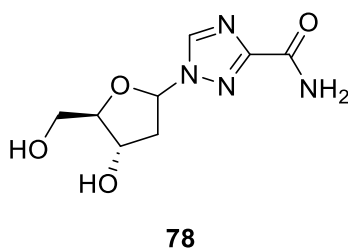
75a-h

R= H, 4-OCH₃, 4-CH₃, 4-C₅H₁₁, 4-CF₃, 4-F, 3-F, 2-F

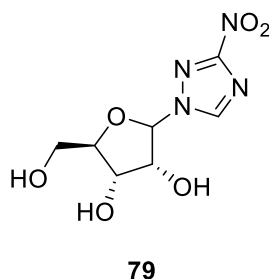
A novel series of 3,4,5-trisubstituted 1,2,4-triazole derivatives was synthesized and tested for HIV-1 RT inhibitory activity. The bioassay results showed that compounds **76a**, **b**, and **77** were the most active NNRTIs.¹²³



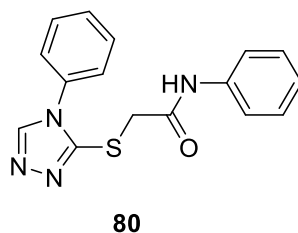
New approaches for viral therapy have been developed to overcome the rapid emergence of resistant strains of retrovirus. Vivet Boudou *et al.* tested the activity of 1-(2'-deoxy--D-ribofuranosyl)-1,2,4-triazole-3-carboxamide (2'-deoxy-ribavirin) compound **78** on HIV-1.^{124,125}



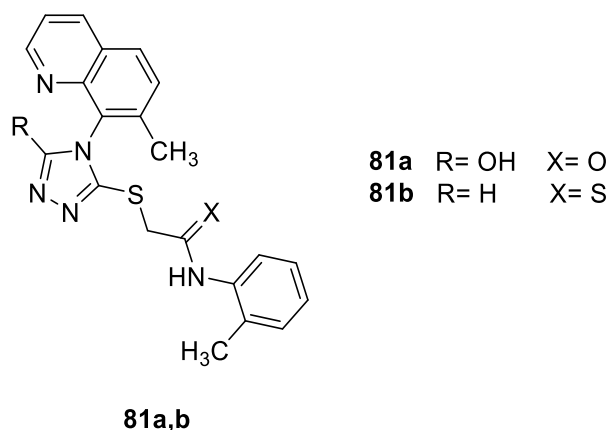
Kumarapperuma *et al.*¹²⁶ synthesized a group of new ribavirin analogues to be tested against RNA viruses. Of the synthesized compounds, **79** showed the best activity.



The synthesis of novel sulfanyltriazole derivative **80** was reported for further screening as an anti-HIV agent. This compound unexpectedly showed very potent anti-HIV activity that can be considered as a lead for further optimization.^{127,128}

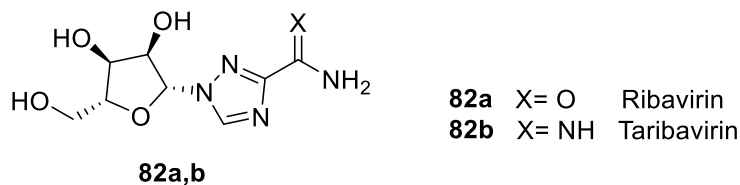


De La Rosa and co-workers were able to synthesize triazole derivatives **81a,b** that were found to be highly active against nevirapine HIV-resistant strains with compound **81a** as the most active compound.¹²⁹

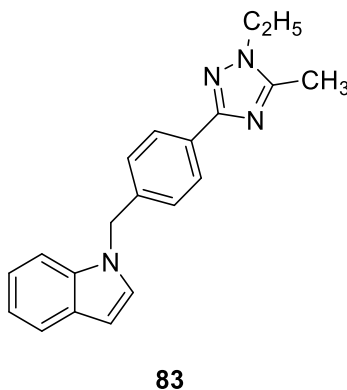


Ribavirin (**82a**) marketed as Hepavirin, Panvirin or Rebetol is a well-known antiviral drug used mainly for the treatment of HCV infections. This drug contains 1,2,4-triazole ring in its basic skeleton. It was first made in 1972 by researchers from international chemical and nuclear corporations and proved to have excellent activity against a wide range of RNA and DNA viruses. It was approved in the U.S.A. in 1998 and is now produced by Schering-Plough.¹³⁰

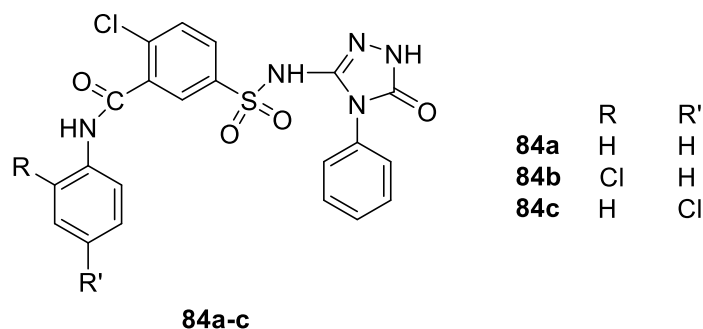
Taribavirin (**82b**) also known as Viramidine is a Ribavirin prodrug in phase III human trials showed to be active against the influenza virus. It is better liver targeting than ribavirin, designed to concentrate in the liver, and expected to replace it in the treatment of hepatitis infections. Although it showed 38% viral inhibition compared to 52% for approved ribavirin, but it showed more safety from hemolytic anemia than ribavirin, that's why Valeant indicated the drug was on track by the end of 2007.¹³¹



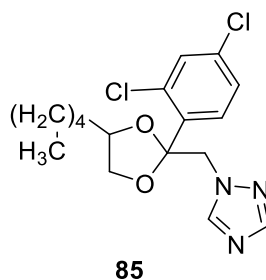
Al-Soud *et al.*¹³² synthesized a new series of 1,2,4-triazole derivative to be tested against HIV. All the prepared compounds were inactive except **83** which showed activity against HIV.



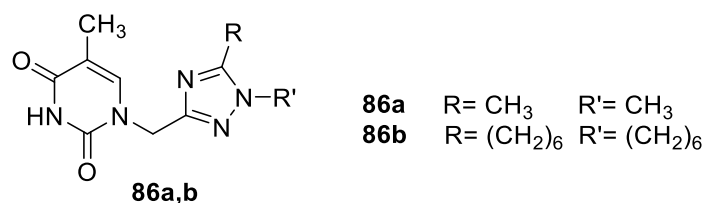
Pomarnacka and Kedra¹³³ synthesized 1,2,4-triazolone derivatives **84a-c** which proved to have moderate anti-HIV activity.¹³⁴



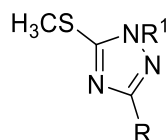
Compound **85** is a pharmaceutical compound that can be used as an antiviral as well as inhibiting the growth of tumors and cancers in mammals.¹³⁵



Al-Soud and Al-Masoudi synthesized 1-[(1,5-disubstituted)-1*H*-1,2,4-triazol-3-yl)methyl]thymines **86a,b** for their antiviral evaluation. These compounds showed moderate activity against HIV-1 (IIB-strain), HIV-2 (rod strain) and CMV.¹³⁶

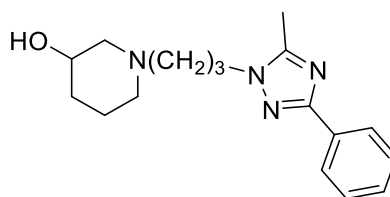


The compounds **87a-c** and their *N*-glycosides were synthesized and examined for antiviral action against RNA-3 poliomyelitis.¹³⁷



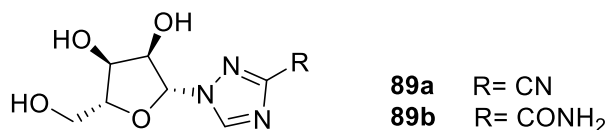
R = H, Me, or Et and R¹ = H

The triazole compound **88** inhibited bacteriophages on an *Escherichia coli* culture as well as decreasing the growth of tobacco mosaic virus in infected tobacco leaves.¹³⁸



88

The cyanotriazole nucleoside analogue **89a** was able to reduce the Dengue virus replication at a concentration lower than that of ribavirin. This compound represents a promising drug candidate for the treatment of infections caused by a flavivirus. On the other hand, the D-ribofuranosyl-1,2,4-triazole-3-carboxamide (**89b**) was found to be highly active against measles virus.¹³⁹

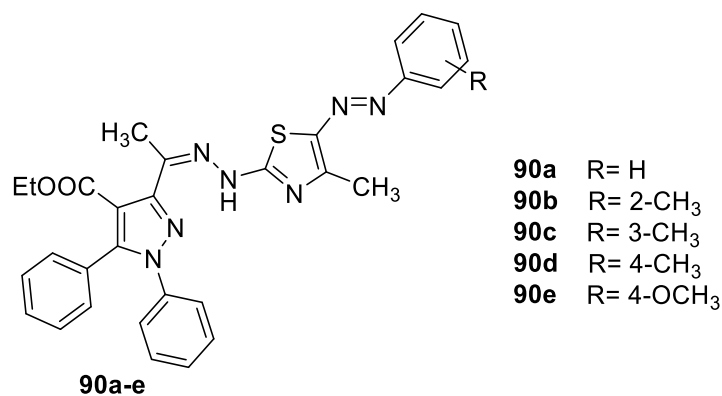


89a R= CN
89b R= CONH₂

89 a,b

5. Thiazole-containing Compounds as Antiviral Agents

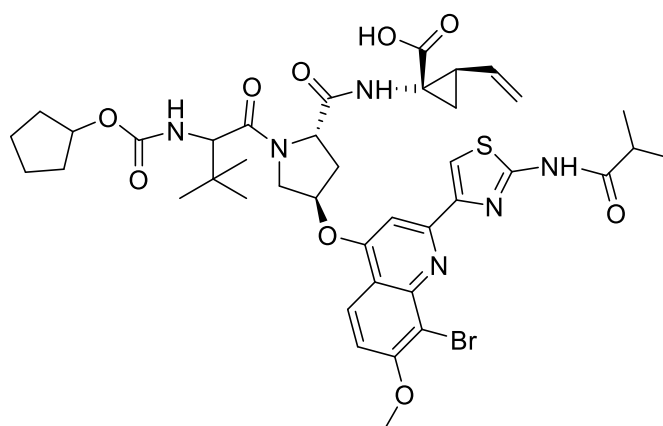
M. Abdalla *et al.*¹⁴⁰ synthesized a series of new thiazoles **90a-e** that exhibited strong to moderate antiviral activity against rabies virus with **90e** the most active one.



90a R= H
90b R= 2-CH₃
90c R= 3-CH₃
90d R= 4-CH₃
90e R= 4-OCH₃

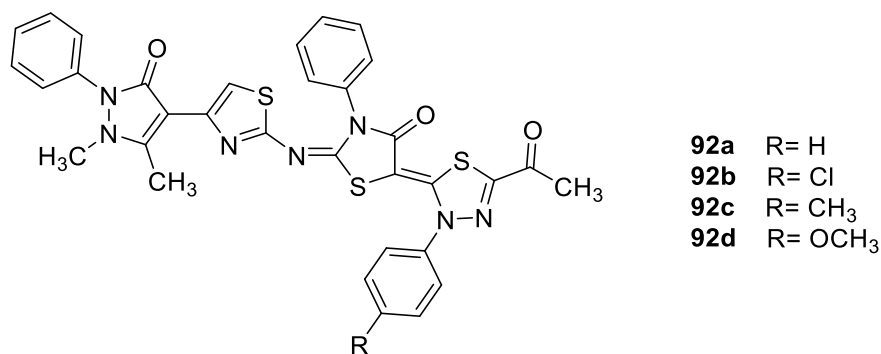
90a-e

Faldaprevir (**91**) is another experimentally tested agent in phase III trials containing thiazole ring for treatment of HCV infections through inhibition of NS3-NS4A protease enzyme.¹⁴¹



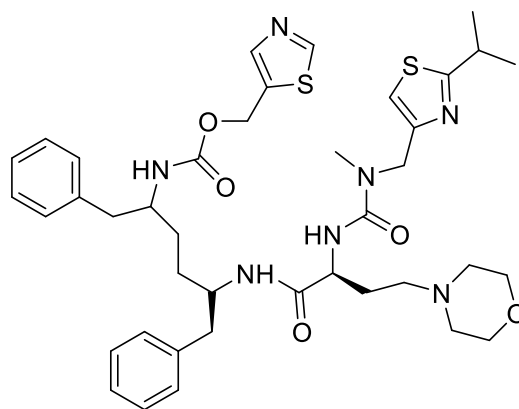
91

Dawood *et al.*¹⁴² synthesized a new series of thiazole derivatives **92a-d** that exhibited potent antiviral activity against HCV.



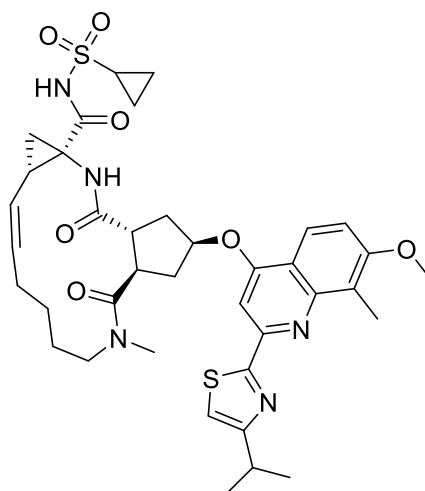
92a-d

Cobicistat (**93**) marketed as Tybost is a licensed drug, approved in 2015 and produced by Bristol-Myers Squibb for treatment of HIV-1 infections as a part of a combination therapy.¹⁴³



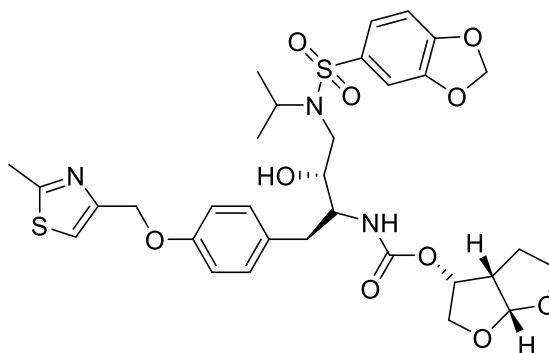
93

Simeprevir (**94**) marketed as Olysio or Sovriad is considered as HCV-protease inhibitor agent, used in combination with interferon- α and ribavirin. It was first developed by Medivir and Johnson & Johnson's Pharmaceuticals.¹⁴⁴



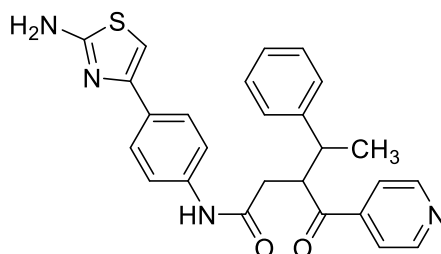
94

Brecanavir (**95**) code-named GW640385, HIV-protease inhibitor, but in 2006 GlaxoSmithKline stopped the drug development for problems in the formulation; they were unable to develop a viable oral dosage form that can achieve the drug levels required to treat multi-drug resistant HIV.¹⁴⁵



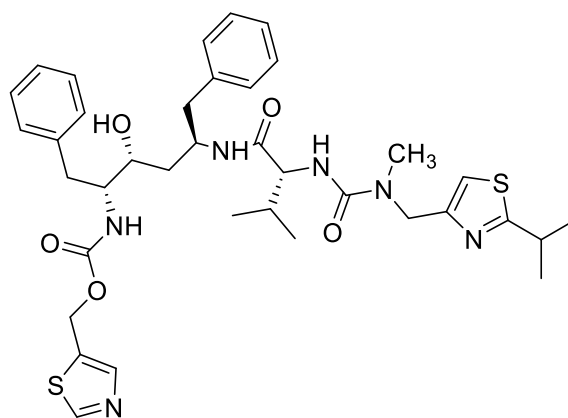
95

Compound **96** was synthesized and found to have excellent anti-HSV activity, that it can be considered as a lead for further development of antiviral agents.¹⁴⁶



96

Ritonavir (**97**) marketed as Norvir, was first used in 1996 for treatment of retroviral infections and in combination with other medications for the treatment of hepatitis C infections.¹⁴⁷



97

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Authors' Biographies



Samar Tawfik received a bachelor's degree in Pharmaceutical Science, at Mansoura University, Egypt, 2006, her Master's degree in Pharmaceutical Organic Chemistry, Mansoura University, 2012, and her Ph.D. in Pharmaceutical Organic Chemistry, Mansoura University, 2017, under the Supervision of Prof. Atef Tantawy. Dr. Samir is working now as an assistant professor of Pharmaceutical Organic Chemistry at Mansoura University. Dr. Samir is interested in the design and synthesis of new compounds to be investigated as antiviral agents, especially those acting as anti-influenza.



Mengyao Liu is a graduate of UC Berkeley majoring in Molecular Cell Biology B.S. She has been with the Feeley-Liu Lab for 3 years and specializes in tissue engineering, tissue culture, and genetic analysis. She runs the basic science and cell culture group and serves as a mentor for the junior investigators in the lab. Currently, she is in her second year of MPS program at California Northstate University.



Abdelbasset Farahat is an Assistant Professor of Pharmaceutical and Medicinal Chemistry in the Department of Pharmaceutical and Biomedical Sciences, Master of Pharmaceutical Sciences at California Northstate University. In 2002, Dr. Farahat received a Bachelor of Pharmacy from Mansoura University Egypt, and then in 2006, he received a Master of Pharmaceutical Sciences from Mansoura University. In 2010 Dr. Farahat received his Ph.D. in Medicinal Chemistry after research at Georgia State University, Atlanta, GA, USA under the supervision of Prof. David W. Boykin. His Ph.D. research focused on the design and synthesis of dicationic compounds to be used as antimalarial and antitrypanosomal agents. In 2011, Dr. Farahat joined the Faculty of Pharmacy, Mansoura University as Assistant Professor. In 2012 he joined Boykin's laboratory at Georgia State University, Atlanta, GA as a Postdoctoral researcher, then research scientist and team leader. In 2018 Dr. Farahat joined Kennesaw State University as Assistant Professor of Medicinal Chemistry. In 2018 Dr. Farahat was awarded The Encouragement State Prize in Medical Sciences from the Academy of Scientific Research and Technology, Egypt. Dr. Farahat has published 69 publications in high impact peer-reviewed journals and is an inventor of three patents.

Dr. Farahat's research focuses on medicinal chemistry and synthetic organic chemistry projects. The focus is primarily on targeting the DNA minor-groove as an approach for antiparasitic drug discovery. This work is mostly directed towards the discovery of antimalarial, antitrypanosomal, antileishmanial, antinaeplerial and antiacanthamoebal drugs. More recently his research has turned to developing heterocyclic dications for DNA minor groove binding which induce topological effects, binding into either the major or minor grooves in specific parasitic sequences to generate a new mode of therapeutic activity.

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