1.3.α, β – unsaturated carbonyl compounds

It is well known that the α, β –unsaturated ketones , are found as naturally-occurring compounds, but it could be considered that their true importance is extended in two branches, the biological activity associated with them, as well as they are widely used as versatile precursors for synthesis of several types of heterocyclic compounds examples are pyrazoles, isoxazoles, pyrimidines and fused heterocyclic derivatives which are of great biological interest especially as antimicrobial and antioxidants.(Jun Wu *etal*., 2014).

These are abundant in edible plants, and they possess conjugated double bonds and a completely delocalized π – electron system on both benzene rings. Molecules possessing such systems have relatively low redox potential and have a greater probability of undergoing electron transfer reactions.α, β – unsaturated carbonyl compounds are synthesized by Claisen- Schmidt condensation of aldehyde and ketone by base catalyzed followed by dehydration to yield the α, β –unsaturated carbonyl compounds.

1.3.1-Preparation of α, β – unsaturated carbonyl compounds.

α, β – unsaturated carbonyl compounds were prepared by condensing aryl ketones with aromtic aldehydes in presence of suitable condensing agents. They have been used as intermediates for the preparations of compounds having their therapeutic value.(Kalirajan *etal*., 2009).

Some of α, β – unsaturated carbonyl compounds were reacted with different reagents i.e. hydroxylamine hydrochloride, urea, thiourea, by condensation in ethanolic basic media to form different heterocyclic derivatives such as isoxazoles, pyrazoles, by cyclization reaction. (Kalirajan *etal*.,2009).

One of the important classes of the reactions which these compounds undergo is the ring closure reactions with hydrazine, guanidine etc. giving heterocyclic derivatives such as pyrazolone, pyrimidine, isoxazole etc. The enone functionality present in them provides an attractive site for 1, 3- nucleophiles affording such heterocyclic ring system. Such reactions are traditionally catalyzed by ethanolic NaOH or ethanolic KOH solutions under reflux conditions .

A series of substituted α, β – unsaturated carbonyl compounds were prepared by reacting 4'-piperazinoacetophenone or acetyl – 2, 5- dichlorothiophene and aromatic aldehyde. (Ghosh *etal*., 2014)

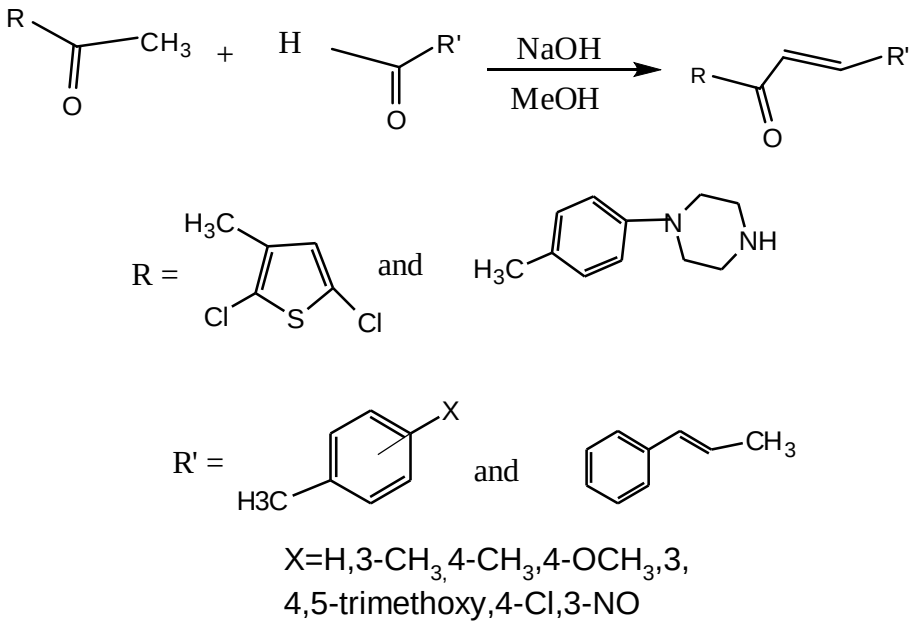


Fig.1.9.Preparation of substituted α, β – unsaturated carbonyl compounds.

Claisen Schmidt condensation method was adopted to give α, β – unsaturated carbonyl compounds. Acetophenone on condensation with aldehyde in the presence of base produced α, β – unsaturated carbonyl compounds. These are

subjected for reaction with hydroxylamine hydrochloride to give isoxaline derivatives of theα, β – unsaturated carbonyl compounds.(Khadar *etal*.,2014)

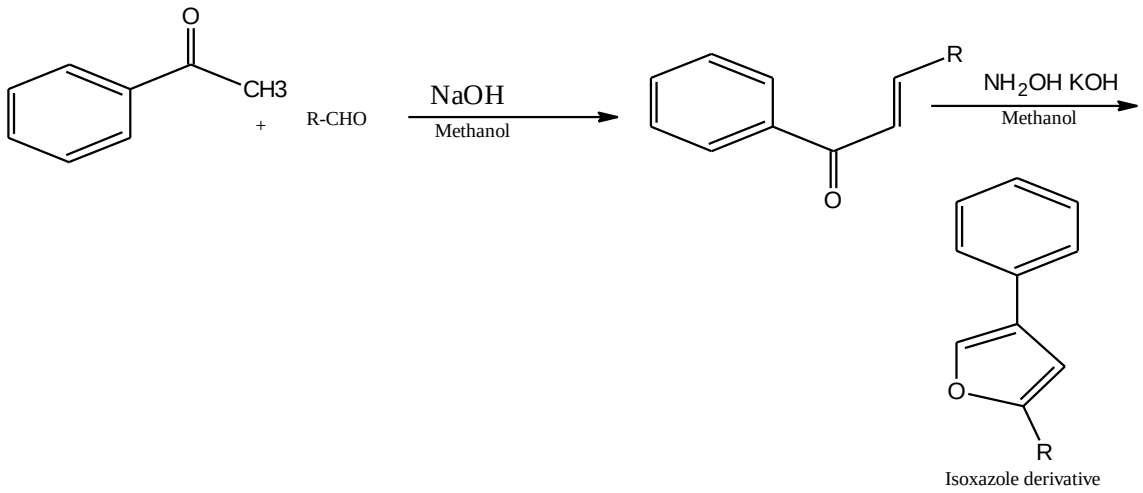


Fig.1.10. Isoxazole derivative structure

The β – unsaturated ketones were synthesized from substituted aromatic aldehydes and acetophenone. (Ghosh *etal*., 2014).

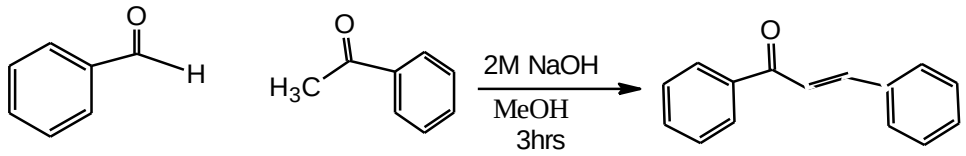


Fig.1.11.Synthesis of α, β – unsaturated ketones

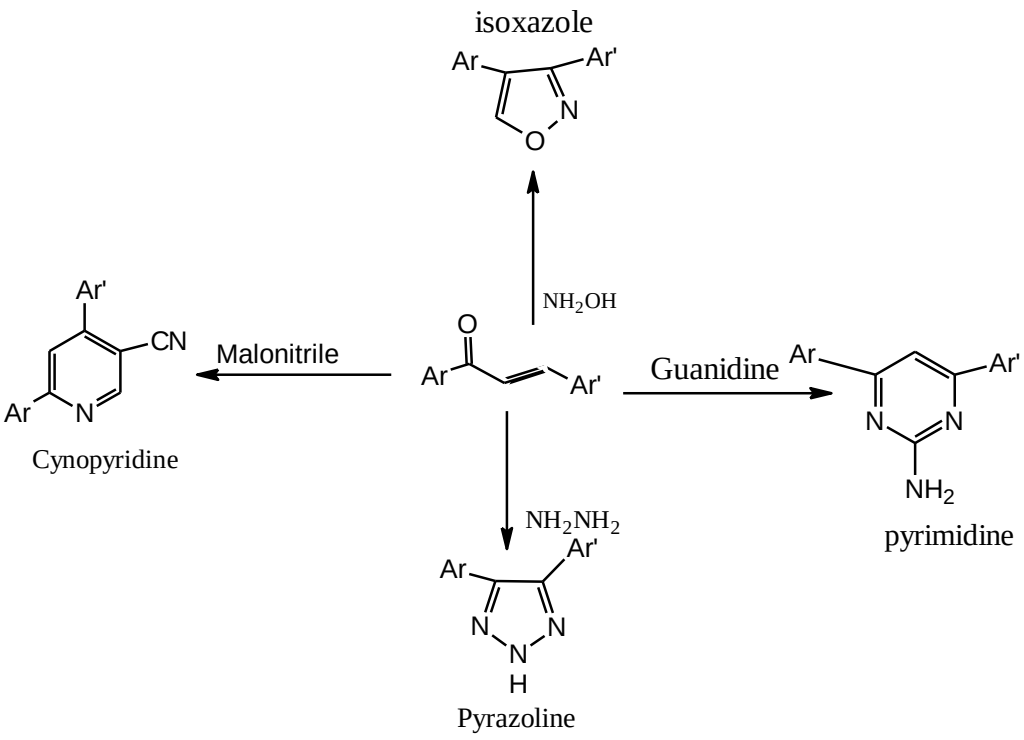


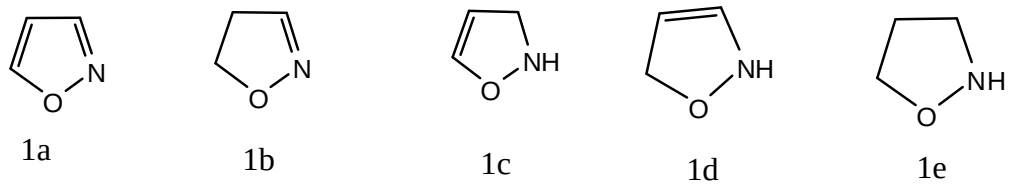
Fig 1.12.Ring closure reaction of α, β – unsaturated carbonyl compounds

1.3.2-Biological activities of α, β – unsaturated carbonyl compounds derivatives

These compounds are associated with different biological activates like insecticidal, anticancer, antiflammatory, antibacterial etc. The presence of unsaturated carbonyl systemof α, β – unsaturated compounds derivatives makes it biologically active. They have shown antibacterial activity against S.aureus, E.Coli, albicans and some other organism (Jalal, 2015;Lahtchev, *etal*.2008).

1.3.3-Isoxazoles:

Isoxazole is a five membered heterocyclic compound containing oxygen and nitrogen in 1,2 position and its partially saturated analogs are called isoxazolines (1a – 1d) and completely saturated analog is isoxazolidine (1e).



1a 1b 1c 1d 1e

Fig 1.13.Isoxazole structure

Isoxazoles are an important class of heterocycles which are largely employed in the area of pharmaceuticals and the pesticidal such as insecticidal, antibacterial, antifungal, antuberculosis, anticancer and ulcerogenic.

Isoxazole derivatives are used in the market as anti-inflammatory drugs, and COX-2 inhibitor, and anti-inflammatory drugs. Other derivatives such as sulfamethoxazole, sullfisoxazole and acivicin have been in commercial use for many years (Jayaroopa, 2013).

The reaction of terminal alkynes with n-Buli, and then with aldehydes, followed by the treatment with molecular iodine, and subsequently hydrazines or hydroxylamine provided the corresponding 3,5-disubstituted pyrazoles or isoxazoles in good yields with high regioselectivity ,through the formation of propargyl secondary alkoxides and α-alkynyl ketone. The reaction is the preparation of 3, 5-disubstuted isoxazole from terminal alkynes, aldehydes, molecular iodine, and hydroxylamine.(Ryo *etal.*,2014).

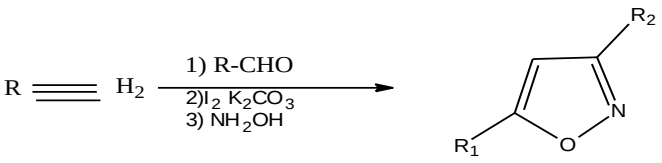


Fig.1.14.3,5-disubstituted isoxazole preparation reaction.

1.3.4-Biological activities of isoxazoles derivatives

Isoxazoles possess interesting medicinal properties and have some industrial utility.Many biologically active isoxazoles and reduced isoxazole derivatives have been reported, viz.,the naturally occurring antituberculosis, antibiotic, cycloserine, the monoamine oxidase inhibitors, isocarboxzid, useful in psychotherapy and isoxazole steroids show anabolic activity e.g. denazole. (Kapubalu *etal*., 2011). Isoxazole derivatives were used as inhibitors for ulcers, lipoxygenase. (Elkanzi *etal.*,2014). Their antimicrobial activity and particularly the antifungal action have been largely attributed to the reactive enone moiety. As a Micheal reaction acceptor the enone unit thiol groups of certain proteins. Most α, β – unsaturated compounds inhibit biosynthesis of yeast cell wall and thus unfold their antifungal potential.(Lahtchev, *etal.* 2008).

The isoxazole nucleus is well known for its medicinal importance and a number of related compounds are known to exhibit antitumor, anti-HIV and cestoidal agents.

Compounds containing an isoxazole scaffold are known to possess antimicrobal, anti-inflammatory, antiviral and antileukemic. (Kumudini *etal*. ,2014).

1.4. Quantitative structure- activity relationships. (QSAR)

1.4.1. Definition of QSAR

QSAR is an effective way of optimizing or correlating certain structural features or molecular descriptors, such as lipophilicity, polarizability,or electronic and steric properties within a congeneric series of molecules with their biological activities.(Mohammed *etal.*,(2009).

QSAR is a statistical model that relates a set of structural descriptors of a chemical compound to its biological activity. QSAR studies have acquired an important position within modern chemistry. In QSAR analysis, one or more molecular descriptors are related with the molecular activity by means of statistical analysis. The main objective of this analysis is the creation of statistical models through which it is possible to predict the biological activity of novel compounds that have not been tested yet.

The main steps involved in the development of QSAR are:

• The selection of the database of compounds with known biological activities (training set).

•The calculation of molecular descriptors.

• The development of a statistical model that relates the activity with calculated descriptors.

• The evaluation of the generated model with a test set. (Vilar *etal*., (2008).

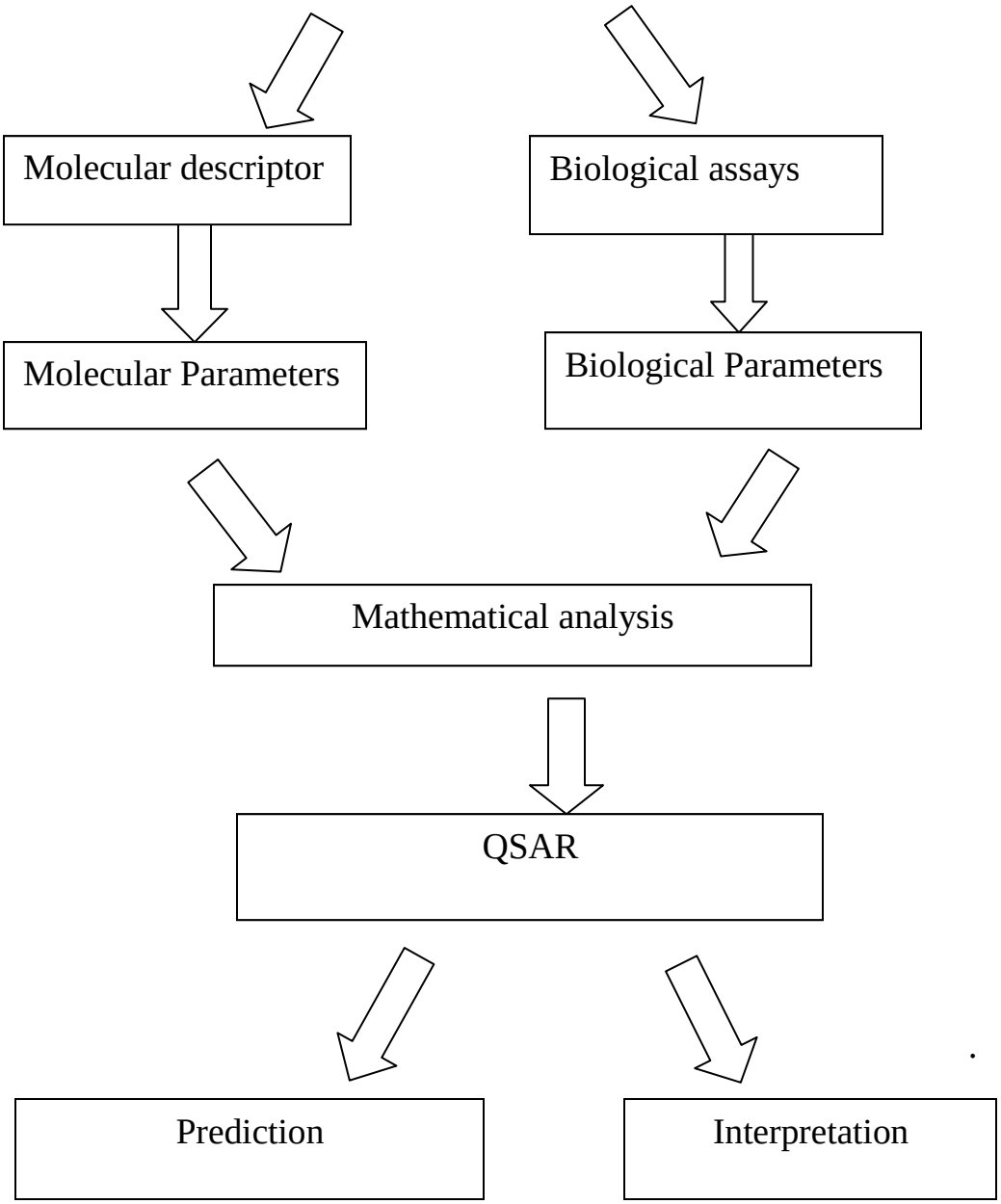


Fig.(1. 15).Main steps involved in the development of a QSAR mode

QSAR describes how a known biological activity can differ as a function of molecular descriptors derived from chemical structure of a set of molecule.

Many physiological activities of a molecule can be associated with their composition and structure. Molecular descriptors which are numerical descriptors of the molecular structures, are used for performing QSAR analysis. (Ponmary *etal*.,2010).

Aims and objectives:

Recently, quinones have been the subject of much interest, because of their various biological, pharmacological, antitumor activities, and they were introduced in many clinically important antitumor drugs.

The present work aims to:

• Preparation of α, β – unsaturated carbonyl compounds derivatives using Claisen-Schmidt and Aldol reactions.

• Preparation ofsome heterocyclic compounds i.e. amino-isoxazoles derivatives from the reaction ofα, β – unsaturated carbonyl compounds with hydroxylamine using Micheal reaction.

• Preparation of the target compounds i.e. *p*-quinones derivatives from the reaction of 2, 3, 5, 6-tertrabromo-1,4-benzoquinone (bromanil), and the prepared isoxazoles.

• Preparation of the heterocyclic compounds by the reaction of 2.5-bromo-3, 6- diamine- (*p*-diacetylphenyl)-1,4-dione.

• QSAR study can be used to predict the biological activities of novel compounds that have not been tested yet.

• Selection of the database of compounds with known biological activities from literature.

• Calculation of the molecular descriptors to establish a statistical correlation that relates the activity with the calculated descriptors.

• Evaluations of the novel synthesized compounds for their anti-cancer properties

• Employment of molecular docking program to predict the ligand-acceptor complex structure of the novel compounds.

• The project aimed to analyze all of the synthesized compounds spectroscopically i.e.α, β – unsaturated carbonyl compound, isoxazoles derivatives and quinones derivatives, using elemental analysis (IR, ^{1}HNMR, MS spectroscopy.