A comparative study of Oxazolones and imidazolones-A review

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ABSTRACT

In assessment of vast importance of heterocyclic compounds in the field of chemistry and pharmaceutical sciences, an attempt is made for comparative studies of oxazolones and imidazolones as they are closely associated with each other. In the present review heterocyclic ring comprising compounds based on oxazolone and imidazolone derivatives as target molecules are chosen for exploring their pharmaceutical activity, microbial activity and molecular docking studies. The existence of quantified functional moieties in strategic position of a molecule to actively bind the receptor site is also studied with the help of molecular docking studies.

Keywords: oxazolones, imidazolones, molecular docking studies

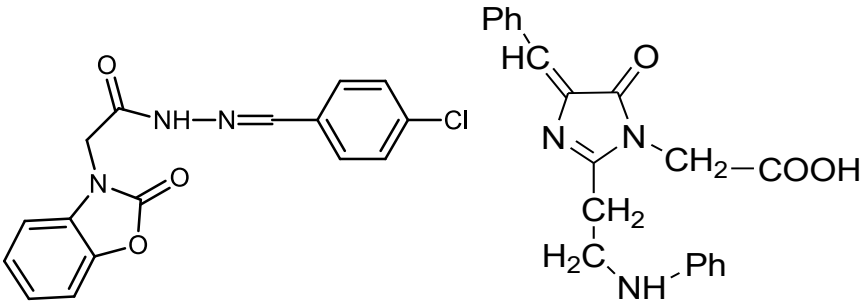
INTRODUCTION

Oxazolones exhibit important biological activities such as antiobesity[1], anti-inflammatory[2], neuroleptic[3], sedative[4], antidiabetic[5], anticancer[6,7], antimicrobial[8], antibacterial[9], analgesic[10], antifungal[11], heterocyclic precursors[12] as well as coupling and photosensitive devices for proteins[13].Oxazolones are well known for their multifunctional behavior as they participate in a number of replacement reactions, cycloadditions, dimerization and other type of reactions leading to formation of a variety of heterocyclic compounds. Imidazolones are five membered carbonyl

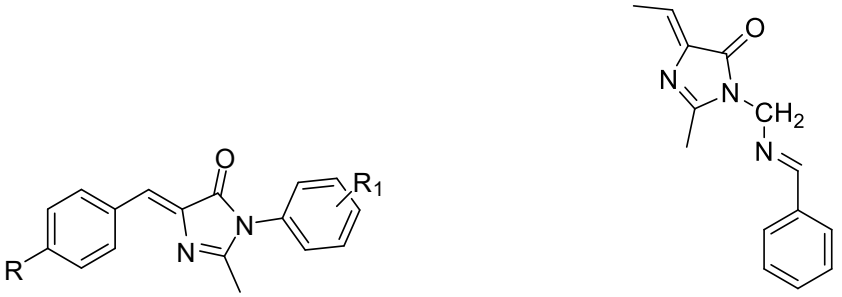
dihydro-imidazoles and classified into 2-,4-,or 5-imidazolones built on the site of carbonyl group. Imidazolone-5-ones clasp a widespread band of pharmacological and biological actions as CNS depressant[14] ,antifungal[15], antihelmentic[16],anticancer[17], anticonvulsant[18], anti-Parkinsonian[19]and monoamine oxidase inhibitory[20] agents.

1.Pharmacological studies of oxazolones and imidazolones

Gosken U.S etal synthesised [21] (4-chlorobenzylidene)-2-(2-oxo-benzooxazol-3(2H)-yl) acetohydrazide which showed better Analgesic and Anti-inflammatory activity. The anti-inflammatory activity of 4-benzylidene, 4,5-dihydro-5oxo-2-(substituted phenyl amino ethyl)-1H-imidazole-1-alkanoic acid[22] was reported by Atul Kumar.

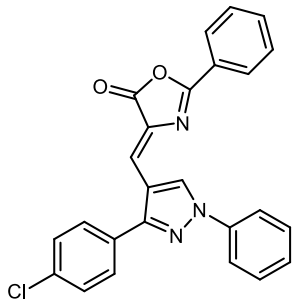


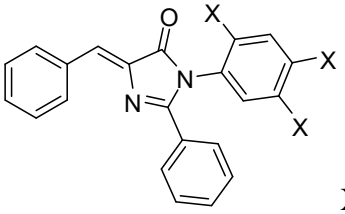
Monoamineoxidase suppressive and Anti-convulsant behaviour of trisubtituted imidazolones were reported by MahimaVerma and his co-workers[23]. Jayantha Kumar *et al.,* synthesized oxazolinone and imidazolinone derivatives for Anti-microbial activity[24]



R =Cl, R_1 = m-$CONH_2$

Argade N.D etal [25] prepared pyrazol substituted oxazolones which exhibited remarkable antimicrobial activity. N.C.Desai *et al.,* synthesized various trichloro phenyl imidazolinone derivatives for anti-microbial activity[26]



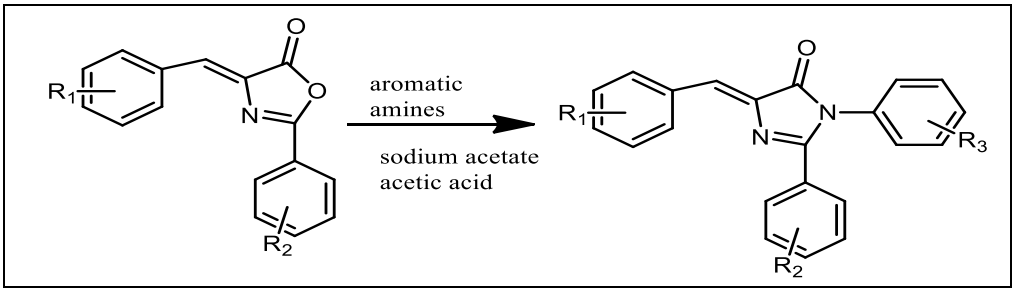


X=Cl^-

2.Preparations of Oxazolones and Imidazolones

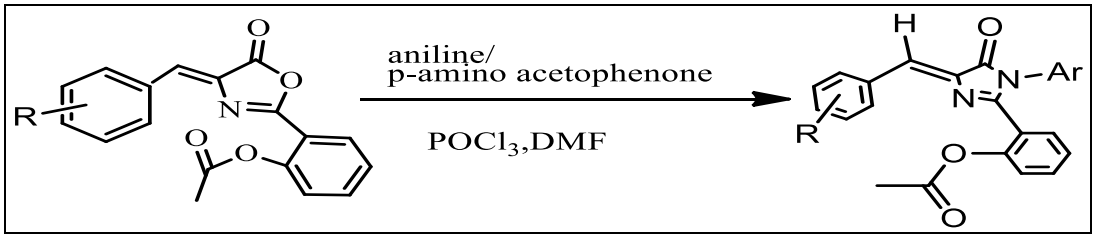
Synthetic approaches and chemical properties of oxazolone chemistry were recognized as imperative synthones for the preparation of diversified otherwise tricky to obtain synthetically useful and novel heterocyclic systems. oxazolones are used as vital intermediates in synthesis of imidazolones. The most common technique adopted for synthesis of imidazolones is from oxazolones as the yield is very good compared with other routes.

Imidazolin-5-ones were prepared by the reaction of 2-oxazolin-5-ones and aromatic amines in the presence of acetic acid and sodium acetate[27]



R_1=O-Cl, P-Cl R_2=O-NO_2, m-NO_2 R_3=H, P-Me, O-Cl, m-Cl

Imidazolone moities were also prepared by the reaction of oxazolones with aromatic amines in the presence of $POCl_3$ in DMF[28] .The oxazolones are prepared from hydroxy derivative of hippuric acid[29] by perkin condensation.

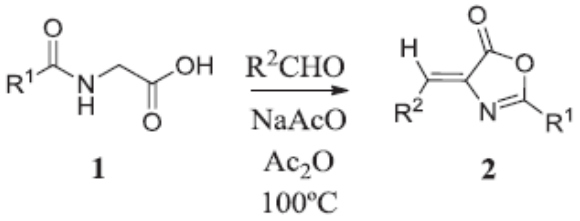


Ar=phenyl, acetyl phenyl R=-OH,-Cl,-Br,-NO_2

3.Response of oxazolones and imidazolones as photoswitches

oxazolones have been used as precursor for the synthesis of GFP derivatives and their photoisomerisation is already known[30,31]. The recent results on the photophysics and photochemistry of Benzylidene-Oxazolones are presented[32]

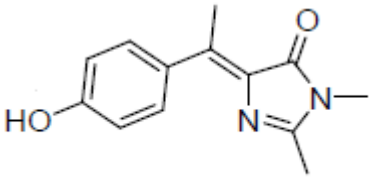
Benzylidene-Oxazolones **2** prepared from amino acid **1** are good moeities for efficient photoswitches as they are easily synthesised, feature good photoisomerisation quantum yields and are thermally stable[33].



R^1= Me, Ar
R^2=Ar

Imidazolones are also synthetic analogues of GFP chromophore and the modifications introduced in these compounds under study turned them into efficient photoswitches.

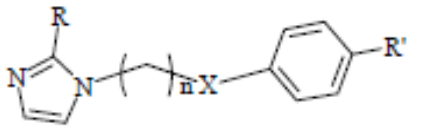
In an attempt to recognize this diversity, the synthetic analogue of the FP chromophore 4′-hydroxybenzylidene-2,3-dimethylimidazolinone[34] has been studied intensely, through both experiment and quantum chemical calculation[35-47]. The extended delocalisation leads to a visible absorbing chromophore which is approximately planar in its electronic ground state and adopts the *cis* isomer. The quantum chemical calculations suggest that excited state population decay occurs at a conical intersection reached by an approximately 90° rotation about the τ or ϕ twisting coordinate[48-50].



4.Antioxidant behaviour of oxazolones and imidazolones

In the free-radical scavenging activity of (**a**)explored by DPPH test, verified that compounds characterized by a keto group displayed a higher quenching capacity than O and CH_3 groups. This may be due to the fact that the adjacent phenyl ring may subsidize to stability of free radical via resonance and by providing accessory site for free radicals[51]. The new imidazole **(b)**compounds were analysed for their antioxidant

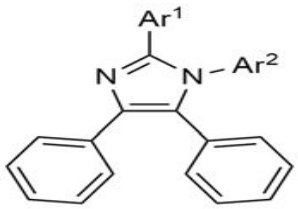
properties by DPPH free radical scavenging assay. The efficacy of the samples as DPPH radical scavengers was established by the measured IC50 values[52].



a

X=CO, O, CH_3

R=H, CH_3,R'=NO_2



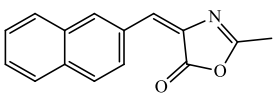
b

Ar^1= 4-OMe-C_6H_4, 4-Me-C_6H_4

Ar^2=H, 4-Cl- C_6H_4

5.Role of oxazolones and imidazolones as inhibitors of corrosion in steel

As per literature assessment it has been established that organic moieties containing N, S and O atoms with conjugated system are good corrosion inhibitors[53]. Various researchers recognized that these molecules certainly adsorb on the metal surface forming a protective layer[54-57].



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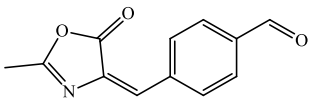
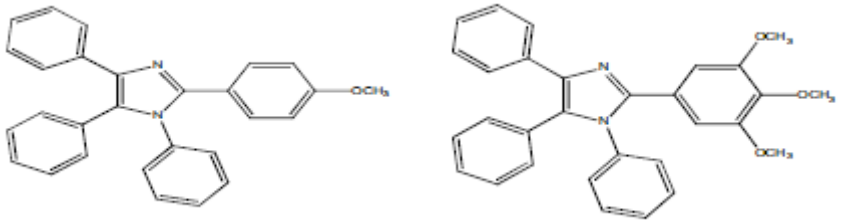


II

Inhibiting properties for carbon steel in three varying HCl concentration on oxazolones was studied. Compound I was found to be more effective than compound II in 1NHCl concentration in terms of %corrosion efficiency. The outcomes of gravimetric analysis, electrical resistance corrosion monitoring methods, UV-Visible, pH studies and surface studies like SEM, SEM-EDX and Langmuir Adsorption further established the positive

aspects of the inhibitor coatings owing to decreased corrosion rate on application of the inhibitors on the steel samples[58].



C_1 **C_2**

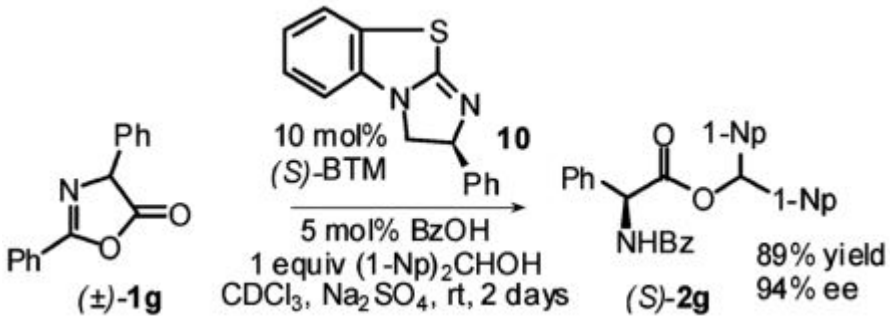
The organic molecules **C_1** and **C_2** revealed excellent protective qualities for protection of mild steel against corrosion in 1M HCl medium, and the inhibition efficiency increases with increase in the inhibitor concentration. Based on polarization measurements, EIS measurements, gravimetric studies and SEM analysis depicted the development of protective film of inhibitors molecule over the metallic surface. The experimental results exhibited strong tendency of adsorption of investigated inhibitors over the steel surface[59].

6.Dynamic kinetic resolution(DKR) of oxazolones and Imidazolones

Dynamic Kinetic Resolution reactions can result in quantitative yields with enantiomeric excesses approaching 100%. Oxazolones are excellent substrates for DKR reactions on account of their low pKa of the C-4 proton and their inherent reactivity towards lipase-catalysed alcoholysis[60].

Yang et al proposed a novel highly enantioselective method for the Dynamic Kinetic Resolution of azlactones. It is specifically suited for the C4-aryl-substituted substrates, thus supplementing the previously available enzymatic and nonenzymatic protocols. Dynamic kinetic resolution [61] of azlactones[62] by way of their enantioselective alcoholysis offers an attractive method to the asymmetric synthesis of α-amino acid

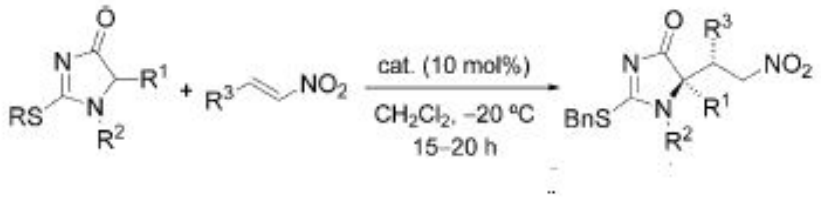
derivatives. Enantioselective acyl transfer catalyst benzotetramisole (BTM) has been found to promote dynamic kinetic resolution of azlactones providing di(1-naphthyl)methyl esters of α-amino acids with up to 96% ee[63].



1g =2,4-diphenylazlactone

2g=di(1-naphthyl)methyl esters of α-amino acids

In 2015, Palomo and coworkers[64] established for the first time that various N-substituted a-amino acid derivatives could be obtained in excellent diastereoselectivities and enantioselectivities through the enantioselective 1,4-addition reaction of imidazolones to nitroolefins.

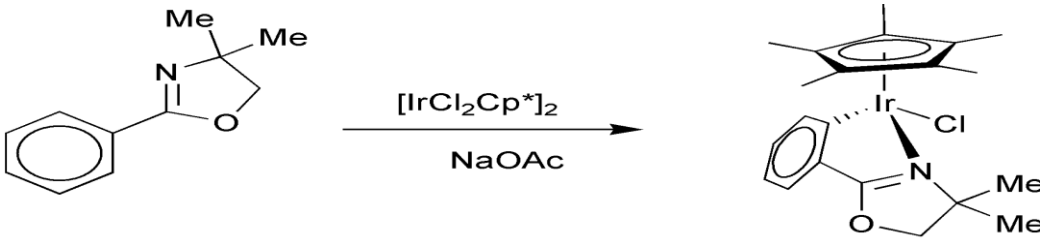


R^1=Me, R^2=Me,R^3=Ph

It was observed that by using the Rawal catalyst[65] the reactions of the N-methyl imidazolones with nitroolefins advanced effectively in terms of yield and stereocontrol,

7.Cyclometallation of oxazolones and Imidazolones

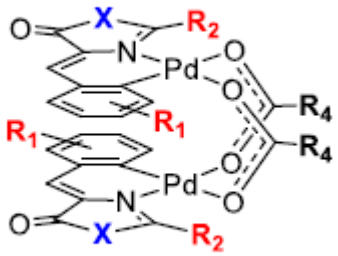
Cyclometallation of phenyl oxazoline **I** with [IrCl**2**Cp*]$_2$ and NaOAc led to formation of **II**. The structure of the complex was predicted by spectral studies.^{1}H NMR spectrum shows two singlets at δ 1.50 and 1.53, two mutually coupled doublets at δ 4.43 and 4.55 due to the oxazoline and only four protons in the phenyl region as anticipated for cyclometallation[66].



I **II**

From the results obtained, it was observed that sodium acetate can promote cyclometallation of oxazolines with [IrCl**2**Cp*]$_2$ even at room temperature.

The orthopalladation of 2-phenyl-4-aryliden-5(4*H*)-imidazolones[67] takes place under experimental conditions wherein a mixture of the imidazolone and $Pd(OAc)_2$ in equimolar ratio is heated at 75 °C in trifluoroacetic acid as solvent for 4 hrs leading to formation of dimers.



R1=2-Cl, 2-Br ; R2=Ph ;X=NCH2C5H4 ;R4=CF3COOH

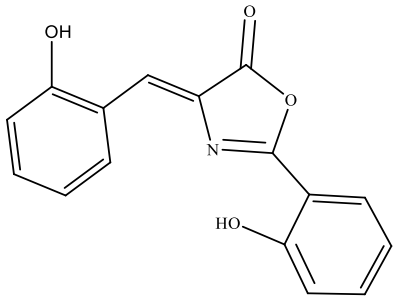
The orthopalladation of a diverse 4-aryliden-5(4*H*)-oxazolones and -imidazolones with different substituents at the arylidene ring takes place through C-H bond activation with

complete regioselectivity, because only the ortho position of the 4-arylidene ring is activated. The resulting orthopalladated complexes have dimeric open-book structures with carboxylate bridges.

8.Molecular docking studies of oxazolones and imidazolones

Molecular Docking is used to predict the interaction of molecules with protein binding sites .This is applicable in drug design.The tools used for docking include structure based drug design, 3D grid where protein and ligand are placed and Glide which predicts ligand and protein binding and understanding of steric and electrostatic interaction ,hydrogen bonding interaction and pi bonding interaction with aromatic groups. Glide helps in predicting favorable interactions between ligand molecules and receptor. The properties and shape of receptor are represented on a grid by setting various fields that offer accurate ligand pose for docking Docking is one of the tools used to discover complementarity between the receptor and ligand[68]. Molecular docking is used to predict the steric, electrostatic or vanderwaal's inreaction or hydrogen bonding interaction between ligand and receptor which gives scope in applying this tool in biological systems[69] .The position and orientation of a ligand relative to the receptor, along with its conformation is referred to as *ligand pose*.Glide uses ligand pose which use an algorithm for evaluating ligand receptor interaction energy[70].

Docking of azlactone derivatives into DNA showed hydrogen bond interaction with G5 nucleotide. These molecules were placed in between the base pairs resulting in π- π interaction. The dock score for compound **I** is -6.184kcal/mol. It showed hydrogen bond interaction with G5 and T14 apart from π- π interaction[71].



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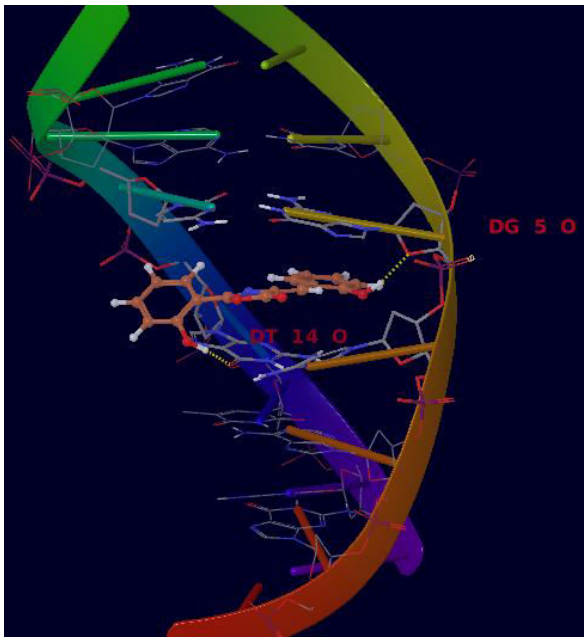
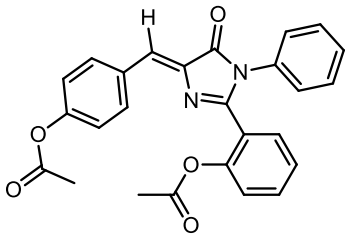
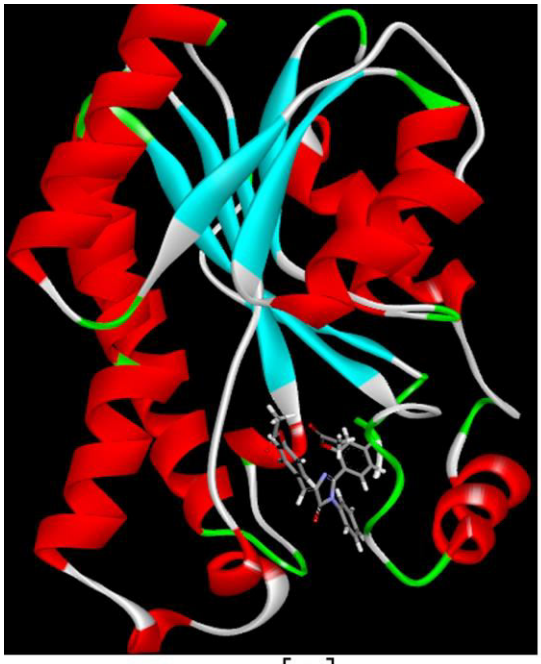


Dock pose of I in the intercalation site of DNA showing hydrogen bond interaction

Substituted imidazole and benzimidazole inhibitors of Staphylococcus aureus and Escherichia coli enoyl acyl carrier protein reductase (FabI) have been reported and crystallized. These structures help in determining the mode of interaction of the inhibitors with the enzyme, to elucidate the mode of interaction and binding of synthesized imidazole derivatives. Molecular docking studies[72] were carried out on X-ray crystal structure of FabI of Staphylococcus aureus (pdb id: 4NZ9) obtained from protein data bank (www.rcsb.org).The molecule **II** showed hydrogen bond interaction with amino acid residue Tyr157, the major interaction with the protein were of hydrophobic nature with amino acid residues Leu102, Tyr147, Val154, Met160, Pro 192 and Ile207.



II



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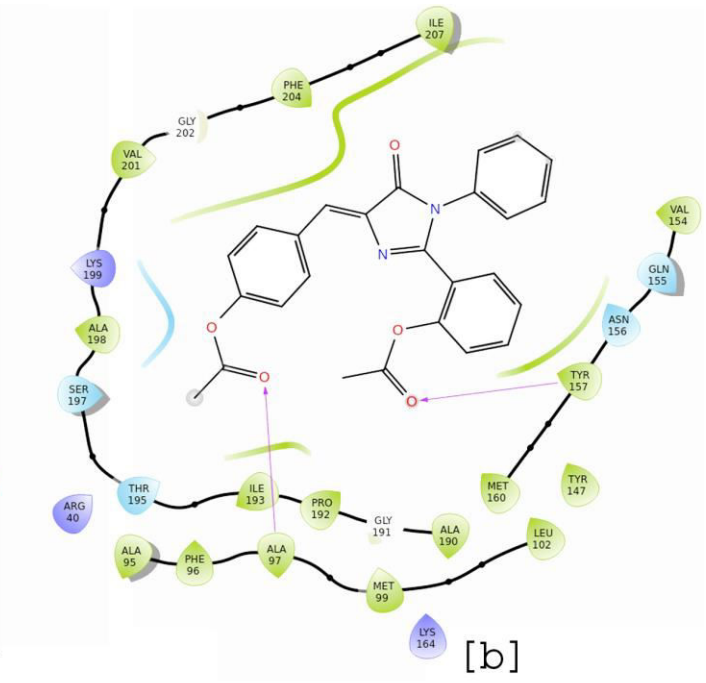
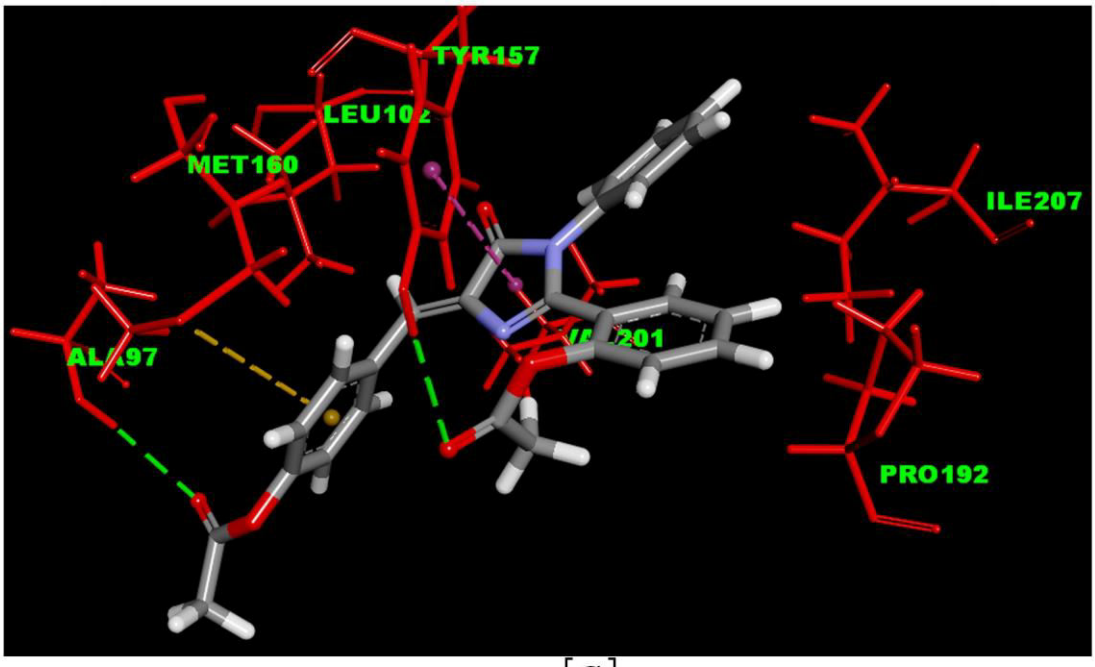

ILE 207
PHE 204
GLY 202
VAL 201
LYS 199
ALA 198
SER 197
THR 195
ARG 40
ILE 193
PRO 192
GLY 191
ALA 190
ALA 95
PHE 96
ALA 97
MET 99
LYS 164
LEU 102
MET 160
TYR 147
TYR 157
ASN 156
GLN 155
VAL 154

[b]


TYR157
MET160
ILE207
PRO192

[c]

Dock pose of molecule **II** (a) in the active site of Fab I, (b) Ligand interaction diagram representing the hydrogen bond interaction and (c) hydrophobic interaction of the molecules with active site amino acid residues.

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