Abstract

The research work carried out during 2001–2005 comprises of crystal and molecular structure analysis of dihydropyridine, coumarin and venlafaxine derivatives. The results have been compiled in the thesis entitled *"Crystal and Molecular Structure Analysis of Therapeutic Compounds"*. The single crystal X-ray diffraction data were collected in-house at the National Single Crystal Diffractometer Facility, Department of Studies in Physics, Manasagangotri, University of Mysore, Mysore.

The abstract of the work is categorised as given below:

Introduction

This chapter gives a brief introduction to the various classes of compounds studied along with the schematic diagrams of each molecule. The importance of these compounds in the therapeutic field and their applications are also mentioned in brief.

X-ray crystallography

The second chapter details the X-ray diffraction phenomenon. It elucidates the use of X-rays in the single crystal X-ray diffraction as a technique to study the crystal and molecular structures of small molecules. The chapter also briefs about the working and details of the two instruments *viz.*, AFC7S diffractometer and DIPLabo Image Plate diffractometer that were used for data collection.

Dihydropyridine derivatives

This chapter discusses the crystal and molecular structures of five dihydropyridine derivatives. IUPAC name, Crystal class, Space group, Empirical formula and structural analysis of each compound is herein summarised:

1. Methyl 5-acetyl-2,6-dimethyl-4-(3-nitrophenyl)-1,4-dihydropyridine-3-carboxylate (**1**): Monoclinic, $P2_1/c$, $C_{17}H_{18}N_2O_5$.

   The molecule possess intra-molecular hydrogen bonds of the type NH$\cdots$O. The inter-ring conformation angles between the pyran ring and the phenyl ring substituted at C4 being 121.8(3)°and 67.7(4)° respectively imply that the phenyl ring bisects the plane of the pyran ring. Also these two rings make an angle of 87.85°, hence they are fairly perpendicular to each other.

2. 2,6-dimethyl-3, 5-di-N-(2′-chlorophenyl) carbamoyl-4-(4″-hydroxy phenyl)-1,4-
   dihydropyridine (**2**): Triclinic, $P\bar{1}$, $C_{17}H_{18}N_2O_5$.

   A molecule of DMF is retained with the compound during crystallization. The structure shows intermolecular hydrogen bonds between the DMF residue and the dihydropyridine derivative. Also, there are inter molecular bonds of the type O-H $\cdots$ O and N-H $\cdots$ O. The angle between the least squares planes of the pyran ring and the phenyl ring substituted at C4 position is 89.3(1)°, making them perpendicular to each other.

3. 2,6-dimethyl-3, 5-di-N-phenylcarbamoyl-4 (3′-nitro phenyl)1,4-dihydro
   pyridine (**3**): Monoclinic, Cc, $C_{60}H_{62}N_{10}O_{10}$.

   The crystal structure exhibits non-crystallographic symmetry between the two moieties (A and B) of **3**. Also two molecules of DMF are retained with the compound during crystallisation. Angles between the pyran ring and the phenyl ring substituted at C4 position are 76.5(3)° and 83.8(3)° for the moieties A and B respectively. The inter-ring conformation angles of the moeities show that the phenyl ring does not bisect the plane of the pyran ring. The molecules exhibit intermolecular hydrogen bond interactions of the type CH$\cdots$O.

4. 3,5-dicarbethoxy-2,6-dimethyl-4-(4′-methoxy)phenyl-1,4-dihydro
   pyridine (**4**): Monoclinic, $P2_1/n$, $C_{20}H_{25}NO_5$.

   The structure exhibits inter molecular hydrogen bonds of the type N-H$\cdots$O. The angle between the least squares planes of the pyran ring and the phenyl ring substituted at C4 position is 86.7(2)°. The inter-ring conformation angle between these two rings being close to 90° implies that the phenyl ring does not bisect the plane of the pyran ring.

5. N-(3-methyl phenyl) 3,5 dicarbethoxy-2,6 dimethyl-4-(4 thio methyl)phenyl-1,4-
dihydropyridine (**5**): Triclinic, $P\bar{1}$, $C_{27}H_{31}NO_4S$.

   The molecule does not exhibit inter/intra-molecular hydrogen bonds. The angle between the pyran ring and phenyl ring at C4 position is 87.7(3)° making them nearly perpendicular to each other. The inter-ring conformation angle indicates that the phenyl ring bisects the plane of the pyran ring.

Coumarin derivatives

This chapter discusses the crystal and molecular structures of three coumarin derivatives. IUPAC name, Crystal class, Space group, Empirical formula and the structural analysis of each compound is summarised:

1. 2-amino-3-ethoxycarbonyl-4-(4′-methoxy Phenyl)-4H- pyrano-[3,2-c]-chromene-6-methyl-5-one (**6**): Triclinic, $P\bar{1}$, $C_{23}H_{21}NO_6$.

   The molecule exhibits intermolecular hydrogen bonds of the type N-H$\cdots$O and C-H$\cdots$O. The molecule possesses a chiral center. The pyrano ring is in a flattened boat conformation with methoxy phenyl substituted at C4 position. The dicarbethoxy group reflects *anti-periplanar* conformation with respect to the pyrano ring.

2. 2-amino-3-ethoxycarbonyl-4-(4′-thiomethyl phenyl)-4H-pyrano-[3,2-c]-chromene-7,8- dimethyl-5-one (**7**): Monoclinic, $P2_1/c$, $C_{24}H_{23}NO_5S$.

   The intermolecular hydrogen bonds are rather short and make an angle less than 140° about the hydrogen atoms. The molecule possesses a chiral center. The pyrano ring is in a flattened boat conformation with thiomethyl phenyl substituted at C4 position. The dicarbethoxy group reflects *anti-periplanar* conformation with respect to the pyrano ring.

3. 2-amino-4(3′-chloro phenyl)-3-ethoxycarbonyl- 4H-pyrano-[3,2-c]-chromene-5-one (**8**): Triclinic, $P\bar{1}$, $C_{23}H_{20}ClNO_5$.

   The molecule exhibits intermolecular hydrogen bond of the type N-H$\cdots$O. The pyrano ring is in a flattened boat conformation with chlorophenyl substituted at C4 position. The dicarbethoxy group reflects *anti-periplanar* conformation with respect to the pyrano ring.

Venlafaxine derivatives

This chapter discusses the crystal and molecular structures of three venlafaxine derivatives. IUPAC name, Crystal class, Space group, Empirical formula and the structural analysis of each compound is summarised:

1. 1-cyano-(4-methoxyphenyl)methyl-cyclohexanol (**9**):

   This compound was crystallised using two different solvents, water and methanol, to obtain the forms **9a** and **9b** respectively.

   (a) (**9a**): Monoclinic, $C2/c$, $C_{15}H_{19}NO_2$.
   The compound is found to exist as a dimer. The structure exhibits intermolecular hydrogen bonds of the type OH$\cdots$N and CH$\cdots$O. The cyclohexanol is in chair conformation. The molecule possesses chiral center.

   (b) (**9b**): Orthorhombic, $P2_12_12_1$, $C_{15}H_{19}NO_2$.
   The structure exhibits intermolecular hydrogen bonds of the type OH$\cdots$N. There is a formation of an infinite one-dimensional chain along the b-axis. The molecule possesses a chiral center. The cyclohexanol is in chair conformation.

2. 1-[2-1-(4-dimethylamino-phenyl)-ethylideneamino]-1-(4-methoxy-phenyl)-ethyl-cyclohexanol (**10**): Triclinic, $P\bar{1}$.

   The molecule exhibits intramolecular hydrogen bond of the type OH$\cdots$N. The cyclohexanol group is in chair conformation.

3. 2-(2,6-difluorophenyl)-4a,5,6,7,8,8a-hexahydro-4a- (4-methoxyphenyl)-4H-benzo[e][1,3]oxazine (**11**): Triclinic, $P\bar{1}$, $C_{22}H_{25}F_2NO_2$.

   The molecule shows intermolecular hydrogen bonds of the type C-H$\cdots$O. Both the flourine atoms contribute to short hydrogen contacts with angles about the hydrogen atom being 114.0° and 102°. The cyclohexanol group is in chair conformation. The key bioactive 1,3-oxazine ring is also in chair conformation.

Summary

This chapter summarises the results of the structure elucidated earlier. The molecular structures of similar compounds are compared. The effects of various substituents on the parent molecule are brought out. Dihydropyridine derivatives with potential therapeutic properties are identified.