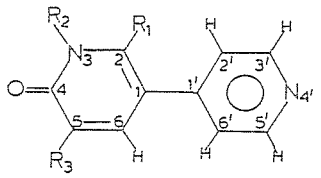
03.1-5 STRUCTURE-ACTIVITY RELATIONSHIPS OF BIPYRIDINE INOTROPIC CARDIAC AGENTS. Vivian Cody and Joe Luft, Medical Foundation of Buffalo, Inc., 73 High St., Buffalo, NY 14203; Faith B. Davis and Paul J. Davis, VA Medical Center, Buffalo, NY, 14215, USA.

Milrinone [2-methyl-5-amino-(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 reported that milrinone, but not amrinone, shares structural homology with thyroid hormone and like thyroid hormone, stimulates rabbit myocardial membrane Ca^{2+}-ATPase activity as shown by Ca^{2+}-dependent ATP hydrolysis in vitro (Mylotte 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) 2-methyl-(3,4'-bipyridin)-6(1H)-one ($C_{11}H_{10}N_2O$; $P2_1/c$, z = 4, a = 7.574 (1), b = 11.132(2), c = 11.437(2)Å, β = 94.90(1)°), (D) 2-methyl-5-bromo-(3,4'-bipyridin)-6(1H)-one ($C_{11}H_9N_2OBr$; P-1, z = 2, a = 6.813(2), b = 7.269(2), c = 12.787(4)Å, α = 97.57(3), β = 92.61(2), γ = 113.74-(2)°), (E) 2,3-dimethyl-5-cyano-(3,4'-bipyridin)-6(1H)-one HBr ($C_{13}H_{11}N_3O$ HBr; Pbca, z = 8, a = 7.2993(8), b = 18.955(3), c = 19.814(3)Å), (F) 2,3-dimethyl-5-cyano-(3,4'-bipyridin)-6(1H)-one ($C_{13}H_{11}N_3O$; $P2_1/c$, z = 4, a = 11.713(4), b = 7.892(3), c = 12.154(4)Å, β = 92.27(4)°). The biochemical data for these compounds show that only the bromo analogue (D) and a 2-CH_3-5-NH_2 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 (E,F) show the largest variation in the twist angle. There is an N-H...O hydrogen bond in C and D. These data show that the presence of the 2-methyl substituent forces the two pyridine rings to adopt a twist conformation which is favorable for Ca^{2+}-ATPase enzyme activity. The nature of the 5-substituent is less critical although these results suggest that a functional group that can mimic iodine in either size or electrochemical properties is preferred. Thus, prerequisites for enzyme stimulation include a 2-methyl for a twist conformation, a free 3-N position, and a 5-substituent.

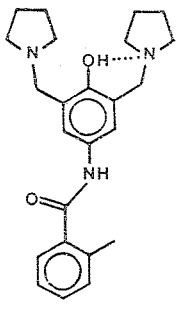


	R1	R2	R3	Φ		R1	R2	R3	Φ
A*	CH_3	H	CN	42;52°	B+	H	H	NH_2	1;-13,-9 -12,-22
C	CH_3	H	H	59	D	CH_3	H	Br	48
E	CH_3	CH_3	CN	43	F	CH_3	CH_3	CN	67

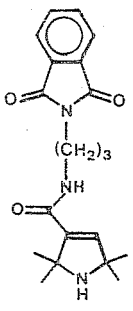
Φ = C2-C1-C1'-C6'
A* Milrinone, Cody, Acta Cryst.; Milrinone HCl, Robertson et.al., J. Med. Chem.
B+ Amrinone H_2O, Robertson et. al.; Amrinone, 4 independent molecules, Cody.

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

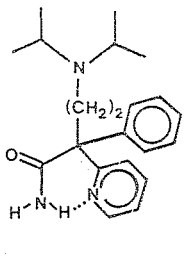
Class I antiarrhythmic agents control irregular heart beat in cardiac disorders by binding to sodium channels and slowing conduction velocity. Class I agents are characterized by three structural units: (a) an aromatic ring that can intercalate between the alkyl chains of phospholipids, (b) an amino 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 2,6-bis-(1-pyrrolidinylmethyl)phenol moiety (A) and one based on 2,2,5,5-tetramethyl-3-pyrrolino-3-carboxyamide (B) are being characterized. These structures have been compared to those of the traditional local anesthetics like disopyramide (C), quinidine, procainamide, 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-methyl-benzamide, $C_{23}H_{31}N_3O{\cdot}HCl$, orthorhombic, Aba2, a=13.882(2), b=29.115(3), c=11.092(1)A, T=223K, Z=8, R=0.042, R_w=0.043. B: N-(ω-N-phthalimidopropyl)-2,2,5,5-tetramethyl-2-pyrrolino-3-carboxyamide, $C_{20}H_{25}N_3O_3{\cdot}HCl{\cdot}1/2CH_3OH$, triclinic, P$\bar{1}$, a=8.995(1), b=10.749(1), c=12.190(1)A, α=96.36(1), β=100.95(1), γ=110.22(1)°, T=223K, Z=2, current R=0.08. C: disopyramide, $C_{21}H_{29}N_3O$, monoclinic, $P2_1/n$, a=17.409(2), b=10.922(2), c=21,565(2)A, β=99.50(3)°, T=243K, Z=8, R=0.060, R_w=0.060.



(A)



(B)

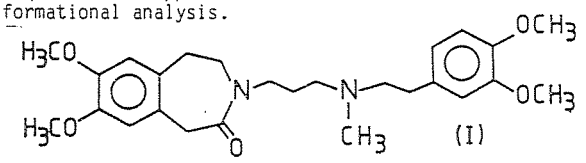


(C)

03.1-7 CONFORMATIONAL ASPECTS OF UL-FS 49, A NEW SPECIFIC BRADICARDIC AGENT.

By P. Luger, Institut für Kristallographie, Freie Universität Berlin; P. Müller, M. Reiffen and A. Prox, Chemical 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 (I). 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 conformer requested the application of different methods of conformational analysis.



(I)

X-ray analysis of the protonated and non protonated 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 3 Å apart from each other. However, according to the results of photoelectronic-(PE)-spectroscopy, an extend form was derived for the gas phase. NMR-experiments, to elucidate the most stable conformation in solution, are currently under investigations. Empirical (MMI, MMPI, ECEPP) and semiempirical (PCILO, MNDO) calculations confirmed both the extended as well as 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 pharmacological data, we conclude that there is a strong correlation between the molecular conformation and bradi cardic activity, with the most potent conformer being very close to the structure found in X-ray analysis.

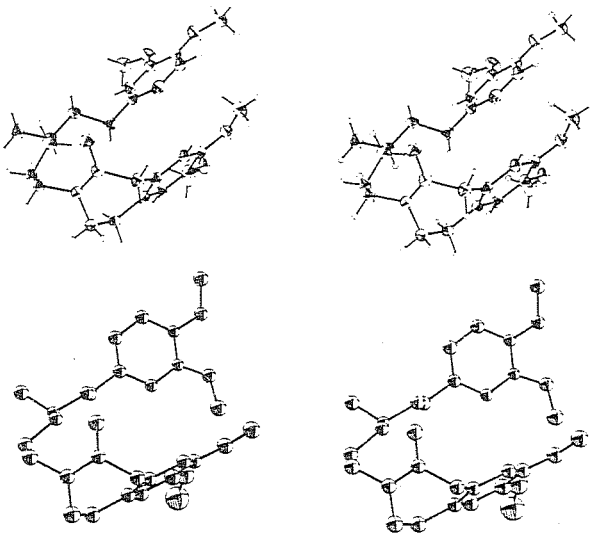


Fig. 1. Protonated (above) and nonprotonated form (below) of UL-FS 49

03.1-8 STRUCTURE-ACTIVITY RELATIONSHIP IN FUROCOUMARIN DERIVATIVES.

By F. Benetollo[a], G. Bombieri[b], A. Del Pra[b] and L. Mosti[c] (a) Istituto di Chimica e Tecnologia dei Radioelementi del C.N.R. Padova, Italy. (b) Istituto di Chimica Farmaceutica, Universita' di Milano, Italy. (c) Istituto di Scienze Farmaceutiche, Universita' di Genova, Italy.

Investigations on the molecular conformation of substituted furocoumarins have been carried out in order to elucidate the role of the substituents with respect to their differing ability to form molecular complexes with DNA in the ground state, where the ligands could undergo intercalation between two base pairs of the macromolecule. Among those ligands which have proved to be biologically active, the following have been characterized by X-ray diffraction analysis in order to correlate molecular structure with their biological activities.

3-chloro-4-morpholinoangelicin. Monoclinic system, space group $P2_1/n$, Z=4, cell dimensions a = 11.776(2), b = 13.832(2), c = 8.793(1) Å, β = 110.73(2)°.

3-chloro-4-aminomethylphenyl-7-tioangelicin. Monoclinic system, space group $P2_1/a$, Z=4, cell dimensions a = 18.313(3), b = 6.123(1), c = 14.124(2) Å, β = 93.41(2)°.

3-phenylangelicin. Trigonal system, space group $R\bar{3}$, cell dimensions a=b=40.964(10), c=3.881(2) Å, Z=18 (hexagonal axes).

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

03.1-9 CRYSTAL AND MOLECULAR STRUCTURE OF 1,4-DIHYDRO-6-METHOXY-7-BENZOYLOXY ISOCOUMARIN.

By K. Sivakumar, K. Subramanian, and S. Natarajan, Department of Physics, Anna University, Madras 600 025, 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-benzoyloxy isocoumarin has been determined. The title compound, $C_{17}H_{16}O_4$ crystallises in the space group $P2_1/c$ with a=10.822(1), b=13.961(1), c=10.047(1) Å and β = 109.57(1); Z=4, D_m=1.312, D_x=1.320 gcm^{-3}. The structure was solved by direct methods using CuK_α diffractometer intensity data. The coumarin ring system was seen in the E-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 hetro ring in coumarin ring system. The conformation of the coumarin ring system is typical of that of other molecules in the series. The hetro ring is in sofa conformation [ΔC_s =1.1]. 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.