Inhibitors of Types I and II Dehydroquinase

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Abstract: Inhibitors of varying potency have been developed for types I and II 3-dehydroquinate dehydratase (dehydroquinase), enzymes from the shikimate and quinate pathways that catalyse the dehydration of dehydroquinate to dehydroshikimate. These inhibitors have resulted from enzyme mechanistic studies and from the direct search for enzyme inhibitors with herbicidal, fungicidal or antimicrobial potential. This review discusses the design of the various inhibitors that have been produced so far and some structure-activity relationships. The majority of these inhibitors are based on dehydroquinate analogues, although some work has also been carried out on dehydroshikimate and bissulfonamides. Some discussion is also presented on advances in the synthesis of these types of compounds.

INTRODUCTION

Chorismate, the precursor of the aromatic amino acids and other aromatic metabolites including flavonoids, lignans and some alkaloids, is produced in nature from phosphoenolpyruvate and erythrose-4-phosphate in a sequence of reactions referred to as the shikimate pathway [1]. This pathway occurs in plants, microorganisms and fungi, but not in mammals, making its inhibition a desirable target for the design of potentially highly selective antimicrobial and herbicidal compounds. The herbicide glyphosate for e.g. inhibits EPSP synthase, the enzyme that catalyses, the formation of 5-enolpyruvylshikimate-3-phosphate (EPSP) in the penultimate step in the shikimate pathway [2]. This review is concerned with the inhibition of 3-dehydroquinate dehydratase (dehydroquinase, DHQase), the enzyme that catalyses the third step in the shikimate pathway, i.e. dehydration of dehydroquinate **1** to dehydroshikimate **2** (Fig. (**1**)). The conversion of dehydroquinate to dehydroshikimate by dehydroquinase also occurs as part of the quinate pathway in fungi in which quinic acid is utilised as a carbon source *via* protocatechuate and the β-ketoadipate pathway.

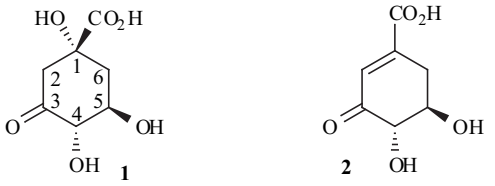

Fig. (1). Structures of dehydroquinic acid **1** and dehydroshikimic acid **2**.

There are two classes of dehydroquinase, known as type I and type II that catalyse the dehydration of **1** by different mechanisms. The two dehydroquinases are unrelated in an evolutionary sense, having completely different three dimensional structures [3] and exhibiting no sequence homology [4]. While type II dehydroquinase occurs on both the shikimate and the catabolic quinate pathways the type I enzyme has only been reported on the shikimate pathway [1].

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MECHANISM OF TYPE I DEHYDROQUINASE

Deuterium labeling experiments have shown that type I dehydroquinase catalysed dehydration of **1** occurs with loss of the less acidic *pro-R* hydrogen (Scheme (**1**)), while the analogous non-enzymatic dehydration occurs with loss of the more acidic *pro-S* hydrogen [5]. The enzyme catalysed *syn* dehydration is thought to proceed *via* imine formation with a highly conserved active site lysine residue (Lys-170) (Scheme (**1**)) [6]. Evidence for an imine intermediate comes from borohydride trapping of this species in the presence of an equilibrium mixture of substrate and product [7]. The reduced enzyme-product adduct has been characterised by electrospray mass spectrometry [8] and the crystal structure solved for the *Salmonella typhi* enzyme [3].

It has been proposed that imine formation results in distortion of the conformation of the substrate from its preferred chair form, increasing the acidity of the *pro-R* proton. A twist boat conformation provides the requisite co-planar orientation of the *pro-R* hydrogen with the π-acceptor orbital of the imine giving rise to the overall *syn*-stereochemistry of the elimination [5,9]. Enzyme inactivation resulting from modification of His-143 by diethyl pyrocarbonate, as well as the observed highly conserved nature of His-143 in type I dehydroquinases, led to the initial proposition that His-143 was the active site general base responsible for abstraction of the *pro-R* proton [10]. However, further studies suggested that although His-143 is clearly involved in imine formation and breakdown, it may not be the general base responsible for proton abstraction, rather it is involved in the deprotonation of the ε-NH_2 of Lys-170 [11]. Chemical modification experiments with phenylglyoxal have also identified an essential hyper-reactive active site arginine (Arg-213 in *E. coli*) that may be involved in carboxylate recognition [12].

MECHANISM OF TYPE II DEHYDROQUINASE

In contrast to the type I enzyme, the conversion of 3-dehydroquinate to 3-dehydroshikimate by type II dehydroquinase does not involve a Schiff-base intermediate. This is indicated by the lack of a conserved lysine residue [13] and the lack of enzyme inactivation observed upon treatment with sodium borohydride in the presence of an equilibrium mixture of substrate and product [14]. The

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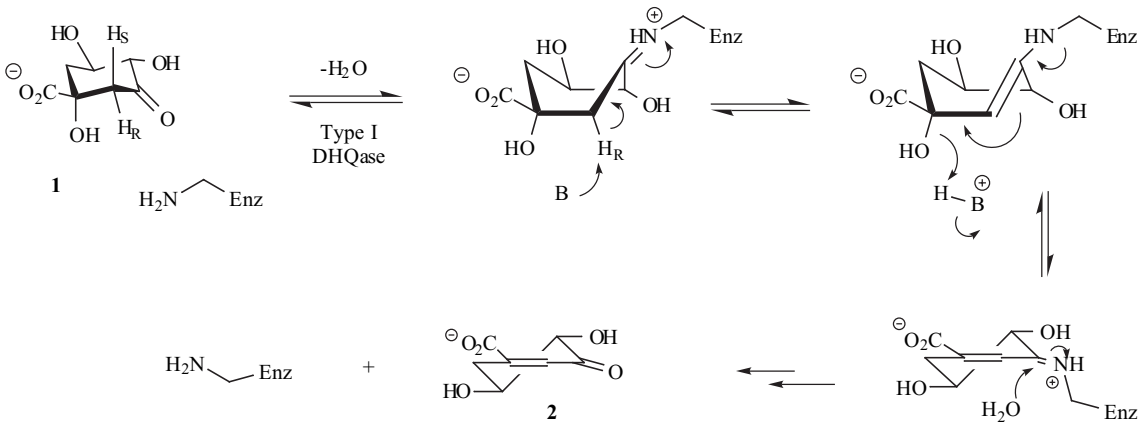
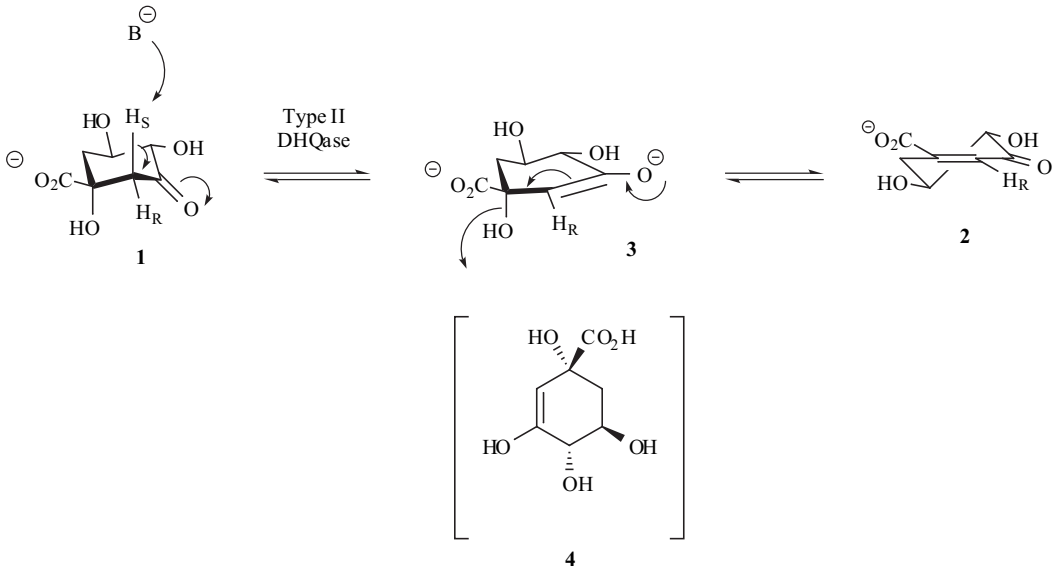


Scheme 1.

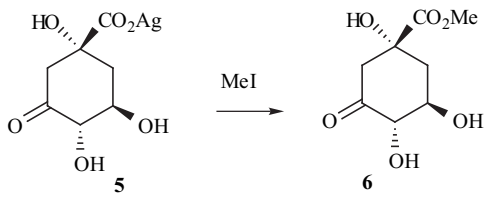


Scheme 2.

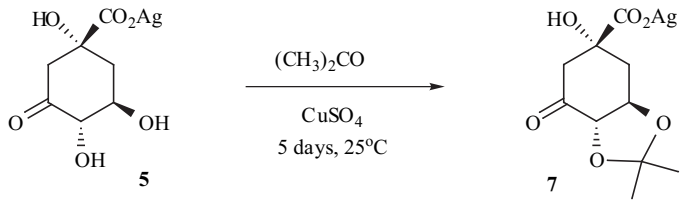
second notable mechanistic difference between the two types of dehydroquinase is that, in contrast to the elimination catalysed by the type I enzyme, the type II dehydroquinase catalysed reaction proceeds with *anti*-stereochemistry and loss of the more acidic axial *pro-S* proton, as confirmed by deuterium labelling experiments [15,16]. A stepwise E_1CB mechanism involving an enolate intermediate has been proposed, supported by kinetic isotope experiments, to explain the stereochemistry of the elimination (Scheme (**2**)) [17]. The subsequent crystallographic identification of a conserved active site water molecule in *S. coelicolor* dehydroquinase, along with the absence of any suitable residue to stabilise an enolate intermediate, suggests that enol **4** rather than enolate **3** was the more likely intermediate [18]. The conserved Tyr-28 has been proposed to be the general base responsible for proton abstraction, with His-106 acting as the general acid in the hydroxyl elimination step. Tyr-28 had been implicated in a catalytic role by inactivation of the enzyme following tetranitromethane modification of this residue [12]. As in the type I enzyme, an essential hyper-reactive active site arginine residue has been identified by phenylglyoxal modification and electrospray mass spectrometry [19].

INHIBITION OF TYPES I AND II DEHYDROQUINASE

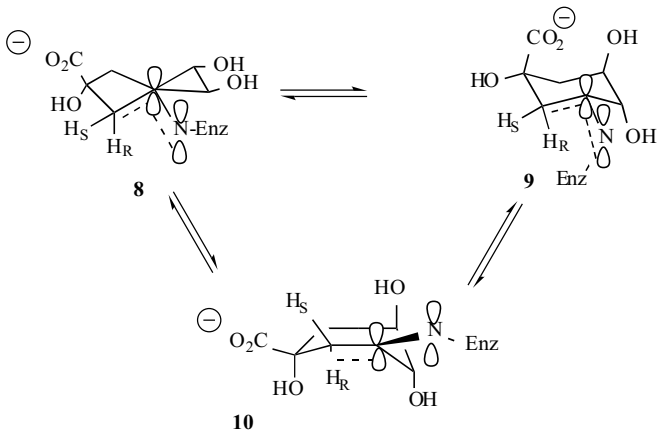
Early mechanistic studies, as discussed above, saw the synthesis of many dehydroquinate analogues that were subsequently screened for inhibitory activity. Most compounds were initially assayed against the type I enzyme. Nugent prepared analogues of dehydroquinate in order to identify the mechanistic source of the *syn* dehydration of **1** (see Scheme (**1**)) [9]. The methyl ester **6**, synthesised as shown in Scheme (**3**), was used to establish if the carboxylate of **1** acted as an internal base in the biosynthesis. This compound, however, proved to be neither an inhibitor nor a substrate of type I dehydroquinase from *E. coli*.



Scheme 3.



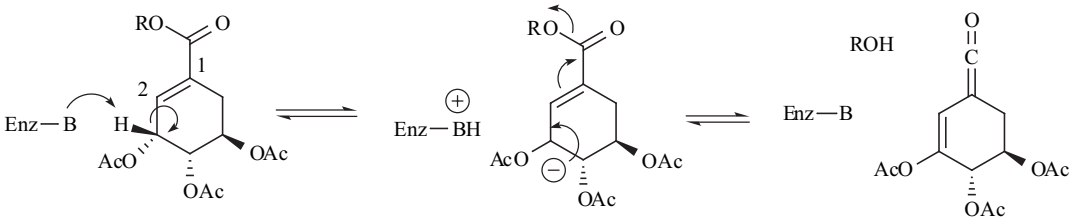
Scheme 4.



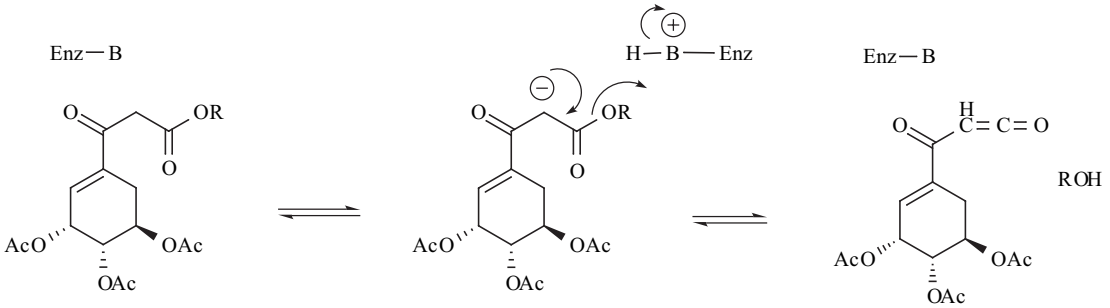
Scheme 5.

Next, dehydroquinate **5** was protected as the C-4/C-5 acetonide **7** as shown in Scheme (**4**), to study the conformational change required in the enzymatic conversion of dehydroquinate to dehydroshikimate. Three possible conformations were proposed to account for the dehydration of dehydroquinate (Scheme (**5**)).

Nugent proposed that, of these possible conformations, the one in which the hydroxyl groups are maintained in a diequatorial position (**8**) would be most favoured. The acetonide **7** was prepared and assayed as an analogue of conformation **8**. Assay of **7** against dehydroquinase from *E. coli* showed it to be a substrate such that hydrolysis of the acetonide is not required for activity. This result is consistent with **8** being the correct conformer for the biosynthesis. In addition, the rate of elimination of the hydroxyl at C-1 in **7** was approximately half that of the



Scheme 6.



Scheme 7.

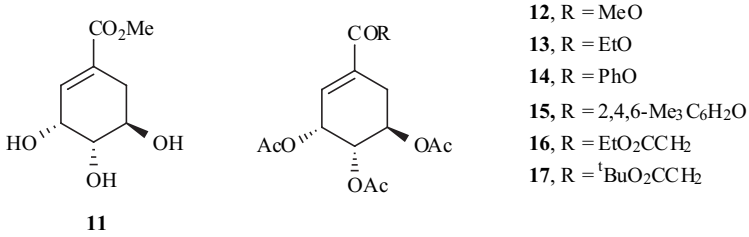


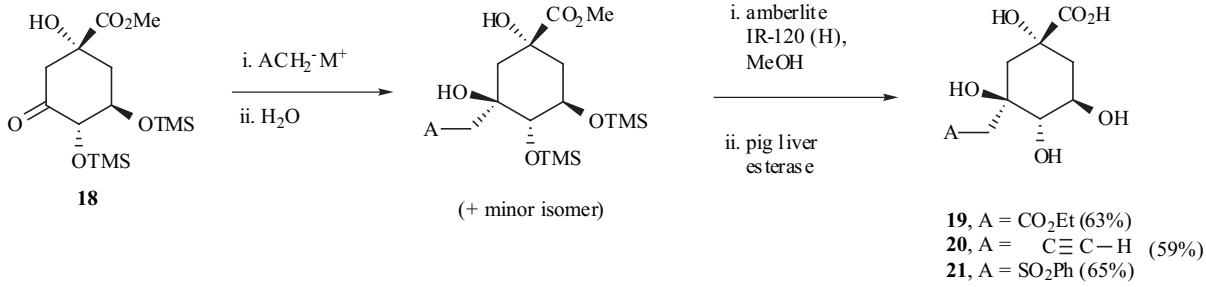
Fig. (2). Ester and β-ketoester-based derivatives.

natural substrate under similar conditions and an equimolar mixture of both these compounds reacted with the enzyme 0.714 times as fast as dehydroquinate only, therefore the acetonide acts as a competitive inhibitor of type I dehydroquinase.

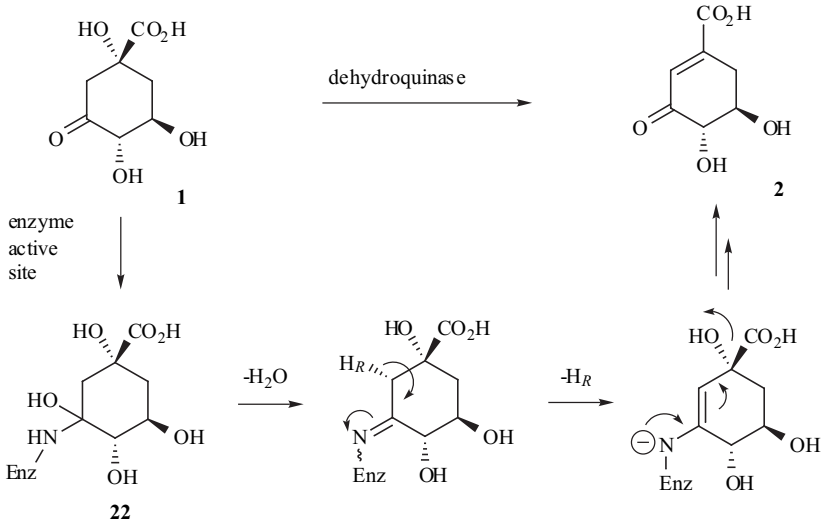
It is known that a reactive ketene functional group, derived from an ester group, can lead to suicide inhibition of a target enzyme [20,21]. By analogy, it has been suggested that an active-site base in the vicinity of C-1 and C-2 of a bound substrate [22] would be able to unmask an electrophile from an ester as in Scheme (**6**) for esters obtained from shikimic acid, and in Scheme (**7**) for β-ketoesters derived from shikimic acid, thus triggering the suicide inhibition of dehydroquinase.

Accordingly, Gorrichon synthesised a series of esters and β-ketoesters **11-17** (Fig. **2**) as putative inhibitors in order to test for suicide inhibition of type I dehydroquinase isolated from corn [23,24]. Esters **11-17** were assayed, however none showed inhibitory activity against dehydroquinase. This result is in agreement with the fact that the methyl ester **6** synthesised by Nugent (see Scheme (**3**)) *w*as neither a substrate nor an inhibitor of dehydroquinase from *E. coli* [9].

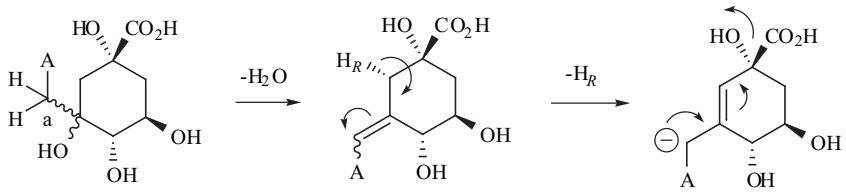
A study by Baltas and Gorrichon on the diastereoselectivity of nucleophilic additions to the carbonyl group of methyl 1,4,5-tris (trimethylsilyl)-3-dehydroquinate **18** provided a basis for another series of inhibition studies [25]. Compounds **19-21** (Scheme (**8**)) that have an electron-withdrawing group at C-3, were synthesised and subjected to inhibition assays. No explanation as to the possible mode of action of these compounds was given in the original publication, however Gorrichon [26] subsequently proposed that they might mimic an enzyme-bound intermediate **22** as shown in Scheme (**9**). The electron-withdrawing group (A) at C-3 in these compounds would be expected to increase the acidity of the α-methylenic protons and thus facilitate the



Scheme 8.



Scheme 9.



Scheme 10.

dehydration process as depicted in Scheme (**10**). The putative modes of binding and inhibition of the enzyme by compounds **19-21** were not, however, described in detail.

All three compounds failed to inhibit type I dehydroquinase from *E. coli*. It was proposed that this was the result of either the steric hindrance of the electron-withdrawing group **A** or the removal of the carbonyl at C-3, which prevented recognition of the substrate [26]. No further studies on this type of compound have been reported.

The first truly systematic studies on the design and synthesis of active-site directed inhibitors of type I dehydroquinase were carried out by Abell et al [27]. This work was based on a putative model for the active site of dehydroquinase (Fig. (**3**)), generated from information acquired during the early mechanistic studies.

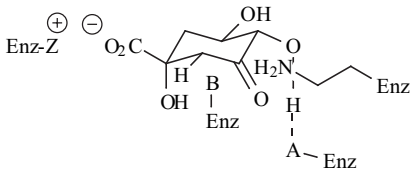
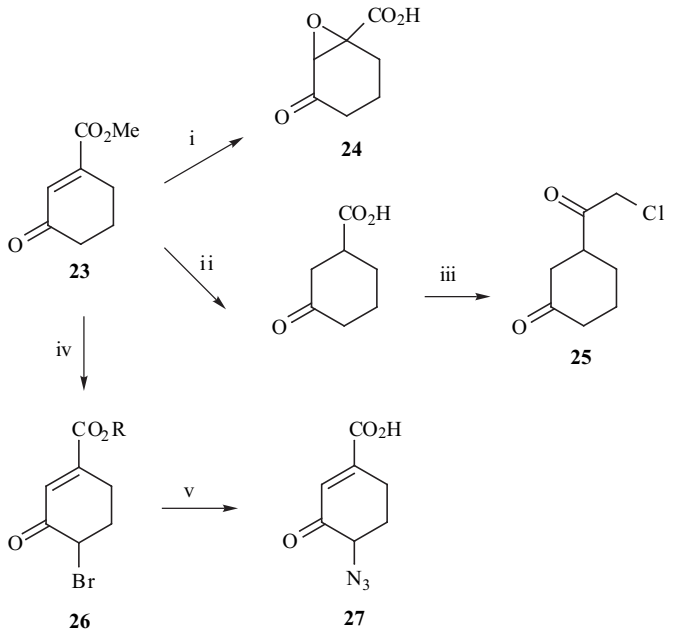


Fig. (3). Model of the active site of type I dehydroquinase.

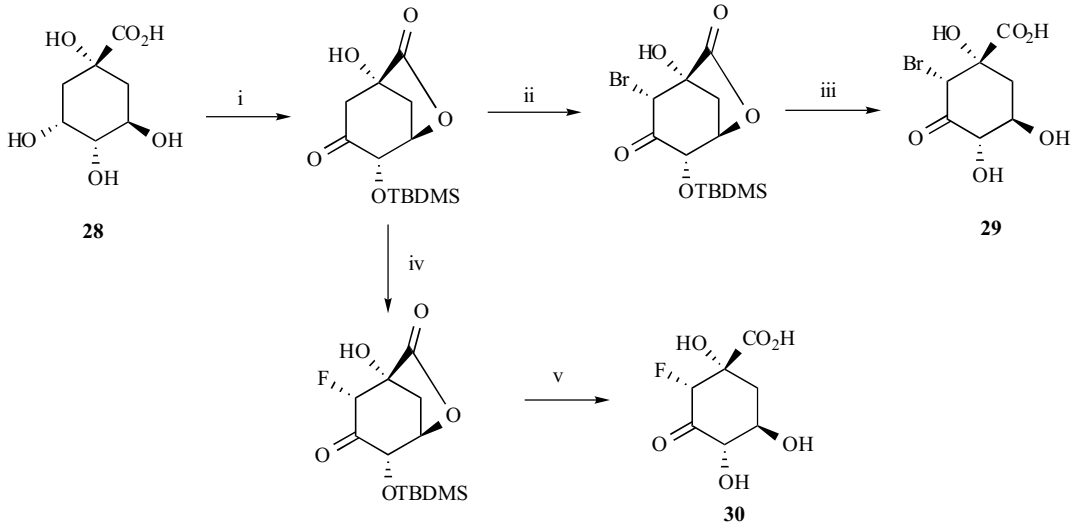
This model incorporated the active site lysine of dehydroquinase that is now known to be involved in Schiff base formation with the ketone of the substrate. At the time of this work, it was proposed that subsequent dehydration occurred *via* a conformational change of the substrate followed by a proton abstraction at C-2 by a general base, possibly a histidine residue. A positively charged residue was also thought to be involved in the binding of the carboxylate group of dehydroquinate, and several other residues to be implicated in hydrogen bonding interactions with the hydroxyl groups at C-1, C-4 and C-5.

A series of affinity-labels **24-27** was designed to investigate this model (Scheme (**11**)). The generic structure of the putative inhibitors consisted of a cyclohexane ring bearing an electrophile, and a carboxylate group and a ketone functionality that mimicks the dehydroquinate natural substrate.

The first compound tested in this series, epoxide **24**, showed rapid active-site directed irreversible inhibition of dehydroquinase. In addition, it exhibited saturation kinetics and presented an inhibition constant K_i of 400 μM, and a maximal rate of inactivation k_i of 2.5 x 10^{-3} s^{-1}. It would seem likely that enzyme inhibition occurs by nucleophilic attack on the epoxide by an active site base but this remains unproven. Next, ester **23**, the precursor of **24**, was converted into the chloromethylketone **25** by Arnsdt-Eistert homologation. This compound showed irreversible inhibition of the dehydroquinase with a K_i of 0.68 mM and a k_i of 5.6 x 10^{-4} s^{-1}. It also displayed saturation kinetics. The C-4 bromide analogue **26** proved inactive against *E. coli* dehydroquinase, however, the corresponding azide **27** acted



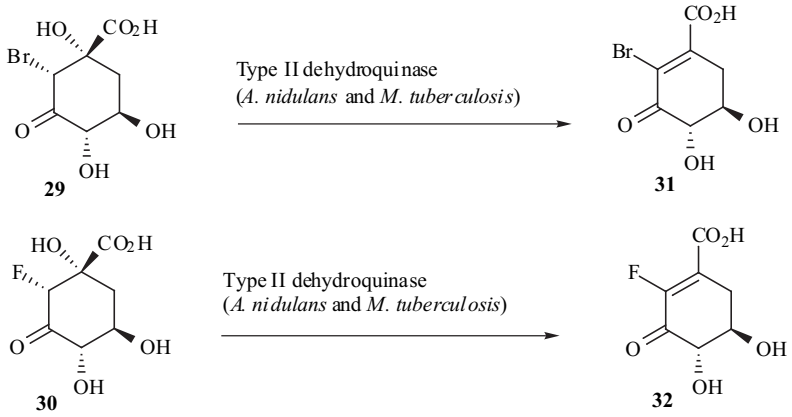
Scheme 11. i. H_2O_2, Na_2CO_3, H_2O, 75%; ii. H_2/Pd/C, MeOH, 60%; K_2CO_3, MeOH, H_2O, 62%; iii. EtCOCl, Et_3N, THF, CH_2N_2, Et_2O, 50%; HCl, EtOH, 62%; iv. LDA, TMSCl, THF, NBS, CH_2Cl_2, 64%; v. NaN_3, Me_2CO, 60%; pig liver esterase, H_2O, pH 7, 74%.



Scheme 12. i. ref [10]; ii. Br_2, dioxane, Et_2O, 89%; iii. AcOH, THF, H_2O, 95%; iv. (a) TMSOTf, Et_3N, toluene, (b) Selectfluor®, DMF, 89%; v. AcOH, H_2O, 90%.

as a photoaffinity label, presumably *via* the generation of a reactive nitrene diradical. The inhibition constant (K_i) for the azide **27** was modest at 1.1 mM, with a maximal rate of inactivation k_i of 3.9 x 10^{-4} s^{-1}. Inhibition by compounds **24**, **25** and **27** was prevented, or significantly reduced, by addition of dehydroquinate substrate. Hence all three labels

Next, (2*R*)-2-bromo- and (2*R*)-2-fluoro-3-dehydroquinic acid **29** and **30*** [28], substrates for type II dehydroquinase, were shown to be mechanism-based inhibitors of type I dehydroquinase [33]. Acid **29** proved to be a weak competitive inhibitor that resulted in slow, irreversible inactivation of the enzyme (K_i = 3.7 mM). Acid **30**, the



Scheme 13.

are competitive inhibitors of the enzyme and corroborated the active site model depicted in Fig. (**3**).

Subsequent work by Abell *et al.* reported the synthesis of (2*R*)-2-bromo- and (2*R*)-2-fluoro-3-dehydroquinic acids **29** and **30** from **28**, as part of a new enzymatic synthetic methodology for the preparation of dehydroshikimates (Scheme (**12**)) [28].

The halogenated dehydroquinates were incubated with type II dehydroquinases from *Mycobacterium tuberculosis* and *Aspergillus nidulans* [29,30] which are known to display distinct kinetic properties. The conversion of both (2*R*)-2-bromo-3-dehydroquinic acid **29** and (2*R*)-2-fluoro-3-dehydroquinic acid **30** to the corresponding dehydroshikimates **31** and **32** proceeded smoothly (Scheme (**13**)) [17]. Surprisingly, the fluoro analogue **30** displayed slow irreversible inhibitory activity with the enzyme from *A. nidulans* (50% over 4 hours).

fluorine analogue of **29**, also caused slow, irreversible inactivation of the enzyme but was a more potent inhibitor than **29** (K_i = 80 μM). The increased potency of the fluorine analogue is believed to be due to the lack of the bulky bromine atom that may block a catalytically important area of the active site. Mass spectrometry showed that the enzymes had been modified by the inhibitors, gaining an additional mass of 126 ± 5 Da due to the formation of the enzyme-inhibitor adduct **33** (Fig. (**4**)) [33,34]. This species would result from enzyme binding to the ketone of the inhibitor followed by decarboxylative elimination of the halide and isomerism to give **33**.

*Halogenated analogues of the natural substrates are often useful inhibitors and suicide substrates [31,32]. In particular, the fluoro substituent is used as an isostere of a proton for which electronic properties differ dramatically, therefore this substitution can contribute to a better understanding of the mechanism of an enzymatic conversion [31].

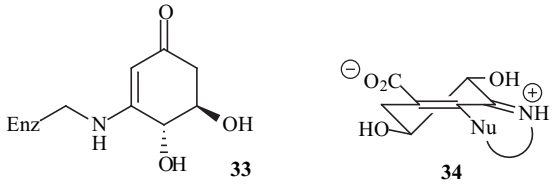
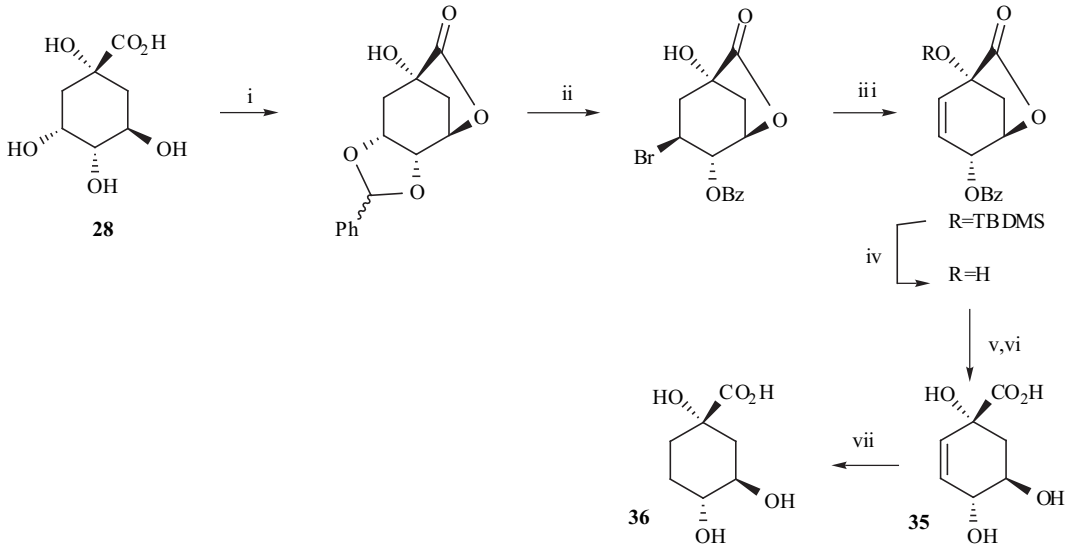


Fig. (4). Enzyme-inhibitor adducts.

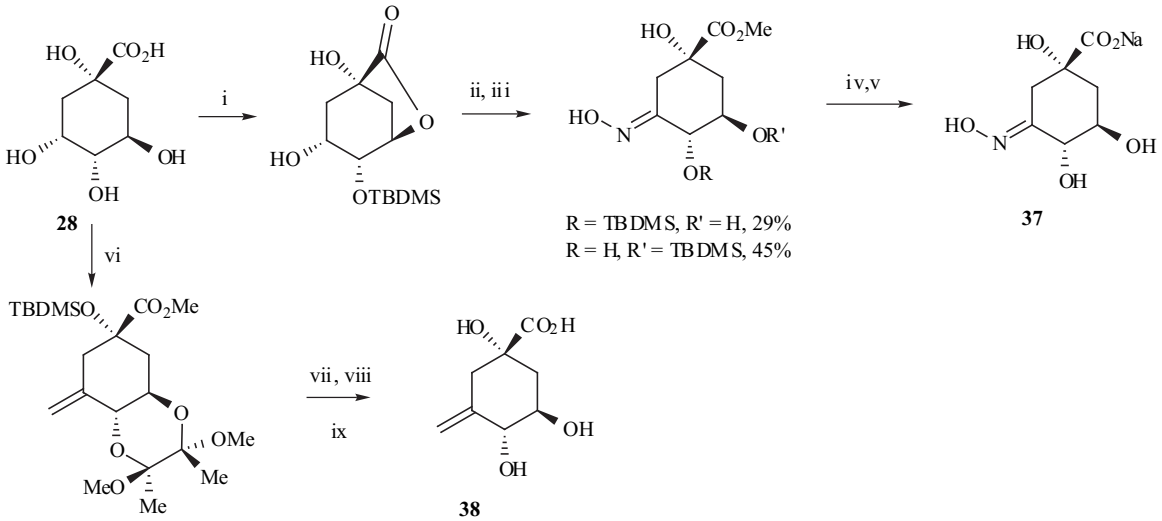
Similarly, incubation of the enzyme with 2-bromo-3-dehydroshikimic acid **31** resulted in slow irreversible inactivation. In this case, the enzyme-inhibitor adduct observed by mass spectrometry revealed an additional mass of 154 ± 5, possibly corresponding to the formation of adduct **34**, where the inhibitor is bound by both an imine linkage and an active site nucleophile **(**Fig. (**4**)). This adduct was postulated to be derived from the dehydroshikimate **31** by formation of an imine followed by conjugate attack at C-2 and subsequent elimination of the bromide substituent.

Next, Abell and co-workers designed and prepared alkene **35** (Scheme (**14**)) and oxime **37** (Scheme (**15**)) as analogues of the enolate intermediate **3** that is characteristic of the type II dehydroquinase mechanism (Scheme (**2**)). Compounds **36** and **38** were also prepared as controls to assess the importance of the *endo* methylene and oxime functionalities in **35** and **37**, respectively, to inhibitor activity (Schemes (**14**) and (**15**)) [29]. In particular, compounds **35** and **36** were designed to study the effect of the partial flattening of the six-membered ring caused by the double bond between C-2 and C-3 of the intermediate **3** (Scheme (**2**)) [29].

The enolate intermediate in the reaction catalysed by the type II enzyme results in a certain degree of ring flattening. As such it was thought that *endo* methylene **35** may be a transition state analogue for type II dehydroquinase. Compound **36**, identical to **35** but lacking the double bond, was prepared as a control. The electronegative oxime functionality of **37** was intended to mimic the negative



Scheme 14. i. PhCHO, $TsOH.H_2O$, benzene, 75%; ii. NBS, AIBN, benzene, 86%; iii. TBDMSCl, DBU, MeCN, 83%; iv. TBAF, THF, 88%; v. NaOMe, MeOH, 96%; vi. Amberlite IR-120 (H), 99%; vii. H_2, Pt, H_2O, 97%.



Scheme 15. i. ref [28]; ii. NaOMe, MeOH; iii. $HONH_3Cl$, NaOAc, MeCN, H_2O; iv. TBAF, THF; v. NaOH, H_2O, 61%; vi. ref [35]; vii. TFA, H_2O; viii. NaOH, H_2O; ix. Amberlite IR-120 (H), H_2O, 76%.

Table 1. Inhibition Constants (μM) for Compounds 35-38 Against Types I and II Dehydroquinase

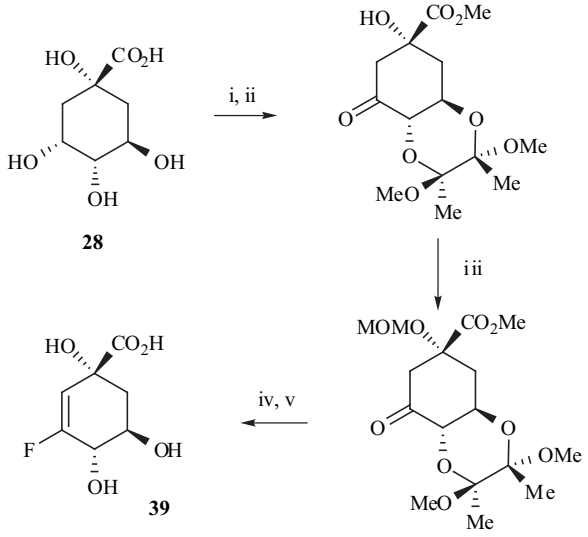
Enzyme	K_m	K_i for 35	K_i for 36	K_i for 37	K_i for 38
Type I *S. typhimurium*	18	3000 ± 000	4500 ± 500	>25000	>25000
Type II *A. nidulans*	150	60 ± 10	1500 ± 200	2200 ± 100	15 ± 2
Type II *M. tuberculosis*	64	200 ± 20	1200 ± 200	700 ± 200	20 ± 2
Type II *S. coelicolor*	650	30 ± 10	600 ± 200	2500 ± 500	500 ± 200

charge of the enolate intermediate **3** to allow hydrogen bonding interactions with the corresponding binding pocket of the enzyme. *Exo* methylene **38**, which lacks the oxime functionality, would not form the added binding interactions and so would not be expected to be as potent an inhibitor as the oxime.

Compounds **35-38** were assayed against type I dehydroquinase from *Salmonella typhimurium* and against type II dehydroquinase from *Mycobacterium tuberculosis*, *Aspergillus nidulans* and *Streptomyces coelicolor*. All compounds proved to be poor inhibitors of the type I enzyme (Table 1). The oxime **37** and the exo methylene derivative **38** were especially poor inhibitors of the type I enzyme with inhibition constants greater than 25000 μM, presumably due to the steric hindrance at C-3. Compounds **35-38** were also tested for inhibition against three type II dehydroquinases. The endo methylene **35** was a reasonably good inhibitor of all three enzymes, especially of dehydroquinase from *S. coelicolor* for which it showed a K_i of 30 ± 10 μM. The inhibition constants for *A. nidulans* and *M. tuberculosis* were slightly higher, and by comparison, the saturated analogue **36** was relatively inactive against dehydroquinase from *S. coelicolor* which supported the notion that a certain degree of ring-flattening is required for stabilisation of a transition state by the enzyme.

The oxime **37** and *exo* methylene **38** showed very different affinities for the type II enzymes. The oxime **37** was a potent inhibitor of dehydroquinase from *A. nidulans* (K_i = 15 ± 2 μM) and *M. tuberculosis* (K_i = 20 ± 2 μM), and considerably less potent inhibitor of the enzyme from *S. coelicolor* (K_i = 500 ± 200 μM). However the *exo* methylene compound **38** showed poor inhibitory activity against all three type II enzymes (K_i ranging from 700 to 2500 μM), possibly emphasising the importance of the hydrogen-bonding effect in the substrate of type II dehydroquinase. Hence compounds **35** and **37**, which resembled most closely the enolate intermediate involved in the type II mechanism were overall the best inhibitors of these enzymes.

Most recently, another example of a mechanism-based inhibitor of dehydroquinase has been reported [36]. A vinyl fluoride analogue of dehydroquinate **39** was synthesised as shown in Scheme (**16**), as a mimic of the proposed enolate intermediate **3** in the type II dehydroquinase catalysed reaction, and assayed against type I and type II dehydroquinases for inhibitory activity. Vinyl fluoride **39** demonstrated improved affinity for the type II enzymes, in particular it is a potent inhibitor of the dehydroquinase from *M. tuberculosis* (K_i = 10 μM). In comparison, alkene **35** (C-2/C-3 double bond) has a K_i of 200 μM, hence emphasising the importance of a vinyl fluoride moiety as an isoelectronic and isosteric replacement for an enolate anion.



Scheme 16. i. $MeC(OMe)_2C(OMe)_2$, $HC(OMe)_3$, CSA, MeOH, 79%; ii. $RuCl_3$, KIO_4, K_2CO_3, H_2O, $CHCl_3$; iii. $CH_2(OMe)_2$, P_2O_5, $CHCl_3$, 60%; iii. DAST, DME, 45%; iv. TFA, H_2O, v. NaOH, H_2O, vi. Amberlite IR-120 (H), H_2O (96%).

Finally, random screening has also been used to identify novel inhibitors of dehydroquinase. For example, in excess of 280 diaminobissulfonamide derivatives [see Fig. (5)], a class of compounds known since the 1960's, were synthesised by combinatorial methods and assayed against type II dehydroquinase from *M. tuberculosis* amongst other enzymes [37,38]. The bissulfonamides are moderate inhibitors of the type II dehydroquinase from *M. tuberculosis,* with IC_{50} values in the micromolar range.

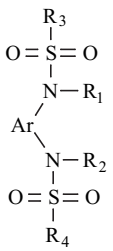
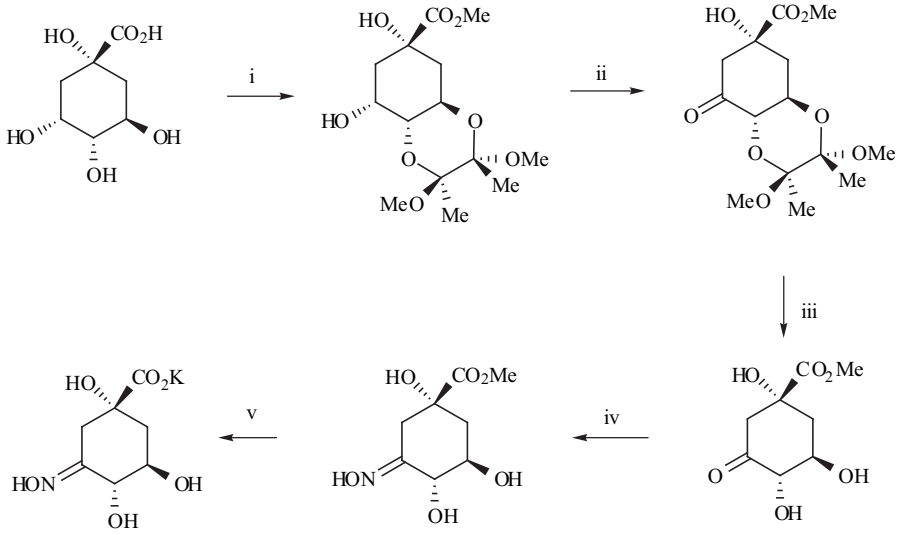


Fig. (5). The bissulfonamide series: Ar= aryl or heteroaryl; R_1 and R_2 = H or alkyl with R_1=R_2 or R_1≠R_2; or R_1 and R_2 together form a C_1-C_3 alkylene group, -CO- or –CS-; and R_3=R_4 or R_3≠R_4, with R_3 and R_4= alkyl-aryl, alkyl-heteroaryl, alkenyl-aryl, alkenyl-heteroaryl, alkynyl-aryl-alkynyl-heteroaryl, aryl or heteroaryl.



Scheme 17. i. $(COMe)_2$, $HC(OMe)_3$, MeOH, D-CSA, 76%; ii. PCC, 88%; iii. TFA, H_2O, 83%; iv. $H_2NOH.HCl$, NaOAc, 96%; v. KOH, H_2O, 97%.

Generally, these compounds inhibit type II dehydroquinase from various organisms, although their mode of interaction with the enzyme has not been described.

These derivatives are notably active against organisms that utilize the type II dehydroquinase only, and also organisms in which both the shikimate and the quinate pathways operate. In addition, examples of this class of compound are reported to be active against dehydroquinate synthetase, another enzyme of the shikimate pathway. Accordingly, the bissulfonamide class provide important leads to potential antibacterial, fungicidal or herbicidal agents. In support, examples of this class have been shown to be effective against a strain of antibiotic resistant *Staphylococcus aureus,* although the target enzyme was not identified.

COMMENTS ON THE SYNTHESIS OF INHIBITORS

It is worth noting that the efficiency of synthesis of dehydroquinate analogues has improved during the course of the inhibition studies discussed in this review. Initially, inhibitors were prepared from dehydroquinic acid which is itself obtained by a tedious and problematic oxidation of quinic acid [39,40]. The one-step protection of quinic acid by concomitant lactonisation and benzylidene acetal protection of the C-3/C-4 *cis*-diol was then introduced (see Scheme (**14**) for an example). This development facilitated the synthesis of analogues of dehydroquinate by avoiding the difficult purification steps associated with the oxidation of unprotected quinic acid, although this method was still somewhat lengthy and low yielding [28]. By contrast, the development of the butane-2,3-bisacetal (BBA) [41] protecting group for the C-4/C-5 *trans*-diol considerably simplified the preparation of analogues of dehydroquinate since it allowed the unprotected hydroxyl group at C-3 to be readily oxidised and further derivatised [42-44]. As an example, the initial synthesis of oxime **37** was achieved in 8 steps (6-9% yield) using a *cis*-diol protection strategy [29]. By comparison, the corresponding potassium salt of this oxime has recently been prepared in five steps and 50% overall yield using the BBA protecting group methodology (Scheme (**17**)) [45].

CONCLUSION

Studies on the mechanism of action of both type I and type II dehydroquinase have yielded a number of putative substrates and inhibitors of each type of enzyme. These compounds have provided both a better understanding of the mode of action of these enzymes and also a basis for the design and synthesis of more potent and specific inhibitors. The vast majority of the inhibitors of both types of dehydroquinase are analogues of dehydroquinate, thus presenting similarities with the proposed enolate intermediate in the dehydration catalysed by the type II enzyme. By contrast, random screening efforts have identified the novel bissulfonamide class of inhibitor that exhibit inhibitory activity against type II dehydroquinase from *M. tuberculosis*.

ACKNOWLEDGMENTS

We thank the Royal Society of New Zealand Marsden Fund for providing a Ph.D scholarship (MG) and a postdoctoral stipend (CLS).

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