1.1 Introduction

Structure analysis by X-ray diffraction technique is one of the most powerful methods of unambiguously determining the complete three-dimensional structure of crystalline substances. Besides confirming the connectivity and stereochemistry of the molecule, X-ray diffraction method is uniquely capable of providing precise information concerning bond lengths, bond angles, torsion angles and molecular dimensions. With the advent of direct methods, the widespread availability of electronic computers and the efficient program packages coupled with the development of computer controlled automatic diffractometers to measure X-ray intensities, X-ray crystallography has emerged as the main source of unambiguous information on crystal and molecular structure of compounds. In order to understand the nature of chemical bond, the functions of molecules in biological contexts and to understand the mechanism and dynamics of reaction, structure analysis by X-ray diffraction techniques is an unique method of determining the complete three-dimensional representation of atoms of molecules in crystals. Hence, the crystal structure determination by single crystal X-ray diffraction was undertaken to obtain a detailed picture of the contents of the crystals of compounds presented in this thesis. This chapter briefly outlines the methods usually adopted for studying single crystal X-ray structure analysis of small molecules. For detailed
information, one may refer to a number of books contributed by various authors (Stout & Jenson, 1968; Sherwood, 1976; Dunitz, 1979; Giacovazzo, 1980; Woolfson, 1987; Hauptman, 1988; Giacovazzo, et al., 1992).

1.2 Unit Cell Parameters and Intensity Data Collection

Single crystal of suitable size of each of the compound studied in this thesis was used for X-ray data collection. All the low temperature measurements* were made on a Nonius KappaCCD diffractometer (Hooft, 1999) using graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) and an Oxford Cryosystems Cryostream 700 cooler. Data reductions were performed with HKL Denzo and Scalepack (Otwinowski & Minor, 1997) for all the low temperature intensity data. The determination of the unit cell parameters and the three-dimensional intensity data collection of the remaining two compounds (ST18 and ST21; Chapters XIV and XV) were carried out using a STOE IPDS image plate systems with ω scan mode and graphite-monochromated Mo Kα radiation (λ = 0.71073 Å) at room temperature. In all the cases, the intensity data were corrected for Lorentz and polarization effects and absorption corrections were applied to those structures with heavy atoms [ST10, ST19 and ST20-multi-scan using SORTAV (Blessing, 1995) and ST21 – integration (X-Red in IPDS) (Stoe & Cie, 1997)].

Function minimized (in the case of Nonius KappaCCD diffractometer data):

\[
\sum w \left[ F_o^2 - F_c^2 \right]^2
\]

where \( w = \left[ a^2 F_o^2 + bP \right]^{-1} \) and

* Only two of the compounds were measured at room temperature (293 K).
\[ p = \frac{F_0^2 + 2F_c^2}{3} \]
\[ F_0^2 = \frac{S(C - RB)}{Lp} \]
and \[ \sigma^2[F_0^2] = \frac{S^2(C + R^2B)}{Lp^2} \]

\( S \) = Scan rate

\( C \) = Total integrated peak count

\( R \) = Ratio of scan time to background counting time

\( B \) = Total background count

\( Lp \) = Lorentz-polarization factor

Any crystal may be regarded as being built up by a three-dimensional translational repetition of some basic structural pattern, which may comprise one or more atoms, a molecule or a complex assembly of molecules. The basic building block in a crystal is the unit cell. Within a single unit cell of a crystal, the atoms are distributed in a certain manner, and so there exists some electron density function \( \rho(\vec{r}) \), which describes the location of the electrons within the atoms of the unit cell. To obtain the electron density \( \rho(\vec{r}) \) from the diffraction data of a crystal, the periodic and continuous electron density can be expressed as a Fourier series

\[ \rho(\vec{r}) = \left[ \frac{1}{V} \right] \sum_{H} F_H \exp[-2\pi i (\vec{H} \cdot \vec{r})] \]  \hspace{1cm} (1.1)

where \( V \) = volume of the unit cell

\( F_H \) = Structure factor of the reflection \( H = hkl \)

\( (\vec{r}) = x \, \vec{a} + y \, \vec{b} + z \, \vec{c} \); \( (x, y, z) \) fractional coordinates with respect to the unit cell axes \( \vec{a}, \vec{b}, \vec{c} \)

\( \vec{H} = h\vec{a}^* + k\vec{b}^* + l\vec{c}^* \); the indices \( (h, k, l) \) are integers relative to the reciprocal lattice axes \( \vec{a}^*, \vec{b}^*, \vec{c}^* \).
1.3 Structure Solution

On knowing the structure factor magnitude and phases, the electron density distribution in the unit cell can be calculated, and when the electron density is known, the three-dimensional structure of the molecule can be elucidated. Structure solutions would thus be trivial exercises in computation except for the fundamental difficulty that crystallographically available X-ray diffraction data contain only the structure factor magnitudes and not their phases. The loss of phase information during intensity data collection is said to be the phase problem in crystal structure determination. Owing to their known atomicity of the crystal structures and the redundancy of observed magnitudes, the phase problem is solvable in principle.

The structure factor is represented by the following equation

$$F_{hkl} = \sum_{j=1}^{N} f_j \exp \left( 2\pi i \left( h x_j + k y_j + l z_j \right) \right)$$

(1.2)

where $f_j$ is the scattering factor for the $j^{th}$ atom. $F_{hkl}$ can be represented by

$$F_{hkl} = |F_{hkl}| \exp(\text{i}\phi_{hkl})$$

(1.3)

where $|F_{hkl}|$ is the structure amplitude and $\phi_{hkl}$ is the associated phase. The structure amplitude can be obtained directly from the square root of the observed intensity. But there is no direct method to find out the associated phase values experimentally. In order to locate the position of atoms one usually computes the electron density at various parts. The position at which the electron density is maximum, gives the position of an atom.

The general expression for electron density function $\rho(x, y, z)$ is given by
\[ p(x, y, z) = \frac{1}{V} \sum_{h} \sum_{k} \sum_{l} F_{hkl} \exp \left[ -2\pi i (hx + ky + lz) \right] \] (1.4)

In order to get the structure it appears from the above equation as if we simply have to map \( p(x, y, z) \) and locate the maxima in it, but the process is not so straightforward; in order to sum the series \( p(x, y, z) \), we have to find out the complex structure factor \( F_{hkl} \).

Using equation 1.3, \( p(x, y, z) \) becomes

\[ p(x, y, z) = \frac{1}{V} \sum_{h} \sum_{k} \sum_{l} |F_{hkl}| \exp \left[ -2\pi i (hx + ky + lz) - \phi_{hkl} \right] \] (1.5)

where \( 2\pi \phi_{hkl} = \phi_{hkl} \) is the phase angle, \( V \) is the volume of the unit cell and \( x, y, z \) are the fractional co-ordinates of any point in the unit cell. To evaluate equation (1.5) one needs the exact values of the complex quantity \( F_{hkl} \) in both magnitudes and phases. Our experimental data however gives us only the real quantity \( |F_{hkl}| \). Thus the phase \( \phi_{hkl} \) is necessary if one wants to compute the electron density to locate the position of atoms. This is called "phase problem" in crystallography.

Several methods are available to solve the phase problem and some of them are:

1. Direct methods
2. Heavy atom method
3. Isomorphous replacement method
4. Anomalous dispersion method

The above methods can be successfully applied to locate the approximate positions of all the atoms (trial structure of a molecule) in the unit cell.
1.4.1 Direct Methods

The structure determination of all the compounds studied in this thesis has been carried out using Direct methods.

Direct methods are mathematical techniques used to derive the phase information directly from the observed intensities in arriving at a final map to locate the atoms. These methods determine the values of some linear combination of phases from which individual phases can be determined. The assumptions and various steps involved in the direct methods are summarized below:

1.4.2 Basic Assumptions

The electron density is assumed to be either positive or zero throughout the unit cell. In Direct methods, a real crystal with continuous electron density is replaced by an idealized one, the unit cell of which consists of N discrete equal non-vibrating point atoms i.e. the structure factors $F_{hkl}$ is replaced by the normalized structure factors $E_{hkl}$. In the initial stage, atoms are assumed to be the point type $|F|$ now being replaced by $|E|$, the normalized structure factor amplitude, which does not vary with $(\sin \theta)/\lambda$.

The various steps involved in the direct methods are:

I. Conversion of observed structure factor amplitude to normalized structure factor amplitude $|E_{hkl}|$ which are independent of $\theta$.

II. Setting up of phase relations using triple phase relations (triplets) and four phase relations (quartets).

III. Selection of a few reflections, the phases of which are assigned a priori.

IV. Phase propagation and phase refinement using tangent formula (Karle & Hauptman, 1956).
V. Calculation of best phase sets and expressing the reliability of the phases in terms of Combined Figure of Merit (CFOM)

VI. Calculation of electron density map (E-map) with $|E_{hkl}|$ as the Fourier coefficient.

1.4.3 DIRDIF Procedure

When part of the structure is known, the unknown part of the structure can be solved by using Direct methods. For phase extension and for the refinement of input phases and amplitudes, the difference structure factors, phased by the partial structure are used as input to a weighted tangent-refinement process. The method is referred to as DIRDIF (Beurskens et al., 1983; Beurskens et al., 1990, Beurskens et al., 1996 & Beurskens et al., 1998). This method is useful if the known part is only marginally sufficient to solve the structure. It can also be used if the known atom lies in a special or pseudo-special position (origin ambiguity), or if, for non-centrosymmetric structures, the known atoms form a centrosymmetric arrangement (enantiomorph ambiguity). The observed structure amplitudes and positional parameters of the known atoms are used by the computer program DIRDIF to produce a greatly improved electron density map.

1.5 Structure Refinement

Structure refinement consists of obtaining the best fit between a set of observed measurements and the quantities calculated from a model postulated. Differences between the observed and the calculated values can arise due to random errors (statistical fluctuations) in the observations and defects in the model (systematic errors). The errors introduced into the calculation of the electron density function have inaccuracies in the magnitude and phases of the structure factor $F_{hkl}$. Therefore, the trial structure has to be refined to get a more accurate set of structure factors. A number of
structure refinement processes are in use, the full-matrix least-squares refinement technique is widely used in refining the small molecular structures. The least-squares refinement consists of using the squares of the differences between the observed and calculated values as a measure of their disagreement and one would expect that the more closely the calculated and observed structure factors agree, then the more closely does the trial structure represent the true structure. The discrepancy between the observed and calculated structure factors is therefore an indication of the degree of confidence, which may be ascribed to any given trial structure.

The best agreement is obtained for

\[ D = \sum_{i=1}^{m} w_i \left( |F_o| - |F_c| \right)^2 \]  

where \( w_i \) is the weighting factor

The residue \( R \) or the Discrepancy index is given as

\[ R(F) = \frac{\sum \left| |F_o| - |F_c| \right|}{\sum |F_o|} \]  

summed over all observed reflections and \( R_{\text{int}} = \frac{\sum |F_o|^2 - \langle |F_o|^2 \rangle}{\sum |F_o|^2} \) summed only over reflections for which more than one symmetry equivalent was measured.

Lower the \( R \)-value, greater the accuracy of the molecular model. A suitable weighting scheme is applied at the end of the refinement procedure and the weighted \( R \) factor is given as (SHELXL97 Manual, Sheldrick, 1997).
The goodness of fit $S$ is always based on $F^2$

Standard deviation of an observation of unit weight (goodness of fit):

$$wR^2 = \left( \frac{\sum w(F_o^2 - F_c^2)^2}{\sum wF_o^2} \right)^{1/2}$$

\[ (1.8) \]

where $N_o$ is the number of observations and $N_v$ is the total number of parameters refined. For a correct structure, the goodness of fit is close to unity. All the structures studied in this thesis were refined based on $F^2$ of all data by full matrix least-squares techniques using *SHELXL97* (Sheldrick, 1997).

### 1.6 Molecular Conformations

The internal parameters of a molecule are the parameters that characterize the molecular conformation and hence they are known as conformational parameters. They are bond length, bond angle and torsion angle. Of these three, the torsion angle is the most important one since a variation of the torsion angles about the single bond leads to different conformations of a molecule. The torsion angle is defined as follows:

The torsion angle otherwise known as the dihedral angle of four atoms A, B, C, D with a chemical bond between AB, BC and CD (Fig.1.1) is defined as the angle ($\tau$) between the two planes through A, B, C and B, C, D. As it varies from $-180^\circ$ to $180^\circ$, its sign is defined according to the convention of Klyne and Prelog (1960). The initial conformation corresponding to $\tau = 0$ is that in which all the atoms are
coplanar and the end atoms A and D are cis with respect to BC. In any orientation of CD, the torsion angle $\tau$ is given by the rotation in degrees it has undergone from the ($\tau = 0$) original position. The torsion angle is considered positive when it is measured clockwise from the front substituent A to the rear substituent D and negative when it is measured anti-clockwise. $\tau$ (D-C-B-A) has the same sign and magnitude as $\tau$ (A-B-C-D) (Luger, 1980).

1.7 Symmetries in Five- and Six-membered Rings

A quantitative evaluation of the conformation of rings of any size from which a comparative analysis can be easily made is obtained from a mathematical combination of torsion angles. This analysis is based upon consideration of approximate symmetry possessed by most rings (Duax et al., 1976). The two types of symmetry that define the ring conformation are mirror planes perpendicular to the dominant ring plane and two-fold axes lying in the ring plane. Either of these symmetry elements may be present at any of the three locations described in Fig. 1.2. The location of symmetry element in a ring depends on the number of atoms comprising that ring. In rings containing even number of atoms, symmetry elements may pass through two ring atoms located directly across the ring from each other (Figs. 1.2a,d) or bisect two opposite bonds (Figs. 1.2b,e). If there are an odd number of atoms in the ring, all the symmetry elements pass through one atom and bisect the opposite bond (Figs. 1.2c,f). The most commonly observed conformations of five- and six-membered rings are shown in Figs. 1.3a,b, respectively, along with the mirror and two-fold rotational symmetries for the five- and six-membered rings.

Six-membered rings possess twelve potential symmetry elements that must be considered in order to determine the
conformation of the ring. The planar ring is highly symmetric and contains all possible symmetry (a mirror plane and a two-fold axis of symmetry at each of the six possible locations). The chair conformation possesses the next highest symmetry, having three mirror planes of symmetry and three two-fold axis of symmetry. The boat and twist-boat conformations each has two mutually perpendicular symmetry elements. The sofa and half-chair conformations each has only a single symmetry element.

1.8 Conformation of Ring Structures

The conformational analysis of interest in crystallography varies from molecule to molecule. It mainly depends on the type of molecule. If a molecule contains rings, the planarity or otherwise of the ring is an important conformational feature. The non-planar rings are described in terms of well-known objects in common use like the chair, the boat, the envelope and the sofa.

1.8.1 Five-membered Rings

The five-membered rings generally assume (i) the envelope conformation in which four atoms are on a plane while the fifth atom is displaced from the plane, forming the flap or (ii) the half-chair conformation in which two atoms lie on either side of the plane of remaining three atoms (Fig. 1.3a).

1.8.2 Six-membered Rings

The six-membered rings assume varieties of conformations some of which are shown in Fig. 1.3b (Duax, et al., 1976). Simplest way of finding the conformations is to look at the torsion angle within the ring. In the case of chair conformation, the torsion angles will be alternating between +60° and -60° (In actual examples the modulus of the torsion angle can be in the range of 50° to 70°). For a boat
conformation, two of the non-consecutive torsion angles will be zero and these will be separated by the torsion angles around +60° and -60°. In the half-chair form, two consecutive torsion angles will be zero and these will be separated by the torsion angles around +60° and -60°. In a sofa conformation, five out of six atoms will be in one plane. These factors can be effectively used to describe and compare the conformation of the molecule occurring in different compounds, in a quantitative way. The conformation of the rings can also be identified using the puckering degrees of freedom. In the six-membered rings there are three puckering degrees of freedom, a single amplitude-phase pair \((q_2, \phi_2)\) and a single puckering coordinate \(q_3\). Alternatively, these coordinates may be replaced by a "spherical polar set" \((Q, \theta, \phi)\) where \(Q\) is the total puckering amplitude and \(\theta\) is an angle \((0 \leq \theta \leq \pi)\) such that

\[
q_2 = Q \sin \theta \\
q_3 = Q \cos \theta
\]

This coordinate system permits the mapping of all types of puckering (for a given amplitude \(Q\)) on the surface of a sphere (Fig. 1.4). The polar positions \((\theta = 0\) or \(180^\circ)\) correspond to a chair conformation with \(q_2 = 0\) and \(q_3 = \pm Q\). The positions on the equator of the sphere (Fig. 1.4) have \(\theta = 90^\circ\) so that \(q_3 = 0\) and \(q_2 = Q\). As the phase angle \(\phi\) varies the conformation traverses a series of six boat conformations \((\phi = 0, 60, 120, 180, 240\) and \(300^\circ)\) and six twist-boat conformations \((\phi = 30, 90, 150, 210, 270\) and \(330^\circ)\).

In the case of molecules with rings where the ring is known to be planar, the deviations of the atoms from the least-squares plane is an important feature of molecular conformation and provides information about the effects of substitution on the planarity of the
Figure 1.1
Figure 1.2 (a-f): The signs of torsion angles in six- and seven-membered rings describe the symmetrical positioning of atoms related by symmetry operations.

(a), (b) & (c): Torsion angles related by mirror planes (---) have opposite signs.

(d), (e) & (f): Torsion angles related by 2-fold rotational axes (-----) have the same sign.
Figure 1.3a: The most commonly observed conformations of five-membered rings and the corresponding mirror and twofold rotational symmetries are indicated on the right (Duax et al., 1976).
Figure 1.3b: The most commonly observed conformations of six-
membered rings and the corresponding mirror and twofold rotational
symmetries are indicated on the right (Duax et al., 1976).
Figure 1.4: One octant of the sphere on which the conformations of six-membered rings can be mapped (for a constant Q). Special conformations are indicated: C = chair for $\theta = 0^\circ$, $\phi = 0^\circ$; B = boat for $\theta = 90^\circ$, $\phi = 0^\circ$; TB = twist boat for $\theta = 90^\circ$, $\phi = 90^\circ$; HB = half-boat; HC = Half-chair.
ring. Two possible representations are employed: (i) the equation to the least-square plane and the deviation of the atoms the plane are given; (ii) the torsion angles about the various bonds of the ring are listed out. For completely planar molecules, all the torsion angles will be zero. Hence, the deviation of the observed torsion angle from this ideal value gives the amount of non-planarity present in the structure. The algebraic sum of the torsion angles will, however be zero.

1.9 Intra- and Intermolecular Interactions

In crystalline state, the molecules are stabilized by intra- and intermolecular interactions like hydrogen bonds, van der Waals forces and possibly some close contacts between two non-bonded atoms. Before the 19th century, chemists were concentrating their attention more on the making and breaking of covalent bonds. From the middle of the 20th century onwards, scientists started focusing on the non-covalent interactions. Such interactions are of great biological interest because of the fact that the biological structures are usually made from loose aggregates that are held together by weak, non-covalent interactions. These interactions are dynamic in nature and are responsible for most of the processes occurring in living systems.

Non-covalent interaction has made a substantial shift of interest, from a focus on atoms and bonds between atoms to a focus on molecules and bonds between molecules, and has encompassed all areas of chemistry including the presently thriving area of materials chemistry. Supramolecular chemistry and crystal engineering are closely related fields. Both involve the non-covalent interactions as their basis and have expanded the frontiers of chemical science dealing with many physical and biological phenomena (Lehn, 1978, 1995; Russell et al., 1998). The repetitive units of these small sized hydrogen-bonded motifs are called supramolecular synthons
(Desiraju, 1995) and they hold the key to successful crystal engineering (Desiraju, 2001).

1.9.1 Hydrogen-bonding

Hydrogen-bonding is the most reliable design element in the non-covalent assembly of molecules with donor and acceptor functionalities and as such it is the most important interaction in crystal engineering and supramolecular design.

Hydrogen-bonding occurs between a proton donor group $\text{D-H}$ and a proton acceptor group $\text{A}$, the $\text{D-H...A}$ interaction being called as a 'hydrogen bond'. Generally, a hydrogen bond can be characterized as a proton shared by two lone electron pairs. Hydrogen bond energies are 15-40 kcal/mol$^{-1}$ for strong bonds, 4-15 kcal/mol$^{-1}$ for moderate bonds and 1-4 kcal/mol$^{-1}$ for weak bonds (Jeffrey, 1997). The van der Waals cut-off criterion requires that in a hydrogen bond, the distance between $\text{H}$ and $\text{A}$ must be smaller than the sum of the van der Waals radii of $\text{H}$ and $\text{A}$ (Desiraju & Steiner, 1999). The different types of hydrogen bonds are shown in Scheme 1.1.

![Scheme 1.1](image)
1.9.2 Describing Hydrogen-bonded Motifs: Graph Sets

A language based upon graph-theory for describing and analyzing hydrogen bond networks in three-dimensional solids was introduced by Etter, Bernstein and co-workers (Etter, 1990 1990a, 1991; Bernstein et al., 1995). A generic graph-set descriptor is shown in Scheme 1.3.

\[ G_d^a(n) \]

where \( G = \) Graph set designator C/R/D/S
\( d = \) Number of donor atoms
\( a = \) Number of acceptor atoms
\( n = \) Total number of atoms present in the hydrogen-bonded motif

**Scheme 1.3.** A generic graph-set descriptor

The process of assigning a graph set begins by identifying the number of different types of hydrogen bonds present in the structure and then by defining the bonds by the nature of its donors and acceptors. The hydrogen-bonded motif is characterized by any one of the four designators, R (ring), D (dimer), C (chain) and S (self, for intramolecular hydrogen bond). The numbers of donors and acceptors used in each motif are designated as subscripts and superscripts respectively and the total number of atoms present in the repeat unit is denoted in brackets. The graph-set notations for some hydrogen-bonded motifs are shown in Scheme 1.4. A benefit of using graph sets is that it brings the focus on to the hydrogen-bonded pattern and not simply on the geometrical constraints of non-covalent interactions. The future retrieval and analysis of crystal data from the Cambridge
Structural Database (CSD) on the basis of hydrogen bonding patterns are also some of the important uses of graph-set assignments.

[R2(8) and R4(8)]

Scheme 1.4
Graph-set notations for some hydrogen-bonded motifs.

One of the objectives of the present work is to study the conformations of molecules reported in this thesis and the hydrogen-bonding pattern.
Part I

Chapter-II

Significance and Preparation of Compounds

2.1 Introduction

In this chapter, the significance and the preparation of the compounds reported in this thesis are presented. There are three types of series of compounds, which are biologically important. The structures of the compounds are analysed in this thesis. Part II of the thesis deals with the crystal structure analyses of six potential antiamnesic agents such as 2-(2-Naphthyloxy)acetate derivatives and two of their closely related compounds. The crystal and molecular structure of nine steroidal derivatives are reported in the Part III of the thesis. In Part IV, the crystal and molecular structures of four 1,2,4-triazole derivatives are presented.

2.2 Significance of Potential Antiamnesic Agents

The conformations of molecules with antiamnesic activity have attracted considerable interest (Amato et al., 1991b). Increasing effort has been devoted to the search for drugs that can be used for the prevention or treatment of human cognitive disorders (Angelucci et al., 1993). Cognition enhancers are drugs able to facilitate attentional abilities and the acquisition, storage and retrieval of information and to attenuate the impairment of cognitive functions associated with various neurodegenerative states, such as Alzheimer's disease (hereafter AD) (Gualtieri et al., 2002). Development of cognition enhancers is still a difficult task because of the complexity of brain functions. Hence, several classes of memory enhancers are used,
which include acetylcholinesterase inhibitors (Gruzendler & Morris, 2001), acetylcholine precursors, muscarine receptor agonists and antagonist (Mucke & Castaner, 1998), nicotinic receptor agonists (Vernier et al., 1999), psychostimulants and nootropics (Parnetti et al., 1997; Thamotharan et al., 2003h).

The brains of people with severe cognition disorder show a consistently depleted cortical and hippocampal cholineacetyl transferase (ChAT) and a decrease in cell density and number in the nucleus basalis of meynert, the major source of cholinergic innervation of the human cortex (Sims et al., 1983; Perry, 1986; Heize, 1987). The cholinergic hypothesis of geriatric dysfunction asserts in essence that the cognitive deficits and memory impairment observed in AD patients are due, at least in part, to deficient cholinergic function (Showell et al., 1991). The cholinergic system has stimulated interest in agents that could enhance central cholinergic transmission. Based on the cholinergic hypothesis, a number of drugs having various mechanistic implications (Moos et al., 1988) have been evaluated against AD.

The improvement of cholinergic transmission is a rational and well documented approach to the improvement of cognition and memory. Cognition activators are drugs currently employed for the symptomatic treatment of pathological brain aging phenomena, which are usually referred to as senile cognitive decline or age-associated memory impairment (Gamzu et al., 1989; Bandoli et al., 1992; Thamotharan et al., 2003i). In the light of the growing incidence of such illness among the older population, several families of compounds are being tested in laboratory and clinical trials. The
nootropics* (mind-targeted) family is the forerunner in the field (Giurgea, 1982), and the key feature of this family is the presence of the pyrrolidin-2-one ring. This moiety is a requisite for several active compounds currently used in the therapy of pathological brain-aging phenomena (Piracetam, Oxiracetam and Pramiracetam). The ring-extended \( N \)-analogues of 2-pyrrolidinone, viz. 2-aryl-3-piperazinone compounds, have been found to possess the characteristic nootropic pharmacological profile (Amato et al., 1991). Therefore, the crystal structures of eight closely related compounds of antiamnesic agents are presented in Part II.

(Late) Prof. D. P. Jindal and his group from the Pharmaceutical Institute of Sciences, Punjab University, Chandigarh, India, have prepared and kindly supplied these compounds for crystal structure analyses. The single crystals suitable for X-ray analysis were prepared by the author in the Department of Physics.

### 2.3 Significance of Steroids

Steroids form a group of structurally related compounds, which are widely distributed in animals and plants. The most important classes of steroids include (1) the sex hormones, which are responsible for the development and maintenance of primary and secondary sex characteristics; (2) the adrenal cortical hormones, which are essential for maintenance of salt and water balance and carbohydrate metabolism; (3) bile acids present in animal bile and used in chemical synthesis of anti-inflammatory agents; (4) sterol constituents of cell membranes and (5) cardiotonic agents useful in the treatment of congestive heart failure. In addition to the regulatory functions that

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*The term 'nootropic' indicates that the novel class of drugs for treatment of main age-related syndromes such as memory deficits, Alzheimer's disease, Alzheimer-type senile dementia*
steroids perform, they play a significant role in the body responses to emotional and physical stress and disease conditions. The intimate involvement of steroids in the cause and cure of cancer is illustrated by therapeutic effect of treating victims with massive quantities of specific steroids and steroid analogues. Regression of breast cancer in women through estrogen, androgen and corticoid administration, the regression of breast cancer in men through androgen and artificial estrogen administration and corticosteroid therapy of lymphomas and leukemias are a few of the most common examples of hormonal cancer therapy (Duax et al., 1976; McMurry, 1984; Finar, 1996; Wallimann et al., 1997).

The functions and activities of steroids are determined by their compositions, constitutions, configuration and conformation. Composition defines the number and kinds of atoms that make up the molecule and is readily represented by its chemical formula. Constitution refers to the connectivity of the molecule and is best illustrated by diagrammatically showing which are the atoms bonded to one another. Molecular configuration defines the chirality of all asymmetric centres of carbon in the molecule. Conformation refers to the total geometric distribution or disposition of the atoms in three dimensions (Duax et al., 1976 & 1979).

Androsterone was the first steroid with male sex hormone activity to be discovered. Its isolation in 1931 by Butenandt and other aspects of early research in this area, are reviewed by Fieser & Fieser (1959). Androsterone is actually a metabolic product derived from testosterone, by which it is far surpassed in androgenic activity. The androsterone molecule is of structural interest, however, in that it comes closest among the naturally occurring steroid hormones to
representing the completely saturated fundamental steroid nucleus (High & Kraut, 1966).

2.3.1 Steroid Nomenclature

Steroid molecules are characterized by a basic skeleton or nucleus consisting of three six-membered rings and one five-membered ring. The nomenclature for steroids has been completely systematized by IUPAC-IUB (1972) conventions. In Fig. 2.1 the basic steroid nucleus is given along with standard numbering and ring designation. Of the two possible substituents on any of the given carbon atom in the steroid nucleus, the one emanating from the nucleus on the same side as C18 and C19 methyl groups is designated as β-oriented, whereas the one on the opposite side is said to be α-oriented (Fig.2.2). Substituents lying in the plane of the steroid nucleus are equatorial, whereas those extending away from the central plane are axial substituents (Weeks et al., 1971a).

All steroids can be assigned with unique names defining composition, constitution and configuration. In spite of the diverse classes of steroid compounds, they are mostly interconvertible by partial synthesis involving introduction, elimination and transformation of side chains and functional groups. In addition to many hundreds of steroids isolated from plants and animals, thousands more have been synthesized in pharmaceutical laboratories in the search for new drugs. The idea is to start with a natural hormone, carry out chemical modification of the structure, and then see what biological properties the modified steroid has (Duax et al., 1976).
2.3.2 Steroidal Alkaloids

The steroidal alkaloids have also been referred to as azasteroids, and may be divided into one group of compounds in which nitrogen is in the steroid nuclear skeleton, and the other group in which the nitrogen is in one or more side chains. There has been considerable interest in the synthesis and biological study of several heterocyclic steroids as extremely potent anti-inflammatory agents (Gupta et al., 1996, and references therein). It is known that 2'-phenyl-11β,17α,21-trihydroxy-16α-methyl-20-oxo-4-pregnenol[3,2-c]pyrazol-21-yl acetate and its p-fluorophenyl analogue are, respectively, 60 and 100 times more active than hydrocortisone (Hirschmann et al., 1963, 1964), and the importance of the [3,2-c]pyrazole function has been demonstrated by a number of investigators (Fried et al., 1963; Hirschmann et al., 1963; Hannah et al., 1975). Both cortivazol and nivazol have the [3,2-c] pyrazole structural component, and the 3-keto function is absent, while both have been described as potent anti-inflammatory steroids (Gupta et al., 1996, and references therein).

The crystal and molecular structures of a few of this type of steroidal derivatives are reported in Part 3 of this thesis. Although both ring-A-modified steroids 2'-(p-fluorophenyl)-4-azapyrazolo[4',3':2,3]-5α-androstan-17β-yl acetate and 2'-(p-fluorophenyl)-4-azapyrazolo[4',3':2,3]-5α-androstan-17β-ol were found to be more active than hydrocortisone, the acetoxy derivative was found to be less active than the hydroxy derivative. Crystallographic analyses have been carried out in order to study the influence of the fused pyrazole moiety on the steroid skeleton (Thamotharan et al., 2003a).

When a ring has been contracted and this is indicated by prefix ‘nor’, preceded by a small capital letter indicating the ring affected.
When ring-fission has occurred with addition of a hydrogen atom to each new terminal group and this is indicated by the numbers showing the position of the bond broken, followed by the prefix 'seco'. One nor and seco steroidal analogue is presented in this thesis.

2.3.3 Stereochemistry of the steroids

If we examine the fully saturated sterol, we find that there are eight dissimilar chiral centres in the nucleus (3, 5, 8, 9, 10, 13, 14 and 17) leading to the possibilities of $2^8 = 256$ optical isomers. The stereoisomerism of the steroids is conveniently classified into two types, one dealing with the way in which the rings are fused together, and the other with the configuration of substituent groups, particularly those at the C3 and C17 positions (Finar, 1996).

2.3.4 Absolute configuration of steroids

There are six chiral centres in the nucleus (5, 8, 9, 10, 13 and 14), and therefore there are $2^6 = 64$ optically active forms theoretically possible. In practice, however, many of these cannot exist because of steric limitations.

(Late) Prof. D. P. Jindal and his group from the Pharmaceutical Institute of Sciences, Panjab University, Chandigarh, India, have prepared and kindly supplied the synthetic steroid derivatives for crystal structure analyses. The single crystals suitable for X-ray work were prepared by the author in the Department of Physics. The crystal structures of nine androstene derivatives are reported in Part III of the thesis.
Figure 2.1: Basic steroid nucleus consists of three fused cyclohexane (A, B and C) and one cyclopentane (D) like rings.
Figure 2.2: Of the two possible substituents on any given carbon in steroid nucleus, the one emanating from the nucleus on the same side as C18 and C19 methyls is designated as β-oriented, whereas the one on the opposite side is said to be α-oriented. (Structure of 3β-Chloro-5-androsten-17β-ol, Weeks, et al., 1971a)
2.4. **Significance of 1,2,4-Triazole Derivatives**

Triazoles are five-membered rings, which contain two carbon and three nitrogen atoms. Two structural isomeric triazoles are known, 1,2,3-(1,2,5-) and the 1,2,4-(1,3,4-), the former being known as osotriazole, and the latter as triazole. Each of them exists in two dissimilar tautomeric forms.

![Osotriazole](image1.png)  ![Triazole](image2.png)

Replacement of the imino hydrogen atom by an alkyl or aryl group prevents tautomerism, and thereby gives rise to the possibility of two 1-substituted triazoles and two 1-substituted osotriazoles.

Amino-functionalized triazole derivatives serve as starting compounds for heterocyclic syntheses. The triazole moiety possesses many pharmacological properties, e.g. antimicrobial (Habib et al., 1997), antiviral, antimycobacterial and anticonvulsant (Gülerman et al., 1997). It is also a highly potent eosinophilia inhibitor (Naito et al., 1996) and is used as a fungicide (Crofton, 1996) and a herbicide (Tada et al., 1995). Some triazole derivatives have been evaluated for their anti-bacterial activity against both Gram-positive and Gram-negative bacteria (Bs et al., 1996). Triazole derivatives have been synthesized as possible antidepressants, tranquilizers and plant-growth regulators (Bradbury & Rivett, 1991; Hirota et al., 1991; Walser et al., 1991).

Extensive studies have been carried out on substituted 1,2,4-triazole derivatives (Cornelissen et al., 1992; Kunkeler et al., 1996;
Research findings indicate that the 1,2,4-triazole moiety is found to be associated with diverse pharmacological activities such as analgesic, anti-asthmatic, diuretic, antifungal, pesticidal and anti-inflammatory activities.

Part IV of the thesis describes the crystal and molecular structures of four 1,2,4-triazol-3-one derivatives. The four compounds were prepared and kindly supplied by Prof. Bharati Badami, Department of Chemistry, Karnatak University, Dharwad, India and the single crystals suitable for X-ray work were prepared by the author in the Department of Physics.

2.5.1 Preparation of 1-(2-Naphthyloxy)methylcarbonylpiperidine, C17H19NO2: ST1 [Chapter III]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with piperidine and the oily product was treated with ice-cold water. The resulting precipitate was filtered off, dried and recrystallized from petroleum ether to afford crystals of ST1. (Yield: 0.524 g, 84.14%; m.p. 353-357 K).
2.5.2 Preparation of 3-Methyl-1-(2-naphthyloxymethylcarbonyl) piperidine, C$_{18}$H$_{21}$NO$_{2}$: ST2 [Chapter III]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with 3-pipocoline and the oily product was treated ice-cold water. The resulting precipitate was filtered off, dried and recrystallized from acetone to afford crystals of ST2 (Yield: 0.498 g, 76.01%; m.p. 363-365 K).

![Chemical Structure of ST2](image)

2.5.3 Preparation of 4-(2-Naphthyloxymethylcarbonyl)morpholine, C$_{16}$H$_{17}$NO$_{3}$: ST3 [Chapter IV]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with morpholine and the oily product obtained was treated with water, and the resulting precipitate was filtered off, dried and recrystallized from acetone to afford crystals of ST3 (Yield: 0.532 g, 84.8%; m.p. 416-418 K).

![Chemical Structure of ST3](image)

2.5.4 Preparation of 4-Methyl-1-(2-naphthyloxymethylcarbonyl) piperazine, C$_{17}$H$_{20}$N$_{2}$O$_{2}$: ST4 [Chapter IV]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with N-methylpiperazine and the oily product obtained was treated with water, and the resulting precipitate was filtered off, dried and recrystallized from acetone to afford crystals of ST4 (Yield: 0.514 g, 78.17%; m.p. 383-385 K).
2.5.5 Preparation of \(N\)-(2-naphthyloxymethylcarbonyl)pyrrolidine, C\textsubscript{\textit{16}}H\textsubscript{\textit{17}}NO\textsubscript{\textit{2}}: ST\textsubscript{\textit{5}} [Chapter V]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with pyrrolidine. The oily product obtained was treated with water. The precipitate obtained was filtered, dried and recrystallized from acetone to afford crystals of ST\textsubscript{5} (Yield: 0.51 g, 86.39%; m.p. 397-399 K).

2.5.6 Preparation of \(N,N\)-Dimethyl-2-(2-naphthyloxy)acetamide monohydrate, C\textsubscript{\textit{14}}H\textsubscript{\textit{15}}NO\textsubscript{\textit{2}}\cdot\text{H}_{\text{2}}\text{O}: ST\textsubscript{\textit{6}} [Chapter V]

For the preparation of the title compound, Methyl 2-(2-naphthyloxy)acetate (0.5 g) was reacted with \(N,N\)-dimethylamine. The resulting oily product obtained was treated with water. The precipitate which formed was filtered off, dried and recrystallized from acetone to afford crystals of ST\textsubscript{6} (Yield: 0.245 g, 46.21%; m.p. 345-349 K).
2.5.7 Preparation of 1-[2-(4-Nitrophenoxy)acetyl]pyrrolidin-2-one, C$_{12}$H$_{12}$N$_2$O$_5$: ST7 [Chapter VI]

A solution of (4-Nitrophenoxy)acetyl chloride (1.0 g) in dichloromethane was stirred with pyrrolidinone. The dichloromethane was removed and crushed ice was added to the contents. The solid residue obtained was filtered off and recrystallized from methanol, affording crystals of ST7 (Yield: 0.78 g, 63.71%; m.p. 413-415 K).

![Chemical Structure](image)

2.5.8 Preparation of 2-[(2-Oxopyrrolidin-1-yl)carbonylmethyl]-2,3-dihydro-1H-isoindole-1,3-dione, C$_{14}$H$_{12}$N$_2$O$_4$: ST8 [Chapter VI]

A solution of (1,3-dioxo-1,3-dihydroisoindole-2-yl)acetyl chloride (1.0 g) in dichloromethane was stirred with pyrrolidinone. The dichloromethane was removed and crushed ice was added to the contents. The solid material obtained was filtered off and recrystallized from methanol to afford crystals of ST8 (Yield: 0.81 g, 66.5%; m.p. 473 K).

![Chemical Structure](image)
2.5.9 Preparation of 16-[3-Methoxy-4-(2-piperidin-1-ylethoxy)-benzylidene]-17-oxoandrosten-5-en-3β-ol acetate monohydrate, C₃₆H₄₉NO₅·H₂O: ST9 [Chapter VIII]

A mixture of 16-[3-methoxy-4-(2-piperidin-1-ylethoxy)benzylidene]-17-oxo-5-androsten-3β-ol (0.5 g, 0.868 mmol), acetic anhydride (1.0 ml) and dry pyridine (2.0 ml) was heated on a steam bath for 2 h. The contents of the reaction mixture were then poured into ice-cold water and basified with liquid ammonia. The precipitate obtained was filtered off, washed with water, dried and recrystallized from hexane (333-353 K), affording crystals of ST9 (Yield: 0.38 g, 70.5%; m.p. 399-401 K).

2.5.10 Preparation of 16-[4-(3-chloropropoxy)-3-methoxy-benzylidene]-17-oxoandrost-5-en-3β-ol, C₃₀H₃₉ClO₄: ST10 [Chapter VIII]

To a solution of dehydroepiandrosterone (0.75g, 2.60 mmol) in methanol (10 ml), sodium hydroxide pellets (1.5g) were added and dissolved. 4-(3-Chloro)-propoxy-3-methoxy benzaldehyde (1g, 4.373 mmol) was added dropwise and stirred for 2h. The completion of reaction was monitored using TLC. Ice-cold water was added to the reaction mixture and precipitate was filtered, washed, dried. It was recrystallized from acetone (Yield: 1.5 g, 86.7%, m.p. 483-485 K).
2.5.11 Preparation of 16-[3-Methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3β-pyrrolidinoandrostan-5-en-17β-ol monohydrate, C₃₇H₅₄N₂O₃·H₂O: ST11 [Chapter VIII]

To a stirred suspension of 16-[3-methoxy-4-(2-pyrrolidin-1-ylethoxy)benzylidene]-3-pyrrolidinoandrostan-3,5-androstan-17-one (0.5 g, 0.871 mmol) in methanol (75 ml), sodium borohydride (1.0 g) was added in small amounts over a period of 2 h at room temperature. Stirring was continued for further 4 h. Excess of solvent was removed under vacuum and reaction mixture was poured into ice-cold water (100 ml). The precipitate obtained was filtered, washed with water, dried and recrystallized in methanol-acetone to afford ST11 (Yield: 0.38 g, 75.54%, m.p. 469-472 K).
2.5.12 Preparation of 2’-(p-fluorophenyl)-4-azapyrazolo[4’,3’:2,3]-5α-androstan-17β-yl acetate, C_{27}H_{34}FN_{3}O_{2}: ST12 [Chapter IX]

To a refluxing solution of 17β-acetoxy-3-chloro-4-aza-5-androst-2-en-2-aldehyde (0.5 g, 1.32 mmol) in aldehyde free ethanol (250ml) was added glacial acetic acid (1.5 ml) dropwise. The solution was refluxed for 10 min. and then p-fluorophenylhydrazine hydrochloride (0.25 g) was added and refluxed for 5 h. The solution was concentrated to about 20 ml and poured into ice-cold water, dried and recrystallized from acetone (Yield: 0.25 g, 41.9 %; m.p. 511-513 K).

2.5.13 Preparation of 2’-(p-fluorophenyl)-4-azapyrazolo[4’,3’:2,3]-5α-androstan-17β-ol, C_{25}H_{32}FN_{3}O: ST13 [Chapter IX]

A mixture of 2’-(p-fluorophenyl)-4-azapyrazolo[4’,3’:2,3]-5α-androstan-17β-yl acetate (0.2 g, 0.443 mmol) and potassium carbonate (0.5 g) in 10% aqueous methanol (50 ml) was stirred at room temperature for 3 h. The slurry obtained was poured into ice-cold water. The precipitated product was filtered, washed, dried and recrystallized form acetone (Yield: 0.125 g, 68.9%, m.p. 513-515 K).
2.5.14 2'-p-Fluorophenyl-17a-aza-D-homo-4-androsteno[17,16-c]pyrazol-3-one, C_{26}H_{30}FN_{3}O: ST14 [Chapter X]

A solution of 2'-p-fluorophenyl-17a-aza-D-homo-5-androsteno[17,16-c]pyrazol-3β-ol (0.5 g, 1.186 mmol) in cyclohexanone (5 ml) and toluene (100 ml) was slowly distilled as aluminium isopropoxide (1 g) in toluene (10 ml) was added to remove moisture. Distillation was continued for 0.5 h. The reaction mixture was refluxed for 4 h and allowed to stand overnight. The solution was filtered, filtrate was steam distilled and residue obtained was recrystallized from ethyl acetate to afford ST14 (Yield: 0.35 g, 70.42%; m.p. 499-501 K)

2.5.15 Preparation of 2'-p-Fluorophenyl-5-androsteno[16,17-d]triazol-3β-ol, 2(C_{25}H_{30}FN_{3}O). CH_{3}OH: ST15 [Chapter X]

A solution of 3β-acetoxy-2'-p-fluorophenyl-5-androsteno[16,17-d]triazole (0.2 g, 0.45 mmol) in methanol (30 ml) and potassium hydroxide (0.2 g) was refluxed for 30 min. The reaction mixture was poured into ice cold water and neutralized with glacial acetic acid. The product obtained was filtered, washed, dried and recrystallized from methanol to afford ST15 (Yield: 0.18 g, 99.28%; m.p. 487-489 K).
2.5.16 Preparation of 16-(4-Isopropylbenzylidene)androst-4-ene-3,17-dione, C_{29}H_{36}O_{2}: ST16 [Chapter XI]

16-(4-Isopropylbenzylidene)-17-oxo-5-androsten-3β-ol (1.0 g) was dissolved in dry toluene (150 ml) by refluxing and then cyclohexanone (10 ml) was added. Traces of moisture were removed by azotropic distillation. The distillation was continued at a slow rate while adding a solution of aluminium isopropoxide (1.0 g) in dry toluene (15 ml) drop wise. The reaction mixture was refluxed for 4 h. it was allowed to stand overnight at room temperature. The slurry was filtered and the residue was washed thoroughly with dry toluene. The combined filtrate and the washings were steam distilled until the complete removal of organic solvents was affected. The solid residue was collected by filtration next day, dried and recrystallized from acetone at cold temperature to give ST16 (Yield: 0.80 g, 80.39%, m.p. 453-459 K).

![Diagram](image)

2.5.17 Preparation of 3β-Acetoxy-13α-(5-methyl-1,3,4-oxadiazol-2-yl)-13,16-seco-17-nor-5-androstene-16-nitrile, C_{23}H_{31}N_{3}O_{3}: ST17 [Chapter XII]

A solution of 3β-hydroxy-16-oximino-5-androsten-17-one hydrazone (4 g, 12 mmol) in acetic anhydride (40 ml) was refluxed for 45 min., poured into iced cold water, filtered, washed, dried and purified by fractional crystallization from ethanol to afford the crystals of ST17. Single crystals of ST17 were obtained by recrystallization from ethanol (Yield: 2 g, 42%; m.p. 501-502 K).
2.5.18 Preparation of 4-Amino-2-(p-chlorophenyl)-5-methyl-3,4-dihydro-2H-1,2,4-triazol-3-one, C$_9$H$_9$CIN$_4$O: ST18

[Chapter XIV]

The compound ST18 was prepared by heating 3-(4-chlorophenyl)-5-methyl-1,3,4-oxadiazolin-2-one with hydrazine hydrate in ethanol. The solid obtained was recrystallized from absolute ethanol (m.p. 458-459 K).

2.5.19 Preparation of 2-(4-Chlorophenyl)-4-(2-hydroxyethyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one, C$_{11}$H$_{12}$ClN$_3$O$_2$: ST19 [Chapter XIV]

The compound ST19 was prepared by heating 3-(4-chlorophenyl)-5-methyl-2-oxo-Δ$^4$-1,3,4-oxadiazole with ethanolamine. The solid obtained was recrystallized from ethanol and suitable crystals were selected for X-ray diffraction (m.p. 388-403 K).
2.5.20 Preparation of 2-(4-Bromophenyl)-5-methyl-2,3-dihydro-4H-1,2,4-triazol-3-one, C$_9$H$_8$BrN$_3$O: ST20 [Chapter XV]

The compound ST20 was prepared by refluxing 2-(4-bromophenyl)-5-methyl-1,3,4-oxadiazolin-2-one with formamide. The solid obtained was recrystallized from benzene by slow evaporation (m.p. 503 K).

2.5.21 Preparation of Ethyl 4-[1-(4-bromophenyl)-3-methyl-5-oxo-4,5-dihydro-1H-1,2,4-triazol-4-yliminomethyl] phenoxyacetate, C$_{20}$H$_{19}$BrN$_4$O$_4$: ST21 [Chapter XV]

The compound ST21 was prepared by heating 4-amino-2-(p-bromophenyl)-5-methyl-2,4-dihydro-3H-1,2,4-triazol-3-one with p-hydroxybenzaldehyde to give the corresponding hydrazone, and then further reaction with ethyl bromoacetate in the presence of dry K$_2$CO$_3$ and KI. The solid obtained was recrystallized from acetone (m.p. 428-431 K).