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Significance of Enone Moiety in Ligand-Protein Interaction:A Review

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Abstract: Enone moiety (-C=C-CO-) is an important functionality of bioactive compounds having diverse types of biological activities. It is constructed by attaching a double bond (ene) in conjugation to a keto group (one) asan α,β-unsaturated carbonyl group *via* different types of condensation reactions. This moiety provides two electrophilic sites as β-C and C=O for nucleophiles thus undergoes different types of chemical reactions. The electrophilicity of enone moiety has been recognised as an important characteristic for interactions of small molecules (ligands) with target protein to modified biological response for anticancer, antidiabetic, antibacterial, antifungal, antimalarial, antiviral etc. Here, we reviewed interactions of enone moiety with different amino acid residues of targets proteins.

INTRODUCTION

Enone moiety (-C=C-CO-) is a functional group in which an alkene (-C=C-) and ketone (C=O) are directly connected to each other to form a conjugated system. In a molecule enone moiety is generally constructed by reaction between an ale (-CHO) and α-methylenecarboyl ($-CH_2$-CO-) compounds *via*Claisen-Schmidt condensation [1], or by desulphonation of β-ketosulfones [2], α-methylenation of ketones [3], reaction between ketone and dimethylsulphoxide [4], alcohols and phosphonium salts of ketones [5], reaction of alkyne and aldehyde [6], phosphoniumylides (Witting reaction) [7] etc. Enone moiety provides two electrophilic sites, one as β-carbon (-C=) and other as carbonyl carbon (C=O) for nucleophilic attack and known as Michael acceptor. However, the reactivities of two electrophilic sites depend on substituents on alkene and carbonyl carbon [8]. In biological system when an enone containing molecule enters at its target site enone moiety functions similarly as Michael acceptor for nucleophilic groups of different amino acids surrounding the binding site. By participating in covalent interaction, enone moiety modifies the functions of biological proteins and thus, biological responses. This, strategy has been used for design and development of different types of therapeutic ligands as an agonist or antagonist for biological proteins. Thus, enone moiety containing molecules have been shown various biological activities such as anticancer [9], antidiabetic [10], antibacterialand antifungal [11],

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antimalarial [12], antiviral [13], antioxidantandcytoprotectiveetc(**Fig. 1**)[14].In the present paper, we reviewed the interactions of enone moieties present in a ligand with different amino acids residues of proteins to alter their biological responses.

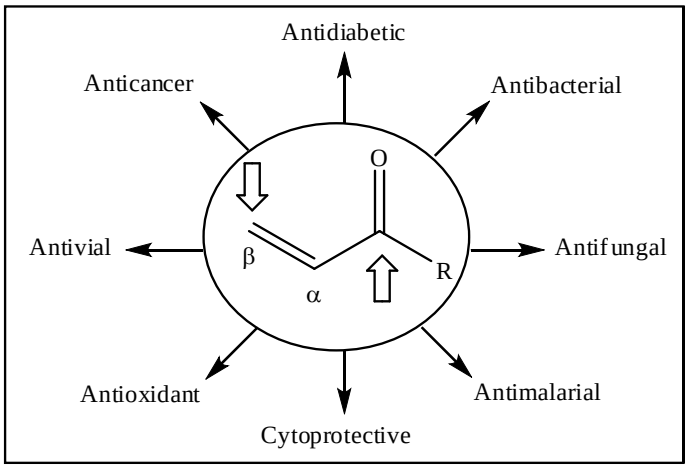
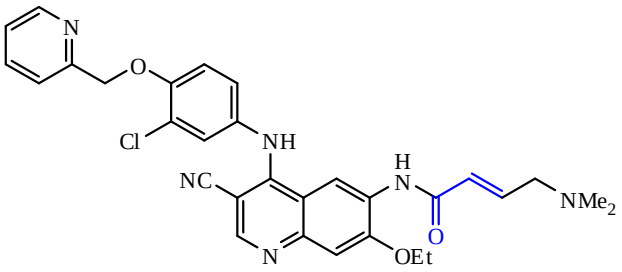


Fig. 1: Enone moiety for development of potential bioactive molecules (arrows indicating electrophilic sites for nucleophilic addition).

Anticancer activity

The EGFR/HER-2 are well known receptor tyrosine kinases and their higher level has been recognised in the development of cancer. HKI-272 (**1**, neratinib) and EKB-569 (**2**, pelitinib) are the chemotypes are potential inhibitors of EGFRs/HER-2 (**Fig. 2**). In 2017, neratinib has been already approved by USFDA for treatment of early stage HER2-overexpressing breast cancers [15].They are known to inhibit EGFRs irreversibly by covalent bond formation through Michael addition at enone moiety. In HER-2, Cys805 is located in close proximity at a distance of 3.43 A from enone and its thiol is capable for thia-Michael addition [16-18].



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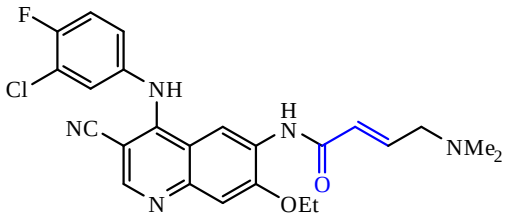

(2)

Fig. 2: Structures of EGFR/HER-2 inhibitors neratinib (**1**) and pelitinib (**2**).

Recently, Wang's group reported antitumor activity of spirodihydrothiopyran-oxindole derivatives (**3**) which acts by inhibiting p53-degrading enzyme Mdm2.These compounds contain enone moiety and having higher potency than corresponding spirotetrahydrothiopyran oxindoles (**4**). The ligand-protein binding study indicated that presence of enone moiety resulted in turning of phenyl group at right angle from spiral nucleus and fitting in Phe19 cavity at binding site on Mdm2. This special orientation helpsto

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potentiatehydrophobic interaction. While, in the absence of enone the phenyl ring binds to Leu26 binding cavity Mdm2 (**Fig. 3**) [19, 20].

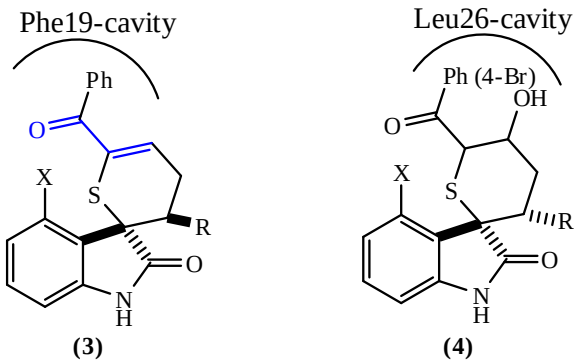

Fig. 3: Presence of enone moiety modifies binding pattern of spirothiopyran-oxindoles.

Proteosome inhibitors are important class of structurally diverse molecules having anticancer activity. In a study Trivella *et al.* reported that presence of enone moiety potentiate the proteosome inhibitory activity of peptides (**5-7**) [21]. This moiety provides site as Michael acceptor for -OH group of Thr1 residue in the biding cavity of proteosome. Crystallographic and quantum chemical study indicated covalent bond formation *via* 1,2- or 1,4-addition between enone and Thr1 which in turn forms cyclic adduct of molecule. These covalent interaction as 1,2-addition and 1,4-addition found to be responsible for reversible and irreversible inhibition, respectively(**Fig. 4a-b**).The absence of enone in a peptide (**8**) resulted in abolishment of proteosome inhibitory activity.

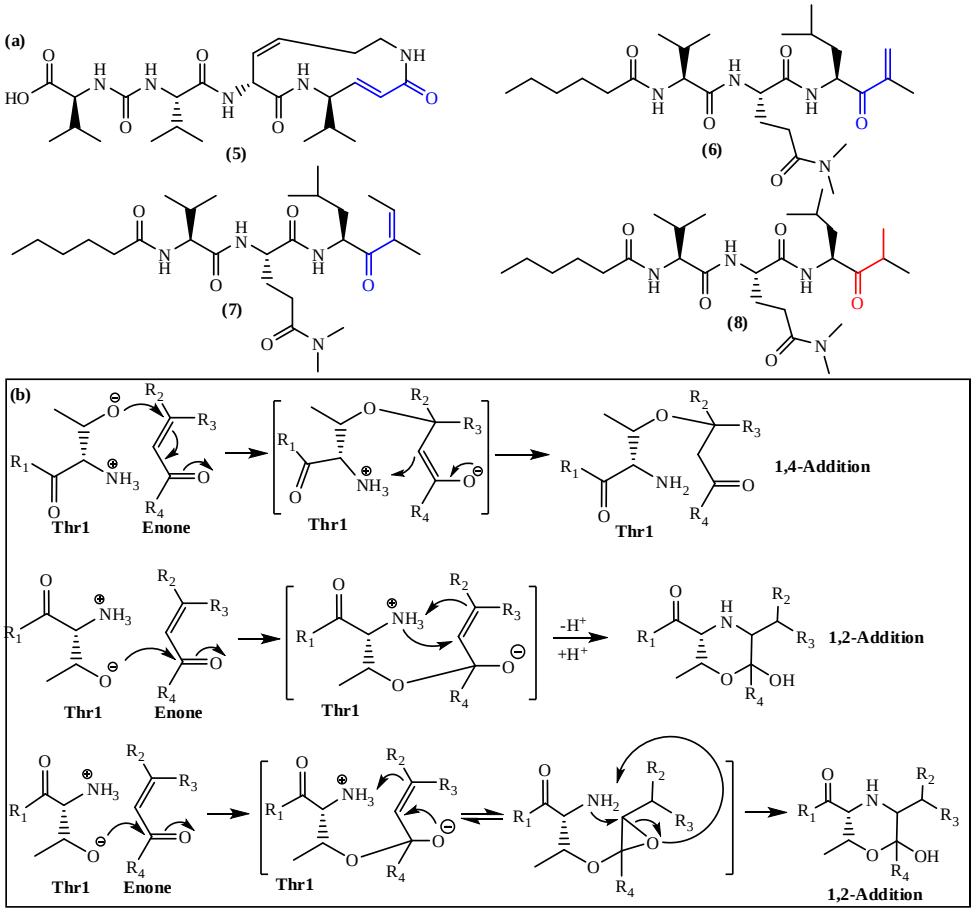

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Fig. 4: Structures of peptides 3-6 (a) and mechanisms of 1,2 and 1,4-addition of Thr1 (b).

Phosphoinositide 3-kinases (PI3Ks) and mammalian target of rapamycin (mTOR) are involved in the development of cancer. Previous studies have been demonstrated inhibition of PI3K and mTOR by wortmannin (**9**) and LY294002 (**10**) in a covalent manner through conjugated addition to lysine residue (**Fig. 5a**) [22-24].

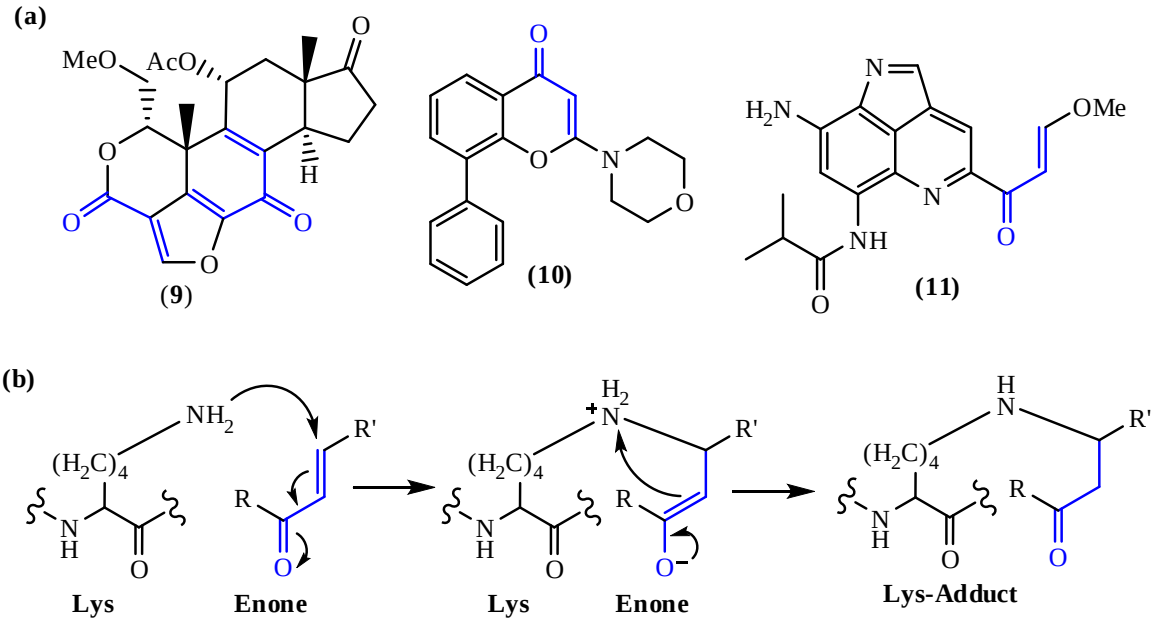

Fig. 5: Structures of PI3-kinase/mTOR inhibitors and mechanism of aza-Michael addition of lysine residue.

Recently, Castro-Falcon *et al.* identified neolymphostin A (**11**) from marine actinomycetes bacterium strain *Salinispora arenicola* CNY-486 as selective and potential dual inhibitor of PI3-kinase/mTOR(**Fig. 5a**) [25]. The mass spectrometry tandem MS/MS study showed that neolymphostin A covalently binds to Lys802 residue of PI3Kα. Moreover, docking of neolymphostin A into PI3Kα also indicated that electrophilic site (C-11) of enone side chain is oriented at a distance of 3.29 Å to N-atom of Lys802 side chain suggesting covalent interaction. The docking of neolymphostin A into mTOR showed that Lys2187,which is homologous to Lys802 of PI3Kα, positioned itself near electrophilic carbon of enone distance of 6.08 Å to N-atom of Lys2187 side chain of mTOR through a C-C single bond rotation. Further, induced fit docking showed 3.98 Å distance between reactive enone and N-atom of Lys2187.Thus, above studies indicated participation of enone moiety in covalent bonding with lysine residues *via* aza-Michael addition and is essential feature for inhibition of PI3Kα and mTOR (**Fig. 5b**) [26].

Antibacterial activity

Scientist at Merk & Co. isolated platensimycin (**12**) as antibiotic from *Streptomyces platensis* that acts by inhibiting FabF enzyme in the bacteria (including *Mycobacteria*). Further, several analogs of platensimycin have been reported with structural modification at several sites in the molecule. The conformational orientation of cyclohexenone ring in platensimycin decides its H-bond interaction and binding with bacterial enzymes to exhibit the desired biological

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activity [27].The SAR study of platensimycin analogs indicated that enone moiety (**12**,**13**) is essential for higher potency as compared to their hydroxylated congeners (**14**)in saFabF2 assay (**Fig. 6**) [28, 29].

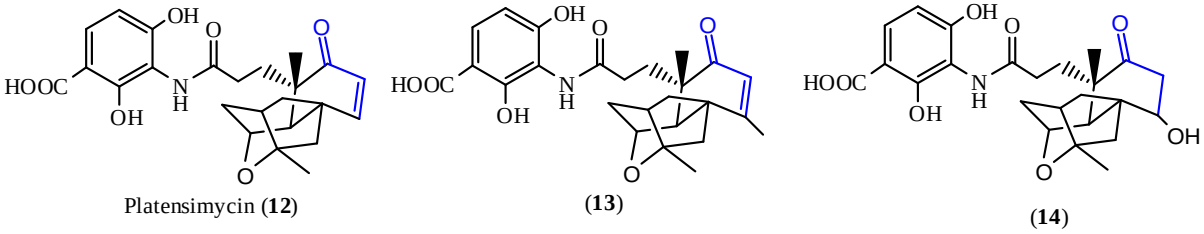

Fig. 6: Structures of FabFinhibitors platensimycin (**12**) and its analogs (**13, 14**).

MurA is an enzyme that catalyses the biosynthesis of peptidoglycan precursors in bacteria. In a study, Bachelier *et al.* have been identified cnicin (**15**) and cynaropicrin (**16**) as potential irreversible inhibitors of MurA (**Fig. 7**) [30]. Structure activity relationship study indicated that unsaturated ester (enone) moieties of **15** and **16** are essential for enzyme inhibition by forming adduct with -SH group of Cys115 of MurA.

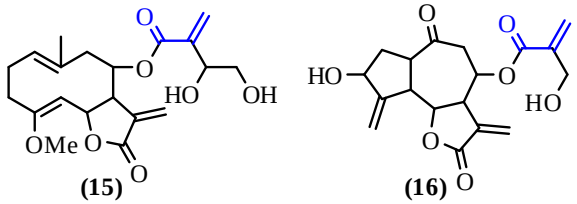

Fig. 7: Structures of cnicin (**15**) and cynaropicrin (**16**).

Anti-diabetic activity

The PPARγ agonists are well known for their hypoglycaemic activity to treat diabetes. 15-deoxy-$\Delta^{12,14}$-PGJ_2 (15d-PGJ_2, **17**) is a prostaglandin D_2-derived product that has been known to agonise to PPARγ and DP2 receptor response. PPARγ also inhibits NF-κB DNA interactions and activates IκB kinase to exert its anti-inflammatory effect. In 15d-PGJ_2 (**17**)presence of cyclopent-2-enone moiety is found to undergo covalent binding to IκB kinase and NF-κB through Michael addition and finally exerts biological response (**Fig. 8**)[31, 32]. It has been foundthat 15d-PGJ_2 interacts covalently with H-Ras protein in 3T3 cells by addition of Cys184 [33]. Recently, Reddy *et al.* reported that 15d-PGJ_2 forms covalent adduct with Cys249 of PPARγ [34].

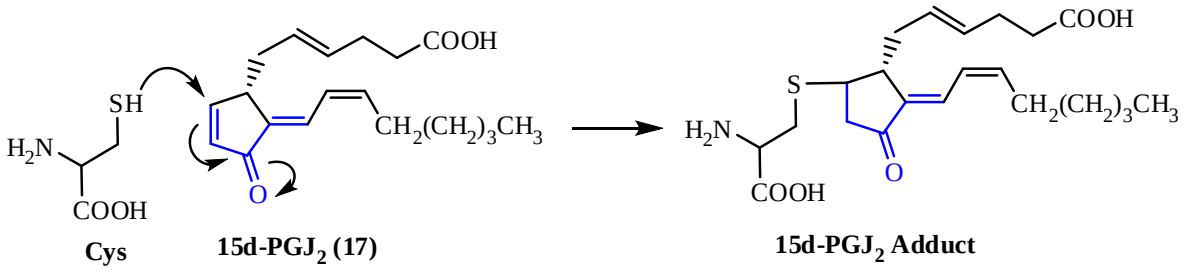

Fig. 8: Interaction of 15d-PGJ_2 (**17**) with target proteins- PPARγ, NF-κB, IκB kinase etc.

Earlier, Schopfer *et al.* have been reported nitro containing unsaturated fatty acids (**18**) covalently bind to PPARγ through Michael addition at Cys285 [35]. These compounds

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partially agonisesPPARγ and lower the blood glucose level in a mice model.Similarly, Utsugi *et al.* have been reported cinnamate-GW9662 hybrid compound (**19**) that binds to PPARγ covalently. The rhodamine-maleimide assay indicated that thiol of Cys285 of PPARγforms covalent bond with unsaturated ester tail of compound**18***via* Michael addition (**Fig. 9**) [36].

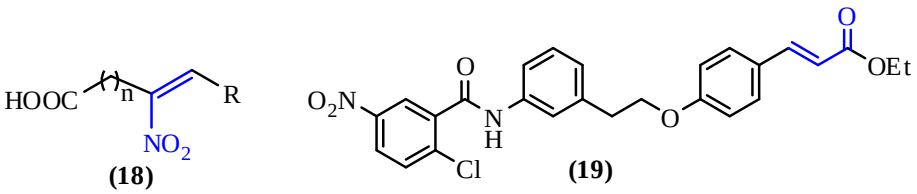

Fig. 9: Structures of PPARγ agonists compound (**18**) and (**19**).

Antioxidant and cytoprotective activity:

NAD(P)H:quinone oxidoreductase 1 (NQO1)acts as an antioxidant and cytoprotective in biological system [37]. The production of NQO1 is regulated by Keap1/Nrf2/antioxidant response elements to perform its activity. Thus, inhibitors of Keap1 have been reported to prevent its binding with Nrf2 to enhance the NQO1 gene expression. Ghorab *et al.* reported appropriately substituted sulphonamides as inhibitors of Keap1 [38]. The SAR study indicated that presence enone moiety in compounds (**21** and **22**) make them active as inducer of NQO1 as compared to parent compound (**20**) which is inactive (**Fig. 10a**). Further, molecular docking study showed that enone moiety potentiate the binding of ligand to Keap1. Previouslyit hasbeen shown that electrophilic olefins are able to react reversibly with sulfhydryl groups (nucleophiles)several proteins and presence of a -CN group enhance the reactivity of olefinsto make them potent inducer [39]. Similarly,molecules with cyano enones have been covalent binding to Cys residues of Keap1 to induceNrf2 gene expression. Thus, it suggests that enone moiety participates in reactions with sulfhydryl group of Keap1 through covalent 1,4-thia Michael addition (**Fig. 10b**) [40, 41].

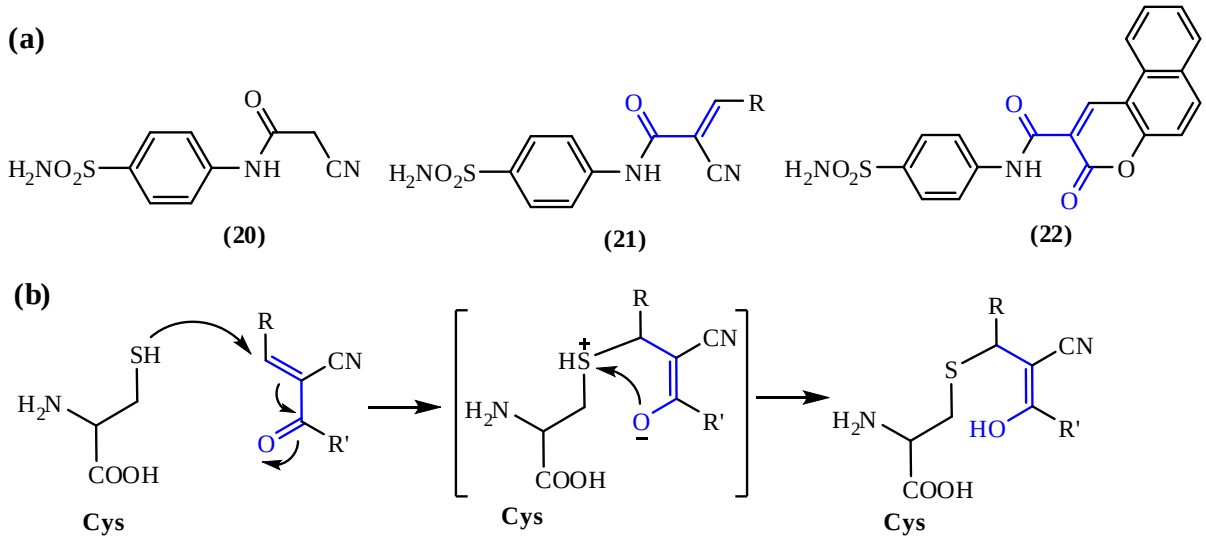

Fig. 10: Structures of Keap1 inhibitors (**20-22**) and mechanism of 1,4-thia Michael addition.

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Calpain is a Ca^{2+}-dependent proteolytic enzyme family and calpain inhibitors act as neuroprotectives. In a study, Lu *et al.* reported thalassospiramides (**23**) as potential inhibitors of calpain [42]. The study of molecular mechanism showed that thalassospiramides covalently bind to the -SH group of Cys115 residue of calpain at α,β-unsaturated carbonyl moiety by a 1, 4-Michael addition reaction. Similarly, peptide**24** has been shown to inhibit calpain-1 (**Fig. 11**) [43].

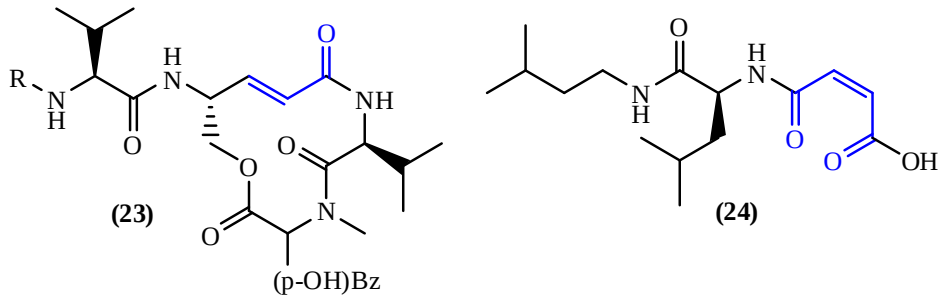

Fig. 11: Structures of calpain inhibitors (**23**) and (**24**).

Antimalarial activity

Falcipains are cysteine proteases of *Plasmodium falciparum* which degrade hemoglobin of host to and provide free amino acids for growth of parasite [44]. Thus, inhibitors of falcipains have been shown potential as antimalarial agents. Falcipain 2 inhibitor (**25**) has been used as potential antimalarial drug and terminal α,β-unsaturated ester moietyis essential feature for antimalarial activity [45]. Similarly,etacrynic acid derivatives**26**and **27** have been reported as potential inhibitors of both falcipain-2/3 and Michael acceptor (enone) moiety was found to be essential for their activity (**Fig. 12**)[46].The mechanism of action indicated that these compounds (**25-27**) acts by forming covalent Michael adduct with -SH group of Cys42 in the binding cavity at falcipain-2. His174residue deprotonates thiol to tholate of Cys42 and carbonyl oxygen participates in H-boding with Trp206 side chain to enhance electrophilicity of enone moiety [47].

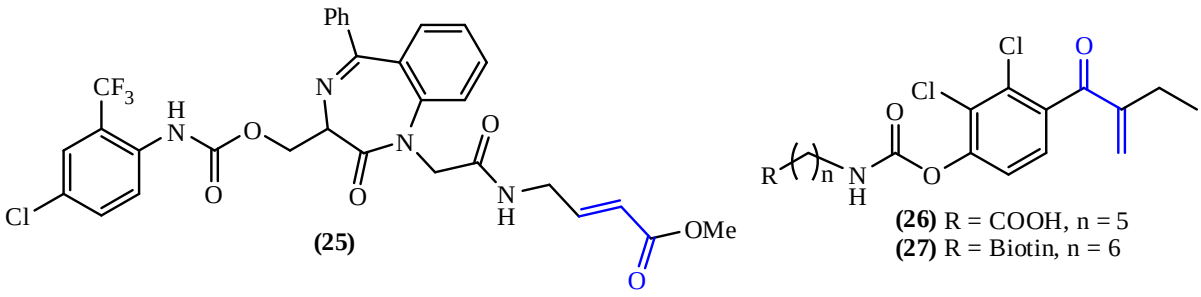

Fig. 12: Structures of falcipain inhibitors (**21-23**).

Antiviral activity

Inhibition of viral protease by small molecules has been found to be important strategy for development of novel antiviral therapeutics. Earlier study reported compound **29** and **30** as irreversible inhibitors of hepatitis C viral (HCV) protease. The structure activity relationship and binding studies showed that compound **29** and **30** having Michael acceptor are potent

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inhibitors of HCV protease with IC_{50} values of 4 and 2 nM, respectively, than compound devoid of Michael acceptor (**28**, IC_{50} 1147 nM). Mutation supported mechanism of action showed that both **29** and **30** inhibits HCV protease by covalent binding of enone to thiol group Cys159. Further, co-crystallized HCV protease with compound **29** confirmed a C-S covalent bond formation between Cys159 and enone moiety of terminal acrylamide side chain (**Fig. 13**) [48, 49].

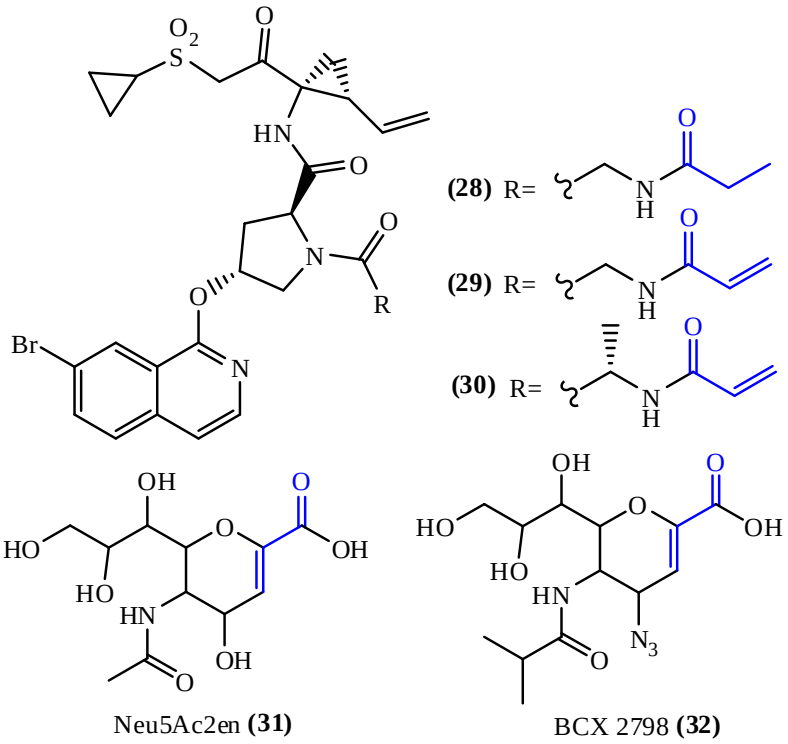

Fig. 13: Structures of irreversible inhibitors of HCV protease (**28-30**) and haemagglutinin-neuraminidase (**31, 32**).

Human parainfluenza virus infection causes lower respiratory tract disease in children and currently there is no available therapeutic drug for treatment. The haemagglutinin-neuraminidase (HN), a viral surface glycoprotein, is an ideal target to develop antiviral. Several small molecular inhibitors of haemagglutinin-neuraminidase have been reported with characteristic enone moieties such as Neu5Ac2en (**31**), BCX 2798 (**32**) and its derivatives [50]. However, their mechanism of action from point of view of Michael adduct formation is remains unexplored.

CONCLUSION

The enone moiety is an important functional group in the ligand that directly involves in ligand-protein interaction by providing an electrophilic site for different nucleophilic groups of protein such as -SH, -OH, $-NH_2$ etc. This interaction resulted in the formation of ligand-protein adduct due to covalent bonding *via* Michael addition. Thus, covalent binding of ligand to protein may lead reversible or irreversible inhibition to modify the biological events for different types of biological activities. It has been explained with help of several latest examples of nucleophilic addition on enone moiety along with mechanism using different

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types of nucleophiles from amino acid residues of proteins. The enone adduct formation has been found to be responsible for diversity of biological activity as compared to absence of enone. Thus, this review will be helpful to use enone moiety as electrophilic site by attaching it at appropriate position in different chemical scaffolds for design of novel bioactive molecules.

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