

A Review of Structure Activity Relationship of Amiodarone and Its Derivatives

Moiz A. Siddiqui¹, Amjad Khan^{2,3*}, Mehreen Zaka³

¹Department of Chemistry, Angels International College, Faisalabad, Pakistan

²Discipline of Clinical Pharmacy, School of Pharmaceutical Sciences, University Sains Malaysia, Penang, Malaysia

³Department of Biotechnology, Quaid-i-Azam University, Islamabad, Pakistan

Email: *amjadpharma@ymail.com

Received 26 January 2016; accepted 27 June 2016; published 30 June 2016

Copyright © 2016 by authors and Scientific Research Publishing Inc.

This work is licensed under the Creative Commons Attribution International License (CC BY).

<http://creativecommons.org/licenses/by/4.0/>



Open Access

Abstract

Structure Activity Relationship forms the basis of Rational Drug Design in the circles of pharmaceutical and medicinal chemistry. Appropriate knowledge of functional outcomes of structural modifications is crucial in conferring desired pharmacological properties to a chemical compound. Amiodarone is a classical antiarrhythmic agent with a long list of adverse effects. This article attempts to review the structure activity relationship of some of the homologues of amiodarone in order to determine the most clinically desirable molecule.

Keywords

Amiodarone, Dronedarone, Structure-Activity-Relationship

1. Introduction

Structural modifications are made in a molecule and compounds are substituted to either improve their pharmacokinetic profile or to enhance their receptor affinity in order to increase pharmacological response. Insertions of certain functional groups to specific positions in a molecule result in specific outcomes. In order to properly quantify these outcomes in terms of pharmacological behavior, detailed SAR studies are vital in determination of a desired compound with ideal properties. Cimetidine, the prototypical histamine-2 receptor antagonist was the first “rationally designed” drug in which particular functional group substitutions were made on the basis of the knowledge of the target receptor to create a pharmacologically active compound [1].

*Corresponding author.

Amiodarone

Amiodarone is an antiarrhythmic agent discovered in 1962 commonly used for cardiac dysrhythmias. Singh and Williams (1970) accounted for its anti-anginal properties [2] while the clinical proof of its efficacy in supraventricular and ventricular arrhythmias was given by Rosenbaum *et al.*, in 1976 [3]. It is currently indicated in ventricular tachycardia, ventricular fibrillation [4] and atrial fibrillation following an open heart surgery [5]. Despite its unmatched efficacy, the use of Amiodarone is associated with a long list of adverse effects, some being fatal such as pulmonary fibrosis. Most of its ADR's are dose- and duration-dependant however, a few are idiosyncratic. Naccarelli *et al.* (1986) presented a detailed account of ADR's of Amiodarone ranging from ophthalmic, dermatological, gastrointestinal, thyroid, cardiovascular, neurological, teratogenic, hepatic and pulmonary toxicities [6].

2. Mechanism of Action

Amiodarone's action can be divided into acute and chronic phases. In acute phase, Amiodarone exerts its effects by blocking inward Sodium and Calcium currents suppressing excitability of cardiomyocytes. It also blocks ligand and voltage gated Potassium channels. In chronic phase, mediated also by its exceptionally long half-lived active metabolite, desethylamiodarone, it causes down-regulation of Kv1.5 mRNA resulting in a drug-induced modulation in gene-expression of potassium-channels [7].

3. Chemistry

Amiodarone is a benzofuran derivative with a chemical formula of (2-{4-[(2-butyl-1-benzofuran-3-yl) carbonyl]-2,6-diiodophenoxy}ethyl)diethylamine. Its structure can be divided into 3 portions, a butylbenzofuran moiety linked with a carbonyl group to a diiodobenzene moiety linked by an ether bridge to a tertiary ethylamine as shown in **Figure 1** [8].

4. Structure-Activity Relationship

N-dealkylated metabolite of Amiodarone, Mono-Desethylamiodarone (MDEA), shows similar pharmacological profile but has a potential for greater toxicity [8]. It contains a secondary amine at the terminal end instead of a tertiary amine as shown in **Figure 2**.

Dronedarone, another clinically available analogue of Amiodarone, shares the basic benzofuran ring which is substituted by a methylsulphonamide. It also differs in the N-alkyl chain length. A prominent difference is the absence of Iodine atoms in the central benzene ring [9]. Dronedarone has generic name Multaq marketed by a multinational Sanofi Aventis Company, Paris, France. Chemically, dronedarone is proved to be effective for pharmacologic cardioversion. In clinical trials, dronedarone was set up to be superior to amiodarone in terms of having a comparatively faster and short half-life, reduced lipophilicity, and insignificant non-cardiovascular toxicity. Dronedarone has a molecular formula $C_{31}H_{44}N_2O_5S$ with molecular mass of 556.758 g/mol. The chemical name of dronedarone is N-(2-Butyl-3-(p-(3(dibutylamino)propoxy)benzoyl)-5 benzofuranyl) methanesulfonamide (**Figure 3**) [10]. The similarity of Amiodarone with triiodothyronine (**Figure 4**) is the basis for hypo- and hyperthyroid disorders associated with its use [6].

The intention behind the replacement of iodine group is to reduce the risk of non-target organ adverse effects

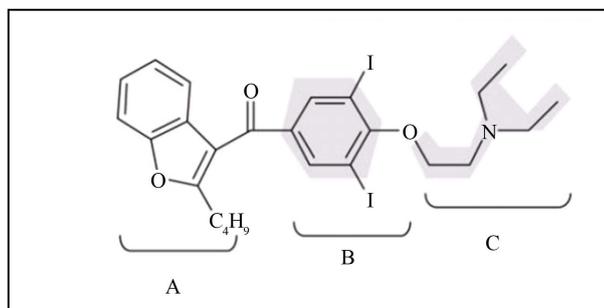


Figure 1. Amiodarone.

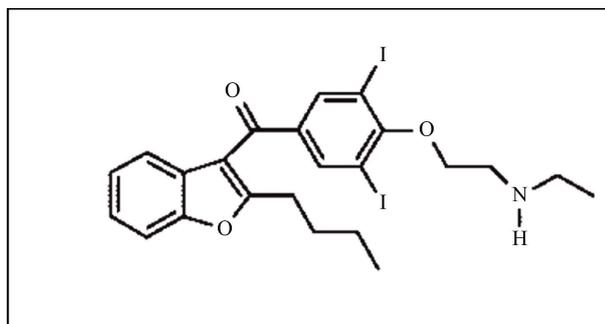


Figure 2. MDEA.

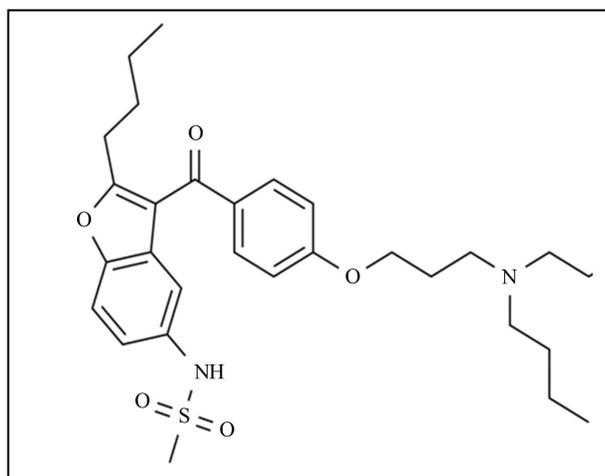


Figure 3. Dronedaronone.

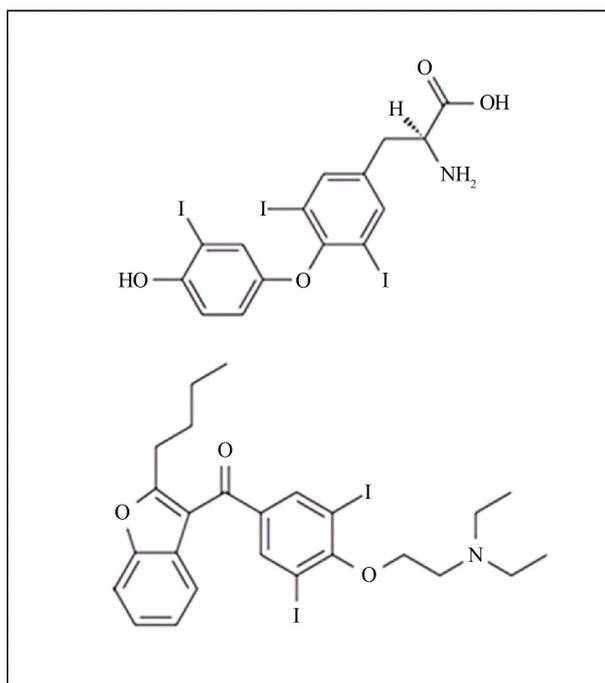


Figure 4. Top: Triiodothyronine; Bottom: Amiodarone. Note the structural similarity of the central diiodobenzene ring.

caused by amiodarone therapy and the presence of methylsulphonamide entity reduces lipophilicity, thus decreases the risks of neurotoxicity and shortens the dronedarone's half-life significantly [10]. Zimalbaum (2009) compared the structural and functional characteristics of Amiodarone and Dronedarone shown in **Table 1**. Lipophilicity of Dronedarone is less than amiodarone. It has very small volume of distribution. The exclusion half-life ($t_{1/2}$) of dronedarone is fairly smaller (13 - 19 h) in comparison to half-life of amiodarone which is numerous weeks. The dose of dronedarone may be less complex than amiodarone due to the pharmacokinetic profile (**Table 2**).

While exhibiting a much better ADR profile than amiodarone, dronedarone was associated with an increased risk of mortality [12] due to heart failure during clinical trials specially, among patients with reduced left-ventricular function apparently causing several deaths, ending the trial prematurely. Also, in 2011, FDA reported an apparent link between dronedarone and acute liver failure [13]. In order to overcome the problem of long elimination half-life of amiodarone, several structural modifications have also been made most noticeably by Morey *et al.*, in 2001. Introduction of methyl acetate entity at position 2 of the benzofurane ring replacing the butyl chain renders the drug susceptible to ester hydrolysis increasing its metabolism and decreasing half-life [14]. Ester homologue of Amiodarone is shown in **Figure 5**.

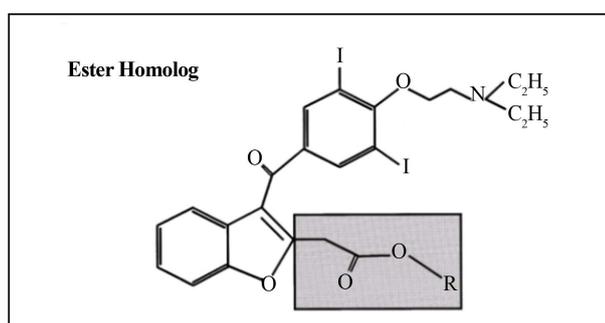


Figure 5. Ester homologue of amiodarone. The butyl side chain of benzofurane is replaced by methyl acetate.

Table 1. Structural and functional characteristics of dronedarone vs. amiodarone [11].

Drug	Toxic effects					Common drug interactions
	Liver	Lungs	Thyroid	Skin	Gastrointestinal tract	
Amiodarone	+	+	+	+	+	Digoxin, Warfarin
Dronedarone	-	-	-	-	++	Digoxin, Statins

Table 2. Comparison of amiodarone and dronedarone [15]-[21].

Drug	Vaughan Williams	Indication	Onset of action	Half life	Protein binding and metabolism	Route of elimination
Dronedarone	All four classes of Vaughan Williams	To decrease the chances of hospitalization in case of sudden/continual AF/AFL with current episode of AF/AFL & related CV risk factors [17]	4 - 8 h	13 - 19 h	>98% by CYP3A and CYP2D6 [23]	~renal (6%) and feces (84%) [24]
Amiodarone	All I - IV classes, but predominantly Class III	Paroxysmal supra-ventricular tachycardia (paroxysmal SVT); Recurrent ventricular fibrillation; Supra-ventricular arrhythmias; Unstable ventricular tachycardia; Recurrent supra-ventricular tachycardia; Management of acute AF and long term treatment to prevent recurrence of AF [22]	Few days to weeks (1 - 3)	40 - 55 days	>96%, by CYP3A4 and CYP2C8 [25]	Metabolized by liver & biliary excretion [26]

Table 3. Effect of ester chain elongation on half-lives of different analogues [14].

R	T1/2 (mins)
methyl	12
ethyl	6
iso-propyl	30
sec-butyl	90
neo-pentyl	240

However, this modification drastically lowers the t1/2 to 12 minutes only, making the drug useless for chronic use hence, further modifications were made in the ester side chain to make it bulkier in order to increase the steric effect for esterases and delaying inactivation. Analogues were created by adding methyl groups in the ester side chain elongating the length to form ethyl, isopropyl, sec-butyl and neo-pentyl acetates. The 5 Carbon containing neo-pentyl acetate analogues exhibited the longest half-life of 240 minutes due to increased hindrance to esterases for metabolism. **Table 3** summarizes this effect. However, in contrast to increasing half-life with elongation of ester side chain length, the increasing number of Carbon atoms also decreased the pharmacological effects with neo-pentyl acetate homologue being inactive altogether [14].

5. Discussion

Since its inception into cardiovascular medicine, Amiodarone, to date, remains a gold standard for difficult-to-treat ventricular tachycardia and fibrillation. It contains the electrophysiological properties of an ideal anti-arrhythmic agent. However, its large volume of distribution, high tissue accumulation and exceptionally long half-life cause serious adverse effects and make it a drug of last resort. Dronedarone, a promisingly less toxic derivative caused increased mortality during trials and esterified homologues suffered activity problems. It is apparent that the benzofuran ring coupled with a benzoyl moiety is essential structural entities for activity while modifications can be made at other positions on the molecule and a safer derivative can be developed which retains most of the activity, as no other drug in this class exhibits a multi-channel blocking effect which is pharmacodynamically ideal for an anti-arrhythmic agent. Till then, Amiodarone remains unchallenged due to its superior clinical efficacy.

Acknowledgements

We are thankful to Institute of Postgraduate Studies (IPS) of University Sains Malaysia (USM) for fellowship support [Ref. no. P-FD0011/15(R)].

Conflict of Interest

The authors confirm that this article content has no conflicts of interest.

References

- [1] Freemantle, M. (2005) Top Pharmaceuticals That Changed the World. *Chemical and Engineering News*, **83**, 3.
- [2] Heijman, J. and Dobrev, D. (2013) Pleiotropic Actions of Amiodarone: Still Puzzling after Half a Century. *Naunyn-Schmiedeberg's Archives of Pharmacology*, **386**, 571-574. <http://dx.doi.org/10.1007/s00210-013-0865-0>
- [3] Rosenbaum, M.B., Chiale, P.A., Halpern, M.S., Nau, G.J., Przybylski, J., Levi, R.J., Lazzari, J.O. and Elizari, M.V. (1976) Clinical Efficacy of Amiodarone as an Antiarrhythmic Agent. *American Journal of Cardiology*, **38**, 934-944. [http://dx.doi.org/10.1016/0002-9149\(76\)90807-9](http://dx.doi.org/10.1016/0002-9149(76)90807-9)
- [4] Kudenchuk, P.J., Cobb, L.A. and Copass, M.K. (1999) Amiodarone for Resuscitation after Out-of-Hospital Cardiac Arrest Due to Ventricular Fibrillation. *The New England Journal of Medicine*, **341**, 871-878.
- [5] Guarnieri, T., Nolan, S., Gottlieb, S.O., Dudek, A. and Lowry, D.R. (1999) Intravenous Amiodarone for the Prevention of Atrial Fibrillation after Open Heart Surgery: The Amiodarone Reduction in Coronary Heart (ARCH) Trial. *Journal of the American College of Cardiology*, **34**, 343-347. [http://dx.doi.org/10.1016/S0735-1097\(99\)00212-0](http://dx.doi.org/10.1016/S0735-1097(99)00212-0)
- [6] Naccarelli, G.V., Rinkenberger, R.L., Dougherty, A.H. and Fitzgerald, D.M. (1989) Adverse Effects of Amiodarone.

- Medical Toxicology and Adverse Drug Experience*, **4**, 246-253. <http://dx.doi.org/10.1007/BF03259911>
- [7] Kodama, I., Kamyia, K. and Toyoma, J. (1999) Amiodarone: Ionic and Cellular Mechanism of Action of the Most Promising Class III Agent. *American Journal of Cardiology*, **84**, 20-28. [http://dx.doi.org/10.1016/S0002-9149\(99\)00698-0](http://dx.doi.org/10.1016/S0002-9149(99)00698-0)
- [8] Quaglino, D., Ha, H.R., Duner, E., Bruttomesso, D., Bigher, L., Follath, F., Realdi, G., Pettenazzo, A. and Baritussio, A. (2004) Effects of Metabolites and Analogues of Amiodarone on Alveolar Macrophages: Structure Activity Relationship. *American Journal of Physiology—Lung Cellular and Molecular Physiology*, **287**, L438-L447. <http://dx.doi.org/10.1152/ajplung.00434.2003>
- [9] Kathofer, S., Thomas, D. and Karle, C.A. (2005) The Novel Antiarrhythmic Drug Dronedaron: Comparison with Amiodarone. *Cardiovascular Drug Reviews*, **23**, 217-230. <http://dx.doi.org/10.1111/j.1527-3466.2005.tb00167.x>
- [10] Iram, F., Ali, S., Ahmad, A., Khan, S.A. and Husain, A. (2016) A Review on Dronedaron: Pharmacological, Pharmacodynamic and Pharmacokinetic Profile. *Journal of Acute Disease*, **5**, 102-108. <http://dx.doi.org/10.1016/j.joad.2015.10.002>
- [11] Zimetbaum, P.J. (2009) Dronedaron for Atrial Fibrillation—An Odyssey. *The New England Journal of Medicine*, **360**, 1811-1813. <http://dx.doi.org/10.1056/NEJMp0902248>
- [12] Køber, L., Torp-Pedersen, C., McMurray, J., Gøtzsche, O., Lévy, S., Crijns, H., Amlie, J., Carlsen, J. and Dronedaron Study Group (2008) Increased Mortality after Dronedaron Therapy for Severe Heart Failure. *The New England Journal of Medicine*, **358**, 2678-2687. <http://dx.doi.org/10.1056/NEJMoa0800456>
- [13] FDA Drug Safety Communication (2011) Severe Liver Injury Associated with the Use of Dronedaron (Marketed as Multaq). <http://www.fda.gov/Drugs/DrugSafety/ucm240011.htm>
- [14] Morey, T.E., Seubert, C.N., Raatikainen, M.J.P., Martynyuk, A.E., Druzgala, P., Milner, P., Gonzalez, M.D. and Dennis, D.M. (2001) Structure-Activity Relationships and Electrophysiological Effects of Short Acting Amiodarone Homologues in Guinea Pig Isolated Heart. *Journal of Pharmacology and Experimental Therapeutics*, **297**, 260-266.
- [15] Hohnloser, S.H., Halperin, J.L., Camm, A.J., Gao, P., Radzik, D. and Connolly, S.J. (2014) Interaction between Digoxin and Dronedaron in the PALLAS Trial. *Circulation: Arrhythmia and Electrophysiology*, **7**, 1019-1025. <http://dx.doi.org/10.1161/CIRCEP.114.002046>
- [16] Huemer, M., Sarganas, G., Bronder, E., Klimpel, A., Garbe, E. and Haverkamp, W. (2015) Torsade de Pointes Tachycardia in a Patient Ondronedaron Therapy. *Pharmacotherapy*, **35**, e61-e65. <http://dx.doi.org/10.1002/phar.1573>
- [17] Piccini, J.P., Hasselblad, V., Peterson, E.D., Washam, J.B., Califf, R.M. and Kong, D.F. (2009) Comparative Efficacy of Dronedaron and Amiodarone for the Maintenance of Sinus Rhythm in Patients with Atrial Fibrillation. *Journal of the American College of Cardiology*, **54**, 1089-1095. <http://dx.doi.org/10.1016/j.jacc.2009.04.085>
- [18] U.S. Food and Drug Administration (2011) FDA Drug Safety Communication: Severe Liver Injury Associated with the Use of Dronedaron (Marketed as Multaq). U.S. Food and Drug Administration, Maryland. <http://www.fda.gov/drugs/drugsafety/ucm240011.htm>
- [19] Wood, S. (2011) Deaths Doubled with Dronedaron in PALLAS: FDA and EMA Updates. Medscape, New York. <http://www.theheart.org/article/1255799.do>
- [20] ClinicalTrials.gov. (2014) Optimal Timing of Dronedaron Initiation after Conversion in Patients with Persistent Atrial Fibrillation (ARTEMIS Load). <http://clinicaltrials.gov/ct2/show/NCT01140581>
- [21] Freemantle, N., Lafuente-Lafuente, C., Mitchell, S., Eckert, L. and Reynolds, M. (2011) Mixed Treatment Comparison of Dronedaron, Amiodarone, Sotalol, Flecainide, and Propafenone, for the Management of Atrial Fibrillation. *Europace*, **13**, 329-345. <http://dx.doi.org/10.1093/europace/euq450>
- [22] Klieber, S., Arabeyre-Fabre, C., Moliner, P., Marti, E., Mandray, M., Ngo, R., *et al.* (2014) Identification of Metabolic Pathways and Enzyme Systems Involved in the *in Vitro* Human Hepatic Metabolism of Dronedaron, a Potent New Oral Antiarrhythmic Drug. *Pharmacology Research & Perspectives*, **2**, e00044. <http://dx.doi.org/10.1002/prp2.44>
- [23] Rosa, G.M., Ferrero, S. and Brunelli, C. (2014) Pharmacokinetic and Pharmacodynamics Profile of Dronedaron, a New Antiarrhythmic Agent for the Treatment of Atrial Fibrillation. *Expert Opinion on Drug Metabolism & Toxicology*, **10**, 1751-1764. <http://dx.doi.org/10.1517/17425255.2014.974551>
- [24] Chopra, S., Badyal, D.K. and Baby, C.P. (2013) Dronedaron: A New Therapeutic Agent for Atrial Fibrillation. *JK Science*, **15**, 3-6.
- [25] Damy, T., Pousset, F., Caplain, H., Hulot, J.S. and Lechat, P. (2004) Pharmacokinetics and Pharmacodynamics Interactions between Metoprolol and Dronedaron in Extensive and Poor CYP2D6 Metabolizers Healthy Subjects. *Fundamental & Clinical Pharmacology*, **18**, 113-123. <http://dx.doi.org/10.1046/j.1472-8206.2003.00216.x>
- [26] U.S. Food and Drug Administration (2010) Cordarone (Amiodarone HCL) Tablets: Package Insert. U.S. Food and Drug Administration, Maryland. http://www.accessdata.fda.gov/drugsatfda_docs/label/2010/018972s0421bl.pdf