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Synthesis and biological activity investigation of azole and quinone hybridized phosphonates

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ABSTRACT

Phosphonates, azoles and quinones are pharmacophores found in bioactive compounds. A series of phosphonates conjugated to azoles and quinones with variable carbon chain lengths were synthesized in 3–4 steps with good yield. Antifungal assay of these compounds showed that ethyl protected phosphates have excellent inhibitory activity against phytopathogenic fungus *Fusarium graminearum*, and the free-base phosphates have good activity against human pathogenic fungi *Aspergillus flavus* and *Candida albicans*. Structure- activity relationship (SAR) studies showed activity increases with longer carbon chain length between phosphonate and anthraquinone analogs consisting of azole and quinone moieties. These newly synthesized compounds also have mild antibacterial activities to Gram positive bacteria, including methicillin-resistant *Staphylococcus aureus* (MRSA). Cytotoxicity analysis of these compounds against HeLa cells reveals that the phosphoric acid analogs are less toxic compared to ethyl protected phosphonates. Three leads compounds have been identified with prominent antifungal activity and low cytotoxicity.

Compounds containing quinone moieties are in great interest because of their wide biological activity[1]. Mitomycin C[2], streptonigrin[3], and anthracyclines[4] are the quinone based anticancer drugs used in the clinical practice (Fig. 1). Along with anticancer properties, compounds containing the quinone motif are also antifungal and anti-bacterial.[5–8] Azole compounds have also attracted great attention due to their broad-spectrum biological activities, especially as antifungal agents like fluconazole, metconazole and itraconazole (Fig. 2).[9,10]

Inspired by the success of quinone and azole compounds, we have pursued the synthesis of cationic anthraquinone analogs (CAAs), a hybrid of naphthoquinone and 1,2,3-triazole (Fig. 3).[11–15] These compounds can be prepared in 2–3 steps and have a wide range of biological activities from anticancer to antibacterial and antifungal activity. For example, when attached with a linear alkyl chain, the CAAs, **1** are mainly antibacterial. With the attachment of aryl groups, compound **2** becomes primarily anticancer and antibacterial. The dimeric CAAs, **3** behave mainly as antifungal and antibacterial agents. These compounds all have a redox active naphthoquinone core, which plays the pivotal role in the exerted biological activities.

Organophosphorus compounds are known to exert diverse biological effects[16] including antibacterial[17], herbicidal[18], and anti-inflammatory[19] activities. To increase the biological availability and stability, phosphonates are commonly employed as analogs of organophosphorus compounds with a C-P bond. Organophosphorus compounds are also used as anticancer[20], and antiviral[21] prodrugs. Organophosphorus compounds with O-P bonds can be easily hydrolyzed in physiological conditions[22], whereas phosphonates with C-P bonds are stable under these conditions.[23] Similar to organophosphorus compounds, phosphonates are also used as antifungal, anticancer, and antiviral prodrugs, such as fosfluconazole, estramustine phosphate, fludarabine phosphonate, and fosamprenavir (Fig. 4).[24] Conjugation of these phosphonate groups improves the solubilities of the parent drugs. Phosphonates conjugated to other biologically important moieties have shown antifungal and antibacterial activities (Fig. 5).[25,26] Motivated by these applications of phosphonates, we began to systematically investigate the biological implications of conjugating phosphonates and anthraquinone analogs.

The synthetic design in this work was to combine the redox active naphthoquinone core, predecessor of the CAA core, and phosphonate with various linkers. The synthesis began with an Arbuzov reaction using dibromoalkanes and triethylphosphite (Scheme 1). Reacting the resulting bromoalkyl phosphonates with sodium azide provided

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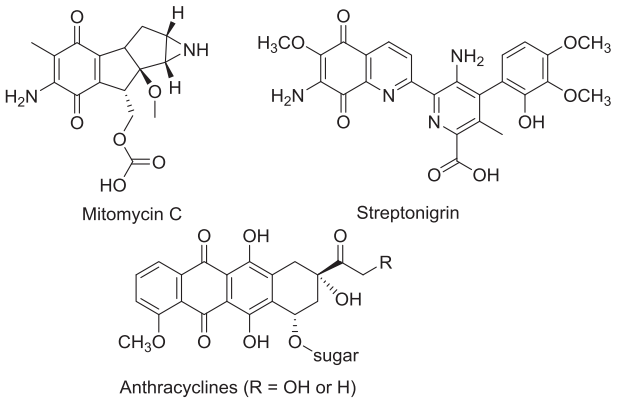


Fig. 1. Structure of quinone-based anticancer drugs.

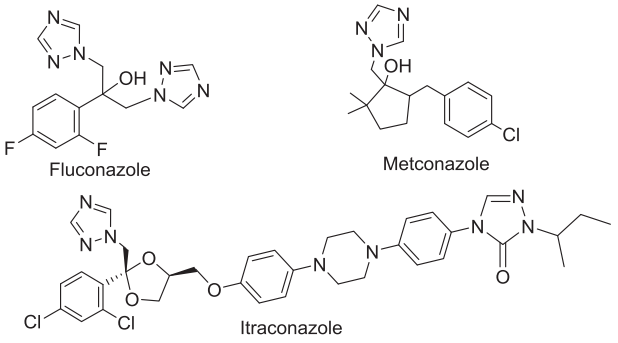


Fig. 2. Structure of azole-based antifungal agents.

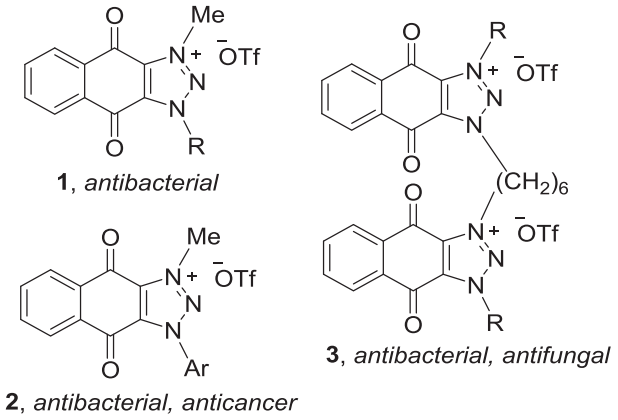


Fig. 3. Structure and activity of CAAs.

compound **8a–8f** ready for a [2 + 3] cycloaddition with 1,4-naphthoquinone. During this cycloaddition, the cyclization was followed by an oxidation *in situ* in the presence of excess naphthoquinone, and yielded compounds **9a–f**.[12] Following the cycloaddition/oxidation process, the ethyl groups of the phosphonate were removed using trimethylsilyl iodide (TMSI). Deprotection of ethyl groups of **9c** led to the formation of the desired product mixed with inseparable impurities. Therefore, no corresponding adducts in the forms of phosphoric acid or potassium phosphonate were tested. The resulting phosphoric acids, **10a**, **10b**, and **10d-10f,** were purified and fully characterized. However, to improve solubility, these phosphoric acids were converted to potassium salts using IR120 ion exchange resin, and assayed as potassium salts, **11a**, **11b**, and **11d-11f**. Compounds **9a-9f**, ethyl ester of phosphonates, can be viewed as prodrugs of compounds **11a**, **11b**, and **11d-11f**. (potassium phosphonates), and both were evaluated for their biological activities. In short, there are two main structural differences among the synthesized compounds: 1) chain-length connecting the triazole and

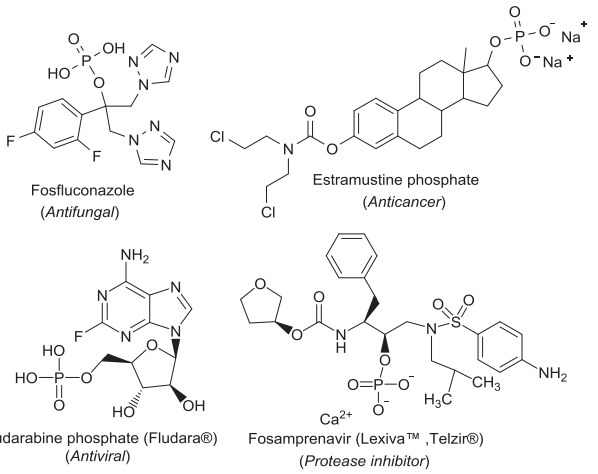


Fig. 4. Structure of bioactive organophosphorus compounds.

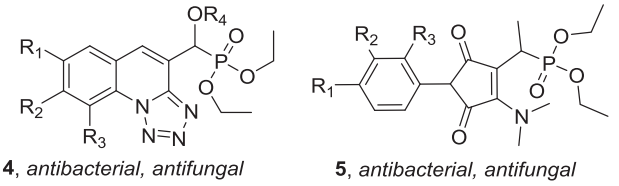
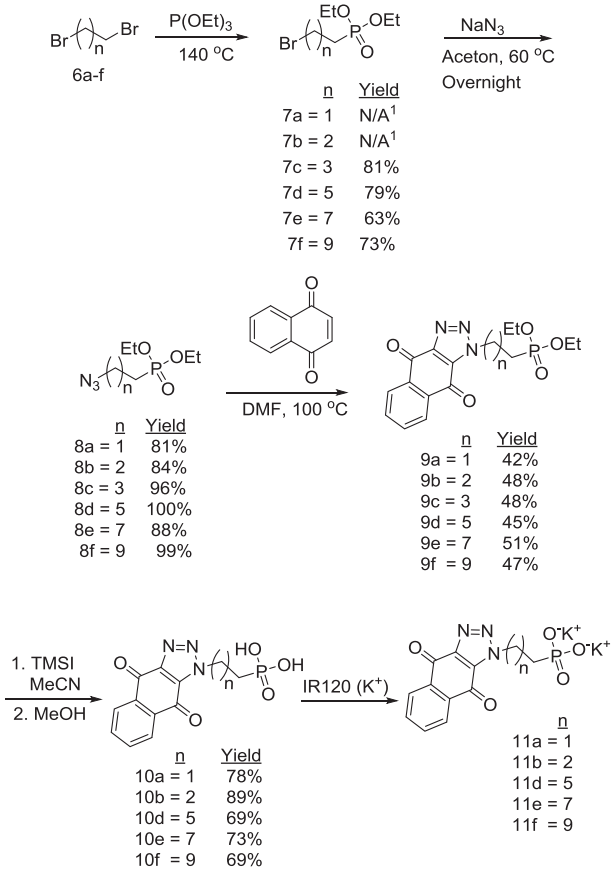


Fig. 5. Phosphonate conjugated biologically active compounds with antibacterial and antifungal activities.

N/A[1]: Not applicable, compound was purchased from commercial source.



Scheme 1.