Chapter 1

Introduction

The thesis work reports crystal and molecular structure analysis of therapeutic compounds viz., dihydropyridine derivatives, coumarin derivatives and venlafaxine derivatives. Objectives of the study are

1. to confirm the molecular structures of the compounds using X-ray diffraction technique.

2. to elucidate the molecular conformation.

1.1 Dihydropyridine derivatives

The study of dihydropyridines(DHP) began early in 1882, when Hantzsch [1] disclosed the first synthesis of these compounds.

1,4-dihydropyridines are known for their action as calcium channel blockers and are used for treating various cardiovascular diseases. The activity is believed to arise from binding with a receptor site located in the α_1 subunit of the L-type voltage gated channels present in skeletal and cardiac muscle [2]. For DHP molecules, structure-activity[3] relationship studies have indicated specific conformational details which correlate with high binding efficiency (figure 1.1.1).

i) The A ring should be in a flattened boat form.

ii) The B ring ring should be in a pseudo-axial position relative to the floor of the boat.

iii) Rings A and B should display an orthogonal relationship.

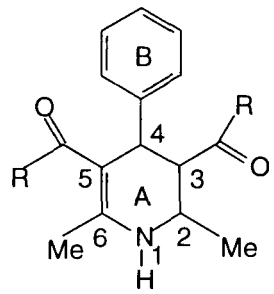


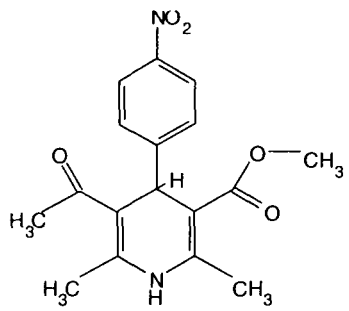
Figure 1.1.1: Scheme of DHP

iv) Electron withdrawing substituents on the B ring improve activity in the order *ortho* > *meta* >> *para*.

v) Substituents on the B ring should be in the 'prow' position and not projecting backwards over the B ring.

Most of the 1,4-dihydropyridine compounds possess different functional groups on C4 phenyl ring. It is observed that changes in substitution pattern at the C3, C4 and C5 positions for the first generation calcium channel antagonists like Nifedipine, alters potency, tissue selectivity and conformation of the 1,4-dihydropyridines. Other recent 1,4-dihydropyridines like Nicardipine, Nitrendipine, Nimodipine, Tiamdipine, Amlodipine etc.; have reached the pinnacle in the drug market.

Molecular structures of the following DHP derivatives have been reported in the thesis.



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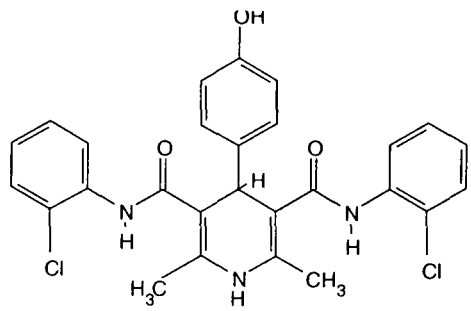

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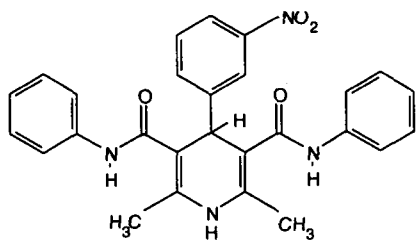

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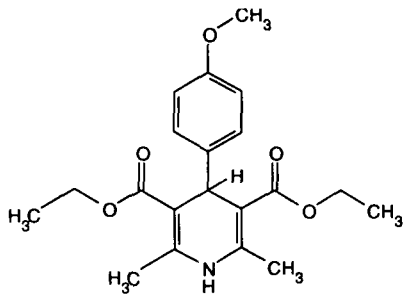

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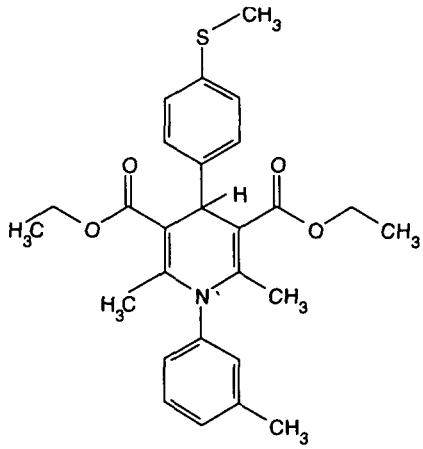


5)

1. Methyl 5-acetyl-2,6-dimethyl-4-(3-nitrophenyl)-1, 4-dihydropyridine-3-carboxylate.

2. 2,6-dimethyl-3, 5-di-N-(2′-chlorophenyl) carbamoyl-4-(4″-hydroxy phenyl)-1,4-dihydropyridine.

3. 2,6-dimethyl-3, 5-di-N-phenylcarbamoyl-4 (3'- nitrophenyl)-1,4-dihydropyridine.

4. 3,5-dicarbethoxy-2,6-dimethyl-4-(4′-methoxy)phenyl-1,4-dihydropyridine.

5. N-(3-methyl Phenyl)3,5-dicarbethoxy-2,6-dimethyl-4-(4′-thio methyl) phenyl-1, 4-dihydropyridine.

1.2 Coumarin derivatives

Coumarin is the parent organic compound of a class of naturally occurring phytochemicals found in many plant species. This oxygen heterocycle is best known for its fragrance, described as a vanilla-like odor or the aroma of freshly mowed hay. Identified in the 1820s, coumarin has been synthesized in the laboratory since 1868 and used to make perfumes and flavorings. It is also used to prepare other chemicals–in particular anticoagulants and rodent poison. Coumarins are used or present in perfumes, cosmetics, cigarettes, alcoholic beverages and laser dyes [4–6].

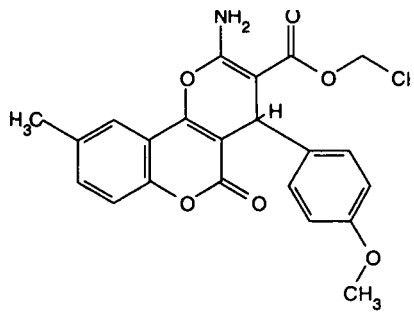
Chemically, coumarin can occur either free or combined with the sugar glucose to produce a coumarin glycoside. Medically, coumarin glycosides have been shown to have blood-thinning, anti-fungicidal, and anti-tumor activities. Dicumarol, a coumarin glycoside better known as warfarin, is the most commonly used oral anticoagulant medication.

4-hydroxy coumarin serves as a powerful tool for constructing 3,4-positionally fused heterocyclic systems [7]. Study of the fused heterocycles at C3-C4 position of coumarin was taken up, as the compounds exhibited good activity against various HIV strains like HIV-1 (IIIB) and HIV-2 (rod).

Development of resistance is a major problem associated with traditional therapeutic approaches towards AIDS. One promising means of overcoming this is to direct agents at multiple points which are required for HIV replication [8]. Simultaneous mutation of more than one critical enzyme would be necessary for this type of multidrug resistance. Among HIV enzymes, three have been identified as major targets for therapeutic development. Inhibitors for reverse transcriptase and protease, are available either on the market or in clinical trial. The third enzyme, integrase, is equally appealing as a site for antagonist action; however, this enzyme has not yet been as extensively investigated as the first two. Recent reports have appeared on HIV integrase inhibitory potency of a variety of compounds. In many cases, multiple aromatic rings and aryl orthohydroxylation are required for good inhibitory potency. Examples of these compounds include flavones, such as quercetin [9], caffeic acid phenethyl ester (CAPE) [9] and analogues [10] as well as certain "tyrphostins" [11] arctigenin-based compounds and bis-catechols such as β-conidendrol [12]. These inhibitors may be described in general as consisting of two aryl units, at least one of which contains the 1,2-dihydroxy pattern, separated by an appropriate linker segment.

Molecular structures of the following Coumarin derivatives have been reported in this thesis.

1. 2-amino-3-ethoxycarbonyl-4-(4′-methoxy phenyl)-4H- pyrano-[3,2-c]-chromene-6-methyl-5-one.



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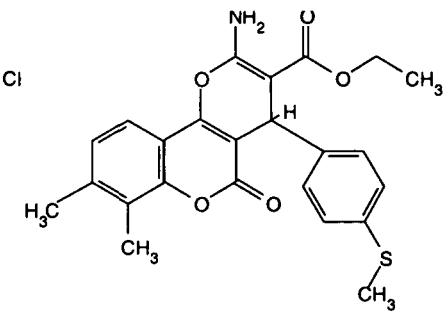

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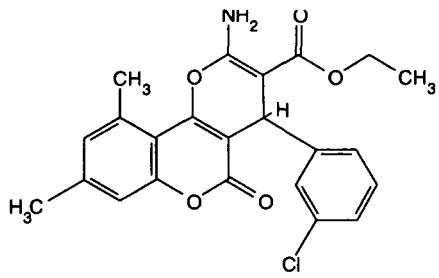


3)

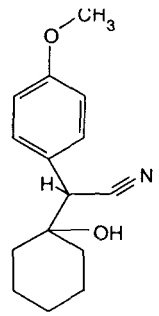
2. 2-amino-3-ethoxycarbonyl-4-(4′-thiomethyl phenyl)-4H-pyrano-[3,2-c]-chromene-7,8-dimethyl-5-one.

3. 2-amino-4(3′-chloro phenyl)-3-ethoxycarbonyl- 4H-pyrano-[3,2-c]-chromene-5-one.

1.3 Venlafaxine derivatives

Venlafaxine is a structurally novel, nontricyclic compound. Venlafaxine is thought to impart antidepressant effects by inhibiting the neuronal uptake of serotonin, norepinephrine, and to a lesser extent dopamine[13, 14]. It lacks monoamine oxidase inhibitory activity, and more importantly, lacks the anticholinergic, sedative, and cardiovascular preclinical adverse effect profile of the commonly marketed antidepressants. Venlafaxine has no affinity for rat brain muscarinic-cholinergic, histaminic, or α_1-adrenergic receptors[15].

Molecular structures of the following Venlafaxine derivatives have been reported in this thesis.



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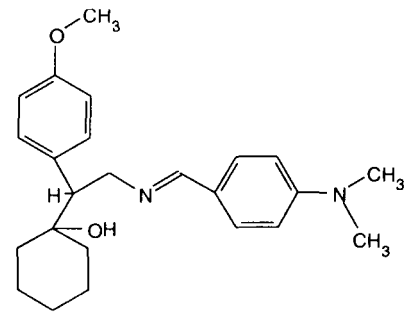

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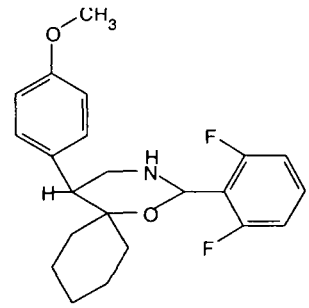

3)

1. 1-cyano-(4-methoxyphenyl)methyl-cyclohexanol.

2. 1-[2-1-(4-dimethylamino-phenyl)-ethylideneamino]-1-(4- methoxy-phenyl)-ethyl-cyclohexanol.

3. 2-(2,6-difluorophenyl)-4a,5,6,7,8,8a-hexahydro-4a- (4-methoxyphenyl)-4H-benzo[e][1,3]oxazine.

1.4 About the Facility

The National Single Crystal X-ray Diffractometer Facility at the Department of Studies in Physics, University of Mysore is equiped with two diffractometers.

1. Rigaku AFC7S

2. DIPLabo IP

All the x-ray diffraction data includeded in the thesis were collected and processed in house. Chapter 2 ellaborates on the technique and instrument used to obtain the molecular strutures.

1.5 References

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