



## REVIEW

### Synthesis, Anticancer and Antiviral Activity Studies of 1,3,4-Oxadiazoles: A Review

K. DEVI<sup>1</sup>, A. SRINIVASA RAO<sup>1,\*</sup>, Y. RAJENDRA PRASAD<sup>1</sup>, K. RAJU<sup>2</sup> and D. GEETA MOUNIKA<sup>1</sup>

<sup>1</sup>Shri Vishnu College of Pharmacy (Autonomous), Affiliated to Andhra University, Bhimavaram-534202, India

<sup>2</sup>AU College of Pharmaceutical Sciences, Andhra University, Visakhapatnam-530003, India

\*Corresponding author: E-mail: drasrpharma@gmail.com; drasr@svcp.edu.in

Received: 18 August 2021;

Accepted: 11 October 2021;

Published online: 14 February 2022;

AJC-20676

1,3,4-Oxadiazole is a five membered heterocyclic nucleus and a versatile lead structure, where its derivatives showed broad and potent biological functions especially as anticancer and antiviral agents which are associated with various mechanisms such as inhibition of different enzymes, kinases and growth factors. The present review summarizes various synthetic procedures and highlights the targeted inhibitory activities of 1,3,4-oxadiazoles as potential anticancer and antiviral agents along with their structure activity relationship. Molecular modeling and pharmacokinetic studies on 1,3,4-oxadiazoles proved a change in their polarity, flexibility and metabolic stability led to their improved biological activity potential. Among all the substituted 1,3,4-oxadiazoles, the mono- and 2,5-disubstituted derivatives showed considerable biological activities especially as anticancer and antiviral agents. Hence, scientists/researchers considered these as future lead molecules to treat cancer and viral infections along with other diseases. In future, the oxadiazole motif is likely to be incorporated in various other therapeutic molecules.

**Keywords:** 1,3,4-Oxadiazoles, Anticancer activity, Antiviral activity.

## INTRODUCTION

Cancer is 2<sup>nd</sup> life threatening and a leading cause of death worldwide after cardiovascular disorders. It is also a genetic disease when mutations that take place in genes lead to uncontrolled cell division. Various anticancer drugs approved by USFDA to treat different cancers [1]. Virus is an obligate intracellular parasite containing a single nucleic acid either RNA or DNA and the encoding viral genome surrounded by protein coat. Viruses are found to be infecting all types of living cells like humans, animals and yeasts; they are reproduced only by infecting a host cell [2].

The heterocyclic systems having 5 and 6-membered rings with hetero atoms like N, O, S, P, Si and B exhibited important biological properties [3,4]. In which, the five membered oxadiazoles having two nitrogen atoms and one oxygen atom with general formula  $C_2H_2N_2O$  showed prominent biological activities [5,6]. The main aim of this review is to describe the various synthetic strategies used, anticancer and antiviral biological activity profiles with their therapeutic targets and structure

activity relationship (SAR) studies reported in the literature till 2020. Many researchers are focusing their attention to explore this 1,3,4-oxadiazole pharmacophore to its multiple potential against several activities as they have exhibited broad spectrum activity. In this regard, oxadiazole motif is likely to be introduced in other therapeutic molecules in future by the researchers across the world as an advancement tool in medicinal chemistry to get new chemical entities.

**Chemistry:** Oxadiazoles classified into four groups according to the position of nitrogen and oxygen atoms *e.g.* (i) 1,2,3-; (ii) 1,2,5-; (iii) 1,3,4-; and (iv) 1,2,4-oxadiazoles (Fig. 1) [7].

The biological activities and the structural modifications suggested that 1,3,4-oxadiazoles are having most potent antiviral and anticancer agents and also these isomers are important bioisosteres of amides and esters [8]. Along with these activities, oxadiazoles also exhibited activities like antibacterial [9], anti-inflammatory [10], hypoglycemic [11], antianxiety [12], antidepressant [13], antiproliferative [14], antifungal [15] and anti-tubercular activity [16]. Oxadiazoles are weak bases due to various effects like inductive and low electron density. 1,3,4-

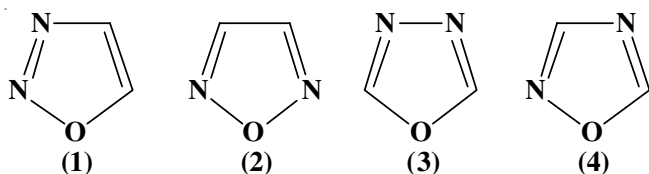
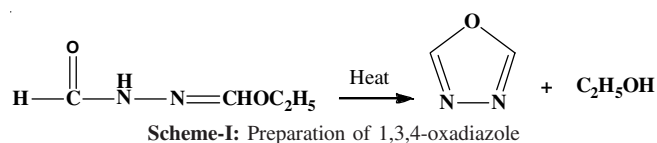


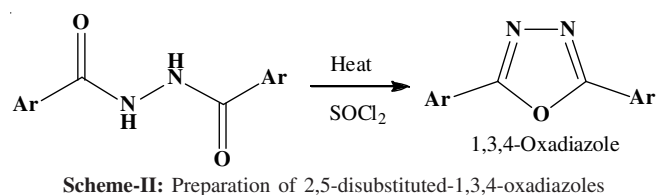
Fig. 1. Various structures of oxadiazoles

oxadiazoles undergo number of reactions like electrophilic, nucleophilic substitution as well as thermal and photochemical reactions [17,18].

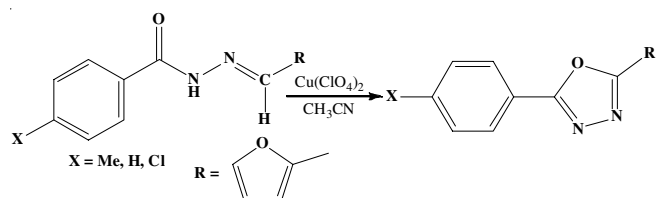
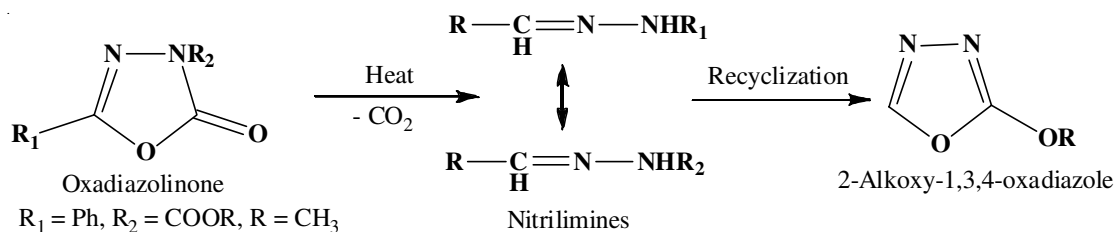
**Synthesis of 1,3,4-oxadiazole:** 1,3,4-Oxadiazole is a liquid with boiling point 150 °C and it was first synthesized by Ainsworth *et al.* [19] in 1965, using thermolysis of ethyl-formate formyl hydrazone at atmospheric pressure (**Scheme-I**).



1,2-Diacylhydrazines contain phenolic hydroxyl groups, reacted in the presence of thionyl chloride to produce 1,3,4-oxadiazole (**Scheme-II**) [20].



In another route, 1,3,4-oxadiazoles can also be formed by reaction of *N*-acyl hydrazones with  $\text{Cu}(\text{ClO}_4)_2$  in  $\text{CH}_3\text{CN}$  by oxidative cyclization [21]. Conversion of  $\text{Cu}^{2+}$  into diamagnetic  $\text{Cu}^+$ , which get stabilized in the presence of  $\text{CH}_3\text{CN}$  produce high potential due to stabilization of  $\text{Cu}^+$  by promoting solvent coordination. Finally  $\text{Cu}^+$  act as oxidant in  $\text{CH}_3\text{CN}$  leads to oxidative cyclization of *N*-acyl hydrazone converts to yield 1,3,4-oxadiazole (**Scheme-III**).

Scheme-III: Oxidative cyclization of *N*-acylhydrazone by  $\text{Cu}^{2+}$  in  $\text{CH}_3\text{CN}$ 

Scheme-IV: Preparation of 2-alkoxy-1,3,4-oxadiazoles

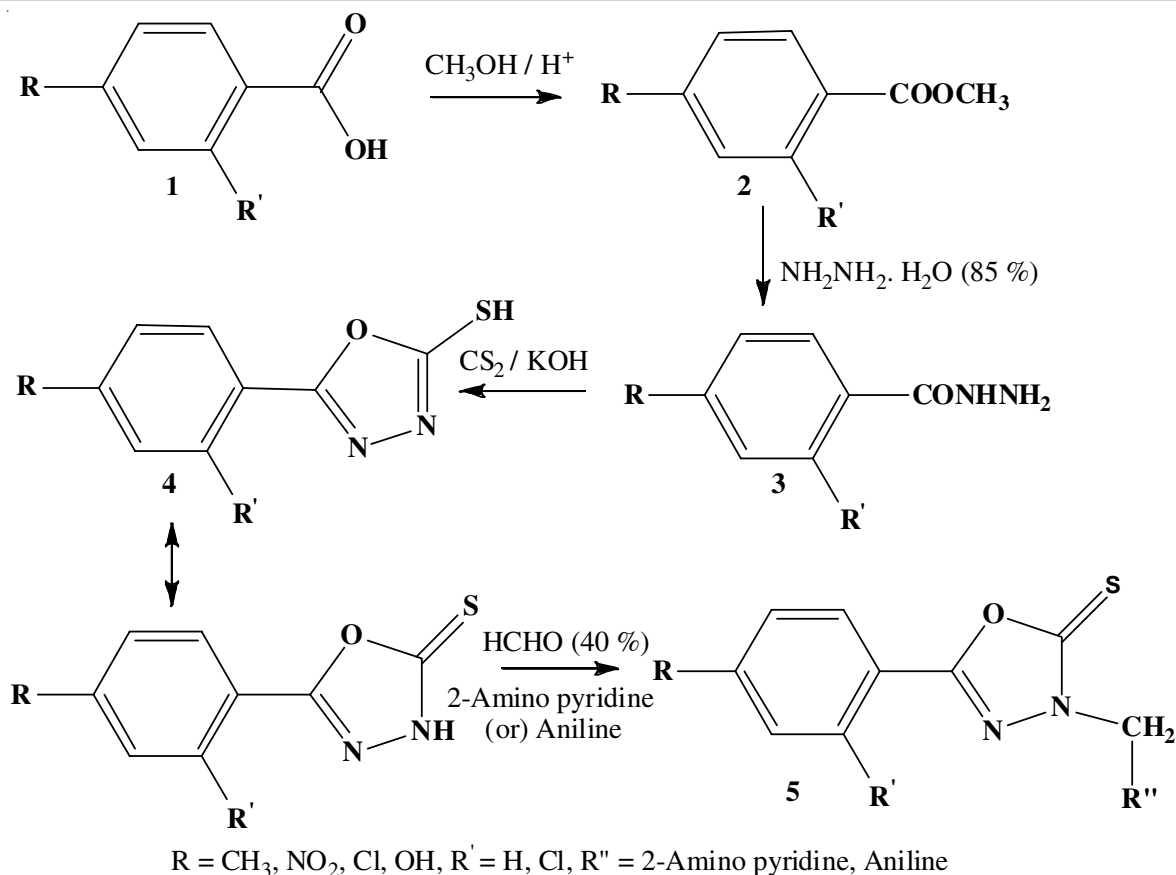
1,3,4-Oxadiazoles are generally thermally stable and the stability was increased by substitution of aryl and perfluoro alkyl groups. Thermal reaction of oxadiazolinones at high temperature results in the loss of carbon dioxide to produce nitrilimines and further recyclization yields 2-alkoxy-1,3,4-oxadiazoles (**Scheme-IV**) [19].

1,3,4-Oxadiazoles synthesized by using aromatic acids get esterified with methanol in the presence of sulfuric acid obtained compound, which was refluxed with hydrazine hydrate in the presence of ethanol to give aroyl hydrazines and further refluxed with  $\text{CS}_2$  and  $\text{KOH}$  in presence of ethanol cyclized to form aryl derivatives of 1,3,4-oxadiazole-2-thiones (**5**) produced with high yield. 1,3,4-Oxadiazoles react with formaldehyde (40%) along with primary amine (2-aminopyridine or aniline) to produce 3,5-substituted aryl derivative of 1,3,4-oxadiazole-2-thiones (**Scheme-V**) [22].

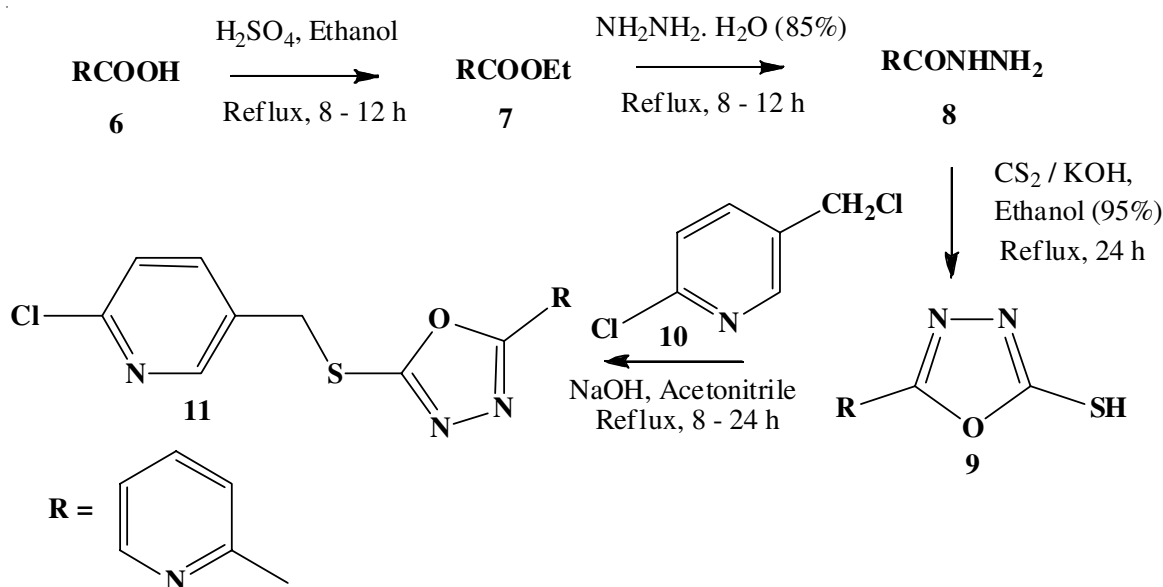
Esterification of carboxylic acids **6** in the presence of ethanol and concentrated sulfuric acid to produce esters **7**. Aroyl hydrazides **8** produced by reaction of esters **7** with 85% of hydrazine monohydrate in presence of ethanol. When aroyl hydrazides **8** reacted with  $\text{CS}_2$  and  $\text{KOH}$  in presence of 95% ethanol under reflux to produce intermediate 1,3,4-oxadiazoles (**9**). Synthesis of 2,5-disubstituted 1,3,4-oxadiazole (**11**) obtained by refluxing compounds **9** with 2-chloro-5-(chloromethyl)-pyridine (**10**) using sodium hydroxide in acetonitrile (**Scheme-VI**) [23].

1,3,4-Oxadiazoles also synthesized using key compound **14**. In first process taking quinoline-2-carboxylic acid in the presence of methanol and concentrated sulfuric acid by reflux produce ester (**12**). When ester **12** was reacted with hydrazine hydrate in ethanol under reflux obtained compound **13** and it gets reacted with  $\text{CS}_2$  and  $\text{KOH}$  in the presence of ethanol gave intermediate compound **14**. This was reacted with primary or secondary amines in presence of formaldehyde in anhydrous ethanol gave compound **15** (**Scheme-VII**) [24,25].

Synthesis of 1,3,4-oxadiazoles done by using different routes of synthesis. The reaction of acyl hydrazides with  $\text{CS}_2$  and  $\text{KOH}$  in ethanol gave 5-substituted-1,3,4-oxadiazole-2-thiol (route A) [26]. Acyl hydrazides when condensed with aliphatic or aromatic acids in presence of dehydrating agents like  $\text{H}_2\text{SO}_4$ ,  $\text{POCl}_3$ ,  $\text{SOCl}_2$  to produce 2,5-diaryl(alkyl)-1,3,4-oxadiazoles (route B) [27]. Dehydrocyclization of acyl semicarbazide ( $\text{X}=\text{O}$ ), acyl thiosemicarbazide ( $\text{X}=\text{S}$ ) and semicarbazone intermediates in the presence of various dehydrating agents like solution of  $\text{I}_2$  in  $\text{KI}$ ,  $\text{I}_2$  in presence of  $\text{NaOH}$ ,  $\text{Br}_2$  in  $\text{CH}_3\text{COOH}$  yields 5-substituted-1,3,4-oxadiazol-2-amines (route C) [28]. 5-Substituted-2-amino-1,3,4-oxadiazoles are



Scheme-V: Synthesis of 1,3,4-oxadiazole-2-thiones



Scheme-VI: Synthesis of 2,5-disubstituted-1,3,4-oxadiazoles

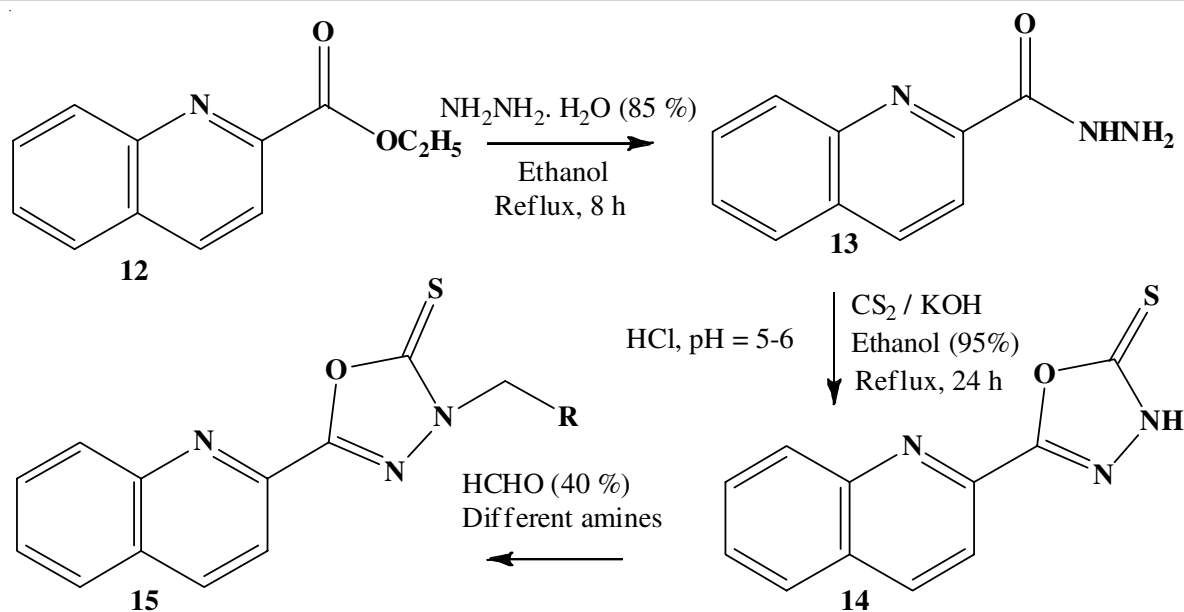
also produced by reacting acyl hydrazides with cyanogen bromide (route D) (Scheme-VIII) [29].

Synthesis of 1,3,4-oxadiazoles are possible using (*N*-isocyanimine)triphenyl phosphorane as starting material *via* intramolecular interaction by using aza-wittig condensation. The acetyl chloride reacted with starting material to produce specific yield of intermediate, and it further reacts with formic acid in

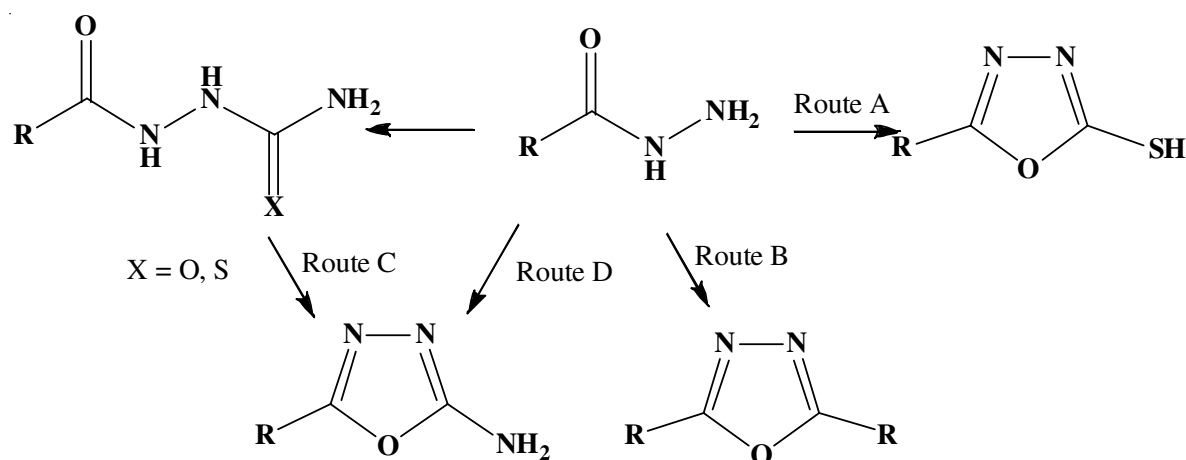
the presence of triethylamine give 1,3,4-oxadiazole derivatives (Scheme-IX) [30].

Another way is Huisgen route useful to synthesize 2,5-disubstituted-1,3,4-oxadiazoles, which includes arylation of 5-aryl tetrazoles (Scheme-X) [31].

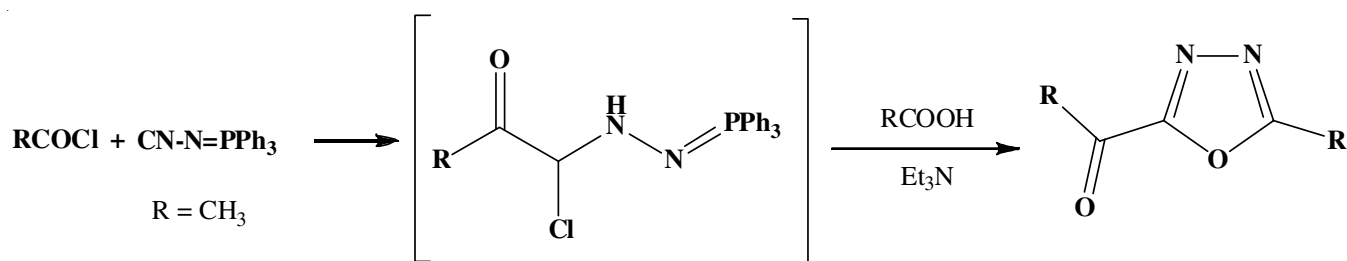
Synthesis of 1,3,4-oxadiazoles (21) is possible from aromatic acid 16. When the aromatic acid 16 esterified produce



Scheme-VII: Synthesis of 2,5-disubstituted-1,3,4-oxadiazol-2-thiones

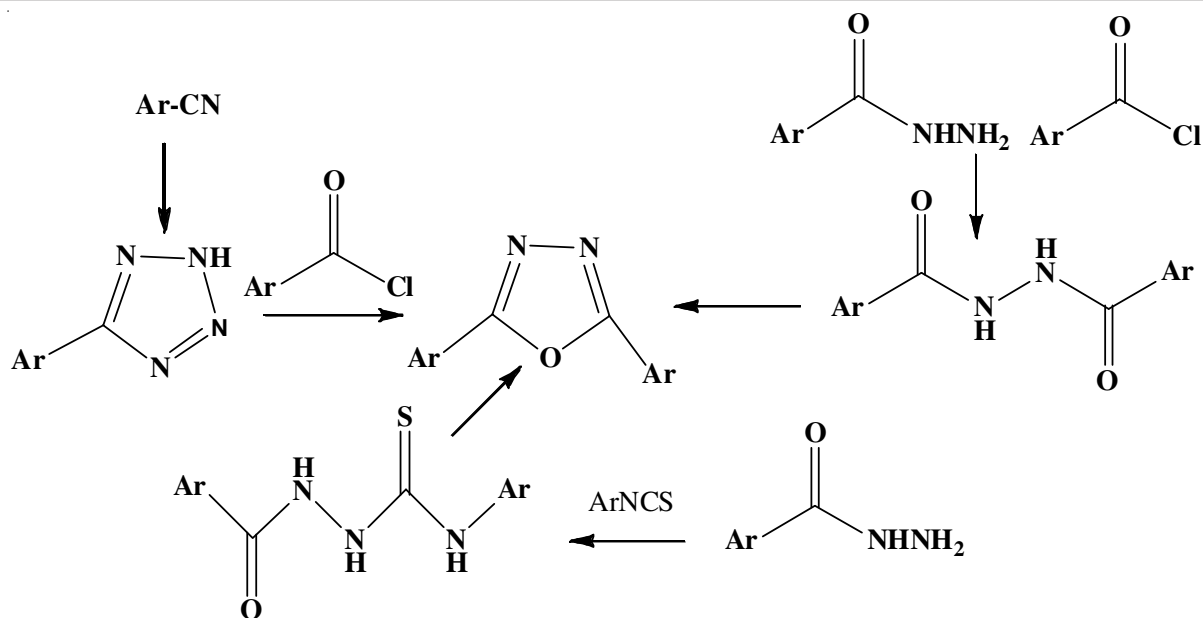


Scheme-VIII: Synthetic route for preparation of 1,3,4-oxadiazoles

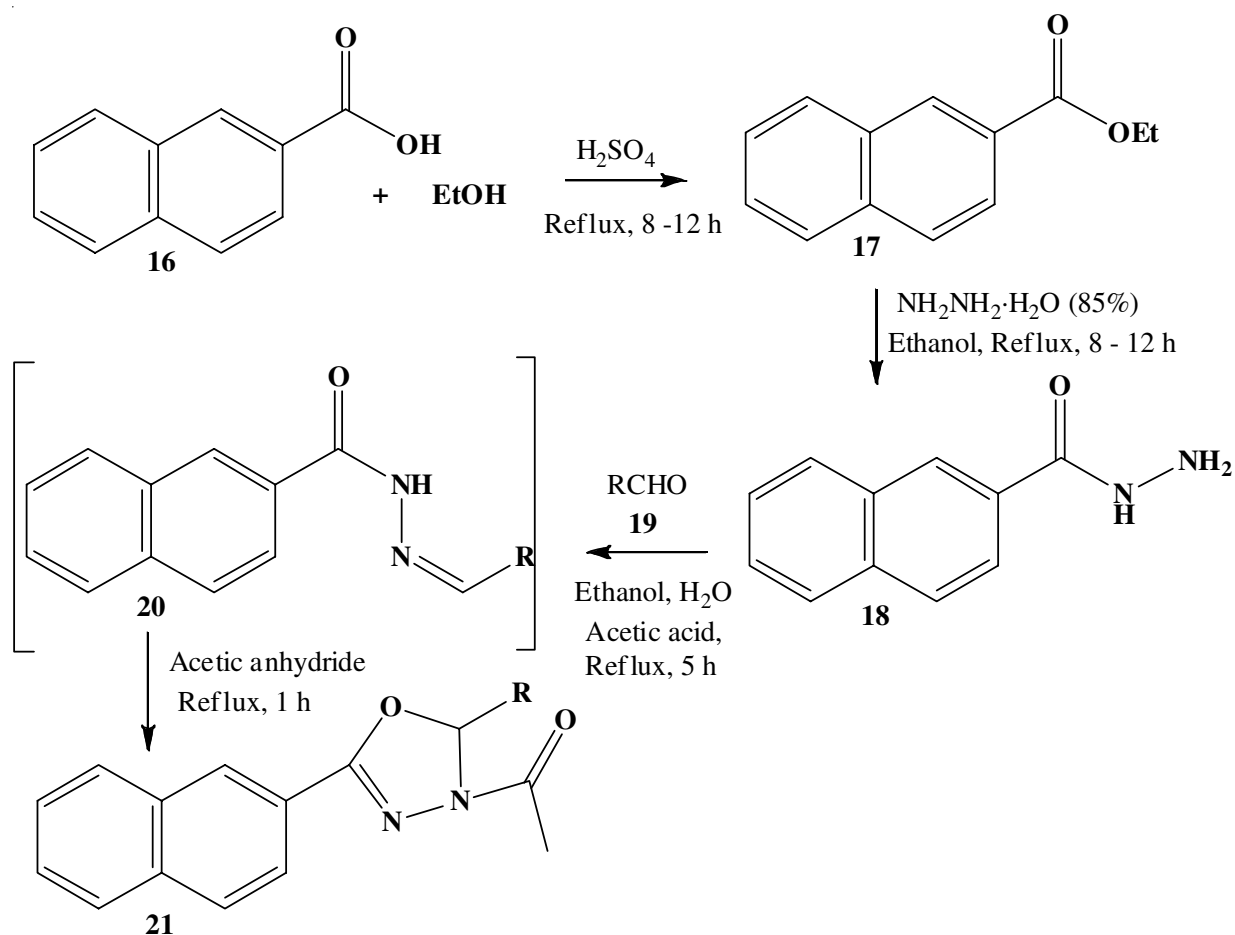
Scheme-IX: Using (*N*-isocyanimine)triphenylphosphorane to synthesize 1,3,4-oxadiazoles

compound **17**. Naphthyl hydrazide **18** was formed when reacting compound **17** with 85% hydrazine monohydrate in the presence of ethanol. Further, compound **18** reacting with various aldehydes produce compound **20** as intermediate when refluxing with both water and glacial acetic acid in the presence of ethanol for about 5 h and finally 1,3,4-oxadiazoles (**21**) are formed when refluxing hydrazone intermediate **20** with acetic anhydride for about 1 h (Scheme-XI) [32].

When methyl ester of salicylic acid (**22**) reacts with hydrazine monohydrate gives salicylic acid hydrazine (**23**). This hydrazine reacts with  $\text{CS}_2$  in the presence of KOH and conc. HCl yields 5-(2-hydroxyphenyl)-2,3-dihydro-1,3,4-oxadiazole-2-thione (**24**), which upon reacting with formaldehyde and various primary and secondary amines to produce 5-(2-hydroxyphenyl)-3-substituted-2,3-dihydro-1,3,4-oxadiazole-2-thiones (**25**) with high yields (Scheme-XII) [33].



Scheme-X: Preparation of 2,5-disubstituted-1,3,4-oxadiazoles

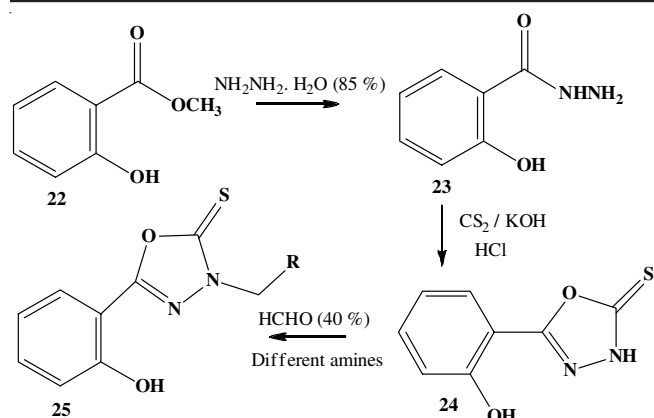


Scheme-XI: Preparation of 2,3-dihydro-1,3,4-oxadiazoles

### Other routes for the synthesis of 1,3,4-oxadiazoles

A. Cyclization of 1,4-disubstituted thiosemicarbazide in the presence of either  $I_2/NaOH$  or dicyclohexylcarbodiimide (DCC) [34].

B. Condensation of 1,2-diacylhydrazines using various reagents including boron trifluoride etherate [35], triflic anhydride [36], phosphorus pentoxide [37], thionyl chloride [38], sulfuric acid [39,40] and polyphosphoric acid (PPA) [41].

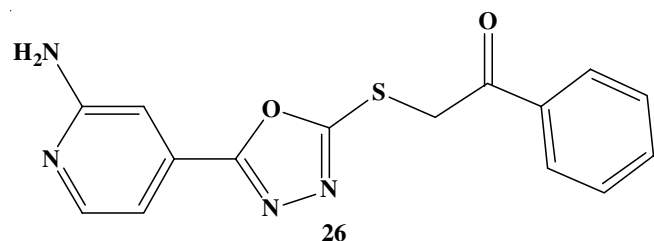


Scheme-XII: Synthesis of 2,5-dihydro-1,3,4-oxadiazole-2-thiones

### Anticancer activity of 1,3,4-oxadiazoles

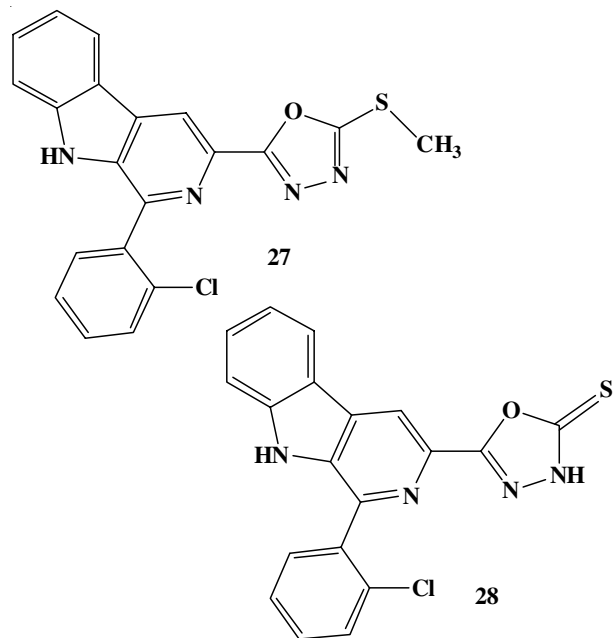
Cancer is genetic disease, which cause normal cell to grow to be cancerous due to imperfect DNA. The effected gene leads to raise cellular abundance as well as absolute to spawn the cells.

In 2014, a series of novel 1,3,4-oxadiazole derivatives contain pyridine and acylhydrazone moieties were synthesized and proved as a new and potential telomerase inhibitors. The compounds exhibited broad spectrum anticancer activity against four cancer cell lines *i.e.* liver (HEPG2), breast (MCF7), colon (SW1116) and gastric (BGC823) [42]. 1,3,4-Oxadiazole derivatives carried various pharmacophore with basic in nature found to be useful for producing cytotoxic activity. In addition to 1,3,4-oxadiazole skeleton, the presence of thiazole or pyrazole moiety produced better antitumor activity, rather decreased activity was observed by the presence of thiazolidin-5-one or thiophene moiety [43]. Some novel 2,5-diaryloxadiazole linked pyrrolo[2,1-*c*][1,4]benzodiazepine conjugates were prepared and studied for their anticancer activity and found to have significant anticancer activity with  $GI_{50}$  (50% growth inhibition) values in the range of  $< 0.1$ - $0.29 \mu\text{M}$  [44]. A novel substituted 1,3,4-oxadiazoles proved as chemotherapeutic agents, which act against breast cancer, leukemia, lung cancer, *etc.* [45]. Researchers reported synthesis of a new 2-(1,3,4-oxadiazol-2-ylthio)-1-phenylethanone derivatives as potential Focal Adhesion Kinase (FAK) inhibitors and studied for their antitumor activity. Compound **26** exhibited most potent activity, which inhibited the growth of MCF-7 and A431 cell lines with  $IC_{50}$  values of 140 nM and 10 nM, respectively [46].

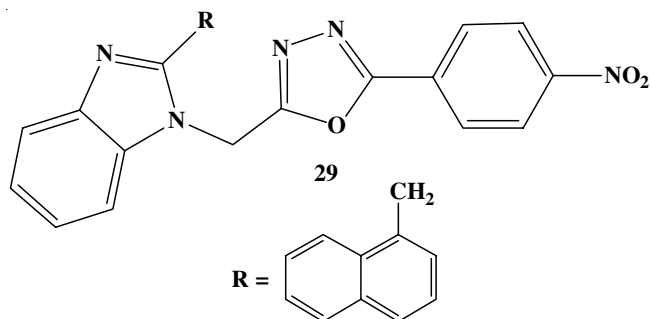


A series of new 1,3,4-oxadiazole derivatives containing benzotriazole moiety showed potential Focal Adhesion Kinase (FAK) inhibitors [47]. Formagio *et al.* [48] synthesized a series

of novel 2-substituted 1,3,4-oxadiazole-5-yl bearing beta-carbolines and screened for their antitumor activity by *in vitro*. Compounds **27** and **28** exhibited high selectivity and potency against human tumor cell lines like melanoma, breast, lung, leukemia, ovarian, prostate, colon and renal.



A new series of 2-(naphthalen-2-yl-oxymethyl)-1-(5-substituted phenyl[1,3,4]oxadiazol-2-ylmethyl)-1H-benzimidazoles were synthesized and examined for anticancer activity in melanoma, leukemia, lung, ovarian, prostate cancer cell lines *in vitro* by Salahuddin *et al.* [49]. Among them, compound **29** bearing  $\text{NO}_2$  group on phenyl moiety at para position exhibited moderate to good anticancer activity. Shaharyar & Akhter [50] reported a series of 5-(2-hydroxyphenyl)-3-substituted-2,4-dihydro-1,3,4-oxadiazole-2-thiones were synthesized and studied for their *in vitro* anticancer activity. These derivatives showed more potent anticancer activity compared to 5-fluorouracil and cyclophosphamide used as reference standards.

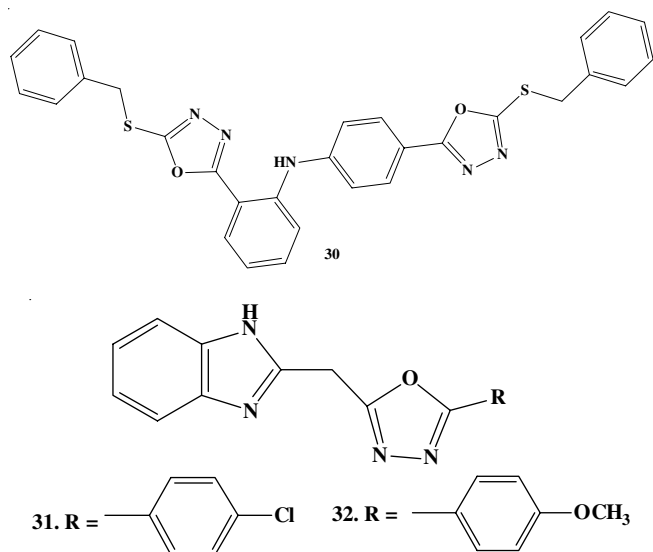


### Antiproliferative activity

**A. Epidermal growth factor receptor inhibitors:** In tyrosine kinase enzyme, the growth factors and their transmembrane receptors have internal activity, which catalyzing the phosphorylation of proteins related with signaling intracellular processes *e.g.* proliferation, differentiation and cell apoptosis.

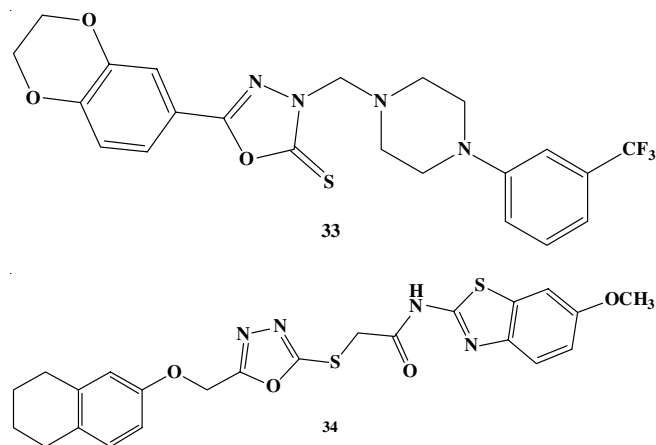
Growth factors with their transmembrane receptors (EGFR-epidermal growth factor receptor, also called as ErbB) take part in significant position in ordinary performance of cells. Because of their inappropriate activation or over expression causes cancer due to uncontrolled cell growth. These receptors also exhibited a role in metastasis and angiogenesis of neoplasm and their suppression leads to tumor regression [51]. Protein dock studies explained that the phosphorylated residues led to producing different signaling pathways such as PI3K (phosphoinositide3-kinase), Ras (renin-angiotensin system) and SFC (supercritical fluid chromatography), which promote processes like cell growth, proliferation, cell survival and increase gene expression [52], inhibition of apoptosis, angiogenesis in human tumor such as breast, lungs, ovarian and squamous carcinoma located on head and neck places [53]. Hence, these receptors are selected as targets for cancer therapy.

Abou-Seri [54] synthesized a series of *bis*-5-mercapto-1,3,4-oxadiazole derivatives and screened for their breast cancer activity on MCF-7 cell line. Compound **30** is the most lipophilic as dibenzyl derivative exhibited better antiproliferative property along with significant EGFR tyrosine kinase inhibitor activity. Akhtar *et al.* [55] derived novel benzimidazole containing 1,3,4-oxadiazoles and analyzed for cytotoxic activity on five cancer cell lines like breast cancer (MCF-7, MDA-MB231), skin cancer (HaCaT), liver cancer (HepG2) and lung cancer (A549). Compounds **31** and **32** showed better cytotoxic activity on breast cancer cells (MCF-7) compared with 5-fluorouracil used as reference standard.

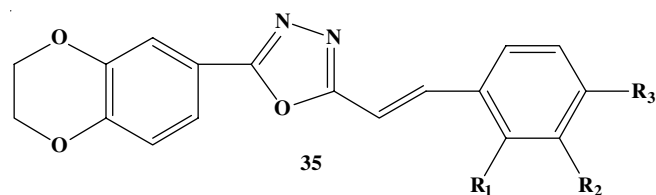


**B. Focal adhesion kinase (FAK):** FAK protein is a cytoplasmic tyrosine kinase and involves in cell cycle regulation, adhesion, migration and cell apoptosis. It played an important role in signal transition from integrin receptors or growth factor receptors to the intracellular protein cascade. Enhanced signaling from FAK may cause uncontrolled proliferation or migration of cells in the process of tumor development and progression [56]. Sun *et al.* [57] published their research work on phenyl-piperazine derivatives of 1,3,4-oxadiazole analogs as FAK inhibitors. The 3-trifluoromethyl-piperazine derivative **33** showed

more activity towards four cancer cell lines tested in cytotoxicity analysis: liver cancer (HepG2), cervical cancer (HeLa), colorectal cancer (SW1116) and stomach cancer (BGC823). Altintop *et al.* [58] reported the analogs of 1,3,4-oxadiazoles with thiazole and benzothiazole moiety as FAK inhibitors. Various compounds analyzed using three cell lines: human lung adenocarcinoma (A549), rat glioma (C6) and mouse embryonic fibroblast (NIH/3T3). Out of which, compound **34** exhibited more prominent antiproliferative activity compared to cisplatin as reference drug against cell lines selected.

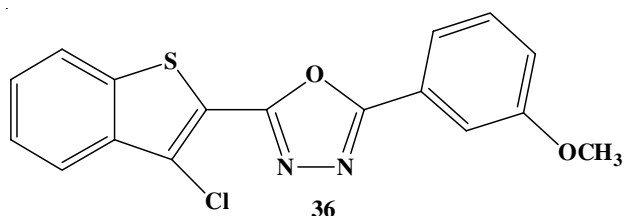


**C. Methionine amino peptidase inhibitors (MetAP):** MetAP is a bifunctional protein plays an important role in regulation of post-translational pathway and synthesis of protein. It acts like metalloprotease, which is responsible for removal of N-terminal initiated methionine from the proteins as well as inhibiting N-terminal myristoylation [59]. N-Myristoylation of proto-oncogene c-Src was used for association of membrane and good signal transduction. Mainly they are divided into two types *viz.* MetAP1 and MetAP2 [60]. Sun *et al.* [61] reported the results of 1,3,4-oxadiazole consisting of 1,4-benzodioxan moiety as novel series **35** found to be inhibit MetAP2 pathway and also led to cell apoptosis. SAR studies explained that the activity was in increasing order when substituting the electron-withdrawing group in the order of F > Cl > Br > NO<sub>2</sub> > CH<sub>3</sub> > OCH<sub>3</sub> and the order of potency was found to be in *ortho* > *meta* > *para*.



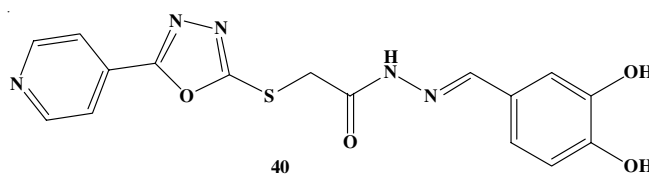
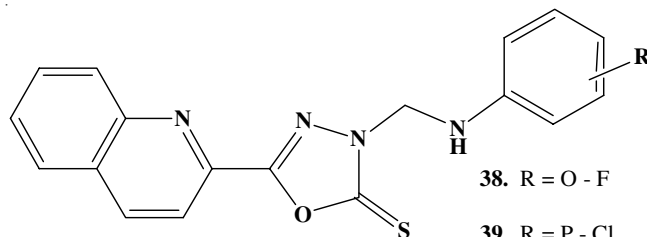
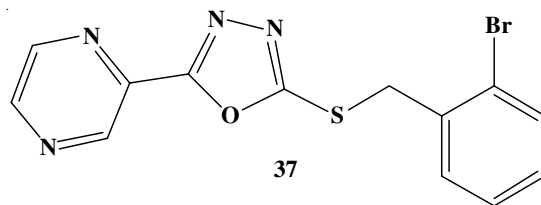
**D. Nuclear Factor (NF-κB) inhibitors:** Nuclear factor κB is an important inflammatory mediator in various diseases even in cancer. It acts as a nuclear transcription factor gets activated by inflammation, DNA damage, *etc.* The expression of cytokines and adhesion factors are responsible for inter-cellular interactions which are regulated by NF-κB. The extreme activation of the NF-κB factor causing several cancers that leads to the genes expression responsible for the proliferation

and protection of cells from factors causing their death by the process of apoptosis [62-64]. Due to this reason, researchers show interest on NF- $\kappa$ B pathway inhibition as promising way of treating cancer. In some of the cases NF- $\kappa$ B inhibitors used in adjuvant therapy because of the NF- $\kappa$ B pathway inhibition can reverse the chemoresistance. Mohan *et al.* [65] described novel 1,3,4-oxadiazole analogs, which showed anticancer activity depending on the level of NF- $\kappa$ B activity in hepato cellular carcinoma cells (HCC). Among them, compound **36** showed more potency as a dose and time-dependent anti-proliferative effect using flow cytometry and protein phosphorylation methods for analyzing the level of NF- $\kappa$ B signaling process in HCC cells. And also this compound causes cell apoptosis mostly through caspase activation pathway.



**E. Telomerase inhibitors:** In various groups of somatic cells the length of telomerase shortens during replication of DNA, which is called as mitotic controlled process, which led to instability and apoptosis in genome [66]. The tumor progression can be interrupted by shortening the telomere by de novo-telomerase, which is possible by the use of telomerase inhibitors. Some researchers in 2012, synthesized 1,3,4-oxadiazole derivatives with pyrazine group and screened for their anticancer activity using four cancer cell lines: liver (HepG2), colorectal (SW1116), cervical (HELA) and stomach cancer (BGC823). High activity was found in compound **37** as anti-proliferative agent against SW1116 cells, when compared with reference drugs 5-fluorouracil and staurosporin [67]. Sun *et al.* [68] synthesized 1,3,4-oxadiazole analogs which contain quinoline group and studied for their anticancer activity on three different cancer cell lines: liver (HepG2), stomach (SGC-7901) and breast (MCF-7). Out of them, compounds **38** and **39** showed 20 times more anti-proliferative activity than 5-fluorouracil. And also the telomerase inhibitor activity was stronger than the staurosporin used as reference standard. Lee *et al.* [69] studied on telomerase inhibitors named pyridine-1,3,4-oxadiazole analogs. Compound **40** exhibited more potent anticancer activity against selected four cancer cell lines: liver cancer (HepG2), breast cancer (MCF7), colorectal cancer (SW1116) and stomach cancer (BGC823) when compared to reference standards 5-fluorouracil and staurosporin.

**Antiviral activity:** Virus is an obligate intracellular parasite. Each viral particle consists of single nucleic acid either RNA or DNA. The encoding viral genome surrounded by protein coat used for enabling replication within living cells. Several privileged structures containing molecules used for treating virus infections, among them 1,3,4-oxadiazole heterocycle containing molecules are considered as a privileged structure based on practical and theoretical interest. These molecules



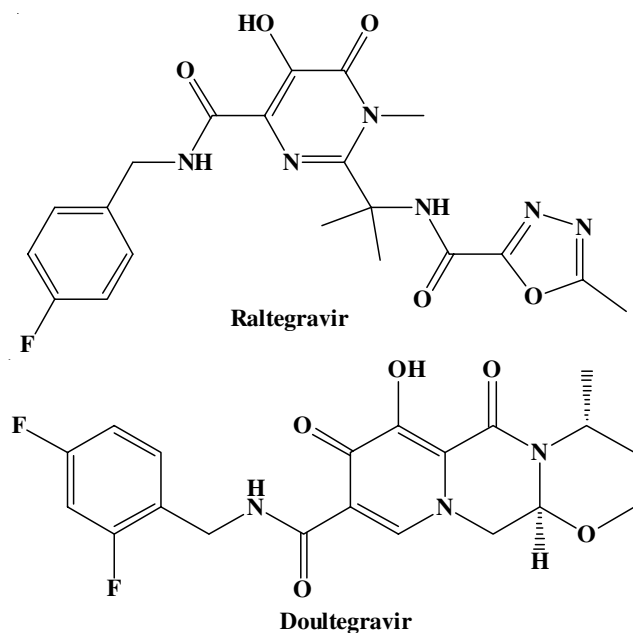
possessing broad and potent antiviral activities include anti-human immune deficiency virus (HIV), anti-hepatitis C virus (HCV), anti-hepatitis B virus (HBV), anti-influenza virus (IV), anti-herpes simplex virus (HSV), anti-hepatitis-A virus (HAV), anti-varicella-zoster virus (VZV) and anti-human cytomegalovirus (HCMV) activities, *etc.* [70-72].

**Hepatitis B virus (HBV):** Literature survey revealed that the hepatitis B virus (HBV) leads to acute and chronic hepatitis *i.e.* hepatocellular carcinoma. About 400 million people worldwide and 1-2% of people are dying each year due to viral infections [73]. The other research teams reported that the only interferon- $\alpha$  and HBV nucleoside reverse transcriptase/polymerase nucleoside inhibitors, lamivudine (3TC), adefovir and entecavir are get approved for the treatment of chronic HBV infection. Interferon- $\alpha$  gives more adverse effects and efficacy is < 30% towards chronic HBV infection [74,75]. Scientists individually described that the 3TC has more applicability and is able to reduce viral load very rapidly as well as this initial fast response of the drug follows slow elimination of residual virus [76,77]. Fischer *et al.* [78] reported that this slower phase causing emergence of drug resistance leads to long-term treatment. Several researchers [79-81] reported that the adefovir showed activity against 3TC-resistant viruses. When applied for long-term monotherapy it showed less activity due to resistance.

**Human immune deficiency virus type-1 (HIV-1):** Moyle *et al.* [82] briefly explained about HIV-1 is a type of Lenti virus and an etiological agent causes AIDS (acquired immune deficiency syndrome) leading to failure of immune system. It is a life threatening infection, which infects vital cells in human immune system such as helper T cells (CD4T cells), macrophages and dendritic cells. HIV-1 encoded by three enzymes essential for viral replication are: viral protease (PR), reverse transcriptase (RT) and the integrase (IN). Several researchers also [83-85] explained that HIV-1 IN plays a major role in insertion of viral DNA into genome of host cells, which first

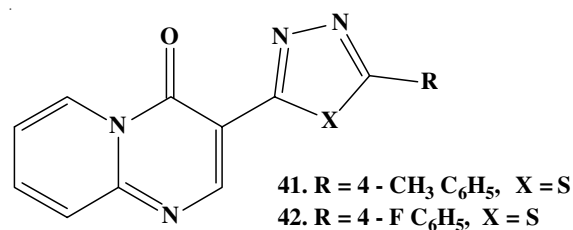


catalyzed for removal of terminal dinucleotide from each 3' end of viral DNA and also mediates strand transfer phenomenon *i.e.*, the joining of the 3' end of the viral DNA to the host DNA. This enzymatic process is dependent on an active site containing  $Mg^{2+}$  held in place with a highly utilized triad of carboxylate amino acid residues (asp64/asp116/ glu152) referred to as a DD(35)E triad. Because of having no counterpart in mammalian cells, the HIV-1 IN considered as a critical target for antiretroviral drugs. In HIV-1 IN inhibitors discovery, only one compound, raltegravir, has FDA approval in October, 2007 [86]. Min *et al.* [87] reported the second HIV-1 IN inhibitor, dolutegravir (S/GSK-1349572) is in phase IIb clinical trial and presently it is sold under the brand name TIVICAY with the approval of USFDA in August, 2013.

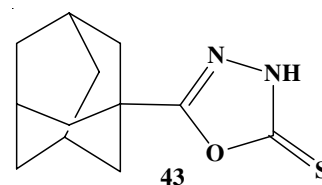


Literature expressed that the raltegravir has viral resistance hence there is a need to discover novel integrase targeting new ligands but scientists have selected HIV-1 IN inhibitors as a base. After several attempts made by the scientists to develop new integrase inhibitors, the keto-enol acid class (diketo acid class) has been found to be the best and has vigorous development because it exhibited marked antiretroviral activities [85]. But this class of compounds exhibited hepatic side effects; hence, there is an attempt to get new bioisosteres such as triazoles and tetra-zole while modifying the carboxylic acid moiety in the keto-enol acid [88,89].

Scientists also clubbed heterocyclic group like pyridine and oxadiazole moiety to improve such activity. A new series of pyrido[1,2-*a*]pyrimidin-4-one derivatives containing 1,3,4-oxadiazole and 1,3,4-thiadiazole rings as metal chelating agents is also reported in the literature [90,91]. As reported SAR of HIV-1 IN inhibitors, it was decided to incorporate different substituted phenyl rings to evaluate the effect of anti-HIV-1 activity along with docking studies. Among all the compounds screened for anti-HIV-1, compounds **41** & **42** showed maximum activity with inhibition rate of 51 and 48% at concentration of 100  $\mu$ M, respectively.

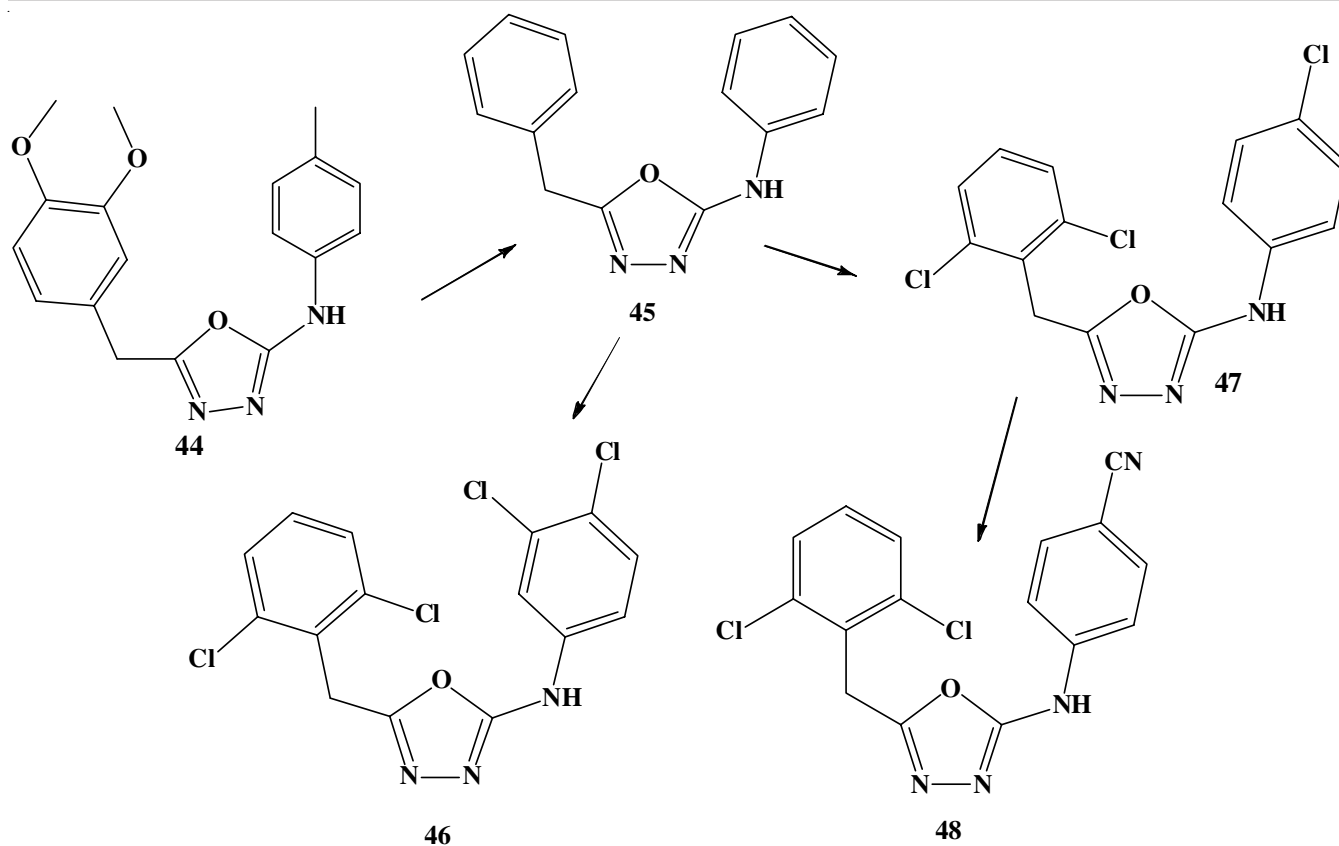


Several adamantane analogs known to be used long time for antiviral activity against influenza A and HIV virus. In this connection, El-Emam *et al.* [92] reported the synthesis and anti-HIV-1 activity of new series of 5-(1-adamantyl)-2-substituted ethylthio-1,3,4-oxadiazole, 5-(1-adamantyl)-3-arylaminoethyl-1,3,4-oxadiazoline-2-thiones, and 5-(1-adamantyl)-3-(4-substituted-1-piperazinylmethyl)-1,3,4-oxadiazoline-2-thiones. Compound **43** produced 100%, 43% and 37% reduction of viral replication at 50, 10 and 2  $\mu$ g/mL concentrations, respectively.

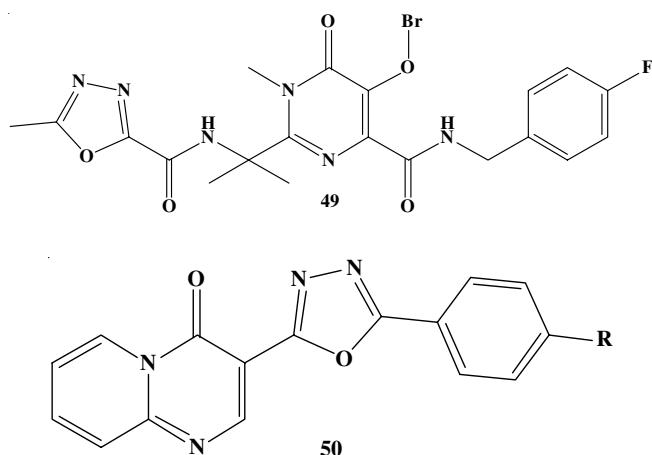


**HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs):** In view of obtaining novel and potent HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs), scientists involved in analysis by virtual screening, performing similarity filter, docking and molecular mechanics obtained 20 top ranked compounds from Muiybridge library of about 70,000 compounds. Compound S10087 (**44**) found to have a powerful core and the BOMB program was used to find rationale modifications. Further structural modification obtained anilinybenzyl-oxadiazole core **45** followed by free energy perturbation (FEP) guided optimization and BOMB program scoring, led to subsequent synthesis and assay of several polychloro analogues with  $EC_{50}$  values, obtained a compound **46** having activity as low as 310 nM in an HIV-infected T-cell assay [93,94]. Further modification of the structure **45** using FEP calculations led compounds **47** and **48**. Compound **48** found to have  $EC_{50}$  value about 130 nM by the same assay [95].

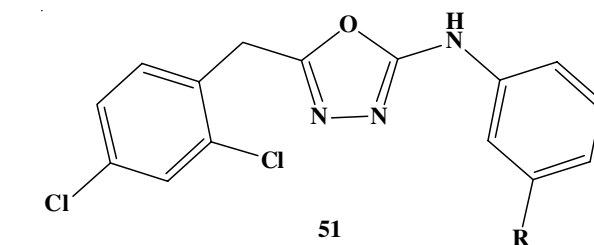
Wang *et al.* [96] synthesized raltegravir analogs with improved microsomal stability as novel IN inhibitors with equal or better anti-HIV activity. Among all, 5-hydroxyl modification of raltegravir analogs showed increased anti-HIV activity. While introducing the acyl group at 5-position of raltegravir also showed antiviral activity. The results showed that maintaining the 6-*O*-methyl group and replacement of 5-methyl-1,3,4-oxadiazole-2-carboxamide group with *N,N*-diethyl-oxo-amino group decreased the anti-HIV activity whereas one of the compound **49** expressed sub-picomolar  $IC_{50}$  value as high potent anti-HIV agent when compared to compounds screened for their activity. On the basis of HIV-1 IN inhibitors pharmacophore, Zabihollahi *et al.* [91] designed and synthesized a new series of pyrido[1,2-*a*]pyrimidin-4-one analogs containing



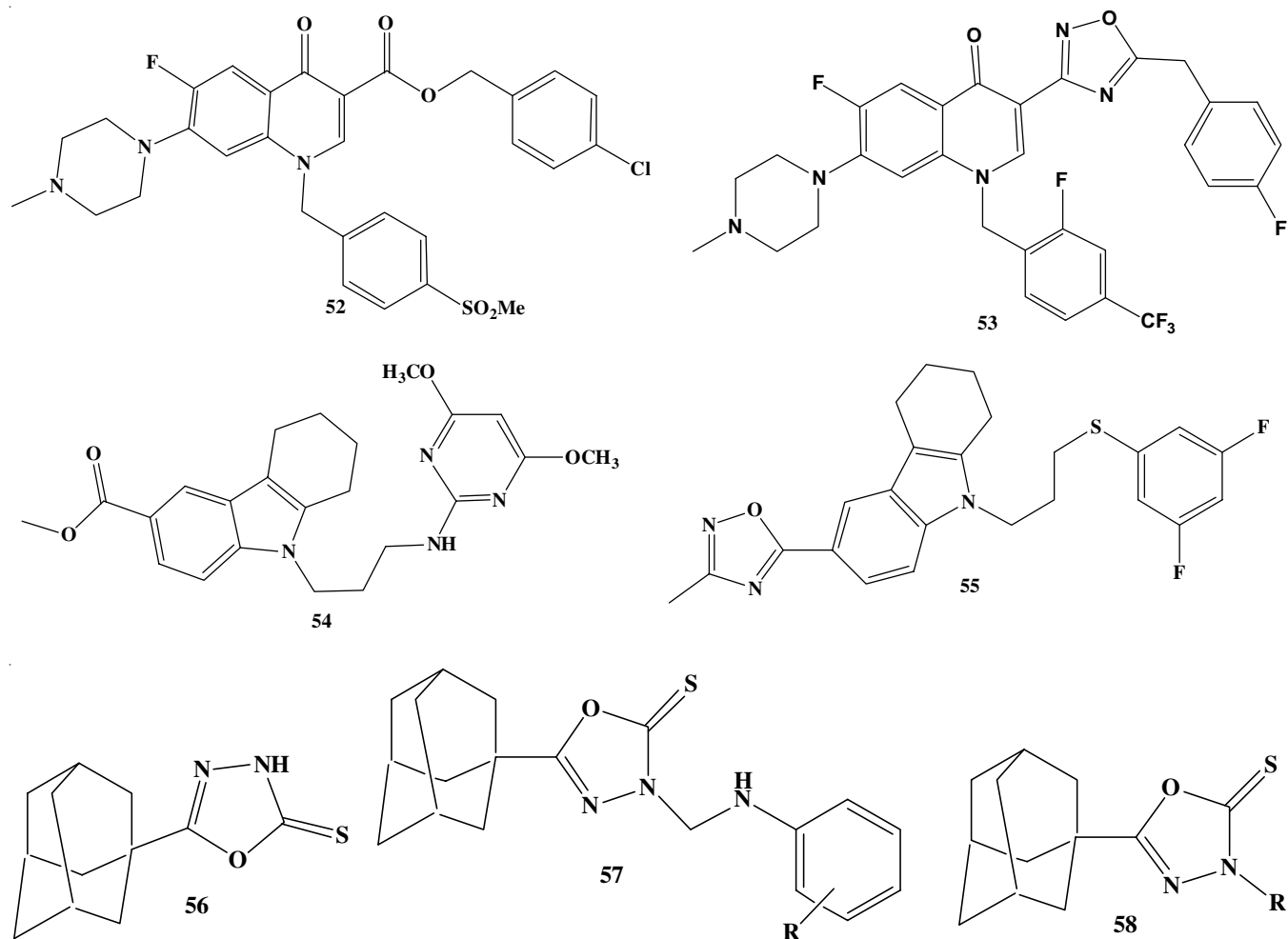
1,3,4-oxadiazole and 1,3,4-thiadiazole rings. Among them, compound **50** showed moderate inhibitory activity against HIV-1 virus (NL4-3) in HeLa cell culture due to presence of 1,3,4-oxadiazole moiety rather than 1,3,4-thiadiazole group.



HIV-1 reverse transcriptase is an ideal target for NNRTIs used for the treatment of antiretroviral therapy. Leung *et al.* [97] studied anti-HIV-1 activities for synthesized 1,3,4-oxadiazole and oxazole analogs against the IIIIB and variant strains of HIV-1 using MT-2 human T-cells. Out of the two series, the oxazole analogs found to be more potent. In the series of 1,3,4-oxadiazoles, compound **51** showed high potent activity which contained, R = CH<sub>2</sub>OCH<sub>2</sub>-4-pyridinyl moiety with EC<sub>50</sub> = 1.6 μM.



**Miscellaneous:** Kumar *et al.* [98] discovered NS5B polymerase inhibitors as a novel class of 3-heterocyclyl quinoline analogs because NS5B act as a key enzyme for hepatitis C virus (HCV) life cycle. Compound **52** was found to be lead compound in quinoline-based analogs. Replacing the ester functional group in compound **52** with hydrolytically stable bisesters obtained oxazole, 1,2,4-oxadiazole, 1,3,4-oxadiazole and tetrazole containing new series. The oxadiazoles showed high potent activity than other heterocycles and compound **53** having EC<sub>50</sub> < 230 nM due to presence of 1,2,4-oxadiazole moiety. Gopi Kumar *et al.* [98] discovered a more potent and orally bioavailable HCV entry inhibitors from compound **54** which is previously reported by Jayashankar *et al.* [99]. In compound **54**, researchers introduced hydrogen-bond acceptors at the 6-position such as methyl sulfone, cyano, nitro as well as introducing bisosteric groups of the methyl esters like oxadiazole, oxazole, triazole and tetrazole moieties. As per the SAR, they found that a hydrogen-bond acceptor is to be essential for the activity and also 1,2,4-oxadiazoles and 1,3,4-oxadiazoles were found to be more tolerable than other groups. The difluoro-substituted phenols or thiophenols showed

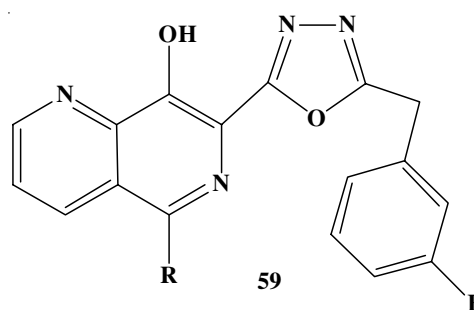


57. R = H, 2-F, 4-F, 2-Cl, 4-Cl, 2-Br, 4-Br, 3-NO<sub>2</sub>, 4-OCH<sub>3</sub>, 2-CN, 2-CF<sub>3</sub>, 2,5-F<sub>2</sub>

58. R = CH<sub>3</sub>, C<sub>2</sub>H<sub>5</sub>, COOC<sub>2</sub>H<sub>5</sub>, C<sub>6</sub>H<sub>5</sub>, 4-FC<sub>6</sub>H<sub>4</sub>, 2-CH<sub>3</sub>OC<sub>6</sub>H<sub>4</sub>, CH<sub>2</sub>C<sub>6</sub>H<sub>5</sub>, 2-CF<sub>3</sub>CH<sub>2</sub>C<sub>6</sub>H<sub>4</sub>

considerable antiviral activity. Compound **55** (ITX 4520) is available as hepatitis C virus entry inhibitor and presently it has been in preclinical process. El-Emam *et al.* [92] designed and synthesized a new series 5-(1-adamantyl)-3-arylamino methyl-1,3,4-oxadiazoline-2-thiones (**57**) and 5-(1-adamantyl)-3-(4-substituted-1-piperazinyl-methyl)-1,3,4-oxadiazoline-2-thiones (**58**) from 5-(1-adamantyl)-1,3,4-oxadiazoline-2-thione (**56**) when treating with formaldehyde solution and primary aromatic amines (or) 1-substituted piperazine in ethanol at room temperature, respectively. Compound **56** and a series of compounds **57** and **58** selected for activity against HIV-1 using the XTT assay on MT-4 cells. Compound **56** was found to be the most potent with 100, 43 and 37% reduction in viral replication at concentrations of 50, 10 and 20 µg/mL, respectively [100].

Ravichandran *et al.* [101] reported synthesis and QSAR studies of substituted 1,3,4-oxadiazole naphthyridines (**59**) and are found to be HIV-1 integrase inhibitors. A group of scientists reported synthesis and biological activity studies of HIV-1 integrase inhibitors having 8-hydroxy-1,6-naphthyridine pharmacophore with an oxadiazole or triazole nucleus. From the results obtained the scientists suggested that these molecules provide initial SAR data as a HIV-1 integrase inhibitors having chela-



tion architecture with potent inhibition by both enzymatically and antiviral assay. Among them C-5 substituted 7-(1,3,4-oxadiazole)-1,6-naphthyridine analogs showed a significant HIV-1 integrase inhibitory activity due to the presence of amido, sulfonamide and aryl substitution at C<sub>5</sub> position. This result suggested that oxadiazole will serve as an amide isostere for metal coordination with in the integrase, which having two metal binding sites [102,103].

### Conclusion

This review has drawn attention on the diverse synthetic routes used to synthesize 1,3,4-oxadiazoles and studied their

biological activity like anticancer and antiviral properties along with their therapeutic targets and brief summary of structure activity relationship studies till 2020 based on the literature survey. Researchers suggested that the anticancer and antiviral activity studies are the major research areas out of their broad spectrum activity studies. The 1,3,4-oxadiazoles are also considered as important intermediates in organic chemistry which employed as electron transporting and hole-blocking materials. Since oxadiazoles exhibited regioisosterism and/or bioisosterism, increases the biological activity by participating in hydrogen bonding interactions with the receptors. Literature revealed that researchers have taken attention on the 1,3,4-oxadiazoles due to their biological potential with authentic and satisfactory synthetic routes of synthesis. Hence, it can be concluded that 1,3,4-oxadiazole derivatives may be exploited further in drug design and development of novel entities to provide better therapeutic potential for variety of fatal diseases like cancer, viral, various other inflammatory conditions, epilepsy, diabetes, *etc.*

#### ACKNOWLEDGEMENTS

The authors are thankful to Shri Vishnu College of Pharmacy (Autonomous), Bhimavaram, India, for providing the facilities and access to online resources for the literature survey.

#### CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

#### REFERENCES

1. T. Olivier, A. Haslam and V. Prasad, *JAMA Network Open*, **4**, e2138793 (2021); <https://doi.org/10.1001/jamanetworkopen.2021.38793>
2. M. Tuyishime, M. Danish, A. Princiotto, M.K. Mankowski, R. Lawrence, H.G. Lombart, K. Esikov, J. Berniac, K. Liang, J. Ji, R.G. Ptak, N. Madani and S. Cocklin, *Bioorg. Med. Chem. Lett.*, **24**, 5439 (2014); <https://doi.org/10.1016/j.bmcl.2014.10.027>
3. K. Al-Othman, M. Abdulla, B. Jeppsson, H. Asakawa, U. Srinivas and S. Bengmark, *Acta Pharm.*, **59**, 223 (2009); <https://doi.org/10.1111/j.1600-0773.1986.tb02749.x>
4. M. Amir, S.A. Javed and H. Kumar, *Indian J. Chem.*, **46B**, 1014 (2007).
5. K.C. Nagaraji, K.C. Chaluvareju, M.S. Niranjan and S. Kiran, *Int. J. Pharm. Pharm. Sci.*, **3**, 9 (2011).
6. S. Zhang, Y. Luo, L.Q. He, Z.J. Liu, A.Q. Jiang, Y.H. Yang and H.L. Zhu, *Bioorg. Med. Chem.*, **21**, 3723 (2013); <https://doi.org/10.1016/j.bmc.2013.04.043>
7. C.R. Biju, K. Ilango, M. Prathap and K. Rekha, *J. Young Pharm.*, **4**, 33 (2012); <https://doi.org/10.4103/0975-1483.93576>
8. J.A. Joule and K. Mills, *Heterocyclic Chemistry*, John Wiley & Sons: Hoboken, New Jersey, USA, Ed.: 5, pp. 569-574 (2010).
9. M.N. Ahmed, B. Sadiq, N.A. Al-Masoudi, K.A. Yasin, S. Hameed, T. Mahmood, K. Ayub and M.N. Tahir, *J. Mol. Struct.*, **1155**, 403 (2018); <https://doi.org/10.1016/j.molstruc.2017.11.011>
10. G. Verma, G. Chashoo, A. Ali, M.F. Khan, W. Akhtar, I. Ali, M. Akhtar, M.M. Alam and M. Shaquiquzzaman, *Bioorg. Chem.*, **77**, 106 (2018); <https://doi.org/10.1016/j.bioorg.2018.01.007>
11. H.S. Abd-Ellah, M. Abdel-Aziz, M.E. Shoman, E.A.M. Beshr, T.S. Kaoud and A.-S.F.F. Ahmed, *Bioorg. Chem.*, **74**, 15 (2017); <https://doi.org/10.1016/j.bioorg.2017.06.003>
12. M.A. Tantray, I. Khan, H. Hamid, M.S. Alam, A. Dhulap and A. Kalam, *Bioorg. Chem.*, **77**, 393 (2018); <https://doi.org/10.1016/j.bioorg.2018.01.040>
13. B. Yadagiri, S. Gurralla, R. Bantu, L. Nagarapu, S. Polepalli, G. Srujana and N. Jain, *Bioorg. Med. Chem. Lett.*, **25**, 2220 (2015); <https://doi.org/10.1016/j.bmcl.2015.03.032>
14. K. Manjunatha, B. Poojary, P.L. Lobo, J. Fernandes and N.S. Kumari, *Eur. J. Med. Chem.*, **45**, 5225 (2010); <https://doi.org/10.1016/j.ejmech.2010.08.039>
15. Z. Hajimahdi, A. Zarghi, R. Zabihollahi and M.R. Aghasadeghi, *Med. Chem. Res.*, **22**, 2467 (2013); <https://doi.org/10.1007/s00044-012-0241-5>
16. W.-M. Xu, S.-Z. Li, M. He, S. Yang, X.-Y. Li and P. Li, *Bioorg. Med. Chem. Lett.*, **23**, 5821 (2013); <https://doi.org/10.1016/j.bmcl.2013.08.107>
17. A.A. Kadi, N.R. El-Brollosy, O.A. Al-Deeb, E.E. Habib, T.M. Ibrahim and A.A. El-Emam, *Eur. J. Med. Chem.*, **42**, 235 (2007); <https://doi.org/10.1016/j.ejmech.2006.10.003>
18. B. Chandrakantha, P. Shetty, V. Nambiyar, N. Isloor and A.M. Isloor, *Eur. J. Med. Chem.*, **45**, 1206 (2010); <https://doi.org/10.1016/j.ejmech.2009.11.046>
19. N.B. Patel and J.C. Patel, *Sci. Pharm.*, **78**, 171 (2010); <https://doi.org/10.3797/scipharm.0912-16>
20. S. Olson, S.D. Aster, K. Brown, L. Carbin, A. Hermanowski-Vosatka, D.W. Graham, C.B. LeGrand, S.S. Mundt, M.A. Robbins, J.M. Schaeffer, L.H. Slossberg, M.J. Szymonifka, R. Thieringer, S.D. Wright and J.M. Balkovec, *Bioorg. Med. Chem. Lett.*, **15**, 4359 (2005); <https://doi.org/10.1016/j.bmcl.2005.06.040>
21. C. Dobrotă, C.C. Paraschivescu, I. Dumitru, M. Matache, I. Baciuc and L.L. Rușă, *Tetrahedron Lett.*, **50**, 1886 (2009); <https://doi.org/10.1016/j.tetlet.2009.02.054>
22. S. Dash, B.A. Kumar, J. Singh, B.C. Maiti and T.K. Maity, *Med. Chem. Res.*, **20**, 1206 (2011); <https://doi.org/10.1007/s00044-010-9455-6>
23. Y.-L. Zhao, Z. Lv, B. Tian, Z. Hou and Z.-R. Geng, *Acta Crystallogr. Sect. E Struct. Rep. Online*, **67**, o251 (2011); <https://doi.org/10.1107/S1600536810052967>
24. J. Sun, M.L. Li, S.S. Qian, F.J. Guo, X.F. Dang, X.M. Wang, Y.R. Xue and H.R. Zhu, *Bioorg. Med. Chem. Lett.*, **23**, 2876 (2013); <https://doi.org/10.1016/j.bmcl.2013.03.068>
25. X.M. Zhang, M. Qiu, J. Sun, Y.B. Zhang, Y.S. Yang, X.L. Wang, J.F. Tang and H.L. Zhu, *Bioorg. Med. Chem.*, **19**, 6518 (2011); <https://doi.org/10.1016/j.bmc.2011.08.013>
26. M. Amir and K. Shikha, *Eur. J. Med. Chem.*, **39**, 535 (2004); <https://doi.org/10.1016/j.ejmech.2004.02.008>
27. X. Zheng, Z. Li, Y. Wang, W. Chen, Q. Huang, C. Liu and G. Song, *J. Fluor. Chem.*, **123**, 163 (2003); [https://doi.org/10.1016/S0022-1139\(03\)00168-4](https://doi.org/10.1016/S0022-1139(03)00168-4)
28. W.A. El-Sayed, O.M. Ali, H.A. Hendy and A.H. Abdel-Rahman, *Chin. J. Chem.*, **30**, 77 (2012); <https://doi.org/10.1002/cjoc.201100029>
29. N.B. Patel and J.C. Patel, *Sci. Pharm.*, **78**, 171 (2010); <https://doi.org/10.3797/scipharm.0912-16>
30. L. Cui, Q. Liu, J. Yu, C. Ni and H. Yu, *Tetrahedron Lett.*, **52**, 5530 (2011); <https://doi.org/10.1016/j.tetlet.2011.08.086>
31. C.O. Kangani, D.E. Kelley and B.W. Day, *Tetrahedron Lett.*, **47**, 6497 (2006); <https://doi.org/10.1016/j.tetlet.2006.07.032>
32. O. Ali, A. Abdel-Rahman and H. Amer, *Synth.*, 2823 (2007); <https://doi.org/10.1055/s-2007-983878>
33. A.S. Aboraia, H.M. Abdel-Rahman, N.M. Mahfouz and M.A. El-Gendy, *Bioorg. Med. Chem.*, **14**, 1236 (2006); <https://doi.org/10.1016/j.bmc.2005.09.053>
34. F.A. Omar, N.M. Mahfouz and M.A. Rahman, *Eur. J. Med. Chem.*, **31**, 819 (1996); [https://doi.org/10.1016/0223-5234\(96\)83976-6](https://doi.org/10.1016/0223-5234(96)83976-6)
35. A. Rauf, S. Sharma and S. Gangal, *Chin. Chem. Lett.*, **19**, 5 (2008); <https://doi.org/10.1016/j.cclet.2007.11.026>
36. S. Cesarini, N. Colombo, M. Pulici, E.R. Felder and W.K.D. Brill, *Tetrahedron*, **62**, 10223 (2006); <https://doi.org/10.1016/j.tet.2006.08.016>

37. S. Liras, M.P. Allen and B.E. Segelstein, *Synth. Commun.*, **30**, 437 (2000); <https://doi.org/10.1080/00397910008087340>
38. M. Al-Talib, H. Tashouh and N. Odeh, *Synth. Commun.*, **20**, 1811 (1990); <https://doi.org/10.1080/00397919008053105>
39. G.S. Poindexter, M.A. Bruce, J.G. Breitenbucher, M.A. Higgins, S.-Y. Sit, J.L. Romine, S.W. Martin, S.A. Ward, R.T. McGovern, W. Clarke, J. Russell and I. Antal-Zimanyi, *Bioorg. Med. Chem.*, **12**, 507 (2004); <https://doi.org/10.1016/j.bmc.2003.10.016>
40. S. Sharma, V.K. Srivastava and A. Kumar, *Eur. J. Med. Chem.*, **37**, 689 (2002); [https://doi.org/10.1016/S0223-5234\(02\)01340-5](https://doi.org/10.1016/S0223-5234(02)01340-5)
41. C. Loetchutinat, F. Chau and S. Mankhetkorn, *Chem. Pharm. Bull. (Tokyo)*, **51**, 728 (2003); <https://doi.org/10.1248/cpb.51.728>
42. F. Zhang, X.L. Wang, J. Shi, S.F. Wang, Y. Yin, Y.S. Yang, W.M. Zhang and H.L. Zhu, *Bioorg. Med. Chem.*, **22**, 468 (2014); <https://doi.org/10.1016/j.bmc.2013.11.004>
43. S. Bondock, S. Adel, H.A. Etman and F.A. Badria, *Eur. J. Med. Chem.*, **48**, 192 (2012); <https://doi.org/10.1016/j.ejmech.2011.12.013>
44. A. Kamal, D. Dastagiri, M.J. Ramaiah, E.V. Bharathi, J.S. Reddy, G. Balakishan, P. Sarma, S.N.C.V.L. Pushpavalli, M. Pal-Bhadra, A. Juvekar, S. Sen and S. Zingde, *Bioorg. Med. Chem.*, **18**, 6666 (2010); <https://doi.org/10.1016/j.bmc.2010.07.067>
45. W.S. El-Hamouly, K.M. Amin and E.E.A. El-Meguid, *Der. Pharm. Chem.*, **3**, 282 (2011).
46. L.R. Zhang, Z.J. Liu, H. Zhang, J. Sun, Y. Luo, T.T. Zhao, H.-B. Gong and H.-L. Zhu, *Bioorg. Med. Chem.*, **20**, 3615 (2012); <https://doi.org/10.1016/j.bmc.2012.03.061>
47. D.D. Schlaepfer, S.K. Hanks, T. Hunter and P. Geer, *Nature*, **372**, 786 (1994); <https://doi.org/10.1038/372786a0>
48. A.S.N. Formagio, L.T.D. Tonin, M.A. Foglio, C. Madjarof, J.E. de Carvalho, W.F. da Costa, F.P. Cardoso and M.H. Sarragiotto, *Bioorg. Med. Chem.*, **16**, 9660 (2008); <https://doi.org/10.1016/j.bmc.2008.10.008>
49. Salahuddin, M. Shaharyar, A. Mazumder and M.J. Ahsan, *Arab. J. Chem.*, **7**, 418 (2014); <https://doi.org/10.1016/j.arabjc.2013.02.001>
50. M. Shaharyar and M.W. Akhter, *Acta Pol. Pharm.*, **66**, 393 (2009).
51. R.B. Bakr, E.K.A. Abdeljal, M.K. Abdel-Hamid and M.M. Kandeel, *Bull. Pharm. Sci.*, **35**, 27 (2012); <https://doi.org/10.21608/bfsa.2012.64596>
52. A. Reid, L. Vidal, H. Shaw and J. de Bono, *Eur. J. Cancer*, **43**, 481 (2007); <https://doi.org/10.1016/j.ejca.2006.11.007>
53. Y. Jin, H.Y. Li, L.P. Lin, J. Tan, J. Ding, X. Luo and Y.Q. Long, *Bioorg. Med. Chem.*, **13**, 5613 (2005); <https://doi.org/10.1016/j.bmc.2005.05.045>
54. S.M. Abou-Seri, *Eur. J. Med. Chem.*, **45**, 4113 (2010); <https://doi.org/10.1016/j.ejmech.2010.05.072>
55. M.J. Akhtar, A.A. Siddiqui, A.A. Khan, Z. Ali, R.P. Dewangan, S. Pasha and M.S. Yar, *Eur. J. Med. Chem.*, **126**, 853 (2017); <https://doi.org/10.1016/j.ejmech.2016.12.014>
56. B.Y. Lee, P. Timpson, G. Horvath and R.J. Daly, *Pharmacol. Ther.*, **146**, 132 (2015); <https://doi.org/10.1016/j.pharmthera.2014.10.001>
57. J. Sun, S.Z. Ren, X.Y. Lu, J.J. Li, F.Q. Shen, C. Xu and H.L. Zhu, *Bioorg. Med. Chem.*, **25**, 2593 (2017); <https://doi.org/10.1016/j.bmc.2017.03.038>
58. M.D. Altintop, B. Sever, G. Akalin Çiftçi, G. Turan-Zitouni, Z.A. Kaplançikli and A. Özdemir, *Eur. J. Med. Chem.*, **155**, 905 (2018); <https://doi.org/10.1016/j.ejmech.2018.06.049>
59. R. Jackson and T. Hunter, *Nature*, **227**, 672 (1970); <https://doi.org/10.1038/227672a0>
60. A. Serero, C. Giglione, A. Sardini, J. Martinez-Sanz and T. Meinel, *Int. J. Biol. Chem.*, **278**, 52953 (2003); <https://doi.org/10.1074/jbc.M309770200>
61. P. Selvakumar, A. Lakshmikuttyamma, J.R. Dimmock and R.K. Sharma, *Biochim. Biophys. Acta*, **1765**, 148 (2006); <https://doi.org/10.1016/j.bbcan.2005.11.001>
62. A.V. Spiros, *Cancer Biol. Med.*, **14**, 254 (2017); <https://doi.org/10.20892/j.issn.2095-3941.2017.0029>
63. E.Z.P. Chai, K.S. Siveen, M.K. Shanmugam, F. Arfuso and G. Sethi, *Biochem. J.*, **468**, 1 (2015); <https://doi.org/10.1042/BJ20141337>
64. Y. Puar, M. Shanmugam, L. Fan, F. Arfuso, G. Sethi and V. Tergaonkar, *Biomedicines*, **6**, 82 (2018); <https://doi.org/10.3390/biomedicines6030082>
65. C.D. Mohan, N.C. Anil kumar, S. Rangappa, M.K. Shanmugam, S. Mishra, A. Chinnathambi, S.A. Alharbi, A. Bhattacharjee, A.P. Kumar, Basappa and K.S. Rangappa, *Oncol.*, **8**, 42 (2018); <https://doi.org/10.3389/fonc.2018.00042>
66. N.W. Kim, M.A. Piatyszek, K.R. Prowse, C.B. Harley, M.D. West, P.L.C. Ho, G.M. Coviello, W.E. Wright, S.L. Weinrich and J.W. Shay, *Science*, **266**, 2011 (1994); <https://doi.org/10.1126/science.7605428>
67. Y.-B. Zhang, X.-L. Wang, W. Liu, Y.-S. Yang, J.-F. Tang and H.-L. Zhu, *Bioorg. Med. Chem.*, **20**, 6356 (2012); <https://doi.org/10.1016/j.bmc.2012.08.059>
68. J. Sun, H. Zhu, Z.M. Yang and H.L. Zhu, *Eur. J. Med. Chem.*, **60**, 23 (2013); <https://doi.org/10.1016/j.ejmech.2012.11.039>
69. J.Y. Lee, K.W. Jeong, S. Shin, J.U. Lee and Y. Kim, *Eur. J. Med. Chem.*, **47**, 261 (2012); <https://doi.org/10.1016/j.ejmech.2011.10.052>
70. E. De Clercq and H.J. Field, *Br. J. Pharmacol.*, **147**, 1 (2006); <https://doi.org/10.1038/sj.bjp.0706446>
71. E. De Clercq, *Curr. Med. Chem.*, **8**, 1543 (2001); <https://doi.org/10.2174/0929867013371842>
72. E. De Clercq, *Biochim. Biophys. Acta*, **1587**, 258 (2002); [https://doi.org/10.1016/S0925-4439\(02\)00089-3](https://doi.org/10.1016/S0925-4439(02)00089-3)
73. K.W. Lin and J.T. Kirchner, *Am. Fam. Phys.*, **69**, 75 (2004).
74. P. Ocama, C.K. Opio and W.M. Lee, *Am. J. Med.*, **118**, 1413.e15 (2005); <https://doi.org/10.1016/j.amjmed.2005.06.021>
75. M.E. Mailliard and J.L. Gollan, *Annu. Rev. Med.*, **57**, 155 (2006); <https://doi.org/10.1146/annurev.med.57.121304.131422>
76. S.J. Stray, C.R. Bourne, S. Punna, W.G. Lewis, M.G. Finn and A. Zlotnick, *Proc. Natl. Acad. Sci. USA*, **102**, 8138 (2005); <https://doi.org/10.1073/pnas.0409732102>
77. T.M.C. Tan, Y. Chen, K.H. Kong, J. Bai, Y. Li, S.G. Lim, T. Ang and Y. Lam, *Antiviral Res.*, **71**, 7 (2006); <https://doi.org/10.1016/j.antiviral.2006.02.007>
78. K.P. Fischer, K.S. Gutfreund and D.L. Tyrrell, *Drug Res.*, **4**, 118 (2001); <https://doi.org/10.1054/drup.2001.0190>
79. P. Angus, R. Vaughan, S. Xiong, H. Yang, W. Delaney, C. Gibbs, C. Brosgart, D. Colledge, R. Edwards, A. Ayres, A. Bartholomeusz and S. Locarnini, *Gastroenterology*, **125**, 292 (2003); [https://doi.org/10.1016/S0016-5085\(03\)00939-9](https://doi.org/10.1016/S0016-5085(03)00939-9)
80. J.P. Villeneuve, D. Durantel, S. Durantel, C. Westland, S. Xiong, C.L. Brosgart, C.S. Gibbs, P. Parvaz, B. Werle, C. Trepo and F. Zoulim, *J. Hepatol.*, **39**, 1085 (2003); <https://doi.org/10.1016/j.jhep.2003.09.022>
81. S.K. Fung, P. Andreone, S.H. Han, K. Rajender Reddy, A. Regev, E.B. Keeffe, M. Hussain, C. Cursaro, P. Richtmyer, J.A. Marrero and A.S.F. Lok, *J. Hepatol.*, **43**, 937 (2005); <https://doi.org/10.1016/j.jhep.2005.05.037>
82. G. Moyle, J. Gatell, C.-F. Perno, W. Ratanasuwana, M. Schechter and C. Tsoukas, *AIDS Patient Care STDS*, **22**, 459 (2008); <https://doi.org/10.1089/apc.2007.0136>
83. J. Colicelli and S.P. Goff, *J. Mol. Biol.*, **199**, 47 (1988); [https://doi.org/10.1016/0022-2836\(88\)90378-6](https://doi.org/10.1016/0022-2836(88)90378-6)
84. M.D. Miller, C.M. Farnet and F.D. Bushman, *J. Virol.*, **71**, 5382 (1997); <https://doi.org/10.1128/jvi.71.7.5382-5390.1997>
85. Y. Pommier, A.A. Johnson and C. Marchand, *Nat. Rev. Drug Discov.*, **4**, 236 (2005); <https://doi.org/10.1038/nrd1660>
86. K. Shimura, E. Kodama, Y. Sakagami, Y. Matsuzaki, W. Watanabe, K. Yamataka, Y. Watanabe, Y. Ohata, S. Doi, M. Sato, M. Kano, S. Ikeda and M. Matsuoka, *J. Virol.*, **82**, 764 (2008); <https://doi.org/10.1128/JVI.01534-07>
87. S. Min, L. Song, J. Borland, S. Chen, Y. Lou, T. Fujiwara and S.C. Piscitelli, *Antimicrob. Agents Chemother.*, **54**, 254 (2010); <https://doi.org/10.1128/AAC.00842-09>

88. T. Kirschberg and J. Parrish, *Curr. Opin. Drug Discov. Devel.*, **10**, 460 (2007).
89. G. Barreiro, J.T. Kim, C.R.W. Guimarães, C.M. Bailey, R.A. Domaal, L. Wang, K.S. Anderson and W.L. Jorgensen, *J. Med. Chem.*, **50**, 5324 (2007);  
<https://doi.org/10.1021/jm070683u>
90. M. Donghi, O.D. Kinzel and V. Summa, *Bioorg. Med. Chem. Lett.*, **19**, 1930 (2009);  
<https://doi.org/10.1016/j.bmcl.2009.02.055>
91. R. Zabihollahi, R. Vahabpour, M.R. Aghasadeghi, A. Memarnejadian, S.M. Sadat, T. Ghazanfari, M. Salehi and K. Azadmanesh, *Acta Virol.*, **55**, 15 (2011);  
[https://doi.org/10.4149/av\\_2011\\_01\\_15](https://doi.org/10.4149/av_2011_01_15)
92. A.A. El-Emam, O.A. Al-Deeb, M. Al-Omar and J. Lehmann, *Bioorg. Med. Chem.*, **12**, 5107 (2004);  
<https://doi.org/10.1016/j.bmc.2004.07.033>
93. P. Zhan, D. Li, X. Chen, X. Liu and E. De Clercq, *Curr. Med. Chem.*, **18**, 29 (2011);  
<https://doi.org/10.2174/092986711793979733>
94. W.L. Jorgensen, *Acc. Chem. Res.*, **42**, 724 (2009);  
<https://doi.org/10.1021/ar800236t>
95. J.G. Zeevaart, L. Wang, V.V. Thakur, C.S. Leung, J. Tirado-Rives, C.M. Bailey, R.A. Domaal, K.S. Anderson and W.L. Jorgensen, *J. Am. Chem. Soc.*, **130**, 9492 (2008);  
<https://doi.org/10.1021/ja8019214>
96. Z. Wang, M. Wang, X. Yao, Y. Li, W. Qiao, Y. Geng, Y. Liu and Q. Wang, *Eur. J. Med. Chem.*, **50**, 361 (2012);  
<https://doi.org/10.1016/j.ejmech.2012.02.015>
97. C.S. Leung, J.G. Zeevaart, R.A. Domaal, M. Bollini, V.V. Thakur, K.A. Spasov, K.S. Anderson and W.L. Jorgensen, *Bioorg. Med. Chem. Lett.*, **20**, 2485 (2010);  
<https://doi.org/10.1016/j.bmcl.2010.03.006>
98. D.V. Kumar, R. Rai, K.A. Brameld, J.R. Somoza, R. Rajagopalan, J. Riggs, J.W. Janc, Y.M. Xia, T.L. Ton, H. Hu, I. Lehoux, J.D. Ho, W.B. Young, B. Hart and M.J. Green, *Bioorg. Med. Chem. Lett.*, **22**, 300 (2012);  
<https://doi.org/10.1016/j.bmcl.2011.11.013>
99. B. Jayashankar, K.M. Lokanath Rai, N. Baskaran and S.H. Sathish, *Eur. J. Med. Chem.*, **44**, 3898 (2009);  
<https://doi.org/10.1016/j.ejmech.2009.04.006>
100. G.K. Mittapalli, F. Zhao, A. Jackson, H. Gao, H. Lee, S. Chow, M.P. Kaur, N. Nguyen, R. Zamboni, J. McKelvy, F. Wong-Staal and J.E. Macdonald, *Bioorg. Med. Chem. Lett.*, **22**, 4955 (2012);  
<https://doi.org/10.1016/j.bmcl.2012.06.038>
101. V. Ravichandran, S. Shalini, K. Sundram and A.D. Sakkalingam, *Eur. J. Med. Chem.*, **45**, 2791 (2010);  
<https://doi.org/10.1016/j.ejmech.2010.02.062>
102. B.A. Johns, J.G. Weatherhead, S.H. Allen, J.B. Thompson, E.P. Garvey, S.A. Foster, J.L. Jeffrey and W.H. Miller, *Bioorg. Med. Chem. Lett.*, **19**, 1802 (2009);  
<https://doi.org/10.1016/j.bmcl.2009.01.090>
103. B.A. Johns, J.G. Weatherhead, S.H. Allen, J.B. Thompson, E.P. Garvey, S.A. Foster, J.L. Jeffrey and W.H. Miller, *Bioorg. Med. Chem. Lett.*, **19**, 1807 (2009);  
<https://doi.org/10.1016/j.bmcl.2009.01.089>