Chapter 6

Summary

The molecular structures of various therapeutic compounds have been discussed in the previous chapters. Based on the knowledge gained so far, it is interesting to know how the molecular structures are correlated with their properties. The structure property correlation of dihydropyridine derivatives has been extensively carried out. It is now possible to identify the molecules which are good candidates as antagonists among the newly tailored derivatives by studying the molecular structures in detail.

6.1 Dihydropyridine derivatives

1,4-dihydropyridines (DHPs, e.g nifedipine) are the most studied class of organic calcium channel modulators and, since their introduction into clinical medicine in 1975, have become almost indispensable for the treatment of cardiovascular diseases such as hypertension, cardiac arrhythmias, or angina [1]. More than 20 years after the introduction of nifedipine, many DHP analogs have now been synthesized and numerous second-generation commercial products have appeared on the market [2].

The bond lengths and angles about N1 and C4 for compounds **1** to **5** are given in table 6.1.1. The two dihydropyridine moieties of **3** are referred to as **3A** and **3B**. Table 6.1.1 shows that the C-N and C-C bond lengths about N1 and C4 are characteristic single bonds. The bond angles about N1 are slightly greater than 120° and that about C4 are around 110°. The bond lengths about C2-C3 and C5-C6 vary between 1.332(8)Å and 1.364(3)Å indicating a characteristic C-C double bond.

Table 6.1.1: Bond lengths and angles about N1 and C4. (Å, °)

Atoms	**1**	**2**	**3A**	**3B**	**4**	**5**
N1-C2	1.384(4)	1.380(3)	1.389(7)	1.38(1)	1.372(5)	1.400(6)
N1-C6	1.383(4)	1.370(3)	1.378(7)	1.38(1)	1.379(5)	1.407(7)
C3-C4	1.513(5)	1.529(3)	1.522(7)	1.54(1)	1.526(5)	1.525(7)
C4-C5	1.536(4)	1.527(3)	1.518(7)	1.499(7)	1.510(5)	1.521(7)
C2-N1-C6	123.2(3)	123.6(2)	123.6(4)	121.6(4)	123.5(3)	121.3(4)
C3-C4-C5	110.7(3)	110.3(2)	111.2(4)	109.6(4)	110.8(3)	109.1(4)

The pyridine rings of compounds **1** to **5** are in flat boat conformation. The degree of puckering at N1 and C4 can be compared by taking the average of the absolute values of successive torsion angles about N1 and C4 respectively. Table 6.1.2 shows the variation of the puckering amplitudes at N1 and C4 accordingly. The sum of absolute torsion angles ($\sum P$) of the dihydropyridine ring and the angle between the least squares planes of dihydropyridine ring with that of the phenyl ring substituted at C4 position (Δ) are also compared in table 6.1.2.

A graph of the average of (C=C−N1−C) torsion angle values versus average of (C=C−C4−C) shows the linear variation of the torsion angles about N1 with respect to C4 (figure 6.1.1). Thus, the amplitude of puckering at N1 and C4 are linear with respect to each other.

Table 6.1.2: Average of absolute torsion angles about N1 and C4 for compounds **1** to **5**, $\sum P$ and Δ

Atoms	**1**	**2**	**3A**	**3B**	**4**	**5**
C=C−C4−C	18.33	20.98	4.01	24.98	29.64	29.51
C=C−N1−C	16.81	10.61	7.39	17.01	15.66	14.02
$\sum P$	105.9°	76.2°	31.6°	95.7°	108.4°	106.8°
Δ	87.9(2)°	89.3(1)°	76.5(3)°	83.9(3)°	86.7(2)°	87.7(3)°

In 1995 a detailed structure-activity profile for a series of DHPM calcium channel modulators was reported leading to a new general binding-site model [3]. It was proposed that calcium channel modulation (antagonist vs. agonist activity) is dependent on the absolute configuration at C4, where the orientation of the 4-phenyl group (R- versus S-enantiomer) acts as a *molecular switch* between antagonist (phenyl-group up) and agonist (phenyl-group down) activity (figure 6.1.2).

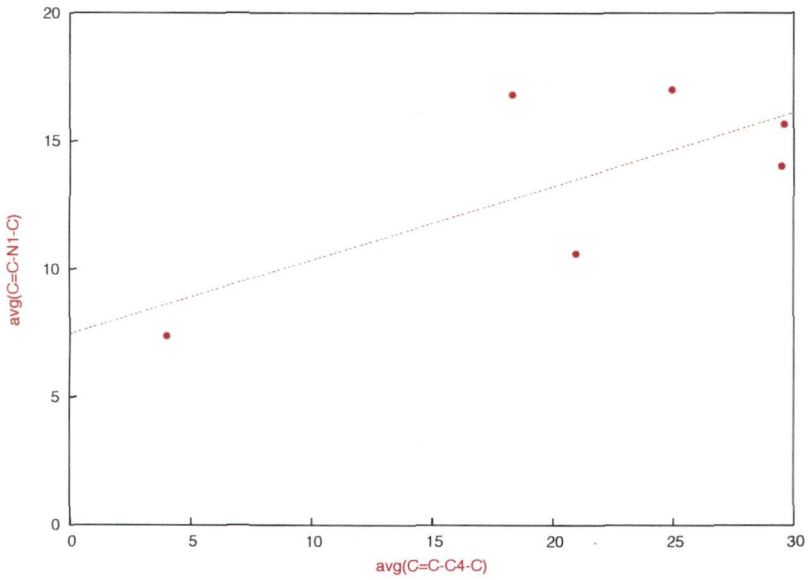

Figure 6.1.1: Average of (C=C−N1−C) torsion angle values versus average of (C=C−C4−C)

Further, in the receptor-bound conformation the substituted phenyl ring should be positioned axially perpendicular to and bisecting the boat-like dihydropyridine ring, with the 4-phenyl substitutent (X) prefering the *syn-periplanar* (relative to C4-H) orientation.A *cis*-carbonyl ester orientation (with respect to the C5-C6 dihydropyridine double-bond) was also found mandatory for optimum calcium channel modulatory activity (figure 6.1.2).

The inter-ring conformation angles of the dihydropyridine ring and the phenyl substitution about C4 of the dihydropyridine rings are listed in table 6.1.3.

The orientation of the phenyl ring at C4 along with that of the carbonyl ester at C3, C5 positions is tabulated in table 6.1.4.

A detailed structure analysis of **1** to **5** reveals that only compounds **1** and **4** may exhibit the antagonist activity. The removal of solvent molecules in **2** and **3** could make them suitable candidates too as the molecular conformation might change.

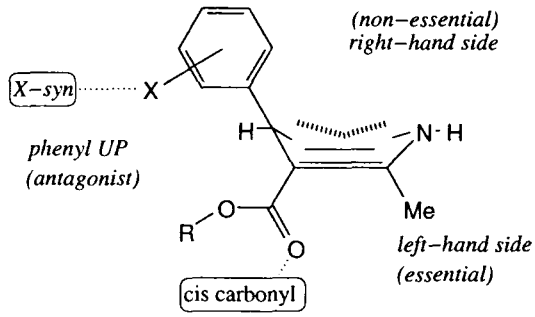

Figure 6.1.2: Receptor-bound dihydropyridine/pyrimidine conformation (antagonist)

Table 6.1.3: Inter ring conformation angles for the compounds **1** to **5**.

	Atoms	Angle (°)
1	C3 C4 C16 C17	−56.8(4)
	C5 C4 C16 C17	67.7(4)
	C3 C4 C16 C21	121.8(3)
	C5 C4 C16 C21	−113.7(3)
2	C3 C4 C29 C30	−68.5(3)
	C5 C4 C29 C30	54.9(3)
	C3 C4 C29 C34	109.2(2)
	C5 C4 C29 C34	−127.5(2)
3A	C3A C4A C27A C28A	39.8(8)
	C5A C4A C27A C28A	−86.1(7)
	C3A C4A C27A C32A	−142.7(6)
	C5A C4A C27A C32A	91.5(7)
3B	C3B C4B C27B C28B	−92.6(5)
	C5B C4B C27B C28B	143.6(5)
	C3B C4B C27B C32B	85.2(6)
	C5B C4B C27B C32B	−38.6(6)
4	C3 C4 C19 C20	93.0(4)
	C5 C4 C19 C20	−142.9(4)
	C3 C4 C19 C24	−86.4(4)
	C5 C4 C19 C24	37.7(5)
5	C3 C4 C19 C20	109.4(6)
	C5 C4 C19 C20	−127.8(5)
	C3 C4 C19 C24	−70.6(6)
	C5 C4 C19 C24	52.3(7)

Table 6.1.4: Orientation of the substituents at C3, C4 and C5 positions of the DHP ring

	1	**2**	**3A**	**3B**	**4**	**5**
C4 (phenyl)	UP	UP	UP	UP	UP	UP
C3	*sp*	*sp*	*sc*	*ac*	*sp*	*sp*
C5	*ap*	*sc*	*ac*	*ac*	*ap*	*sp*
Antagonist	yes	no	no	no	yes	no

ap - anti-periplanar *sc - syn-clinal*
sp - syn-periplanar *ac - anti-clinal*

6.2 Coumarin derivatives

The structures of a large number of HIV-1 integrase inhibitors have in common two aryl units separated by a central linker. At least one of these aryl moieties must contain 1,2-dihydroxy substituents in order to exhibit high inhibitory potency. The ability of o-dihydroxy-containing species to undergo *in situ* oxidation to reactive quinones presents a potential limitation to the utility of such compounds. The recent report of tetrameric 4-hydroxycoumarin-derived inhibitor provided a lead example of an inhibitor which does not contain the catechol moiety [4]. A general arrangement of two aromatic units separated by a central linker has emerged as a common motif for a large number of HIV integrase inhibitors. Also, the findings of Zhao H. et al. [5], show that adding 7-hydroxy groups to the coumarin rings increased inhibitory potency across a wide range of analogues. Modification of the central linker by extending its aryl component also enhanced the affinity. This latter effect may be dependent on both the shape and the hydrophobicity of the central linker unit.

The molecular structures of coumarin derivatives **6** to **8** have been detailed in chapter 4. The bond lengths about the oxygen atom in the pyran ring substituted about 4H of the coumarin base have been compared in table 6.2.1. Also, the bond angles about the rings are compared in table 6.2.1. The bond lengths and angles do not show much variation in the core structure of the derivatives. However variation in bond angles about the substitution at the C4 position of the pyran ring are observed. The variations in the orientations of the substituents can be better analysed by looking at the torsion angles about these bonds. Table 6.2.2 compares the torsion angles about some selected bond of **6**, **7** and **8**. The torsion angle about C14-C17 shows that the dicarbethoxy group is in the *anti-periplanar* conformation with respect to the pyran ring in all the three compounds. Further, the torsion angle about C7-C15 shows that the phenyl substituent at 4 postion of the pyran ring is in *syn-clinal* conformation in all the three compounds.

The pyran rings of **6**, **7** and **8** are all in flat boat conformation and the ring puckering amplidute is maximum for **6**. The deviations of the oxygen O12 and carbon C15 from the least squares plane defined by C6, C7, C15, C14, C13, O12 are tabulated in table 6.2.3. Also the sum of the six successive torsion angles ($\sum P$) of the pyran ring are listed in table 6.2.3 along with the angles (Δ) between the least squares planes of pyran ring and the phenyl substituent. The atoms of the coumarin and pyran groups (C1, C2, C3, C4, C5, C6, O12, C13, C14, C15, C7, C8, O9 and C10) lie in a plane.

Structure property correlation studies for this class of compounds is still very sparce. The structure analysis and their screening for antagonist activity of existing as well as new compounds shall ultimately result in tailoring new and efficient drugs.

Table 6.2.1: Comparison of bond lengths and angles of **6**, **7** and **8**, (Å, °)

Atoms	**6**	**7**	**8**
C8-O9	1.378(2)	1.375(2)	1.366(2)
C8-O11	1.211(2)	1.210(2)	1.210(2)
O9-C10	1.375(2)	1.381(2)	1.377(2)
C6-O12	1.361(2)	1.365(2)	1.360(2)
O12-C13	1.382(2)	1.378(2)	1.374(2)
C15-C22	1.532(2)	1.531(2)	1.529(2)
C17-O18	1.224(2)	1.226(2)	1.221(2)
C17-O19	1.346(2)	1.346(2)	1.347(2)
C8-O9-C10	121.5(1)	122.0(1)	122.1(1)
C6-O12-C13	118.6(1)	118.5(1)	119.1(1)
C7-C15-C22	111.9(2)	110.8(1)	109.7(1)
C14-C15-C22	110.4(1)	113.1(1)	111.7(1)
C14-C17-O18	126.3(2)	126.6(2)	126.4(1)
C14-C17-O19	111.3(2)	111.9(1)	112.1(1)
C15-C22-C23	120.5(2)	120.5(1)	119.2(1)
C15-C22-C27	122.1(2)	121.5(1)	122.3(2)

Table 6.2.2: Comparison of torsion angles of **6**, **7** and **8** (°)

Atoms	**6**	**7**	**8**
C13 C14 C17 O18	−3.3(3)	6.2(3)	0.4(3)
C13 C14 C17 O19	177.1(2)	−172.1(1)	179.5(2)
C15 C14 C17 O18	168.9(2)	−175.9(2)	−177.4(2)
C15 C14 C17 O19	−10.7(2)	5.7(2)	1.7(2)
C8 C7 C15 C22	76.6(2)	−68.7(2)	−70.1(2)
C14 C15 C22 C23	−57.6(2)	57.7(2)	61.9(2)
C14 C15 C22 C27	118.7(2)	−122.4(2)	−116.9(2)
C7 C15 C22 C23	64.0(2)	−65.0(2)	−59.8(2)
C7 C15 C22 C27	−119.8(2)	114.9(2)	121.5(2)
C24 C25 O28 C29	−0.6(3)		
C26 C25 O28 C29	179.9(2)		
C24 C25 S28 C29		−178.9(1)	
C26 C25 S28 C29		2.4(2)	
C22 C23 C24 Cl28			178.8(1)
C26 C25 C24 Cl28			−178.0(1)

Table 6.2.3: Deviations of O12 and C15 with respect to the pyran ring, $\sum P$ and Δ in **6**, **7** and **8** (Å, °).

Atoms	**6**	**7**	**8**
O12	0.098(2)	−0.067(1)	−0.082(1)
C15	0.150(2)	−0.086(2)	−0.105(2)
$\sum P$	96.89	44.22	54.44
Δ	84.3(1)	89.5(1)	88.5(1)

6.3 Venlafaxine derivatives

Venlafaxine has shown effective antidepressant activity in humans [6] and has been developed in recent years as a drug for oral administration in its hydrochloride form. Venlafaxine is a bicyclic phenylethylamine derivative with a pharmacological profile that differentiates it from tricyclic antidepressants and serotonin uptake inhibitors. It is a serotonin and noradrenaline reuptake inhibitor (SNRI) with a weak effect on dopamine uptake [7, 8].

Molecular structures of venlafaxine derivatives, **9** to **11** are given in chapter 5. This section compares some of the crystallographic parameters.

The bond lengths and angles of **9a**, **9b** and **10** are compared in table 6.3.1.

Table 6.3.1: Comparison of bond lengths and angles of **9a**, **9b** and **10**, (Å, °)

Atoms	**9a**	**9b**	**10**
C4-O7	1.426(2)	1.415(3)	1.440(3)
C4-C8	1.557(2)	1.565(3)	1.566(4)
C8-C11	1.518(2)	1.521(4)	1.515(3)
C8-C9	1.470(2)	1.463(3)	1.534(4)
C9-N10	1.133(2)	1.145(3)	1.456(3)
C4-C8-C11	116.1(1)	116.6(2)	113.6(2)
C8-C9-N10	178.4(2)	178.4(3)	112.3(2)
C14-O17-C18	117.6(1)	118.5(2)	118.3(2)

The bond lengths about C9-N10 in **9a** and **9b** reflect the triple bond between carbon and nitrogen. In the case of **10** and **11**, the C-N forms a single bond. The labels of **11** are slightly different due to the presence of the oxazine ring. Hence the bond lengths and angles are not tabulated in table 6.3.1. The bond angle about O18 of **11** is 118.1(3). Thus among the four molecules the bond lengths and angles of the basic venlafaxine moiety do not vary greatly except for C-N. Also, these values are in agreement with those of the venlafaxine hydrochloride form [9].

The torsion angles give a clear picture of the twist or rotaion about various bonds in a molecule. Hence, the molecular geometry can be understood better by comparing the torsion angles. Table 6.3.2 compares the torsion angles about various bonds in **9a**, **9b**, **10** and **11**. The O-CH_3 group substituted on ring 1 (phenyl ring of the venlafaxine) is in *syn-periplanar* conformation (C13-C14-O17-C18) with respect to the phenyl ring for **9a** and **10**. It is in *anti-periplanar* conformation for **9b**. In the case of **11**, the torsion angle about C14-C15-O18-C19 implies that the O-CH_3 group is in syn-periplanar conformation. The oxygen atom O17 of **9a** and O18 of **11** participate in hydrogen bonding whilst that of

9b and **10** do not. The cyclohexane ring is in chair conformation in all the compounds.

The torsion angles about C4-C8-C11-C16 of **9a** and **9b** are close to that observed by Sivalakshmidevi et al. [9]. However for **10** and **11** these vary greatly (table 6.3.2).

Venlafaxine has been identified as a drug molecule since over a decade and a half. Identification of newer more efficient drug is thus in a nacent stage. Hence the structure property correlation studies for this class of compounds is rather scarce. The molecules reported in the thesis are being screened for the activity.

Table 6.3.2: Comparison of torsion angles in **9a**, **9b**, **10** and **11**, (°).

	Atoms	Torsion angle
9a	C5 C4 C8 C9	63.9(2)
	C3 C4 C8 C9	−174.1(1)
	C5 C4 C8 C11	−172.1(2)
	C3 C4 C8 C11	−50.1(2)
	C13 C14 O17 C18	3.4(3)
	C15 C14 O17 C18	−177.5(2)
	C4 C8 C11 C12	−72.0(2)
	C4 C8 C11 C16	109.2(2)
9b	C5 C4 C8 C9	62.8(3)
	C3 C4 C8 C9	−175.6(2)
	C5 C4 C8 C11	−173.4(2)
	C3 C4 C8 C11	−51.8(3)
	C13 C14 O17 C18	−179.1(2)
	C15 C14 O17 C18	0.0(4)
	C4 C8 C11 C12	−71.0(3)
	C4 C8 C11 C16	110.9(2)
10	C5 C4 C8 C9	−52.8(3)
	C3 C4 C8 C9	−176.0(2)
	C5 C4 C8 C11	75.2(3)
	C3 C4 C8 C11	−48.1(3)
	C13 C14 O17 C18	2.2(4)
	C15 C14 O17 C18	−177.8(3)
	C8 C9 N10 C19	−130.0(3)
	C9 N10 C19 C20	−179.2(3)
	C4 C8 C11 C12	99.0(3)
	C4 C8 C11 C16	−78.5(3)
11	C3 C4 C7 C8	−165.1(3)
	C5 C4 C7 C8	70.5(3)
	C12 C7 C4 O11	−179.8(2)
	C14 C15 O18 C19	2.9(6)
	C16 C15 O18 C19	−177.7(3)
	O11 C10 C20 C25	−85.9(4)
	N9 C10 C20 C25	149.9(4)
	C4 C7 C12 C13	−94.4(4)
	C4 C7 C12 C17	89.2(4)

6.4 References

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