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Progress in the total synthesis of epoxyquinone natural products: An update

Goverdhan Mehta*, Saumitra Sengupta**

School of Chemistry, University of Hyderabad, Gachibowli, Hyderabad 5000 046, Telangana, India

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ABSTRACT

Epoxyquinone natural products continue to attract the attention of organic synthesis community worldwide, owing to their increasingly diverse and complex molecular architectures and broad spectrum biological activities associated with them. The last decade, in particular, has witnessed considerable activity and advances towards the total synthesis of this family of natural products with some notable successes. These efforts, deploying appropriate, contextual and emergent synthetic methodologies have led to the total synthesis of numerous epoxyquinone natural products spread over the entire structural landscape, with the added value of generating new chemical diversity space around their scaffold. This flurry of activity since 2005 lends some urgency to provide an update that documents and highlights the achievements in the intervening years and reflects on the new opportunities and challenges that lie ahead.

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* Corresponding author.
** Corresponding author.
E-mail address: gmsc@uohyd.ernet.in (G. Mehta).

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1. Introduction

A large group of secondary metabolites embodying the epoxyquinonoid cores **I-III** are ubiquitously found in nature among various terrestrial and marine sources like fungi, bacteria, insects, plants, molluscs and sponges, to name a few.[1] This family of natural products, collectively recognized as epoxyquinone natural products, are constituted of a deceptively simple but highly oxygenated cyclohexane platform (**I-III**, Fig. 1), that is densely populated with a number of contiguous (often quaternary) chiral centers and reactive functional groups. The stereochemical variations found in epoxyquinol (**II**) and epoxyhydroquinone (**III**) cores are quite intriguing, where all possible permutations in the relative stereochemistry between the hydroxyl groups and the epoxide ring have been encountered. Dimeric epoxyquinones (e.g. **IV**, Fig. 2) represent even more complex architectures, having multiple fused rings around a central bicyclic core, laced with numerous contiguous chiral centers. The molecular and stereochemical complexities of epoxyquinones, together with their diverse biological activities, have presented chemists over the years, a set of interesting targets to test their synthetic creativity and explore the chemical diversity space around their bioactive scaffolds.

1.1. Scope

Earlier work on epoxyquinonoid total synthesis has been covered in two reviews, one appearing in 2004, in which epoxyquinones were featured as part of a broader coverage on cyclohexane epoxides,[1a] and the other that appeared in 2005 mainly dealt with the synthesis of manumycins and the spirodioxynaphthalene linked epoxynaphthoquinones.[1b] In the intervening years,[2a] considerable activity has accumulated in the literature and it is an opportune time to collate and reflect on these advances to facilitate and stimulate further activity in the domain. In order to retain focus, manumycins,[1b,3] epoxynaphthoquinones,[1b,c] cyclohexene oxides like scyphostatin,[4] gabosines and related carbasugars[2b–d] are not included in this coverage.

1.2. Structural landscape

The vast structural diversity of natural epoxyquinones can be broadly classified into epoxy-benzoquinones, epoxy-naphthoquinones and higher homologs. Among them, epoxybenzoquinones constitute the largest class of natural products and based on their substitution pattern, can be subdivided in to four groups (Type **A-D**) as represented in Fig. 3.

A wide variety of pendant substituents are found on the epoxybenzoquinone cores, ranging from small groups like Me or CH_2OH to conjugated enynes to large oligoprenyl chains and cyclic terpene like motifs. Diverse ring annulated structures are also found in some Type **C** & **D** natural products of this family.

A group of dimeric epoxybenzoquinones have also been isolated from various fungi, representative examples of which are shown in Fig. 4.[5] Among them, epoxyquinol A (**11**)[5c,d] has evoked widespread interest among synthetic chemists due to its potent anti-angiogenic property. Dimericbiscognienyne A (**12**)[5e] and pestalofone B (**13**),[5f] having novel enyne substituents and an unusual spirocyclohexene bridge, respectively, are recent additions to this class of natural products.

Epoxybenzoquinones appended with cyclic terpene-like motifs, in particular the drimanyl epoxyquinones,[6–11] are a select group of fungal metabolites that have aroused much current interest. Since the first disclosure of macrophorin A-C in 1983,[6a] drimanyl epoxyquinones have grown to a sizeable number (Fig. 5) displaying a range of structural variations and potent anti-cancer activities.

A few sibling natural products whose structural attributes embody the core epoxyquinone frameworks *viz.* antitumor agent mensacarcin (**19**),[12] the angularly fused natural products SF 2315B (**20**)[13] and fluostatin C (**21**)[14] (Fig. 6) have also attracted the attention of the synthetic community. Ketoanhydrokinamycin (**22**)[15a,b] and FL-120B' (**23**),[15c,d] the only two diazo-containing natural benzofluorenones,[16] close congeners of anti-cancer kinamycins, also harbour an epoxyquinonoid moiety and can be regarded as additional members of this category.

1.3. Bioactivity span

Natural epoxyquinones, exhibit a wide range of biological activities including antifungal, antibacterial, anti-HIV, antitumor and antiangiogenic properties, some of which may be attributed to the presence of reactive functional groups, especially the epoxide moiety.[17] They are also selective inhibitors of a number of therapeutically important enzymes viz. the interleukin-1β converting enzyme (EI-1941-2, **6**),[18] HIV-1 integrase (integrasone, **7**),[19] VEGF (epoxyquinol A, **11**),[2a] human $A\beta_{42}$ (dimericbiscognienyne A, **12**),[5e] etc. A recent review documents several monomeric (e.g. cycloepoxydon)[20] and dimeric epoxyquinones as potent NF-κB inhibitors.[21a] Epoxyphomalin A (**15**) was found to be highly cytotoxic

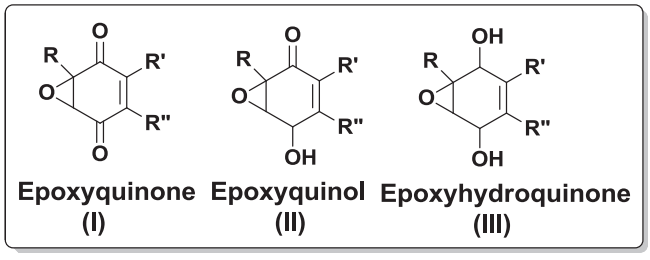

Fig. 1. Natural epoxyquinonoid cores.

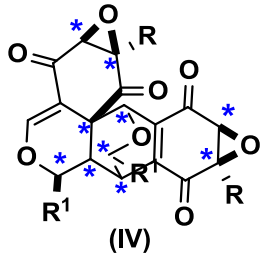

Fig. 2. Natural dimeric epoxyquinone core.

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