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π-Stacked polymers in drug delivery applications

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ABSTRACT

Polybenzofulvenes are π-stacked polymers, which can be synthesized by spontaneous polymerization of the corresponding monomers without the use of catalysts or initiators. Therefore, they can be obtained completely free from byproducts, impurities, or harmful substances. The absence of any relevant toxic effects and cell viability impairments allows PEGylated polybenzofulvene brushes to be potentially functional in a wide range of biological, biomedical, and biotechnological applications. Moreover, the properties of these polymers, in terms of interaction with pharmacological active agents and the ability to self-assemble into nanoaggregates or a quite compact physical gel useful as drug delivery systems (DDSs), can be controlled by varying side chain moieties. Owing to the important role played by self-assembling DDS in the fields of the material and life sciences, the interaction and the delivery ability of polybenzofulvene polymers with model drug or protein molecules was definitively demonstrated. The present paper reviews the applications of polybenzofulvene derivatives in the drug delivery of a range of different drug molecules ranging from small molecules to peptides and proteins.

1. Introduction

Owing to the direct relationship between drug's concentration in the blood and its therapeutic action, a considerable deal of attention of researchers in the pharmaceutical field has been paid over the past four decades to the development of formulations capable of releasing drugs into human body at controlled quantity and rate. In order to achieve this result, non-conventional dosage forms (Drug Delivery Systems, DDSs) have been developed by implementing a modified release. While in the conventional dosage forms the release and the relative blood level trends are affected mainly by the physicochemical features of the drug, DDSs are designed to release the active molecules on the basis of the technological features of their formulations [1].

The most widespread DDSs consist of suitable polymeric supports embedding (by means of weak non-covalent interactions) the drug into the polymeric matrix or linking the active component to the polymeric backbone through covalent bonds in drug–polymer conjugates [2].

After the discovery of the spontaneous polymerization of benzofulvene derivative **BF1**, the work performed in our laboratories has demonstrated that a considerable number of benzofulvene monomers are able to polymerize in the apparent absence of catalyst or initiators by simple removal of solvents to afford polymers showing vinyl structure stabilized by aromatic stacking interactions [3–13]. It is noteworthy that these polymers show interesting features such as rapid and quantitative formation without side reactions and byproducts, high molecular weight, thermoreversible polymerization/depolymerization behavior, high solubility in the most common organic solvents, tunable solubility and aggregation behavior in water, liability to generate nanostructured aggregate, and susceptibility to molecular manipulation.

Thus, the serendipitous discovery of the spontaneous polymerization of benzofulvene derivatives has provided the access to a novel class of polymers, which could represent interesting candidates to play the role of polymeric supports in the development of new DDSs. Therefore, the potential usefulness of polybenzofulvene derivatives in the design of innovative DDSs has been evaluated in

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different approaches, systems, and laboratories [14–16], and the results are summarized in the present review article.

2. The history of polybenzofulvene derivatives

Within the framework of a large research program finalized to the discovery of new antihypertensive drugs [5,17,18], we planned to replace the biphenyl scaffold of losartan (**1**, Fig. 1) with the 4-phenylquinoline moiety of imidazopyridine derivatives **2**. Some compounds of this series were found to show *in vitro* properties comparable to those shown by losartan, but the candidate selected for further preclinical studies (**CR3210**) was characterized by both a low oral bioavailability and a rapid excretion [5]. In the aim of improving the pharmacokinetic features of these imidazopyridine derivatives, the 4-phenylquinoline scaffold of compounds **2** was converted into the 4-phenylisoquinoline one of **3** and 1-phenylindene one of derivatives **4** [5].

In the synthetic approaches to target carboxylic acid **4b** (Fig. 2), we found that the cleavage of *tert*-butyl ester **4a** in acid conditions led to the formation of polymeric materials. In order to characterize the structure of the reaction products, and understand their reactivity, we simplified the structure of **4a** by both eliminating the imidazopyridine moiety and stabilizing the *tert*-butyl ester group into the ethyl ester one of indenol **5**. These studies led to the discovery of the spontaneous polymerization of **BF1** [3] and allowed the features of poly-**BF1** (*e. g.* formation, thermoinduced depolymerization, vinyl polymer structure stabilized by aromatic interactions, and aggregation) to be characterized in detail [4].

The subsequent investigation on **4a** reactivity demonstrated that the cautious reaction of this indenol derivative with formic acid afforded the target acid **4b** containing trace amounts of benzofulvene derivative **BF-AT1**, whereas greater amounts of this latter were obtained by dehydration of starting **4a** or acid **4b** in $CHCl_3$ (or $CDCl_3$) in the presence of *p*-toluenesulfonic acid (PTSA). However differently from **BF1**, we observed that **BF-AT1** was stable as a pure crystalline solid and polymerized spontaneously when the solvent was removed from the mixture of the dehydration reaction of **4a** without the elimination of PTSA [5]. The apparent stability of pure

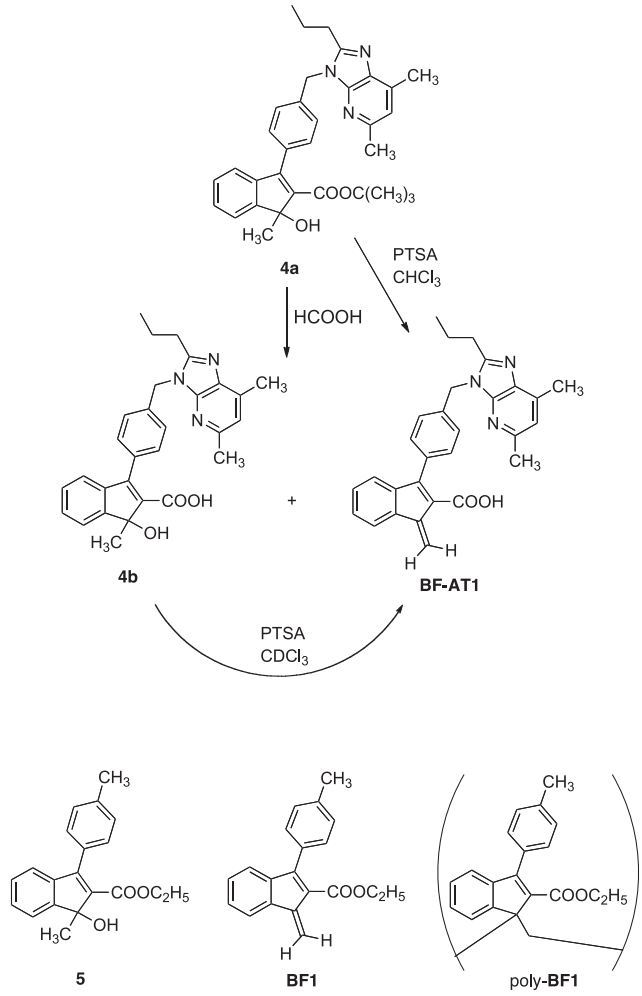

Fig. 2. Chemistry of indenol **4a** and structures of indenol **5**, benzofulvene derivative **BF1**, and of poly-**BF1**.

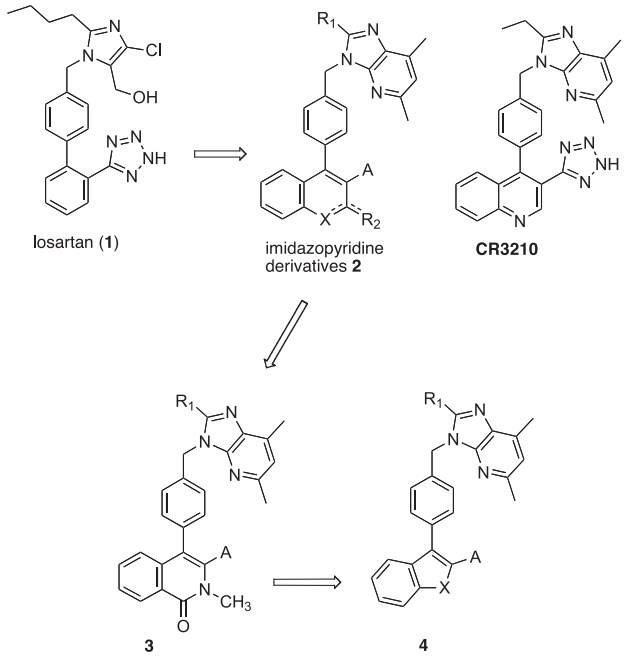

Fig. 1. Design of angiotensin II AT_1 receptor antagonists **2**, **3**, and **4** from losartan.

BF-AT1 was explained by assuming the presence of intermolecular interactions between its COOH and the imidazole nitrogen in the solid state and allowed the interaction with angiotensin II AT_1 receptor to be evaluated in radioligand displacement studies. Interestingly, monomer **BF-AT1** was found to show an angiotensin II AT_1 receptor affinity in the nanomolar range [5]. This result taken together with the thermoreversible polymerization/depolymerization process involving **BF-AT1** (Fig. 3) led to consider poly-**BF-AT1** as a novel polymeric prodrug showing an original release mechanism based on an equilibrium polymerization phenomenon. This assumption was supported by the results of the binding studies, which suggested that depolymerization occurred also in buffer at pH 7.4 [5]. In summary, **BF-AT1** represents a polymerizing AT_1 receptor ligand able to form a thermoreversible polymer capable of releasing the active monomer with a temperature-dependent kinetics until a temperature-dependent equilibrium was reached as it occurs in equilibrium polymerization processes.

These results led us to envision new perspectives in the development of novel polymeric prodrugs and gave strength to our research efforts in the field. As we were aware that the rational design of new bioactive monomers required the precise knowledge of the chemistry of benzofulvene derivatives, we started a comprehensive program of structural modification of **BF1** scaffold aimed at investigating the role of substituents' feature on the polymer properties such as formation, molecular weight