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Interactions of the potent synthetic AT1 antagonist analog BV6 with membrane bilayers and mesoporous silicate matrices

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ABSTRACT

The present work describes the drug:membrane interactions and a drug delivery system of the novel potent AT1 blocker BV6. This designed analog has most of the pharmacological segments of losartan and an additional biphenyltetrazole moiety resulting in increased lipophilicity. We found that BV6:membrane interactions lead to compact bilayers that may in part explain its higher in vitro activity compared to losartan since such environment may facilitate its approach to AT1 receptor. Its high docking score to AT1 receptor stems from more hydrophobic interactions compared to losartan. X-ray powder diffraction (XRPD) and thermogravimetric analysis (TGA) have shown that BV6 has a crystalline form that is not decomposed completely up to 600 °C. These properties are desirable for a drug molecule. BV6 can also be incorporated into a mesoporous silicate drug-delivery matrix SBA-15. The properties of the obtained drug-delivery system have been inspected by XRD, ^{13}C CP/MAS, TGA and nitrogen sorption experiments.

1. Introduction

Coronary heart disease is one of the leading causes of death in the industrialized world. Hypertension is a risk factor for cardiovascular disease (CV) and is associated with an increased incidence of stroke and coronary heart disease. Other risk factors for CV include also high cholesterol, diabetes and obesity. Although there have been many advances in treatment over the past several decades, less than a quarter of all hypertensive patients have their blood pressure adequately controlled with available therapies. Early management of cardiovascular risk factors is fundamental in preventing the development of cardiovascular and renal disease [1,2].

The renin–angiotensin system (RAS) is known to play an important role in the regulation of blood pressure and electrolyte balance. Inhibitors of the RAS would be effective for the treatment of hypertension and congestive heart failure. Although angiotensin-converting enzyme (ACE) inhibitors are highly effective and their use has become well-established for the treatment of hypertension and congestive heart failure, they suffer from some side effects such as dry cough and angioedema caused by the nonspecific action of ACE. On the other hand, angiotensin II (AII) AT1 receptor blockers (ARBs) selectively interfere with the RAS at the AII receptor level and are expected to be more specific and effective agents than ACE inhibitors. The discovery of potent and orally active non peptide AII antagonists such as losartan and eprosartan has encouraged the development of a large number of similar compounds. Among them, candesartan cilexetil, valsartan, irbesartan, telmisartan and olmesartan medoxomil have been launched and were established as angiotensin receptor blockers (ARBs). Treatment with an ARB was demonstrated to reduce CV events and heart failure progression as well as to improve renal disease and prevent diabetes and this constitutes the importance of their development. Despite the plethora of treatment options for the management of hypertension, 55.9% of patients do not have their BP under adequate control. In addition, there is ambiguity concerning the appropriate choice of therapy for hypertensive patients who may present with coexisting conditions such as diabetes. Therefore, an agent with multifunctional purposes would offer an efficacious way of managing hypertension and related complications. Azilsartan medoxomil is a newer-generation ARB with potent antihypertensive effects. On 25 February 2011, the U.S. Food and Drug Administration (FDA) approved azilsartan medoxomil for the treatment of high blood pressure in adults [3–5].

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The molecular basis of their antihypertensive action has been interpreted by a two-step model. In the first step they are incorporated into the bilayers through the lipid–water interface and secondly laterally diffuse to reach the active site of the AT1 receptor in order to exert their biological activity [6].

BV6 (4-butyl-*N*,*N* -bis{[2 -(2*H*-tetrazol-5-yl)biphenyl-4-yl]methyl} imidazolium bromide) is a synthetic rationally designed molecule that exhibited higher activity than losartan (Fig. 1). This molecule comprises three well known pharmacophore segments identical to losartan, in particular the two biphenyltetrazole segments at the N-1 and N-3 of the imidazole ring and the butyl alkyl chain. However, it lacks the chlorine atom and hydroxymethyl group on the imidazole ring. Its higher activity can be postulated to be attributed to: (a) the way it interacts on the lipid bilayer as it is a more lipophilic entity; (b) the additional hydrophobic interactions that it can have at the active site of the receptor (Fig. 2) [7]. Estimated value of LogP for BV6 by ALOGPS 2.1 program was found to be 5.70 (for comparison reasons LogP of losartan was found to be 4.50) [8]. LogP values for all commercial sartans are given in Table 1. BV6 has the highest LogP value after telmisartan.

The cellular membranes are complex entities consisting of various kinds of proteins and lipids as well as cholesterol. Phosphatidylcholines (PCs) are the most abundant lipid species in sarcolemma cardiac membranes [9]. The most frequently found among them are PCs with oleic and linoleic chains, and further dipalmitoylphosphatidylcholine (DPPC). Experimentally, hydrated DPPC lipids are preferred because they spontaneously form multilamellar bilayers in which mesomorphic changes occur in a convenient temperature range between 25 and 50 °C. Their dynamic and thermotropic properties have been extensively explored [10–12] and their partition coefficient especially in the fluid state, resembles that of natural cardiac membranes [9]. Phosphatidyl choline bilayers at low temperatures occur in the gel phase ($L_{\beta'}$) and at higher temperatures in the liquid-crystalline phase (L_{α}). The transition is accompanied by several structural changes in the lipid molecules as well as systematic alteration in the bilayer geometry, for example the *trans*:*gauche* isomerization taking place in the acyl conformation. The average number of *gauche* conformers indicates the effective fluidity, which depends not only on the temperature, but also on perturbation due to the presence of a drug molecule intercalating between the lipids.

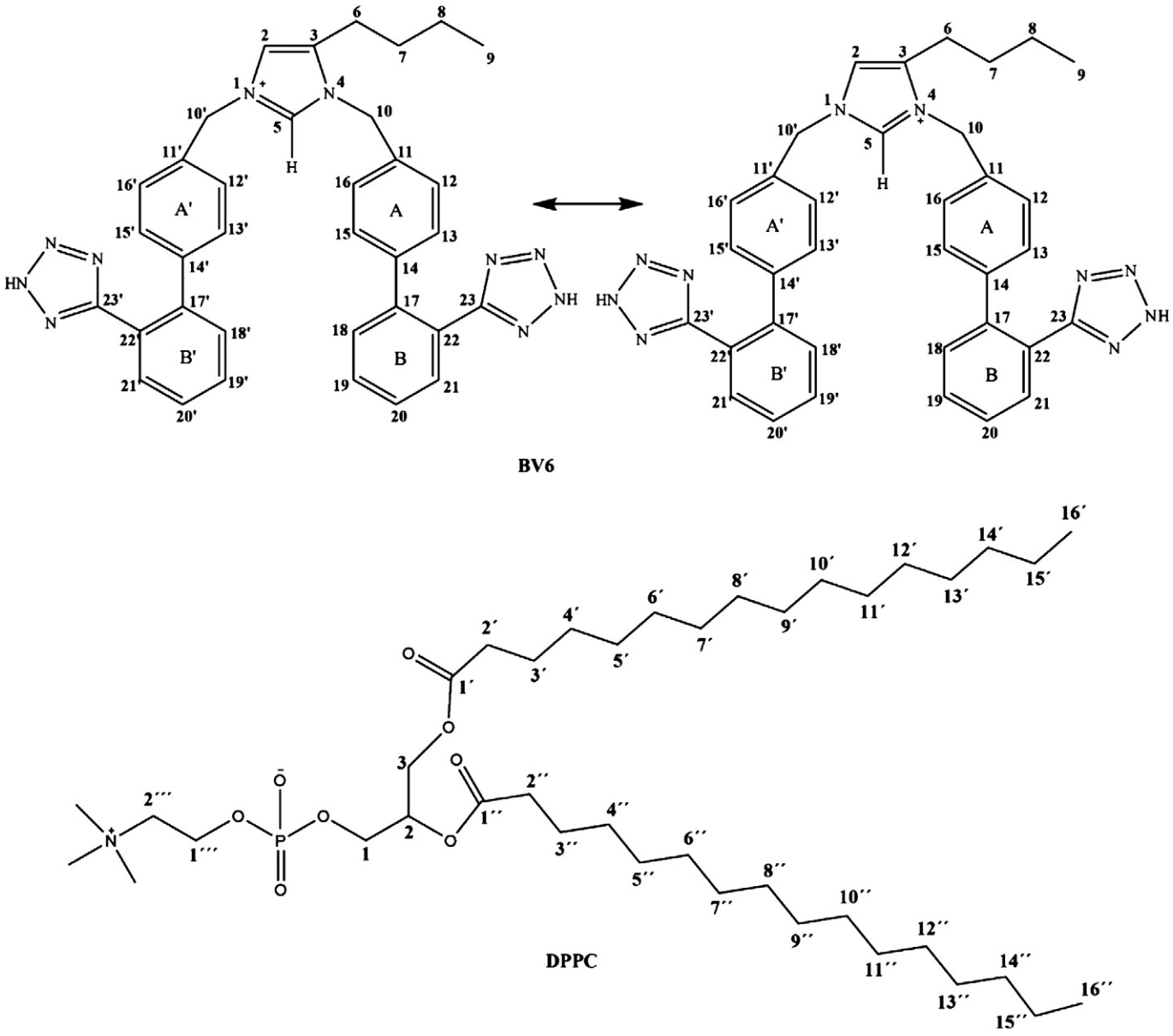

Fig. 1. Chemical structures of BV6 and L_{α}-dipalmitoylphosphatidylcholine.