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Coordination Chemistry Based Approach to Lipophilic Inhibitors of 1-Deoxy-D-xylulose-5-phosphate Reductoisomerase

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Abstract: 1-Deoxy-D-xylulose-5-phosphate reductoisomerase (DXR) in the non-mevalonate pathway found in most bacteria is a validated anti-infective drug target. Fosmidomycin, a potent DXR inhibitor, is active against Gram-negative bacteria. A coordination chemistry and structure based approach was used to discover a novel, lipophilic DXR inhibitor with an IC_{50} of 1.4 μM. It exhibited a broad spectrum of activity against Gram-negative and -positive bacteria with minimal inhibition concentrations of 20−100 μM (or 3.7−19 μg/mL).

Despite great success in the development of antibiotics, bacterial infections are still the number 1 cause of human mortality in the world, killing ~6 million people each year. Furthermore, drug resistant bacteria have reached epidemic levels during the past few decades.[1] Even in developed countries, bacterial infections have now become a serious threat to public health, mainly because of rising drug resistance. On the other hand, production of new antibiotics by the pharmaceutical industry has decreased considerably since 1980.[2] There is therefore a pressing need to find new drugs to combat bacterial infections that are resistant to current therapies.

1-Deoxy-D-xylulose-5-phosphate reductoisomerase (DXR[a]) in the non-mevalonate isoprene biosynthesis pathway (Figure 1) is an attractive target for developing novel anti-infective drugs,[3] since humans do not have the enzyme or its homologues. The non-mevalonate pathway is used by the vast majority of bacteria and apicomplexan protozoa (e.g., malaria parasites) to make essential isopentenyl diphosphate and dimethylallyl diphosphate, which are two common precursors for biosynthesis of all isoprenoids/terpenoids. Fosmidomycin (**1**, Chart 1), a naturally occurring antibiotic,[4] has been found to be a very potent DXR inhibitor.[5] It has also shown antimalarial activity in preclinical studies and recent clinical trials.[6] However, **1** has limited cellular uptake for many bacteria[7] and a short half-life (~1.5 h) in plasma because of its high hydrophilicity.

Much interest has therefore been generated to develop potent DXR inhibitors. However, it has turned out to be a great challenge.[8] Except FR900098 (Chart 1), other derivatives/analogues of **1** with a lipophilic group invariably have considerably reduced DXR inhibitory activity and exhibit no antibacterial activity. Two structurally distinct, bisphosphonate DXR inhibitors (Chart 1) have been reported, but they possess moderate inhibitory activity (IC_{50} of ~4 and 7 μM). In addition, a high-throughput screening of 32 000 compounds only yielded 30 hits with $IC_{50} < 20\,\mu$M. However, the structures of these hits were not disclosed and these compounds therefore cannot be confirmed and further developed. Here, we report the discovery of novel, lipophilic DXR inhibitors with good antibacterial activity, using a coordination chemistry and structure based approach.

DXR is a Mg^{2+}-dependent enzyme, catalyzing the isomerization and reduction of 1-deoxy-D-xylulose-5-phosphate (DXP) to 2-*C*-methyl-D-erythritol-4-phosphate with NADPH as a hydride donor. The crystal structure of the DXR−**1** complex[9] shows that the hydroxamate group of **1** chelates the central Mg^{2+} ion, which is anchored to the protein by coordination to the side chains of the residues Asp149, Glu151, and 230 (see Supporting Information Figure S1). The substrate DXP binds to DXR in a similar manner (see Supporting Information Figure S1).[10] These results suggested that coordination chemistry could be used to design a strong Mg^{2+}-chelating group as a viable approach to DXR inhibition.

Mg^{2+} is a hard metal ion because of its small ionic radius, high electronegativity, and low polarizability. It therefore only forms stable complexes with dioxygen based, hard ligands, such as catechol and hydroxamate. In addition, the stability constant (k_1) of the Mg^{2+}-catechol complex was found to be 1.7×10^5,[11] which is ~3× as stable as the Mg^{2+}-hydroxamic acid complex ($k_1 = 5.2 \times 10^4$),[12] suggesting catechol compounds, such as **2**−**4** in Chart 2, that mimic the structure of **1**, could be DXR inhibitors. Indeed, **2** was found to be an inhibitor of *E. coli* DXR with an IC_{50} of 24.8 μM. Although **3** had only 25.7% inhibitory activity at 100 μM against the enzyme, **4** was found to be a good DXR inhibitor with an IC_{50} of 4.5 μM. A docking study using Glide (in Schrödinger 2008)[13] showed that it could have a similar binding mode as **1**, with catechol chelating the Mg^{2+} and the phosphonate located very close to that of **1**, as shown in Figure 2A. In line with the result, the analogous compound **5**, having a carboxylate group with less electrostatic interactions (compared to a phosphonate), exhibited only weak inhibition against the enzyme.

When **4** was tested against the growth of four bacteria that use the non-mevalonate pathway, i.e., *E. coli*, *Pseudomonas aeruginosa, Bacillus anthracis*, and *Micrococcus luteus*, it exhibited, however, only weak antibacterial activity, with minimal inhibition concentrations (MIC, the lowest concentration of an agent that can inhibit visible bacterial growth upon 24 h of incubation at 37 °C) being ≥1000 μM, as shown in Table 1. The polar, negatively charged phosphonate group (at physiological pH) might limit the cell membrane permeability of **4**, resulting in high MIC values.

To design more lipophilic inhibitors that could have better cell permeability, we further looked into the DXR structure and found, beside the **1**/DXP and NADPH binding sites, a mostly hydrophobic pocket that can be exploited (see Supporting Information Figure S2). Compounds **6** and **7** (Chart 3), which contain a catechol as a Mg^{2+} chelator and a simple lipophilic group (i.e., phenyl or benzyl) that could occupy the hydrophobic pocket, as suggested by our docking studies (Figure 2B), were designed and synthesized.

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[a]Abbreviations: DXR, 1-deoxy-D-xylulose-5-phosphate reductoisomerase; DXP, 1-deoxy-D-xylulose-5-phosphate; MIC, minimal inhibition concentration.

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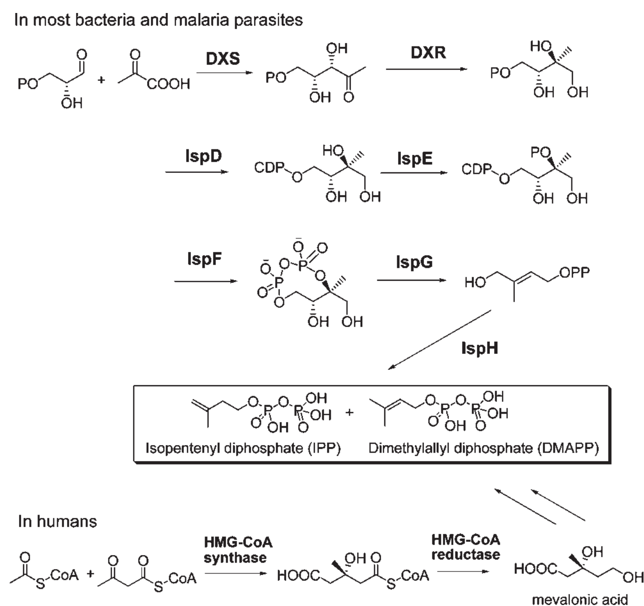


Figure 1. Non-mevalonate and mevalonate isoprene biosynthesis pathways.

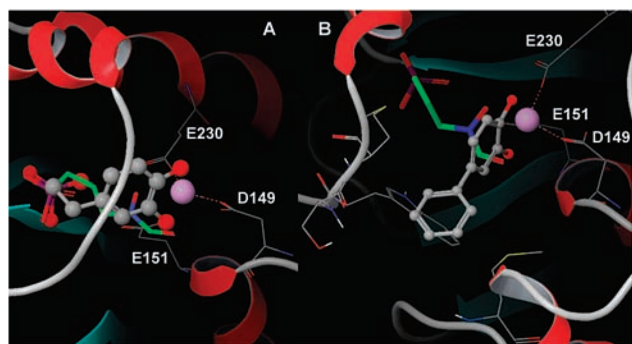


Figure 2. (A) Docking structure of **4** (ball and stick model) in DXR, with superimposed crystal structure of **1**. (B) Docking structure of **6** in DXR, showing its phenyl group in a hydrophobic pocket. Mg^{2+} is shown as a pink sphere.

Chart 1. Structures of DXR Inhibitors

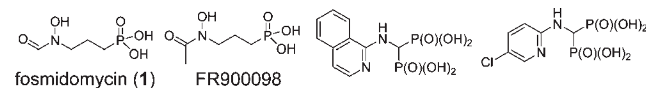
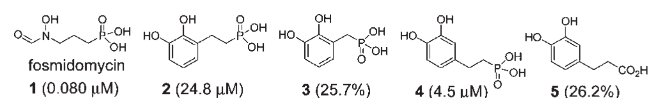


Chart 2. Structures of **1**−**5** and Their IC_{50} Values (or % Inhibition at 100 μM) against *E. coli* DXR in Parentheses

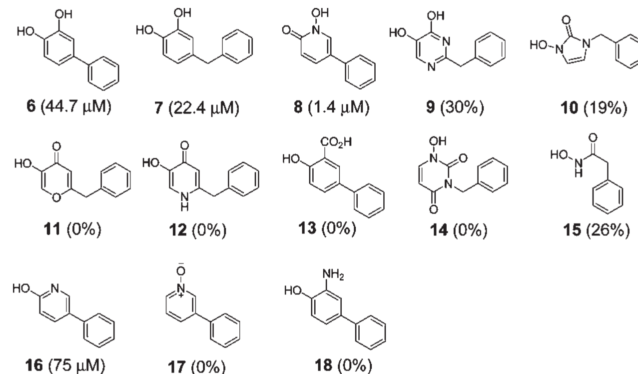


Both compounds were found to be modest DXR inhibitors with IC_{50} of 44.7 and 22.4 μM. However, compared to **4**, they exhibited better antibacterial activity (Table 1) with MICs of 200−1000 μM (or 37−190 μg/mL). Compounds **8**−**15**, each of which has a different dioxygen containing ligand and a phenyl/benzyl group, were made in an effort to identify a better Mg^{2+} chelating group for DXR inhibition. Although **9**−**15** had no or weak activity, **8** containing a 1-hydroxypyridin-2-one group as a Mg^{2+} chelator was found to be a potent DXR inhibitor with an IC_{50} of 1.4 μM.

Table 1. MICs (μM) against Four Bacteria

	Gram-negative bacteria		Gram-positive bacteria	
compd	*E. coli*	*P. aeruginosa*	*B. anthracis*	*M. luteus*
4	> 1000	1000	1000	> 1000
6	500	200	200	200
7	1000	200	200	200
8	100	50	20	100
1	10	20	100	> 1000
ampicillin	5	500	0.1	1
kanamycin	10	200	5	20

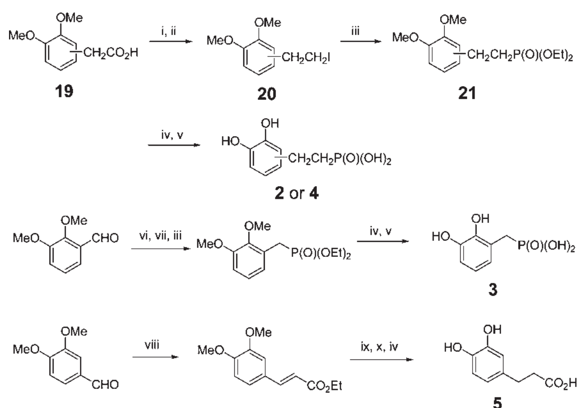
Chart 3. Structures of **6**−**18** and Their IC_{50} Values (or % Inhibition at 100 μM) against *E. coli* DXR in Parentheses



Compound **8** exhibited good activity against all four bacterial species, with MICs of 20−100 μM (or 3.7−19 μg/mL) (Table 1). Three known antibiotics, i.e., **1**, ampicillin, and kanamycin, were included in the test as positive controls. Consistent with previous results,[4] **1** had potent activity against Gram-negative bacteria but displayed weak or no activity against Gram-positive bacteria because of limited cellular uptake.[7] In addition, although **1** (IC_{50} = 80 nM) is ~16× more active than **8** against the *E. coli* DXR (enzyme), **8** is more active against the growth of Gram-positive bacteria. This could be due to (1) increased lipophilicity and/or bioavailability of **8**, (2) improved activity of **8** against DXRs from other bacteria, or both. It is also remarkable that **8** exhibited impressive antibacterial activity (MIC = 50 μM or 9.4 μg/mL) against a clinical isolate of *P. aeruginosa*. The bacterium *P. aeruginosa* is a major hospital-acquired pathogen notorious for its significant intrinsic and acquired antibiotic resistance. This clinical strain is highly resistant to two common antibiotics, ampicillin and kanamycin (MICs of 500 and 200 μM, Table 1). However, it had a similar susceptibility to our novel DXR inhibitor **8**. In addition, **8** exhibited negligible effects against the growth of two noncancerous human cell lines, Beas2B (lung epithelial) and WI-38 (fibroblast), with IC_{50} of > 300 μM. All these features make **8** a promising lead compound for further antibacterial drug development.

Next, **16**−**18** (Chart 3) were prepared to test if both −OH groups (or tautomeric carbonyl) in **8** and **6** are involved in chelating the Mg^{2+}. Compared to **8**, compounds **16** and **17** exhibited > 50× weaker inhibition against DXR. In addition, the lack of activity of **18** also shows that $-NH_2$, a softer ligand, even with an adjacent, hard −OH, is not able to bind the Mg^{2+} strongly. This preliminary mechanistic study, together with the docking results (Figure 2), supports that both oxygen atoms in **8** and **6** chelate the central metal ion, which is key to DXR inhibition.

Scheme 1[a]



[a]Reagents and conditions: (i) $LiAlH_4$, THF; (ii) MsCl, NEt_3, then NaI; (iii) $P(OEt)_3$, 120 °C; (iv) BBr_3, CH_2Cl_2; (v) TMSBr, CH_3CN; (vi) $NaBH_4$; (vii) MsCl, NEt_3; (viii) NaH, triethyl phosphonoacetate, THF; (ix) H_2, 5% Pd/C; (x) NaOH, MeOH.

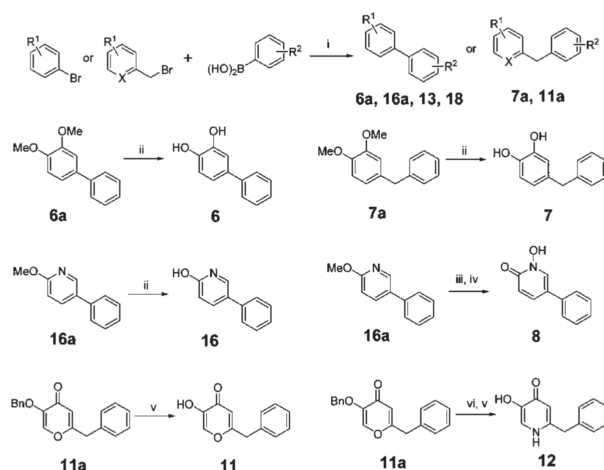
Moreover, it is noteworthy that the hydroxamate group seems to be considered as the ligand of choice for many metalloenzymes and it has been widely used to design their inhibitors. However, hydroxamate compounds, which undergo a variety of rapid metabolic degradations in vivo (e.g., hydrolysis, glucuronidation, and sulfation), generally have poor pharmacokinetic and/or toxicological profiles.[14] Using coordination chemistry to design a wide range of ligands targeting the central metal ion is therefore of particular importance with respect to drug discovery and development. However, this approach has not been widely explored.[15]

Finally, we describe the synthesis of **2**−**18**.[16] Compounds **2**−**5** can be readily prepared according to Scheme 1. Dimethoxyphenylacetic acid **19** was reduced to the corresponding alcohol with $LiAlH_4$, which was converted to iodide **20** by treatment with methanesulfonyl chloride followed by NaI. Arbuzov reaction using **20** and triethyl phosphite afforded **21**, which was then deprotected by successive treatments with boron tribromide and bromotrimethylsilane to give **2** or **4**. Compound **3** was prepared similarly. A Horner−Wadsworth−Emmons reaction using 3,4-dimethoxybenzaldehyde and sodium salt of triethyl phosphonoacetate, followed by hydrogenation and deprotections, gave **5**.

Most compounds in Chart 3 were synthesized with Suzuki coupling as the key step (Scheme 2). Suzuki coupling using an appropriate bromide and a boronic acid gave, after a simple deprotection (if necessary), **6**, **7**, **11**, **13**, **16**, and **18**. Compound **8** was made from the intermediate **16a**, with an $AcOH/H_2O_2$ mediated oxidation and subsequent demethylation. Treatment of the intermediate **11a** with ammonia in ethanol afforded, after hydrogenation, compound **12**.

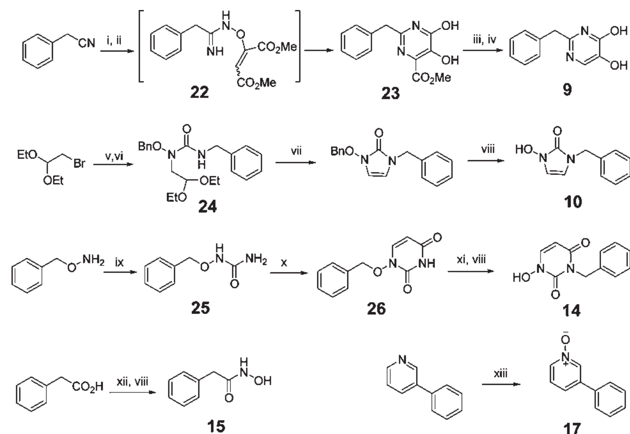
Compounds **9**, **10**, **14**, **15**, and **17** were made according to Scheme 3. Benzyl cyanide was reacted with hydroxylamine and the resulting phenylacetylamidoxime treated with dimethyl acetylenedicarboxylate to give **23**. It was then hydrolyzed and decarboxylated to afford **9**. *O*-Benzylhydroxylamine was alkylated with 2-bromoacetaldehyde diethyl acetal, followed by treatment with benzyl isocyanate, to produce urea **24**. It was cyclized in the presence of 98% formic acid to give, after hydrogenation, **10**. Urea **25**, obtained from *O*-benzylhydroxylamine and potassium cyanate, was reacted with methyl 3-dimethoxypropionate and NaH, affording **26**, which was selectively alkylated and hydrogenated to give **14**. Syntheses of **15** and **17** were readily achieved according to standard protocols.

Scheme 2[a]



[a]Reagents and conditions: (i) $Pd(PPh_3)_4$, K_2CO_3, THF, reflux; (ii) BBr_3, CH_2Cl_2; (iii) $AcOH/H_2O_2$, 70 °C; (iv) AcCl, reflux, then MeOH; (v) H_2, 5% Pd/C; (vi) NH_3, EtOH.

Scheme 3[a]



[a]Reagents and conditions: (i) NH_2OH, MeOH, reflux; (ii) dimethyl acetylenedicarboxylate, 70 °C for 1 h, then 150 °C for 3 h; (iii) NaOH, MeOH; (iv) 6 N HCl, reflux; (v) $BnONH_2$, NEt_3, DMF, 90 °C; (vi) BnNCO; (vii) HCO_2H; (viii) H_2, 5% Pd/C; (ix) KNCO, 10% AcOH/H_2O; (x) NaH, $(OMe)_2CHCH_2CO_2Me$, DMSO, 70 °C; (xi) BnBr, K_2CO_3; (xii) $BnONH_2$, EDC, NEt_3; (xiii) $AcOH/H_2O_2$, 70 °C.

In summary, this work is of interest for a number of reasons. First, although DXR has been identified as a validated anti-infective drug target for over a decade, there has been a great challenge in finding potent, druglike DXR inhibitors. We used coordination chemistry and structure based design to obtain, for the first time, a strong, lipophilic DXR inhibitor **8**, which has a distinct structure from **1**. Second, **8** exhibited a broad spectrum of antibacterial activity, including a multidrug resistant clinical isolate of *P. aeruginosa*, a major nosocomial pathogen. It is also noncytotoxic to human cells. This compound should represent a novel drug lead for further development. Third, the hydroxamate group has been widely applied to design metalloenzyme inhibitors. However, other nonhydrolyzable, aromatic metal-chelating groups have been mostly overlooked.[15] This work shows that coordination chemistry should be considered in designing novel, potentially more metabolically stable inhibitors of metalloproteins, given the generally poor pharmacokinetics of hydroxamate compounds.

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Supporting Information Available: Figures S1 and S2 and Experimental Section. This material is available free of charge via the Internet at http://pubs.acs.org.

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