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Synthesis and anti-influenza activity of five member heterocycles containing compounds: a mini review

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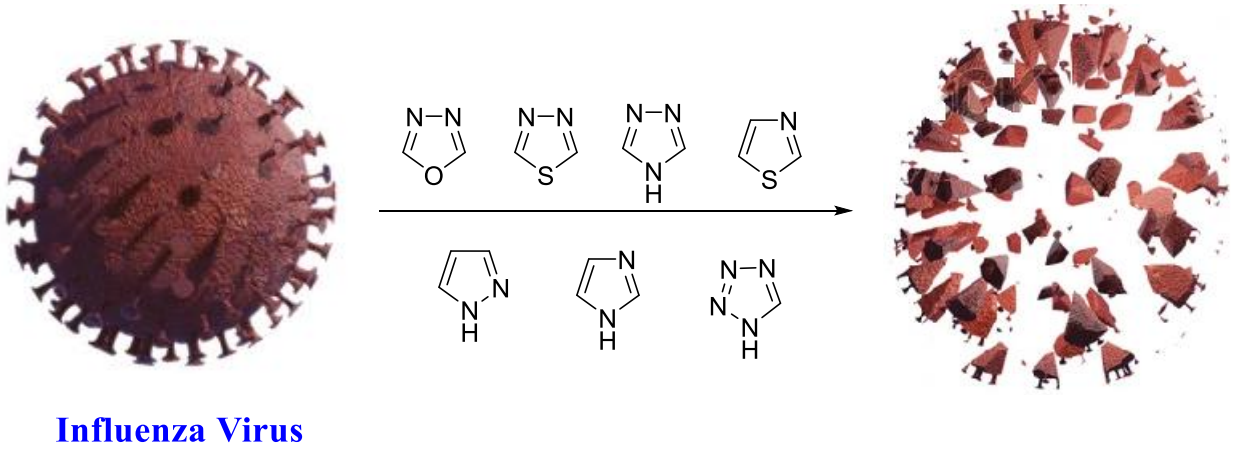
Abstract

This survey covers the literature data published on the chemistry of synthesis of five membered heterocycles containing compounds that show anti-influenza activity. Furthermore, we made a brief review of the anti-influenza activity of these compounds. We believe that this review will be a useful resource for researchers working on developing of anti-influenza agents.



Keywords: Anti-influenza, five members heterocycles, biological activity, thiazoles, oxazoles

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1. Introduction

Influenza is a viral infection caused by various strains of the influenza virus, characterized by a highly contagious, acute respiratory syndrome. It usually presents in a mild form which clears after 3–6 days, but it can also lead to other secondary infections or present in more severe forms, such as pneumonia or acute respiratory distress syndrome, which can be fatal if not treated, particularly in elderly patients. [1-4]
Seasonal influenza is characterized by a sudden onset of fever, cough, headache, muscle and joint pain, severe malaise, sore throat, and a runny nose. Most people recover from fever and other symptoms within a week without requiring medical attention. But influenza can cause severe illness or death especially in people at high risk. Hospitalization and death occur mainly among high-risk groups such as children, elderly patients, patients with chronic respiratory diseases, and pregnant women. Worldwide, these epidemics are estimated to affect 5%–10% of the world's population every year, producing about 3 to 5 million cases of severe illness, and about 290 000 to 650 000 respiratory deaths.[5]

Preventing both the disease and complications can be achieved by vaccination. If treatment with antivirals is administered without delay, the risk of severe complications can be reduced; however, many virus strains develop high resistance and current drugs lose efficacy, so recently, there has been great interest in developing new remedies for combating influenza.[5,6]

Five-membered heterocyclic compounds have shown a wide range of biological activities,[7] namely thiadiazoles, thiazoles, 1,3,4-oxadiazoles, triazoles,[8-21] in addition to the benzimidazole ring.[22] They have been used as scaffolds for the synthesis of a wide range of agents with versatile activities including antibacterial,[23,24] antifungal,[25,26] analgesic, anti-inflammatory,[17] anticancer[27,28] and antihypertensive activity.[29]

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 antiviral research.[30-36]

Many anti-influenza drugs contain five-membered heterocyclic rings in their structure (Figure 1). Nucleozin contains oxazole ring.[37] A loading dose and short-term administration of oral ribavirin significantly improved symptoms and signs of influenza type A or B infection,[38] ribavirin contains triazole ring in its structure. Viramidine, the 3-carboxamidine derivative of ribavirin, is effective against a spectrum of influenza A and B and it also contains triazole moiety in its structure.[39] Verdinexor, a triazole containing drug is a selective inhibitor of nuclear export, reduces influenza A virus replication *in vitro* and *in vivo*.[40] Originally developed and commercialized as an antiprotozoal agent, Nitazoxanide was later identified as a first-in-class broad-spectrum antiviral drug and has been repurposed for the treatment of influenza.[41]

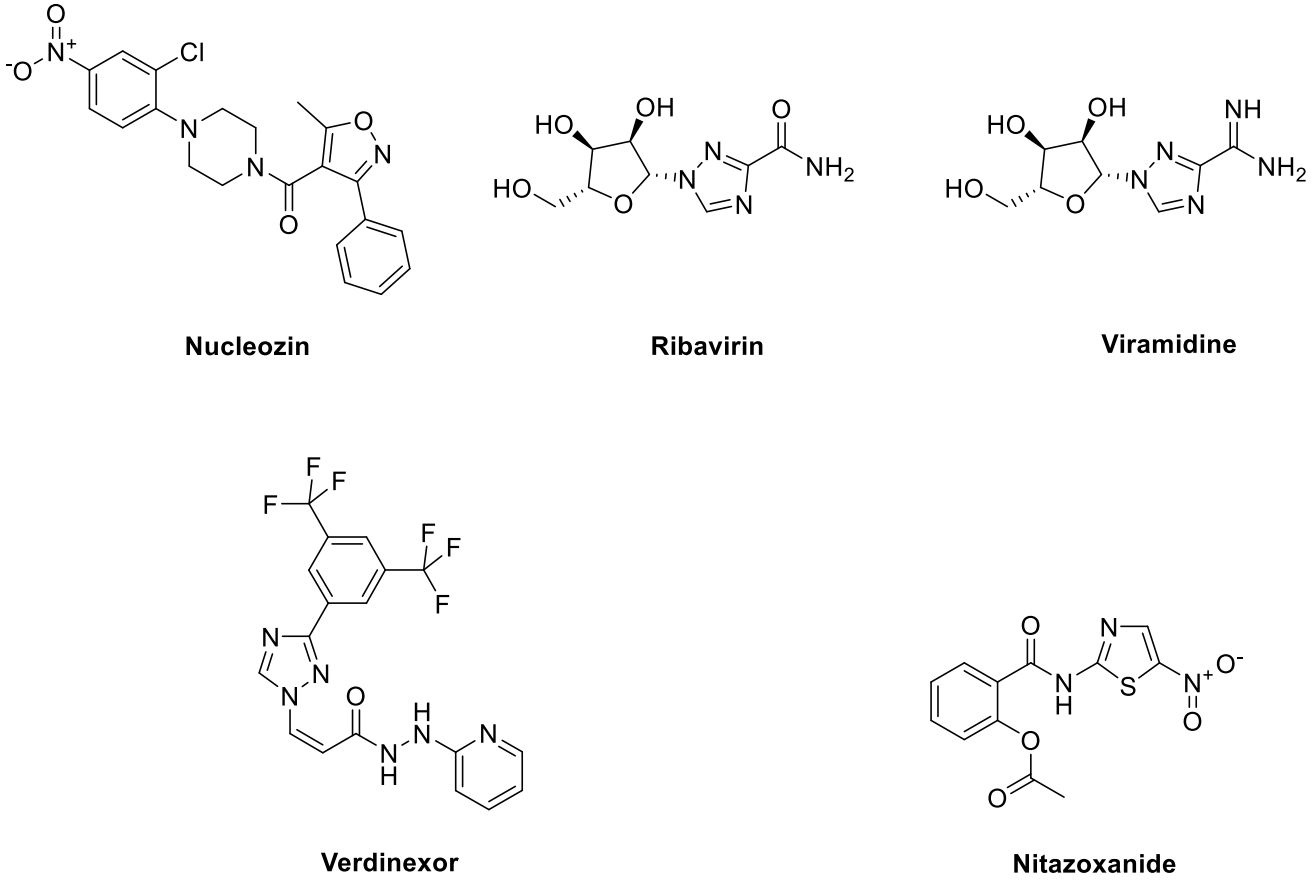
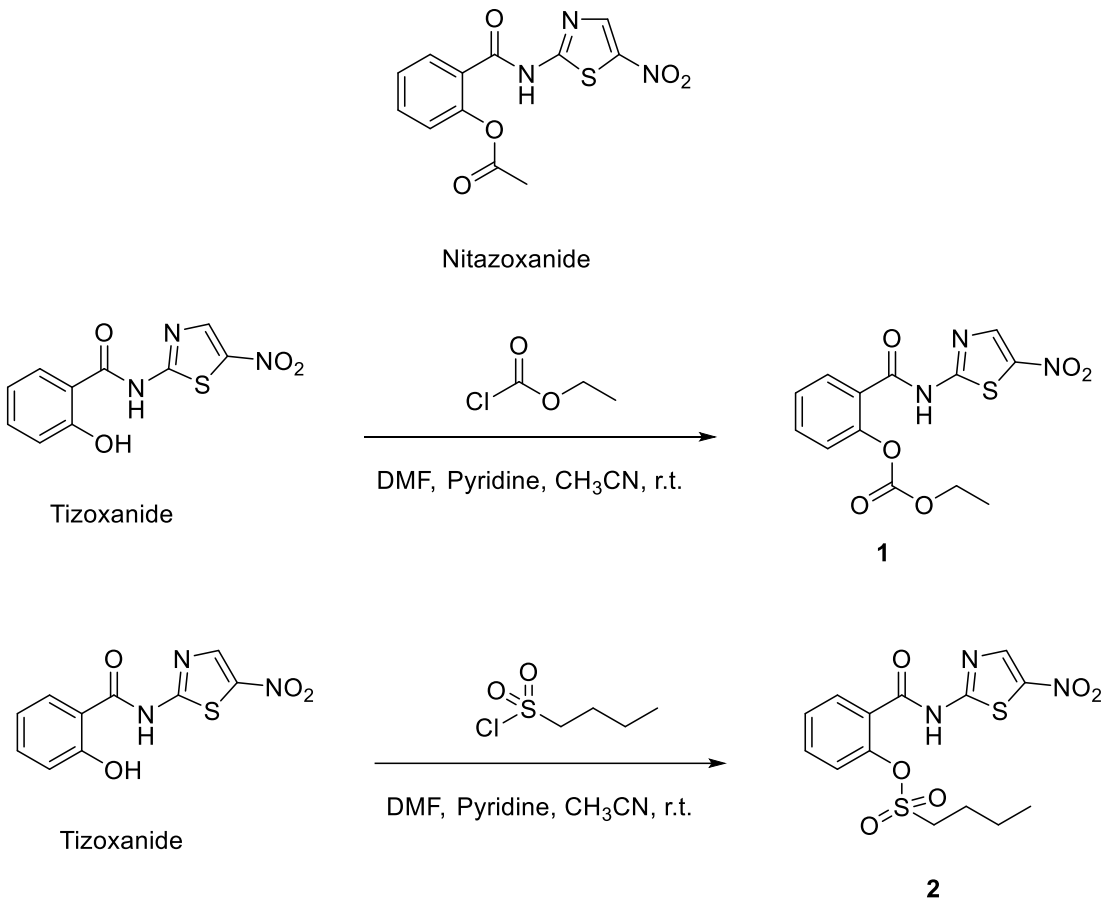


Figure 1. Anti-influenza drugs containing five-member heterocyclic rings.

This review article describes the synthesis and pharmacological activity of new medications under study that contain five-membered heterocyclic rings and show potential benefits in the treatment of influenza.

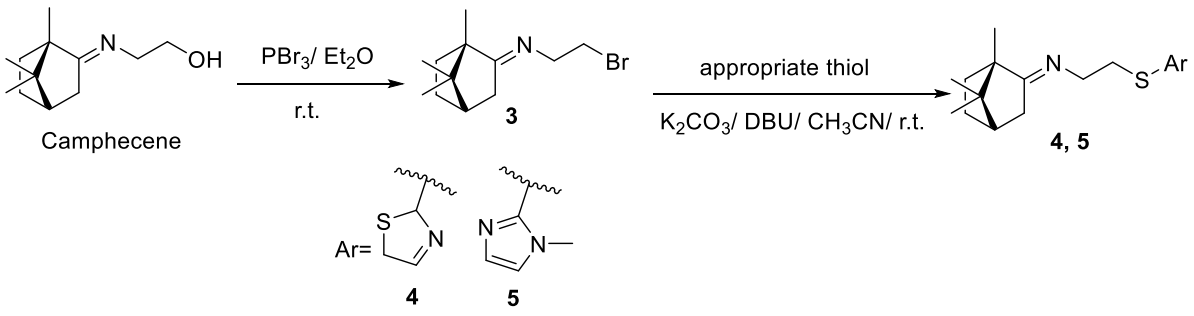
2. Thiazoles

In 2020, Zhao *et al*. reported a series of novel thiazoles derived from an FDA-approved drug, nitazoxanide, (Scheme 1) with antiviral activity against influenza and a broad range of viruses. The preferred candidates compounds **1** and **2** showed significantly enhanced anti-influenza virus potentials, with 10-fold improvement compared to results with nitazoxanide, and were effective against a variety of influenza virus subtypes including oseltamivir-resistant strains. Notably, the combination using compounds **1**, **2** and oseltamivir carboxylate or zanamivir displayed synergistic antiviral effects against oseltamivir-resistant strains. Compound **1** was made by coupling of ethyl chloroformate and tizoxanide in *N,N*-dimethyl acetamide and CH_3CN, while compound **2** was formed as coupling product of 1-butanesulfonyl chloride and tizoxanide in tetrahydrofuran as shown in Scheme **1**.[42]



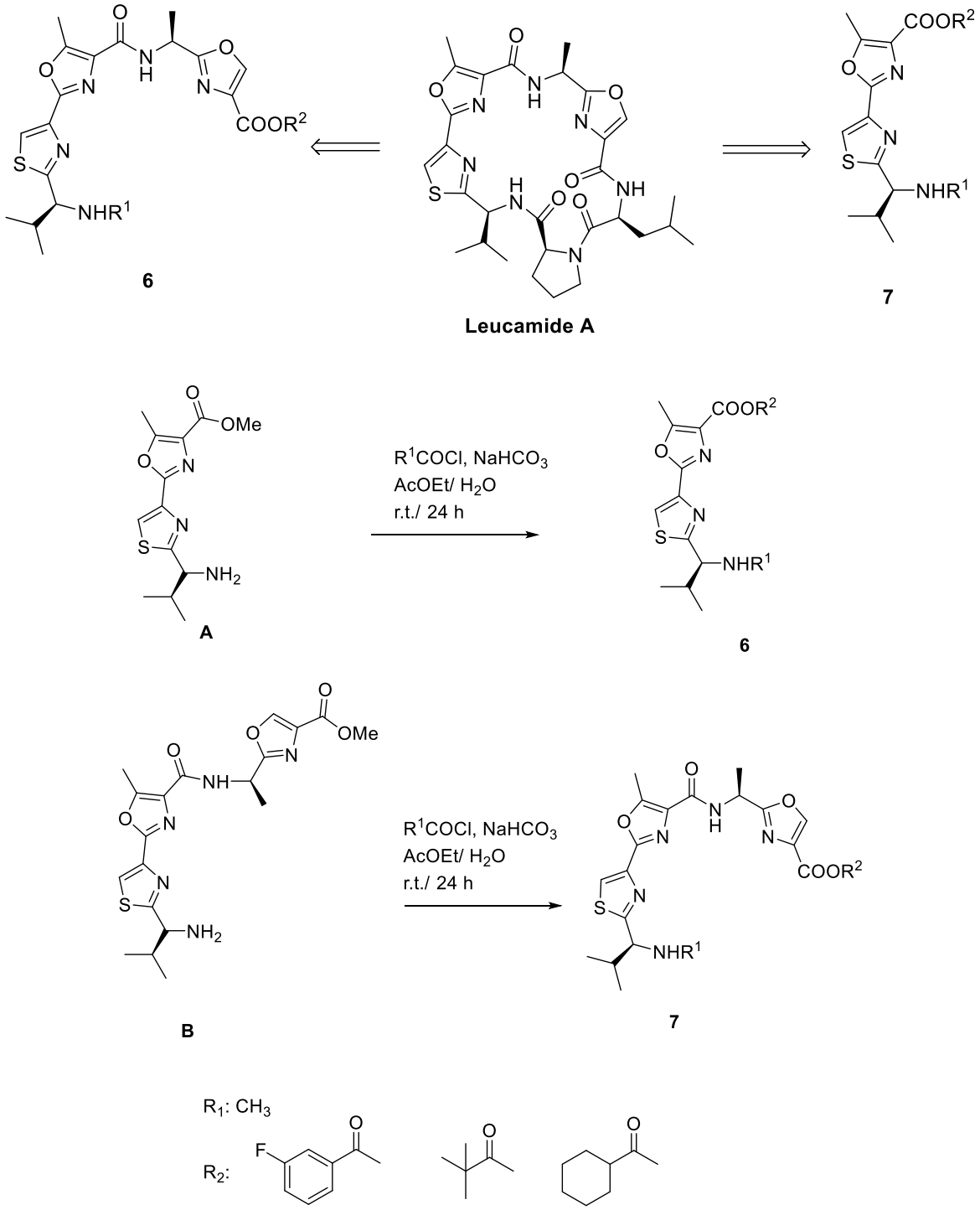
Scheme 1

In 2019, Yarovaya *et al.* synthesized a series of novel camphecene analogues including the introduction of heterocyclic moieties in place of the terminal hydroxyl group of camphecene. All compounds were tested for cytotoxicity and antiviral activity against influenza virus A/Puerto Rico/8/34 (H1N1) in MDCK cells. Among the tested compounds, compounds **4, 5** demonstrated high antiviral activity, with compound **4** showing much less cytotoxicity than other synthesized compounds. Scheme **2** shows the synthesis of the target compounds, where camphecene was treated with phosphorous bromide (PBr_3) in diethyl ether to produce the bromo intermediate **3** that was used directly in further reactions. Key compounds **4, 5** were prepared by nucleophilic substitution of secondary thiols with the bromo compound **3** in the presence of potassium carbonate and 1,8-diazabicyclo[5,4,0]undec-7-ene (DBU) in acetonitrile as a solvent.[43]



Scheme 2

Wang reported the synthesis of a series of novel 4,2-bisheterocycle tandem simplified derivatives of the cytotoxic heptapeptide compound Leucamide A, consisting of a methyloxazole and thiazole subunits. Many of these simplified compounds were found to effectively inhibit the human influenza A virus. Several analogues exhibited moderate biological activity and could serve as leads for further optimizations for antiviral research. Compounds **A** or **B** were treated with acyl chloride to afford the target compounds **6** and **7** as scheme **3** shows.[44]

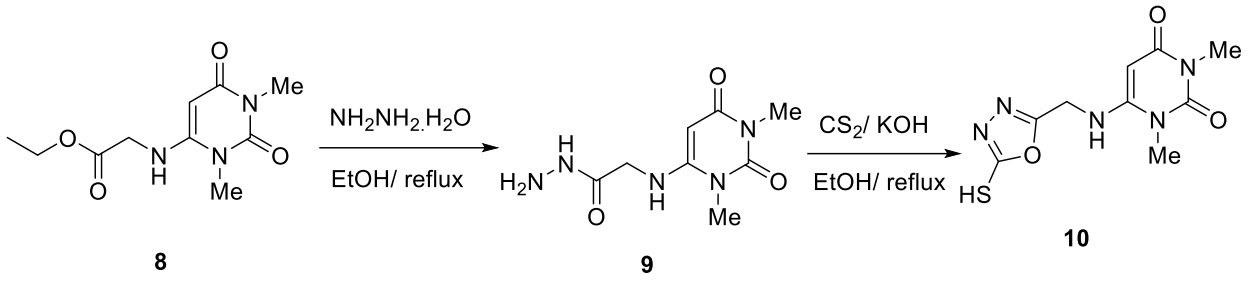


Scheme 3

3. Oxadiazoles

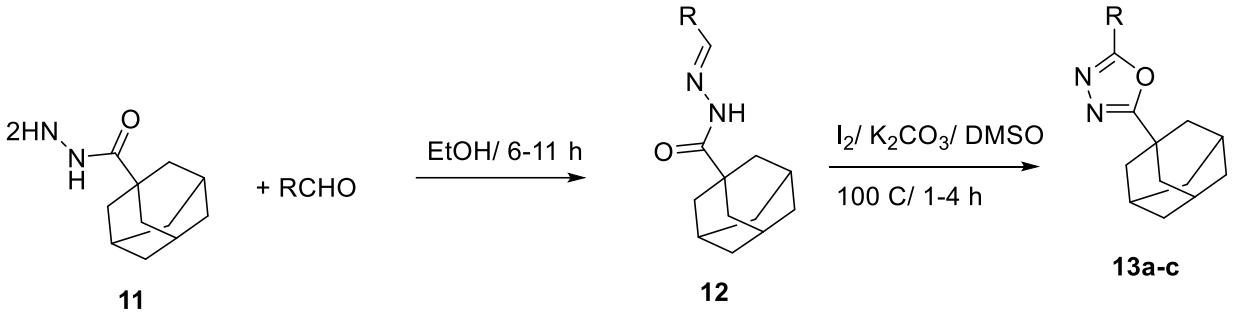
Oxadiazole-linked heterocycles showed moderate to strong anti-influenza activity as follows.

Hala *et al.* in 2020 reported the synthesis of new oxadiazole derivatives for exploring their activity against avian influenza. The reaction of the acid hydrazide **9** with carbon disulfide in presence of potassium hydroxide in ethanol afforded the oxadiazole derivative **10** which showed moderate antiviral activity against avian influenza virus H5N1.[45]



Scheme 4

In 2018, Silverstova *et al.* synthesized two series of new adamantyl derivatives of oxadiazole and triazole; 2-(adamantan-1-*yl*)-5-aryl-1,3,4-oxadiazoles and 2-(adamantan-1-*yl*)-5-aryl-2*H*-tetrazoles. *In vitro* biological studies have shown high inhibitory activity of some of the synthesized compounds against H1N1 influenza A viruses. A mixture of the corresponding aldehyde and the hydrazide **11**, was refluxed to produce the intermediate hydrazone **12**. Iodine and potassium carbonate were added to the hydrazone **12** and the reaction mixture was refluxed to produce the final oxadiazole-linked adamantane **13a-c**.[46]

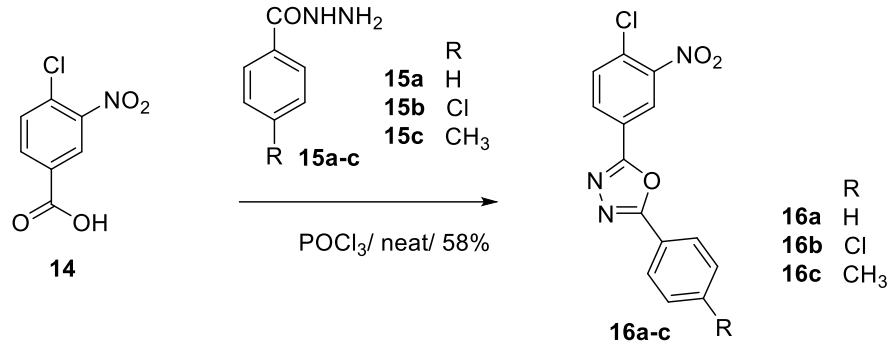


13a R= phenyl
13b R= naphthalen-1-yl
13c R= anthracen-9-yl

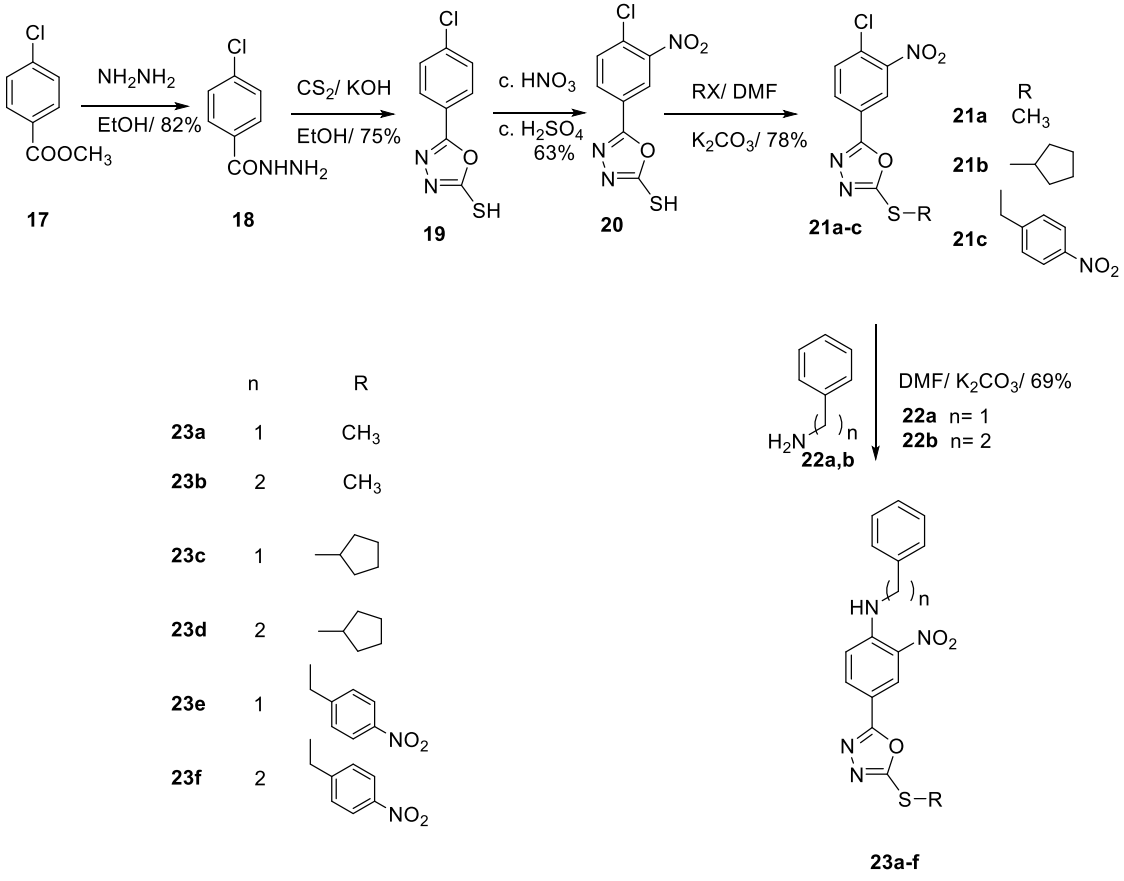
Scheme 5

We have reported a novel series of oxadiazole-based scaffolds that were evaluated *in vitro* against the highly pathogenic influenza H5N1. Four compounds **16b,c, 23b,e** showed excellent anti-influenza activity with the oxadiazole derivative having *p*-tolyl at position 5 of the oxadiazole **16c** being the most active showing 100% inhibition at 100 µg/µl with an IC50= 39 µg/µl. The oxadiazole derivatives **16a-c** were synthesized through cyclization of the acid **14** to the final oxadiazole after heating with different acid hydrazides in phosphorus oxychloride as in scheme **6**.[47]

Scheme **7** shows the synthesis of the oxadiazoles **23a-f** starting with the ester **17** that was produced by esterification of 4-chlorobenzoic acid, then reaction with hydrazine hydrate to furnish the acid hydrazide **18**. The produced acid hydrazide was cyclized by refluxing with CS_2/ KOH in ethanol to afford the 2-thiooxadiazole derivative **19** which underwent nitration using a mixture of concentrated HNO_3 and concentrated H_2SO_4 furnishing the nitro compound **20** in good yield (68%). Alkylation of the produced nitro compound **20** with various alkyl halides in DMF and in presence of K_2CO_3 at room temperature produced compounds **21a-c**. These compounds were further aminated using benzyl or phenethylamine to obtain compounds **23a-f**.



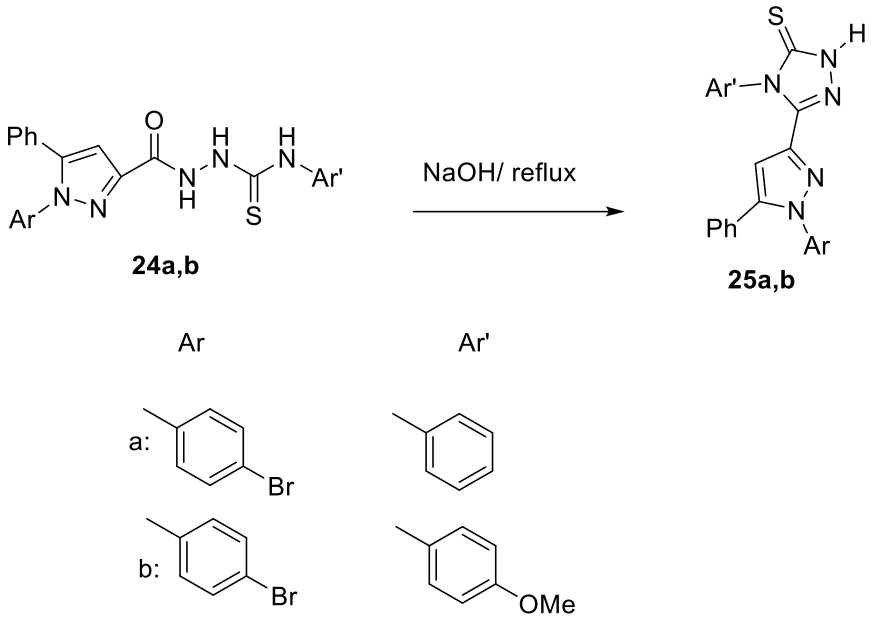
Scheme 6



Scheme 7

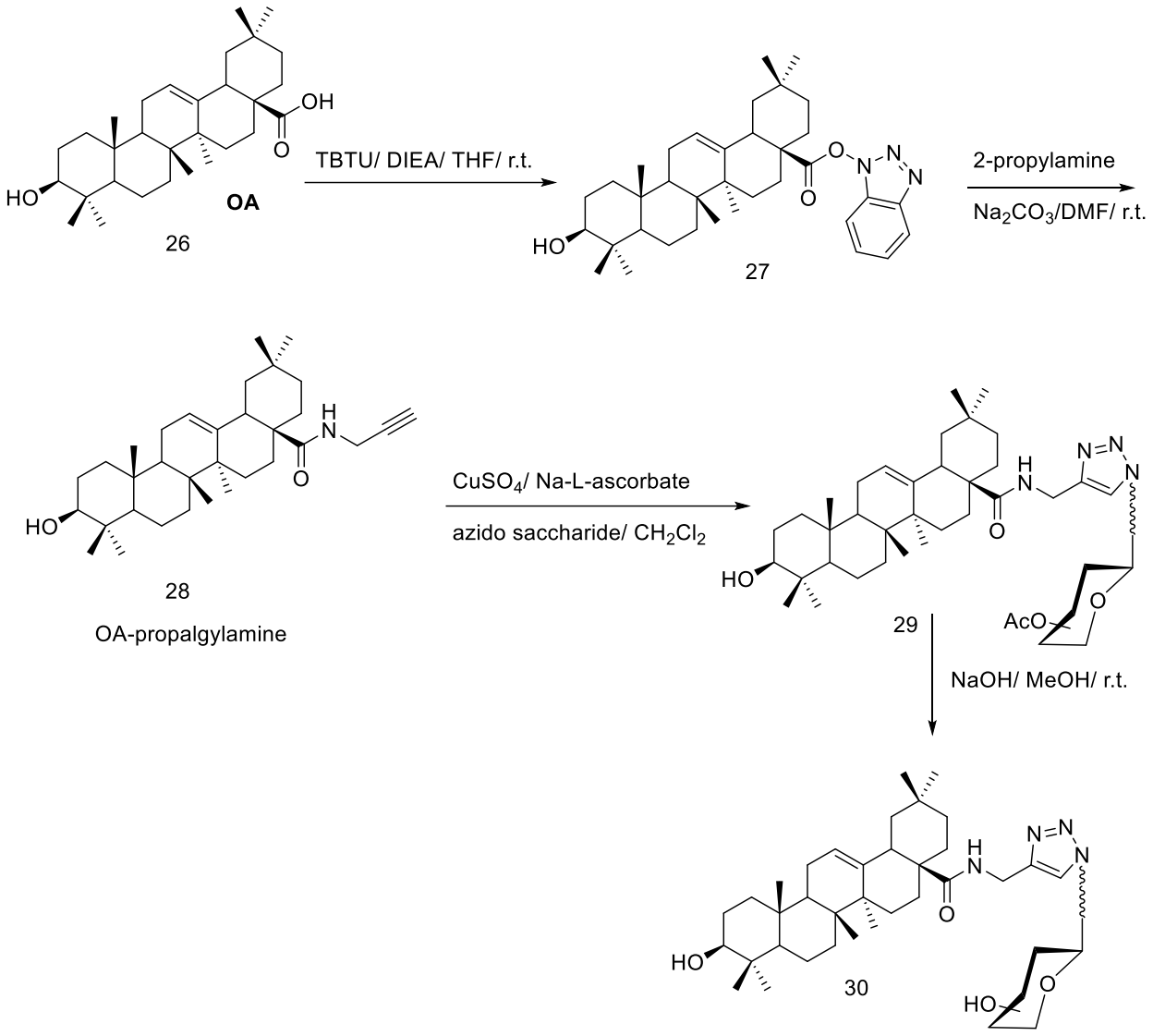
4. Triazoles

In 2013, Flefal *et al.* used 3-[2-(4-bromphenyl)hydrazono]-5-phenyl-furan-2(3*H*)-one for preparation of some novel pyrazole, pyridazinone, oxadiazole, triazole, thiazolidine, and thioxopyrimidine derivatives. Ring closure of thiosemicarbazides **24a,b** using sodium hydroxide solution led to the formation of the corresponding triazolthiones **25a,b**. These two compounds were tested for anti-avian influenza virus activity and revealed remarkable antiviral activity against the H5N1 virus.[48]



Scheme 8

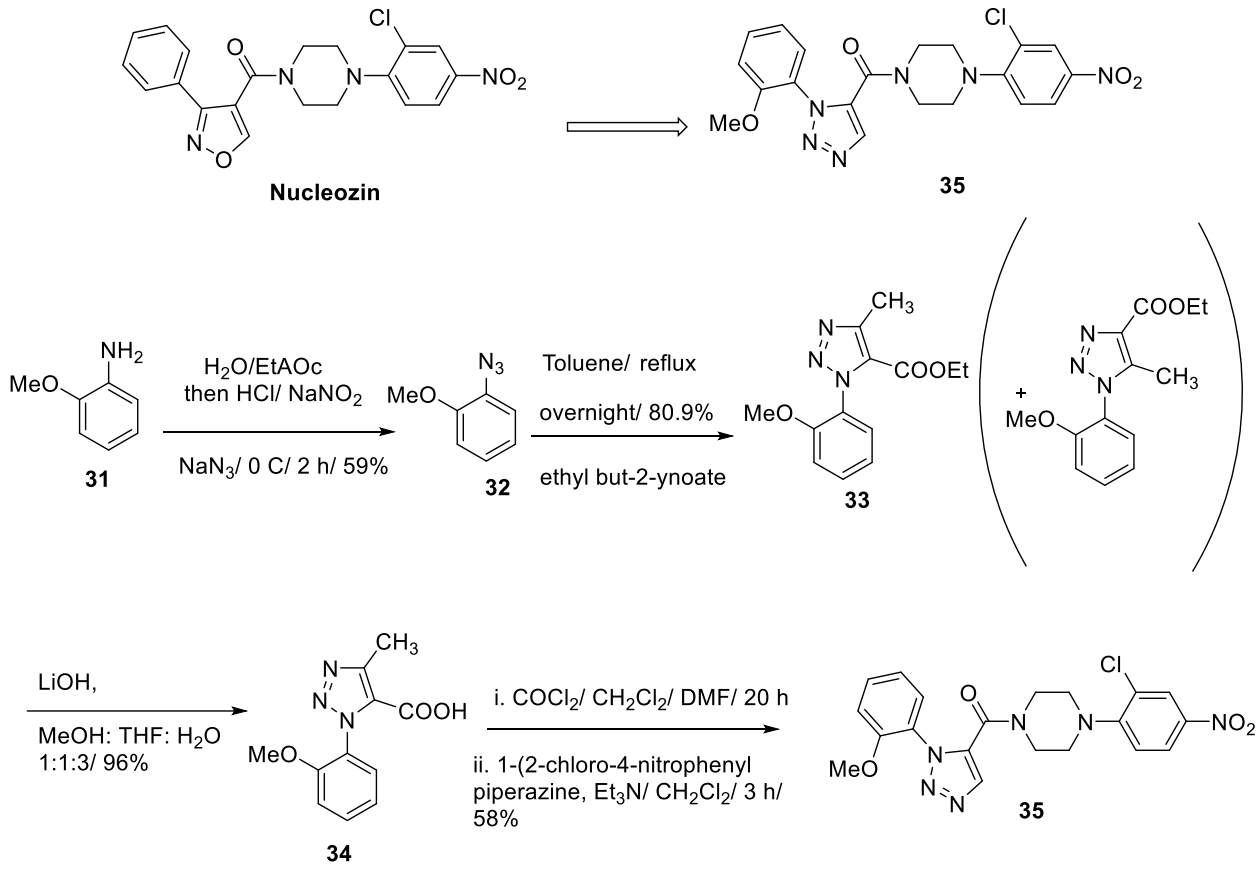
It is well known that the development of entry inhibitors is a promising approach to the inhibition of the influenza virus. In 2019, Yangging *et al.* used oleanolic acid (OA) which was discovered as a mild influenza hemagglutinin (HA) inhibitor. Herein, as a further study, they reported the preparation of a series of OA-saccharide conjugates via the CuAAC reaction, and the anti-influenza activity of these compounds was evaluated *in vitro*. Among them, compound **30**, an OA-glucose conjugate, showed a significantly increased anti-influenza activity with an IC50 of 5.47 μM, and no obvious cytotoxic effect on MDCK cells was observed at 100 mM. Hemagglutination inhibition assay and docking experiment indicated that compound **30** might interfere with influenza virus infection by acting on HA protein. Broad-spectrum anti-influenza experiments showed **30** to be robustly potent against five different strains, including influenza A and B viruses, with IC50 values at the low micromolar level. Overall, this finding further extends the utility of OA-saccharide conjugates in anti-influenza virus drug design.[49]



Scheme 9

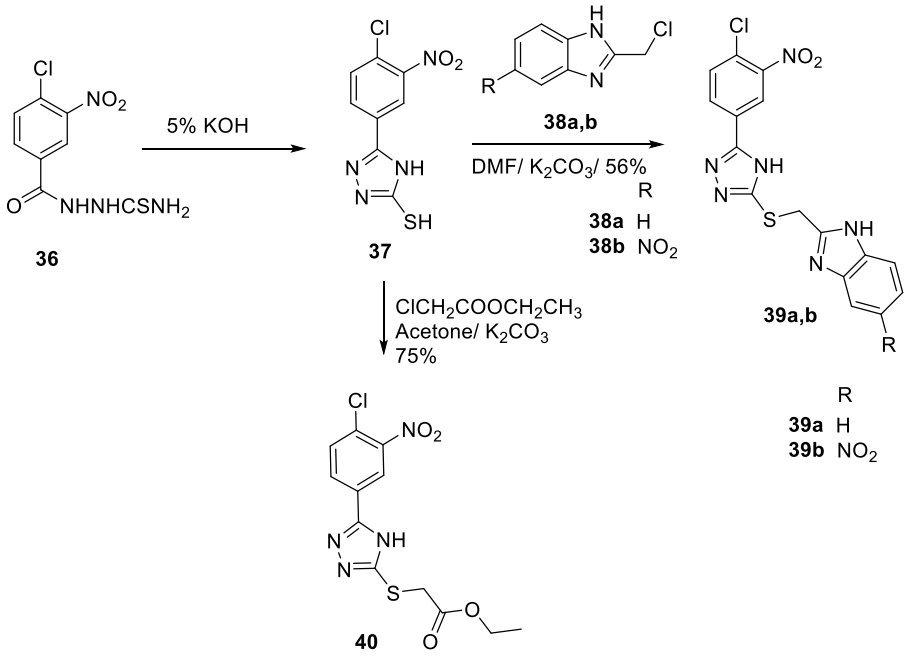
The influenza virus nucleoprotein (NP) is a perfect target for anti-influenza drug research Nucleozin and its related derivatives were found to act as NP inhibitors showing anti-influenza activity. Utilizing Nucleozin as a lead molecule, Huimin *et al.* in 2012 successfully designed and synthesized a series of 1*H*-1,2,3-triazole-4-carboxamide derivatives as new anti-influenza A virus agents. The most potent compound **35** inhibited the replication of various H3N2 and H1N1 influenza A virus strains. Further computational studies and mechanism investigation approved that compound **35** can directly target nucleoprotein of influenza A virus to inhibit its nuclear accumulation. The synthetic pathway of compound **35** is illustrated in scheme **10**.[50]

In our search for effective anti-influenza agents, we synthesized a series of triazole-linked heterocycles, the newly synthesized compounds were tested for their activity against the highly pathogenic avian influenza virus H5N1. The new compounds showed moderate to excellent antiviral activity.



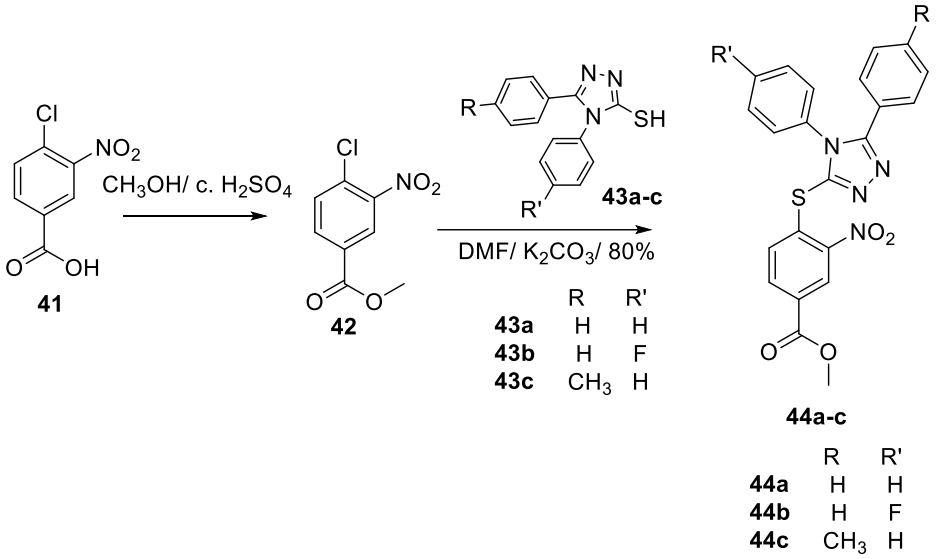
Scheme 10

Scheme **11** describes the synthesis of the triazole derivatives **39a,b** and **40**. Compound **36** was cyclized to the thiotriazole derivative **37** after refluxing with 5% KOH solution. The intermediate thiol was further alkylated either with 2-chloromethyl benzimidazole derivatives **38a,b** to afford the benzimidazole derivatives **39a,b** or with ethyl chloroacetate furnishing the thioester triazole derivative **40**.[47]



Scheme 11

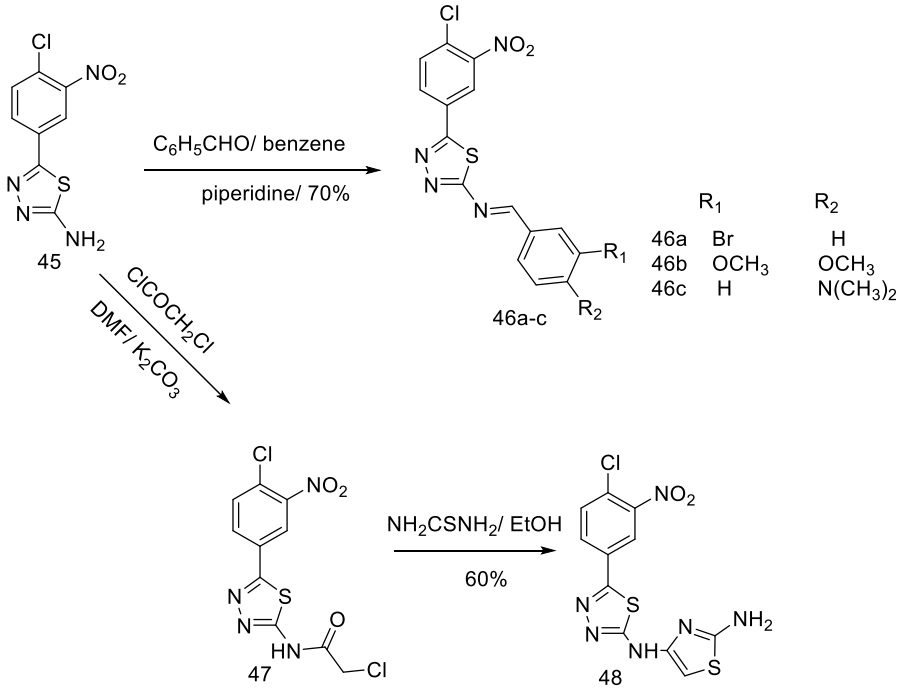
Scheme **12** outlines the synthesis of triazole derivatives **44a-c**. The ester **42** which was prepared by reaction of 4-chloro-3-nitrobenzoic acid **(41)** with methanol/ concentrated H_2SO_4 was further reacted with the triazole derivatives **43a-c** in presence of K_2CO_3 in DMF to obtain the triazoles **44a-c**.



Scheme 12

5. Thiadiazoles

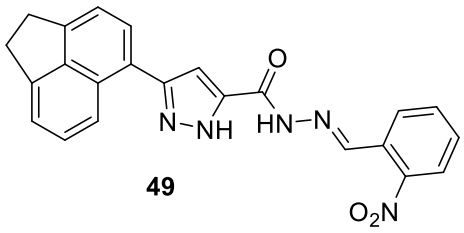
The thiadiazole derivatives synthesized by our group were tested for their activity against avian influenza and showed excellent activity.[47]



Scheme 13

6. Pyrazoles

While in the medicinal chemistry field, only limited reports have appeared involving the study of the anti-influenza activity of the pyrazole-containing compounds. Shin *et al.* searched for novel anti-influenza inhibitors using a cell-based neutralization assay. After screening 20,800 randomly selected compounds, they found that BPR1P0034 (figure 2) has sub-micromolar antiviral activity. Lead optimization and a structure-activity analysis were used to improve potency. Time-of-addition assay was performed to target an event in the virus life cycle. BPR1P0034 is the first pyrazole-based anti-influenza compound ever identified and showed potent (sub-μM) antiviral activity, which offers an opportunity for the development of a new anti-influenza virus agents.[51]



49

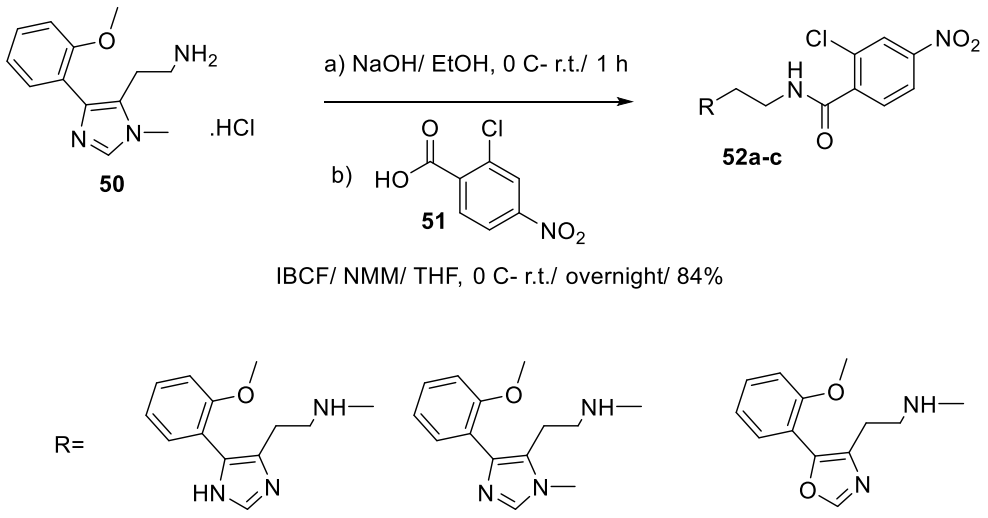
BPR1P0034

Figure 2. BPR1P0034, the pyrazole derivative with anti-influenza activity.

7. Imidazoles

In 2015, Wang *et al.* designed and synthesized a series of new substituted phenyl-coupled heterocyclic ethyl amide derivatives as anti-influenza agents. The activities of these compounds were investigated and compared to those of the commercial antiviral drugs (Arbidol and Ribavirin) against influenza. Among these new compounds exhibiting moderate levels of antiviral activity against influenza A, compounds **52a**-**c** are the most effective ones, and are as efficacious as the positive control Ribavirin and even much more effective than Ingavirin and Arbidol, indicating that they can be lead candidates for further exploration. These results are also consistent with the docking study results in terms of the design of compounds targeting influenza A *via* viral nucleoprotein.

The synthesis of the target compounds is shown in scheme **14**. To the heterocyclic ethylamine hydrochloride, a solution of NaOH was added in ethanol and stirred at room temperature for 1 h. After filtration, the filtrate was evaporated to dryness and redissolved in THF. 2-Chloro-4-nitrobenzoic acid and IBCF were stirred in an ice bath for 30 minutes and followed by the addition of the corresponding free amine in THF, and NMM was added, successively, stirred overnight to obtain the target compounds.[52]



Scheme 14

8. Tetrazoles

Hit compounds with anti-influenza virus activity were selected by *in silico* screening and tested to determine their anti-influenza virus activities via cell-based screening. Potent compounds with anti-influenza virus activities (MIC value <20µM) containing tetrazole moiety are shown in figure 3.[53]

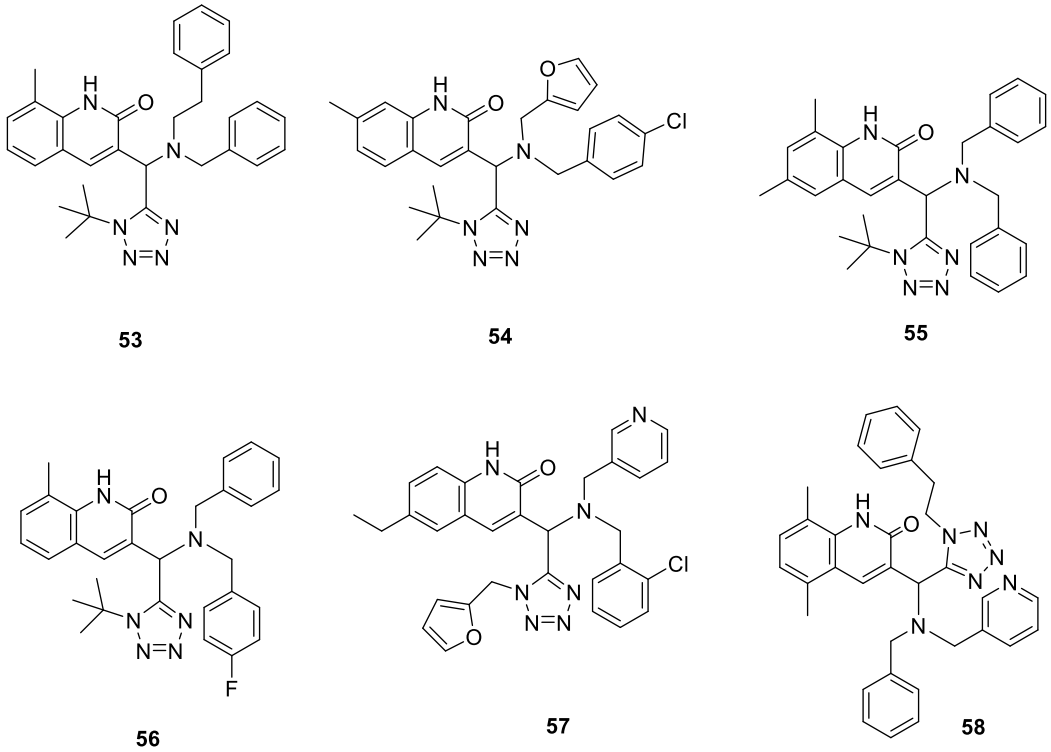


Figure 3. Tetrazole containing compounds with potent anti-influenza activity.

9. Conclusions

This review covers the literature data, best to our knowledge, that study the chemistry of synthesis of compounds, medications under study and drugs that contain five membered heterocycles that show anti-influenza activity. Furthermore, we made a brief review of the anti-influenza activity of these compounds. The authors believe that this review will be a useful resource for researchers working on developing of anti-influenza agents.

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