**03. CRYSTALLOGRAPHY IN BIOCHEMISTRY AND PHARMACOLOGY**

**03.1-5 STRUCTURE-ACTIVITY RELATIONSHIPS OF BIPYRIDINE INOTROPIC CARDIAC AGENTS.** Vivian Cody and Joe Luft, Medical Foundation of Buffalo, Inc., 73 High St., Buffalo, NY 14215, USA.

Milrinone [2-methyl-5-azido-(3,4'-bipyridin)-6(1H)one] (A) and amrinone (B) are members of a new class of oral nonglycosidic, noncatecholamine cardiac positive-inotropic agents developed for the treatment of congestive heart failure. These bipyridine inotropic agents strengthen myocardial contraction by increasing the availability of intracellular calcium. We have shown that milrinone, but not amrinone, shares structural homology with thyroid hormone and like thyroid hormone, stimulates rabbit myocyte membrane Ca2+-ATPase activity as shown by Ca2+-dependent ATP hydrolysis in vitro (Hylote et al., Proc. Natl. Acad. Sci. USA, 82, 7974 (85)). Comparison of these molecular structures showed that there are structural homologies between the phenolic ring of thyroxine and the substituted ring of milrinone, not shared by amrinone. To further delineate the structural features required for this activity, the crystal structures of a number of milrinone analogues were investigated and are compared with the reported structures of amrinone and milrinone (Cody, Acta Cryst., in press; Robertson et al., J. Med. Chem. 29, 635 (86)). The following inotropic agents (C-F) have been studied to determine the conformational aspects of drug specificity. (C) 3-methyl-(3,4'-bipyridin)-6(1H)one (C1H10N3O, P21/c, c = 4, a = 7.574 (1), b = 11.132 (2), γ = 113.437 (2), R = 94.90(13°). (D) 2-methyl-5-bromo-(3,4'-bipyridin)-6(1H)one (C12H12N3O, P21/c, a = 6.613 (1), b = 7.269 (2), R = 12.768 (3), a = 97.573 (3), β = 92.612 (2), γ = 113.74-12°). (E) 2,3-dimethyl-5-cyano-(3,4'-bipyridin)-6(1H)one (BBr, C14H10NO, Pbcn, a = 9.5793 (8), b = 18.9553 (3), c = 19.814 (3), a = 100.95 (1), β = 92.74 (3)). The biochemical data for these compounds show that only the bromo analogue (D) and a 2-Ch3-5-NH2 analogue are active in this myocardial system. Structural analysis of these data show that all of the bipyridine rings are twisted as observed in the structure of milrinone. The two determinations of the N-methyl analogue (Z,P) show the largest variation in the twist angle. There is an N-B...O hydrogen bond in C and D. These data show that the presence of the 2-methyl substituent favors the twisted bipyridine rings to adopt a twist conformation which is favorable for Ca2+-ATPase enzyme activity. The nature of the 5-substituents is less critical though these results suggest that a functional group that can mimic iodine in either size or electrochemical properties is preferred. Thus, the 2,6-bis-(1-pyrrolidinylmethyl)phenyl group, a 2-methyl for a twist conformation, a free 5-N position, and a Z-substituent.

**03.1-6 THE SPATIAL ARRANGEMENT OF IMPORTANT MOLECULAR FEATURES IN CLASS I ANTIARRHYTHMIC AGENTS.** By Marek L. Głowacki and Penelope W. Codding, Departments of Chemistry and of Pharmacology and Therapeutics, University of Calgary, Calgary, Alberta, Canada.

Class I antiarrhythmic agents control irregular heart beat in cardiac disorders by binding to sodium channels and slowing conduction velocity. Class I agents are characterized by three structural units: (a) an aromatic ring that can intercalate between the alkyl chains of phospholipids, (b) an amino group that can ionize under biological conditions, and (c) a linkage region between (a) and (b) that contains a hydrogen bonding group. In this work, the optimal three dimensional arrangement of these crucial features has been sought through X-ray crystallography, molecular mechanics calculations and structural correlations. Two series of synthetic antiarrhythmic agents, one based on the 2,5-bis[1-pyrrolidinylmethyl]phenol moiety (A) and one based on 2,2,5,5-tetramethyl-3-pyrrolidin-3-carboxamide (B) are being characterized. These structures have been compared to those of the traditional local anesthetics like disopyramide (C), quinidine, propanidid, lidocaine and mexiletine to identify the stereochemical requirements for arrhythmia control. These comparisons have been extended by calculating the potential energy surface for both anesthetics (mexiletine) and synthetic compounds (A). Comparisons of the low energy conformers of the active agents thus described indicate that, while flexibility is an important feature of these drugs, there are specific ranges for the distances between the three crucial groups mentioned above. Class I antiarrhythmic drugs have been divided into three subclasses according to the rate of recovery from channel block. We find that the separations between the three molecular features are different for each of these subclasses. Thus, Class I antiarrhythmic activity may be dependent on an induced fit of these flexible agents to a receptor. The similarity in the general three dimensional shape and functionality of these agents suggests that a common receptor mediates the antiarrhythmic action; these findings will be used to propose a model for this receptor site.

Crystal data: A: N-[4-hydroxy-3,5-bis(1-pyrrolidinylmethyl)phenyl]-2-methylbenzamide, C19H14N3O4·HCl, orthorhombic, Aba2, R = 10.82 (2), α = 29.15 (1), c = 11.092 (1), a = 12.223 (1), β = 92.612 (2), γ = 113.74-12°, T = 232K, Z = 8, R = 0.042, R0 = 0.043. B: N-(w-N-phthalimido-3-phenyl-2,3-propanediamine)-2,2,5,5-tetramethyl-3-pyrrolidin-3-carboxamide, C19H13N3O4·HCl·1/2CH3OH, triclinic, P1, R = 0.995 (1), b = 10.7491 (1), c = 12.154 (1), γ = 92.74 (3). 

![Chemical Structure](image-url)
CONFORMATIONAL ASPECTS OF UL-FS 49, A NEW SPECIFIC BRADICARDIC AGENT.
By P. Luger, Institut für Kristallographie, Freie Universität Berlin; L. Müller, M. Reiffen and A. Prox, Chemie Research Department, Dr. Karl Thomae GmbH, Biberach, Federal Republic of Germany

Coronary heart disease is a major cause of morbidity and mortality in Western countries. In the last years cardiovascular drugs with a new pharmacological profile have been described by us as "specific bradicardic" agents. Recently a major breakthrough was made by a novel type of structure, represented by the seven membered ring compound, coded UL-FS 49 (1). Due to the long aliphatic chain, which connects the benzazepinone system with the substituted phenyl ring this compound shows a high conformational flexibility. Therefore, the deduction of its pharmacologically active conformation is a problem which is of great interest.

![X-ray structure of 3-chloro-4-morpholinooangelicin](https://example.com/xray.png)

X-ray analysis of the protonated and nonprotonated form of the molecule in the solid state, revealed a rather unusual U-shaped geometry (Fig. 1), in which both phenyl rings are only about 5 A apart from each other. However, according to the results of photoelectronic (PE)-spectroscopy, an extended form was derived for the gas phase. NMR-experiments, to elucidate the most stable conformation in solution, are currently under investigation. Empirical (MOM, MPM, ECEPP) and semiempirical (PCIL2, MNDO) calculations confirmed both the extended and the globular conformation as energetically favoured with an energy difference of less than 6 kcal.

By comparing the conformational shape of UL-FS 49 and related compounds with their experimentally obtained biological metabolism and selected dye laser activities, the potential for such molecules is high and the search for new potential drug candidates is promising.

3-chloro-4-morpholinooangelicin. Monoclinic system, space group P2₁/a, Z=4, cell dimensions a = 11.776(2), b = 13.832(2), c = 8.793(1) Å, g = 110.73(2)°.

3-chloro-4-aminomethylphenyl-7-tioangelicin. Monoclinic system, space group P2₁/a, Z=4, cell dimensions a = 18.313(3), b = 6.123(1), c = 14.124(2) Å, g = 93.41(2)°.

3-phenylangelicin. Trigonal system, space group P3, Z=18, cell dimensions a=b=40.964(10), c=3.861(2) Å, g = 180° (hexagonal axes).

Conformational analysis by X-ray crystallography, and pharmacological activity of these new furocoumarins will be discussed.

CRYSTAL AND MOLECULAR STRUCTURE OF 1,4-DIHYDRO-6-METHOXY-7-BENZOLOXY ISOCOUMARIN. By K. Sivakumar, K. Subramanian, and S. Natarajan, Department of Physics, Anna University, Madras 600 023, India.

In continuation of our work on coumarins involved in the biological metabolism and selected dye laser activities, the crystal structure of 1,4-dihydro-6-methoxy-7-benzoxy isocoumarin has been determined. The title compound, C₁₈H₁₆O₂, crystallises in the space group P2₁/c with a=10.622(1), b=13.961(1), c=10.047(1) Å and g = 109.37(1); Z=4. D₄=1.312, D₄=1.320 gcm⁻³. The structure was solved by direct methods using CuKα diffractometer intensity data. The coumarin ring system was seen in the B-map with the highest figure of merit. The rest of the non-hydrogen atoms were located in the subsequent difference Fourier maps. The present R factor for 2080 unique reflections is 0.063.

The characteristic feature of the molecule is the system formed by the aromatic ring in benzoyloxy group and the hetero ring in coumarin ring system. The conformation of the coumarin ring system is typical of that of other molecules in the series. The hetero ring is in a sofa conformation. The orientation of the aromatic ring of the benzoyloxy group normal to the coumarin plane is an interesting feature. This has been found in flavonoids and correlated to the biological activity. The methoxy group present in the structure is approximately contained in the plane of the aromatic ring to which it is attached.

Packing in the unit cell emphasizes the non-associated nature of the molecules. The conformational features will be analysed and compared with other structurally related biomolecules in the light of a model for structural activity at receptor site, and the results will be presented in the congress.