Journal of Computer-Aided Molecular Design, 6 (1992) 19–31
ESCOM

J-CAMD 149

Models for the binding of amiodarone to the thyroid hormone receptor

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Received 12 November 1990
Accepted 19 August 1991

Key words: Molecular graphics; Conformational search; Molecular mechanics; Semiempirical molecular orbital calculations

SUMMARY

The antiarrhythmic drug amiodarone has recently been characterized as the first known thyroid hormone antagonist. Its mode of interaction with the thyroid hormone receptor is therefore of interest. A computational analysis of the conformational flexibility of amiodarone using molecular mechanics and the semiempirical molecular orbital method AM1 has been performed. The molecular mechanics studies show that the low-energy conformations of the benzoylbenzofuran portion of amiodarone can be grouped into 4 distinct classes, while the diethylaminoethoxy side chain is extremely flexible. Conformers representative of the 4 low-energy classes were fitted to an extended thyroid hormone receptor model. Four independent modes in which amiodarone could bind to the thyroid hormone receptor site were evaluated.

INTRODUCTION

The thyroid hormones, thyroxine (**1**, T_4) and triiodothyronine (**2**, T_3), are present in all vertebrates, where they play a fundamental role in the regulation of a wide range of processes, including foetal development and the metabolism of lipid, carbohydrate and protein [1]. These hormones have been the subject of intense investigation since T_4 was first isolated and purified in 1914 [2]. This has involved the synthesis and screening of large numbers of thyroid hormone analogues [3] and other compounds [4,5] for activity at the thyroid hormone receptor. Although many thyromimetic compounds have been identified, only recently has a thyroid hormone antagonist, the antiarrhythmic drug amiodarone (**3**), been reported [6].

Amiodarone has long been known to have side effects that involve the thyroid hormone system

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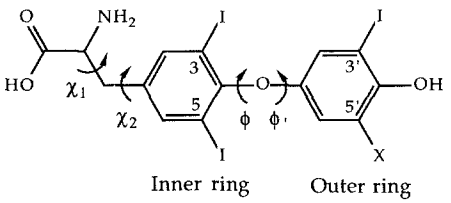
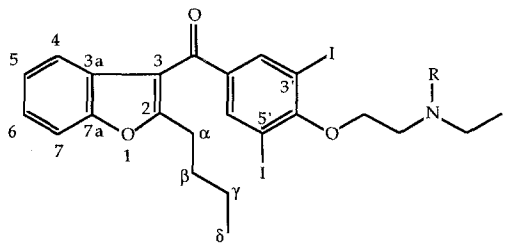




(1) X = I Thyroxine (T_4)
(2) X = H Triiodothyroinine (T_3)

(3) R = Et Amiodarone
(4) R = H Desethylamiodarone

such as alteration of hormone levels and, in severe cases, induction of either hypothyroidism or thyrotoxicosis [7]. This may be partly explained by the ability of amiodarone to bind to the thyroid hormone nuclear receptor and competitively displace T_3. The binding affinity for this site is low, being variously reported as 'modest' [8] and to range from $6.3 \times 10^6\ M^{-1}$ to $7.4 \times 10^5\ M^{-1}$ in different tissues [6]. An in vitro assay in a cultured GC cell line shows that amiodarone inhibits the T_3-stimulated synthesis of messenger RNA, indicating that amiodarone is an antagonist of T_3 at the nuclear receptor [6]. It is interesting that the major metabolite of amiodarone, desethylamiodarone (**4**), also binds to the receptor [8] but with an approximately 10-fold greater affinity. The testing of desethylamiodarone for antagonistic effects has not been reported.

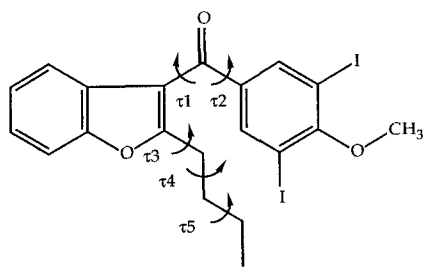
Compounds that act as thyroid hormone antagonists have potential uses as pharmacological tools in the investigation of the thyroid hormone system, and for the treatment of hyperthyroxinaemia. The present drugs for the treatment of this disorder inhibit thyroid hormone biosynthesis and are slow to alter thyroid hormone levels. A thyroid hormone antagonist would act quickly by blocking the receptor and directly inhibiting the effects of excess hormone. Amiodarone itself is of no use for this purpose because of its low affinity for the receptor. For clinical use it also has other undesirable properties, such as having a very low metabolic clearance rate and being concentrated inappropriately in the heart and other organs [7]. It does, however, provide a starting point for the design of novel thyroid hormone antagonists, but a better understanding of its mode of interaction with the thyroid hormone nuclear receptor is necessary before the design of more potent compounds is possible. As a preliminary step in this process, we report here the conformational analysis of amiodarone using both molecular mechanics and semiempirical molecular orbital (MO) calculations. The results of these calculations have been used to evaluate possible binding modes of amiodarone to the thyroid hormone receptor, using an extension of the thyroid hormone receptor model proposed by Jorgensen et al. [9,10].

METHODS

Molecular mechanics calculations and conformational searches were performed with Macromodel 2.5 [11] and the associated program Batchmin 2.6 using the Macromodel implementation of the MM2 force field which includes, in addition to the standard MM2 parameters, parameters appropriate for iodine and the benzofuran ring system. The default minimization method was used, except when close to convergence, when the Full Matrix Newton–Raphson (FMNR) method was

utilized. Conformational searches used the method of Lipton and Still [12] which uses an internal coordinate tree search to generate structures covering the conformational space of the molecule. Each structure is subsequently energy minimized and compared to previously generated minimum-energy structures; a new structure is retained if it does not duplicate previously generated conformers and is within a specified energy of the minimum-energy structure.

To reduce the complexity of the search for low-energy geometries, amiodarone was divided into two conformationally independent portions, structures **5** and **6**. Arbitrary conformations, built and minimized in Macromodel, were used as starting geometries for the conformational search. A step size of 60° was used, as recommended [12] for efficient and comprehensive coverage of the conformational space. Conformers more than 20 kJ/mol above the global minimum-energy structure were discarded.



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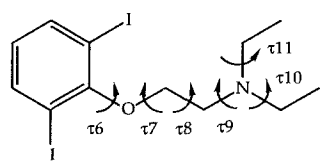

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The thyroid hormone receptor model used in this study was generated from a T_3 template by building T_3 in Macromodel with the diphenyl ether in a skewed ($\phi = 90°$, $\phi' = 0°$) conformation with the 3′ iodine atom distal to (i.e. away from) the inner ring. The structure was then fully geometry optimized. Unoptimized (rigid) rotations of the side-chain dihedral angles χ_1 and χ_2 in 30° increments generated 96 structures which did not have extreme van der Waals contacts. These structures were superimposed and the locations of the carboxylate oxygen atoms were used to define the spatial region accessible to the side chain.

The dihedral angle versus energy contour map in Fig. 1 was generated from energies calculated by the MULTIC routine which performed rigid simultaneous rotations of amiodarone dihedral angles τ_1 and τ_2 [13] in 10° steps.

Semiempirical MO calculations on structure **5** were performed with the program Mopac 5.0 [14] using the AM1 Hamiltonian [15] and the default convergers. All calculations were performed in vacuo and terminated normally. The determination of rotational barriers used the reaction path coordinate facility of Mopac and was carried out using 15° increments. The rotations of τ_1 and τ_2 were commenced from the crystal structure reported by Cody and Luft [16]. Full optimization, except for the dihedral angle being rotated, was performed at each step; the level of convergence of the minimization was specified using the keyword GNORM which was set to 3.0 or lower. If this keyword was not used, the calculations did not continue to adequate precision.

The program Insight II 1.0 was used to display and compare structures [17]. Macromodel was run on a Vax 11/750 or Vax 3400. Insight and Mopac were run on an IRIS 4D/220 GTX workstation.

RESULTS AND DISCUSSION

The conformational analysis of amiodarone has been performed on two levels. Firstly, molecular mechanics calculations have been used to perform a search for low-energy conformers, including the preferred orientations of the butyl and diethylaminoethoxy side chains. Secondly, the more sophisticated and computationally intensive semiempirical molecular orbital method, AM1, has been used to examine pathways of rotation around τ_1 and τ_2, which are important in defining the shape of the backbone of the molecule, the benzoylbenzofuran moiety.

Molecular mechanics calculations

Although a number of theoretical conformational studies of amiodarone have been reported [18,19], they have used abbreviated search procedures to find the low-energy conformers. In this study the 2-butyl benzoylbenzofuran fragment of amiodarone (**5**) has been the subject of a comprehensive conformational search encompassing dihedral angles τ_1–τ_5. Forty conformers within 20 kJ/mol of the global minimum were found. When superimposed, these structures could be grouped into 4 distinct classes depending on the values of τ_1 and τ_3 of each conformer.

Dihedral angle τ_1 was found to be distributed within two ranges, 37°–47° and 213°–223°. Steric interaction between the butyl group and carbonyl group or the butyl group and the phenyl ring prevented a completely planar arrangement of the benzofuran and carbonyl groups from being adopted. The two groups of structures, where τ_1 is closest to 0° and τ_1 is closest to 180°, have been designated the *O-trans*, and *O-cis* forms, respectively [21].

The butyl side chain was found in each case to be approximately perpendicular to the plane of the benzofuran. The value of τ_3 was also found to be independent of the value of τ_1, meaning that the butyl group could readily project from either the same or opposite face of the benzofuran as the carbonyl group. The remaining dihedral angles of the side chain, τ_4 and τ_5, were unrestricted and adopted a full range of staggered conformations.

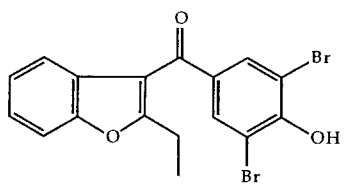
The combination of two possible orientations of the butyl side chain with two low-energy conformations of τ_1 gave 4 low-energy conformational classes of fragment **5**. These are summarized in Table 1.

TABLE 1
SUMMARY OF DIHEDRAL ANGLES IN THE MINIMUM-ENERGY STRUCTURES FOUND BY THE CONFORMATIONAL SEARCH OF AMIODARONE FRAGMENT **5**

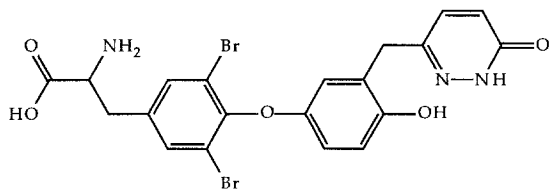
Group	Lowest energy (kJ/mol)	τ_1[a] range (°)	τ_2[b] range (°)	τ_3[c] range (°)
1	148.9	44–70	29–39	224–246
2	155.7	37–47	31–48	66–137
3	155.8	213–223	35–38	235–268
4	154.2	215–223	33–38	72–143
Crystal structure [16]	–	32.1	45.7	78.2

[a] τ_1 = C2, C3, carbonyl carbon, C1′.
[b] τ_2 = C3, carbonyl carbon, C1′, C2′.
[c] τ_3 = Cβ, Cα, C2, C3.

The presence of energy minima when the benzofuran and carbonyl group are in conjugation is consistent with molecular mechanics studies of the related compound benzbromarone (**7**) [20]. Variable temperature NMR studies [21] of amiodarone have been unable to observe the *O-cis* and *O-trans* forms of amiodarone as discrete conformers, even when cooled to −117°C. However, lanthanide-induced shift experiments [22] provide supporting evidence for the presence of both *O-cis* and *O-trans* conformers in solution.



(7) Benzbromarone



(8) SK&F L-94901

A comparison of the theoretical conformational classes with the crystal structure of amiodarone shows that the solid-state structure lies close to the ensemble of conformers designated group 2. The crystal-structure values for τ_2 and τ_3 (45.7° and 78.2°) fall within the range found for the group 2 conformers while the value for τ_1 (32.1°) falls just outside the range found for the group 2 low-energy structures (37°–47°).

The second fragment of amiodarone (**6**) is less conformationally restricted, with bonds τ_6–τ_{11} having little impediment to rotation. Therefore this fragment would be expected to have a large number of low-energy conformations. This was confirmed by a conformational search which found 36 widely varying, low-energy structures within 20 kJ of the minimum-energy structure. It is therefore reasonable to assume that the diethylaminoethoxy portion of amiodarone is essentially unrestricted, and would be able to adopt any accessible conformation upon binding.

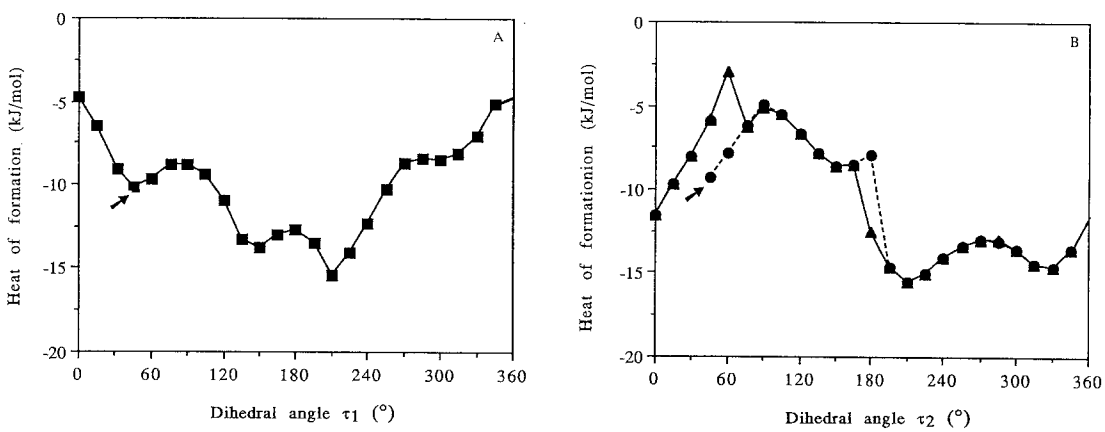


Fig. 1. The calculated heats of formation (AM1) for amiodarone fragment **5** as (A) τ_1 (■) was driven through 360° in 15° increments and (B) τ_2 was driven through 720°, also with a 15° step size (●, first 360°; ▲, second 360°). Rotations were commenced from the crystal structure dihedral angles (arrowed) and were to the right.

Semiempirical molecular orbital calculations

Figure 1A shows the AM1 calculated heats of formation for the amiodarone fragment **5** as dihedral τ_1 was driven through 360° (■) while all other bond lengths and angles were allowed to relax fully. Four energy minima are present at 45°, 150°, 210° and 285°. The minima at 45° and 285° correspond to the *O-trans* forms of amiodarone while those at 150° and 210° are *O-cis* forms. The energy maxima at 90° and 285° coincide with interconversion between *O-cis* and *O-trans* forms. The high-energy points at 0° and 180° arise from the steric interactions between the butyl group and carbonyl group and the butyl group and diiodophenyl ring. The energy difference between the lowest-energy *O-cis* and *O-trans* forms as determined by these in vacuo calculations is 5.3 kJ/mol.

Figure 1B shows the calculated heats of formation of **5** as dihedral angle τ_2 is rotated. The results for two complete rotations are shown. The first (●), which commenced from the AM1 minimized crystal structure of **5**, did not describe a closed loop and the calculation did not return to the initial geometry. Instead the final τ_2 value differed from the starting value by approximately 50° and the final heat of formation was approximately 7 kJ/mol higher. The second rotation (▲), which commenced from the finishing point of the first, did follow a closed loop and the geometry of the final structure was the same as the starting point.

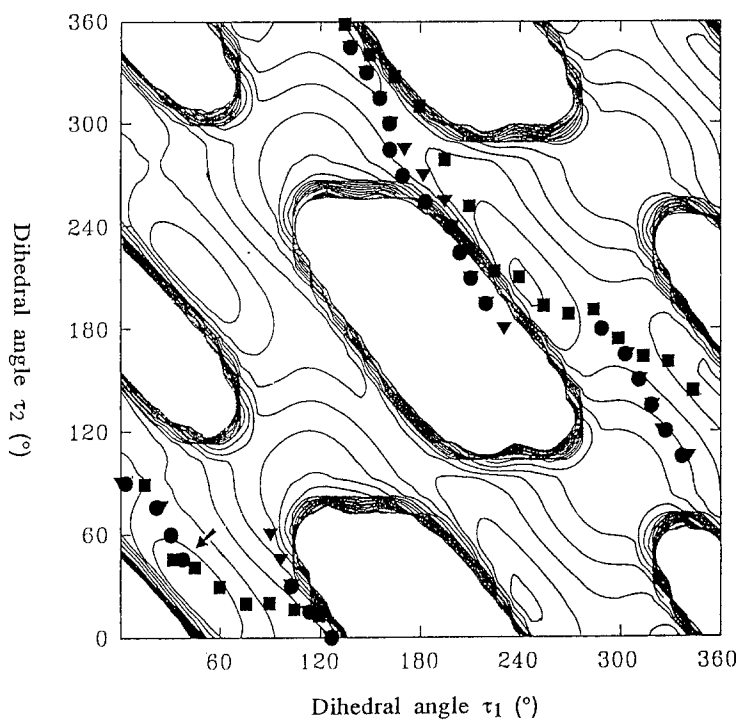


Fig. 2. The trajectories of τ_1 and τ_2 for the two sets of AM1 calculations shown in Fig. 1 are shown superimposed on a molecular mechanics energy map for the rotation of the same two angles. Dihedral angles τ_1 (■) and τ_2 (●, first 360°; ▲, second 360°) were driven through 360° and 720°, respectively. The starting position (crystal structure) is marked by an arrow. Rotation was to the right for τ_1 and bottom to top for τ_2. The molecular mechanics contour levels are at intervals of 5 kJ/mol.

For much of both the first and second rotations similar paths were followed and similar heats of formation resulted. Significant energy minima are observed at 210° and 330°. Both are *O-cis* forms. The abrupt changes in energy at 75°–90° and 165°–180° coincide with the conversion of the undriven angle τ_1 from *O-cis* to *O-trans* and back, respectively.

The trajectories of the AM1 calculations are shown in Fig. 2. To provide an overview they have been superimposed on an energy versus dihedral angle map for τ_1 and τ_2 calculated using 'rigid rotation' molecular mechanics. The symbols used to show each trajectory are the same as for Fig. 1. It can be seen that the course of the AM1 calculations is largely constrained by regions of high energy caused by steric interaction. The minor discrepancies between the two types of calculations, evident where the AM1 trajectories pass into high-energy regions of the energy map, are caused by the nature of the 'rigid rotation' molecular mechanics calculation which does not allow the variation of bond lengths or angles. This is in contrast to the AM1 calculations where full optimization was performed at each step.

It is evident from Fig. 2 that the rotation of τ_1 and τ_2 in both AM1 calculations was cooperative: when τ_1 was driven τ_2 moved in concert and vice versa. It is interesting to note that the AM1 calculations performed on the diphenyl ether linkage of the thyroid hormones [23] reveal a similar concerted rotation of ϕ and ϕ'. This correlation is also observed in crystal structures of thyroid hormones and their analogues [24].

During the course of the driven AM1 calculations the side-chain dihedral angles, τ_3–τ_5, remained largely unchanged. This shows that although the Cα methylene group of amiodarone interacts with the carbonyl group and phenyl ring, the remaining atoms of the side chain do not hinder rotation around τ_1 and τ_2 and hence have little effect on the barriers to rotation around these bonds.

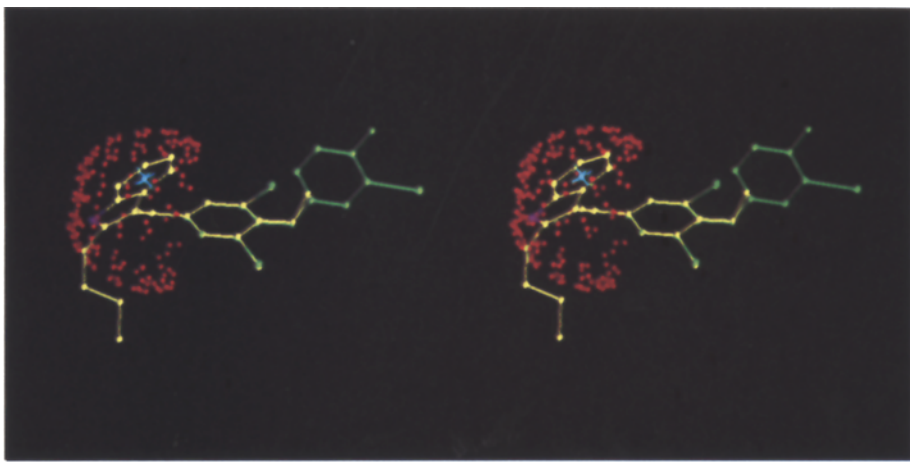
The thyroid hormone receptor model

The generalized thyroid hormone receptor model, formulated by Jorgensen and co-workers [9, 10], identifies 5 key functional groups involved in the interaction of the thyroid hormones with the nuclear receptor. Structure–activity data and theoretical calculations are consistent with the three iodine atoms of T_3 being involved in hydrophobic interactions with the receptor, with the 4′ hydroxyl group forming a hydrogen bond or bonds and with the side-chain carboxylate group forming an ion pair with a positively charged residue of the receptor. The data also show that the 3′ iodine binding site is limited in size and that substitution at the 5′ position reduces affinity for the receptor, probably due to an unfavourable steric interaction.

More recent work by Underwood et al. [25,26] during the development of the noncardiotoxic thyroid hormone analogue SK&F L-94901 (**8**) has shown that while the 3′ binding site is limited in depth to approximately 4.2 Å, it is wide and long enough to accommodate functional groups such as the 3′ substituent of **8** and is able to interact favourably with some polar 3′ groups.

Because T_3 binds strongly to the thyroid hormone receptor it can potentially be used as a template to define the relative locations of important receptor sites. A skewed conformation of the diphenyl ether portion of T_3, which has been identified by theoretical calculations to be the lowest-energy form [23] and is consistently observed in thyroid hormone and analogous crystal structures [24], was used to define the relative locations of the 3 iodine atoms and the hydroxyl group. Because the barriers to rotation about χ_1 and χ_2 are low [10,27], the position of the carboxylate could not be so simply defined. Therefore, in our model we have considered all possible conformations

A



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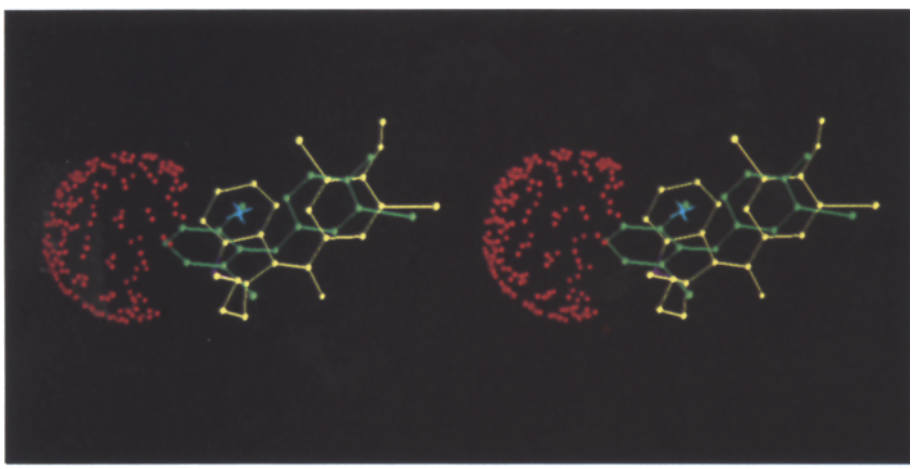

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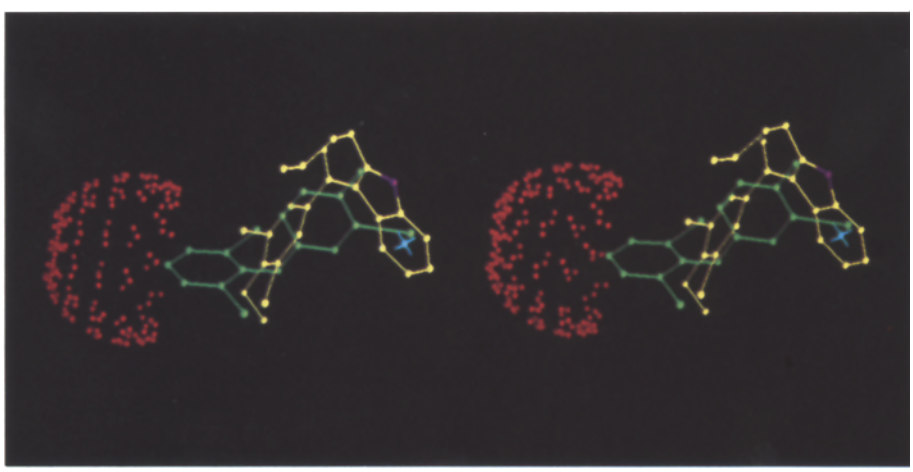

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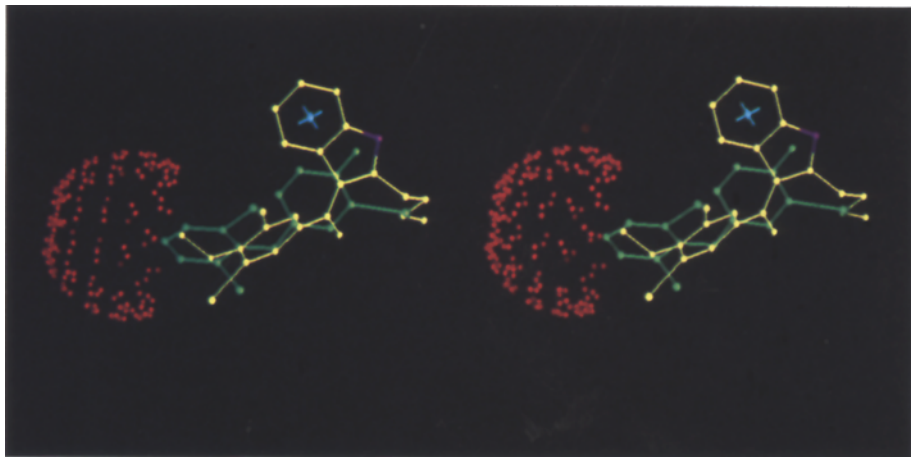


Figs. 3A–D. Models 1–4 for the binding of amiodarone at the thyroid hormone receptor. Amiodarone fragment **5** is shown (yellow) with the benzofuran oxygen (purple) and the receptor point at the centre of the benzofuran aromatic ring (blue) highlighted. This has been fitted to a model T_3 receptor consisting of the diphenyl ether portion of T_3 (green) and the locations accessible to the side-chain oxygen atoms (red).

of the alanyl side chain of T_3, regardless of relative conformational energy. Rotation of side-chain dihedral angles χ_1 and χ_2 in 30° steps produced a comprehensive range of possible structures which, when superimposed, defined the conformational space accessible to the alanyl side chain. The positions of the carboxylate oxygen atoms in the structures generated are shown as red points in Figs. 3A–D. These points define a sphere of radius 3.2 Å centered on the side-chain carbon atom attached to the inner ring.

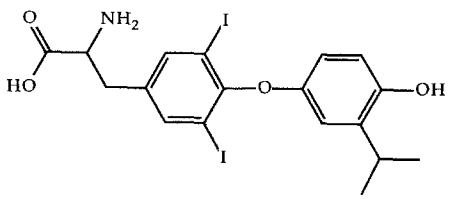
Fitting amiodarone to the receptor model

Although there has been previous speculation about the possible relationships between the thyroid hormones and amiodarone [6,16], previous investigations have not used structures produced by conformational searches for the structural comparison. Also, they have relied largely on superimposition of the steric bulk of the two molecules rather than possible correspondence between functional groups of the molecules. In the current study the low-energy structures derived from a systematic conformational search have been utilized and amiodarone functional groups with similar properties to the key functional groups of T_3 have been used to guide the superimpositions.

When looking for similarities between amiodarone and T_3, it is readily apparent that amiodarone lacks many of the functional groups that have been characterized as important for binding to the thyroid hormone receptor. Most notably, amiodarone has only two iodine atoms and lacks both the hydroxyl and carboxylic acid groups of T_3. This lack of structural similarity makes it seem likely that upon binding, various functional groups of amiodarone are able to substitute for some of the key functional groups of T_3. Structure–activity data of thyroid hormone analogues at the nuclear receptor make it possible to propose appropriate amiodarone functional groups for superimposition onto T_3.

Studies of synthetic thyroid hormone analogues have shown that bulky hydrophobic groups,

particularly alkyl groups such as the isopropyl group of analogue **9**, or aromatic rings such as the fused aromatic ring of the naphthyl group in compound **10**, can substitute for the iodine atoms of T_3 and that the affinity of such analogues can be high [3]. Compound **9** has an affinity for the receptor equal to that of T_3 [3]. Because the butyl group and benzofuran phenyl ring of amiodarone are of approximately the same size as an iodine atom and have the appropriate hydrophobicity to interact with the lipophilic pockets of the receptor, we propose that these groups may substitute for the iodine atoms 'missing' from amiodarone.



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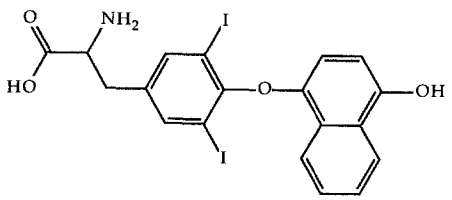

(10)

The lack of a free hydroxyl group in amiodarone may be partially compensated for by the diethylaminoethoxy oxygen, which although unable to donate a hydrogen bond, can still act as a hydrogen-bond acceptor and carries a significant negative charge. It is more difficult to propose a substitute group for the T_3 carboxylic acid group, although it is conceivable that the electronegative benzofuran oxygen may interact with a carboxylate acceptor.

Using the above proposals, four methods of fitting the large, hydrophobic groups of amiodarone onto the iodine atoms of the T_3 receptor model were devised. These are summarized in Table 2, using functional group labels defined in Fig. 4.

Each of these hypotheses was tested by fitting a representative structure from each of the low-energy classes of amiodarone to the thyroid hormone receptor model. In some orientations this allowed the superimposition of additional functional groups such as fitting the diethylaminoethoxy oxygen atom to the T_3 hydroxyl oxygen.

TABLE 2
SUMMARY OF FUNCTIONAL GROUP SUPERIMPOSITIONS[a] FOR 4 METHODS OF FITTING AMIODARONE ONTO T_3

T_3 functional group	Method 1	Method 2	Method 3	Method 4
Carboxylate	B	none	none	none
Inner ring iodines	D	A and C	D	D
Outer ring iodines	none	D	A	C
Phenol oxygen	none	E	B	B

[a] Column 1 lists T_3 functional groups determined to be important in the interaction of T_3 with the thyroid hormone receptor. The remaining columns list amiodarone functional groups (as defined in Fig. 4) fitted to the key T_3 functional groups for each method of superimposition.

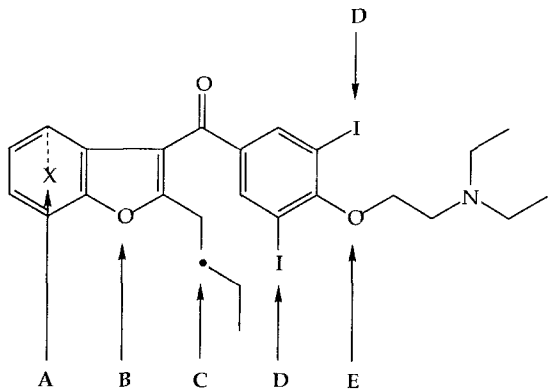

Fig. 4. Amiodarone functional group labels for Table 2, indicating the functional groups used to superimpose amiodarone on T_3.

The problem of superimposing functional groups with multiple atoms on a single atom was overcome by fitting the centre point of the large functional group to the single atom. A guide point added to amiodarone at the centre of the benzofuran aromatic ring allowed superimposition onto the receptor model iodine atoms. Similarly, Cβ was used to approximate the centre of the butyl group.

Figure 3 shows the molecular structures resulting from the fitting of amiodarone fragment **5** to the thyroid hormone receptor model. In each case the receptor model, consisting of the diphenyl ether portion of T_3 (green) and the carboxylate accessible region (red), is shown with the fitted substructure of amiodarone (yellow, with purple benzofuran oxygen atom and blue guide point). Each of the models is described in more detail below.

Model 1 (Fig. 3A) fits fragment **5** to the model receptor site by superimposing the amiodarone diiodophenyl ring onto the inner ring of T_3. The conformer from class 4 was found to give the best fit. This model is similar to previous suggestions [6,16] for fitting amiodarone onto T_3, but in addition, we have also compared the position of the benzofuran oxygen of amiodarone with the locations accessible to the T_3 carboxylate group. It can be seen that when the aromatic rings and iodines of amiodarone and T_3 are superimposed, the benzofuran oxygen coincides with the surface defined by the T_3 carboxylate oxygen atoms. This indicates that interaction of the amiodarone benzofuran oxygen with the same site as the T_3 carboxylate is possible.

Superimposition of the amiodarone diiodophenyl ring on the outer ring of T_3 has also been proposed [16]. This type of orientation suggested that the large, hydrophobic benzofuran aromatic ring and butyl groups of amiodarone be fitted to the T_3 inner ring iodine atoms. Figure 3B shows model 2 where one iodine atom, the diethylaminoethoxy oxygen, the benzofuran aromatic ring and the butyl group of **5** are superimposed on the T_3 receptor model. Conformational class 2 gave the best fit. In this orientation the diethylaminoethoxy group of amiodarone projects beyond the outer ring of T_3, and may possibly occupy the extended 3′ hydrophobic volume defined by Underwood et al. [25,26]. This method of fit results in an iodine atom of amiodarone occupying the 'forbidden' 5′ region of the receptor model, as happens when T_4 binds to the receptor. If amiodarone binds in this manner it would be acting as a T_4 analogue.

Models 3 (Fig. 3C) and 4 (Fig. 3D) fit amiodarone to the T_3 receptor model in the opposite ori-

entation to the first two approaches. Conformational class 4 gave the best fit in both cases. The diphenyl ether backbone of T_3 is treated only as a supporting structure, and the amiodarone iodine atoms are fitted to the T_3 inner-ring iodine atoms. The benzofuran phenyl ring (model 3) or the butyl group (model 4) were placed on the 3′ iodine. These orientations project the diethylaminoethoxy side chain into the region of space occupied by the T_3 side chain.

When the RMS deviation of fit was measured for each of the 4 representative low-energy conformers, it was found that for each proposed orientation, at least one of the low-energy amiodarone conformers could be fitted to 3 or 4 of the key functional groups of T_3 with an RMS deviation of less than 1.0 Å.

With the limited amount of information available on the binding of amiodarone to the thyroid hormone receptor, none of these possibilities can be excluded. It is clear however, that by fitting the benzoylbenzofuran framework of amiodarone over the diphenyl ether backbone of T_3 model 2 provides the largest overlap of molecular volumes. It also provides the best match of similar functional groups in amiodarone and T_3.

In model 2 amiodarone binds so that the phenyl group of the benzofuran ring and the butyl side chain bind to the same site as the iodine atoms in the 3 and 5 positions of T_3, one of the phenyl ring iodines of amiodarone binds to the 3′ iodine binding site of T_3 and the oxygen atom of the diethylaminoethoxy side chain may bind to the T_3 oxygen binding site of the receptor. However, this orientation means that amiodarone has an iodine atom in a position equivalent to the 5′ position of T_3 which has been proposed to be unfavourable. This feature of model 2 may partially account for the low affinity of amiodarone for the thyroid hormone nuclear receptor.

CONCLUSION

This study has undertaken a conformational analysis of the antiarrhythmic drug amiodarone using molecular mechanics and semiempirical MO methods. The molecular mechanics calculations reveal that the low-energy conformers of amiodarone can be divided into 4 distinct classes depending on the orientation of the butyl side chain and the orientation of the carbonyl group in relation to the benzofuran ring. Semiempirical MO calculations in which the amiodarone dihedral angles τ_1 or τ_2 were driven revealed concerted rotation of the benzofuran and diiodophenyl groups. The AM1 calculations showed the energy difference between the *O-cis* and *O-trans* forms of amiodarone to be 5.3 kJ/mol.

The minimum-energy structures derived from the comprehensive conformational search of amiodarone were fitted to an extension of Jorgensen and Andrea's thyroid hormone receptor model [9,10]. By superimposition of functional groups possessing similar steric and electronic properties 4 possible binding modes were devised, each fitting the receptor model with an RMS deviation of less than 1.0 Å.

Model 2, where the butylbenzofuran moiety of amiodarone is superimposed on the inner ring of T_3 and the diiodophenyl group is fitted on the outer ring, provides the best overlap of molecular volumes and gives the closest match of functional groups.

This study has, with the limited amount of information available, made a number of proposals about the nature of amiodarone binding at the thyroid hormone receptor. These proposals can be tested by the synthesis and evaluation of new amiodarone analogues and should be considered in the design of such compounds.

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