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Herbicidal 4-hydroxyphenylpyruvate dioxygenase inhibitors—A review of the triketone chemistry story from a Syngenta perspective

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ABSTRACT

A review, outlining the origins and subsequent development of the triketone class of herbicidal 4-hydroxyphenylpyruvate dioxygenase (HPPD) inhibitors.

1. Introduction

A key objective for modern herbicide research is to discover new products that control the widest possible range of weed species, as flexibly as possible (i.e., can be applied pre- and post-emergence), and at low application rates. In addition, selective herbicides need to be safe to the target crop, and safe to the environment and end-user. The triketone herbicides stack up well against these objectives, in that both weed control spectrum and crop selectivity can be 'tuned' through chemical modification, that they are active pre-and post-emergence, and that low application rates can be achieved. Triketone herbicides have been the subject of an enormous amount of research across the agrochemical industry for many years.[1] The chemical structure of the triketones is typically based around the 2-benzoyl or 2-heteroaroyl cyclohexane-1,3-dione template. The biochemical mode of action of the triketones is inhibition of 4-hydroxyphenylpyruvate dioxygenase (HPPD), which is a key step in the biosynthesis of plastoquinone and tocopherol. Treated plants develop unique bleaching (whitening) symptoms over a few days, followed by necrosis and death.[2]

Syngenta has a long history of triketone research, with ca. 6000 active molecules in its corporate compound collection. This paper reviews the research into triketone chemistry conducted by Syngenta, including its fore-runner companies (Ciba Geigy, ICI Agrochemicals, Novartis, Sandoz, Stauffer Chemical Co, Zeneca Agrochemicals), from the original discovery and early optimisation at the Western Research Center (California, USA) through to more recent work conducted in our current research facilities in Stein (Switzerland) and Jealott's Hill (UK). As some of the work presented was conducted concurrently in different organisations and at different locations, the work has been broken down into discreet subtopics that are presented in a logical, rather than in a chronological order.

2. Discovery of the triketone herbicides

The story of the triketone herbicides began in 1977 when Reed Gray, a scientist working at the Western Research Center, California (then Stauffer Chemical), noted that fewer weeds appeared to grow under the bottlebrush plant (*Callistemon citrinus*) than in surrounding areas. As a result of this observation, he separated compounds from bottlebrush plant extracts using preparative TLC.

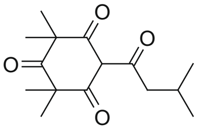

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Figure 1.

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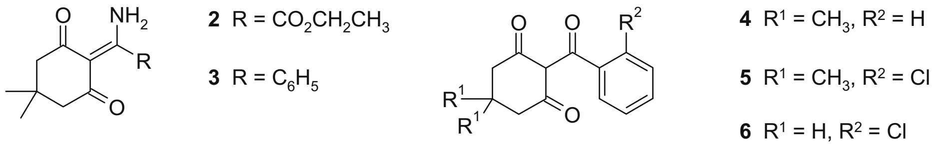
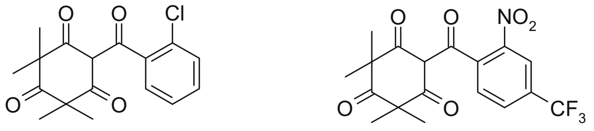


Figure 2.

Grass seeds were then germinated on the developed TLC plates, and a band of stunted, whitened grass allowed the herbicidally active constituent to be located. Structural analysis of an isolated sample of this compound revealed it to be the acyl syncarpic acid, leptospermone **1** (Fig. 1), a known natural product for which no biological activity had previously been reported.[3] Further testing of pure leptospermone in glasshouse tests showed it to be a moderately effective herbicide controlling a narrow range of weed species, predominantly grass weeds, at an application rate of 1000 g ha^{-1} or more. A small set of alkanoyl syncarpic acids were prepared and shown to exhibit similar levels of herbicidal activity to leptospermone. The herbicidal activity of leptospermone and these synthetic analogues was patented in 1980.[4]

Serendipity played more of a role in the next event leading to the discovery of the triketone herbicides. In 1982, chemists working at the Western Research Center were looking to generate novel acetyl-coenzyme-A-carboxylase inhibitors as functional mimics of the commercial herbicide sethoxydim. The enamine **2**, prepared by reaction of dimedone with ethyl cyanoformate, showed some herbicidal activity so the phenyl analogue **3** was targeted (Fig. 2). However, similar reaction of dimedone with benzoyl cyanide gave exclusively the benzoyl dimedone derivative **4**. When tested in the glasshouse, this compound showed no herbicidal activity, though it did show some antidoting effects for soyabean injury caused by thiocarbamate herbicides. As part of a programme aimed at optimising this antidoting effect, a range of analogues bearing substituted benzoyl groups were prepared. One of these compounds, the 2-chlorobenzoyl analogue **5**, was found to be weakly herbicidal. Further exploration quickly revealed that dimedone was not the optimum dione. For example, 2-chlorobenzoylcyclohexane-1,3-dione **6** showed moderate-to-good herbicidal activity against some broad-leaved weeds at 2000 g ha^{-1}. Crucially, this compound showed the same bleaching effects as leptospermone.[5]

Combining the syncarpic acid unit of leptospermone with the benzoyl moiety of **6** led to significant boosts in both the spectrum of weeds controlled and overall herbicidal potency; 2-chlorobenzoyl syncarpic acid **7** (Fig. 3) showed herbicidal activity against a wide range of broad-leaved and grass weeds at 500 g ha^{-1}. Again, the compound showed the same bleaching symptoms as leptospermone **1** and compound **6**.[6] An initial optimisation of the substitution pattern around the benzoyl group established that (i) a 2-substituent is critical for herbicidal activity, and (ii) 2,4-disubstitution is preferred, with a further preference for both substituents being electron-withdrawing groups. For example, 2-nitro-4-trifluoromethylbenzoyl syncarpic acid **8** (Fig. 3) showed good herbicidal activity in the glasshouse at an application rate 62.5 g ha^{-1} or less. The pre-emergence herbicidal activity of this compound against selected broad-leaved and grass weeds is summarised in Table 1.



7 **8**

Figure 3.

3. Synthesis and structure–activity relationships of triketone herbicides

3.1. Benzoyl syncarpic acid derivatives

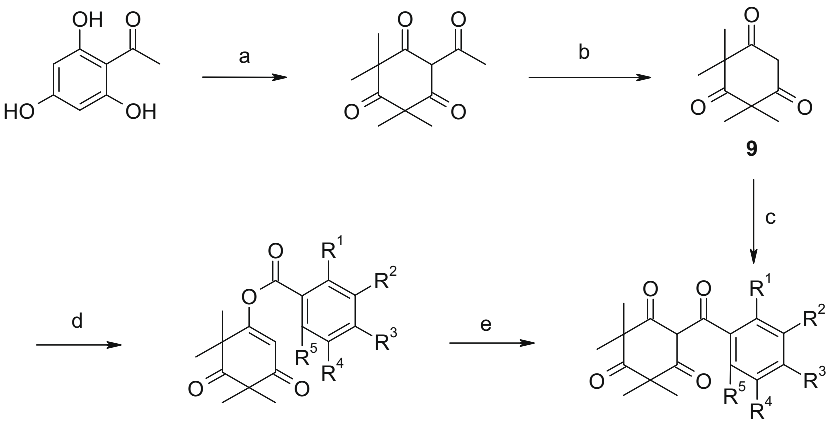
The synthetic route used to prepare a range of benzoyl syncarpic acids is outlined in Scheme 1. Firstly, syncarpic acid **9** was prepared from phloroacetophenone by exhaustive methylation followed by de-acetylation,[7] and this was then benzoylated, either directly using the appropriate benzoyl cyanide, or from the benzoyl chloride via a two-step procedure involving initial O-benzoylation followed by cyanide-catalysed rearrangement.[6] For the latter procedure, 5–10 mol % acetone cyanohydrin and triethylamine was typically used as the source of the cyanide catalyst.[6] On a large scale (>100 g), syncarpic acid was more conveniently prepared from phlorobenzophenone by exhaustive methylation followed by debenzoylation. The benzoic acids used in this work were readily available at the time, either from commercial sources or from our in-house chemical store.

An alternative route to benzoyl syncarpic acids was also investigated, which involved exhaustive methylation of the requisite phlorobenzophenone.[8] However, a major limitation of this approach was that the established method for the preparation of phlorobenzophenones (zinc chloride catalysed addition of a benzonitrile to phloroglucinol followed by acid-catalysed hydrolysis) failed when a 2-substituted benzonitrile was used.

The herbicidal activities of a representative series of substituted benzoyl syncarpic acids in glasshouse tests, which illustrate the general structure–activity relationships for these compounds, are summarised in Table 2. For ease of presentation, herbicidal activity for each compound is expressed as two numbers: the average pre-emergence ED_{90} value for a range of warm-climate broad-leaved weeds (*Abutilon theophrasti, Amaranthus retroflexus, Chenopodium album, Ipomoea hederacea* and *Xanthium strumarium*), and the average ED_{90} value for a range of warm-climate grass weeds (*Brachiaria*

Table 1
Pre-emergence herbicidal activity of compound **8** against selected warm-climate broad-leaved and grass weeds in a glasshouse test (score: 0 = no effect; 100 = complete kill)

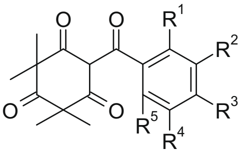
Application rate (g ha^{-1})	Broad-leaved weeds			Grass weeds		
	Chenopodium album	*Amaranthus retroflexus*	*Abutilon theophrasti*	*Sorghum halepense*	*Setaria faberi*	*Echinochloa crus-galli*
250	97	100	100	97	100	100
62.5	100	97	100	100	100	100
32	100	75	100	85	97	97
16	100	75	100	75	70	90



Scheme 1. Reagents and conditions: (a) $NaOCH_3$ (6 equiv), CH_3I (6 equiv), CH_3OH; (b) HCl (aq); (c) ArCOCN, $ZnCl_2$, $(C_2H_5)_3N$, CH_3CN; (d) ArCOCl, $(C_2H_5)_3N$, CH_2Cl_2, rt; (e) $(CH_3)_2C(OH)CN$ (5–10 mol %), $(C_2H_5)_3N$, CH_3CN, rt.

Table 2

Herbicidal activities of a range of benzoyl syncarpic acids (activity is expressed as average pre-emergence ED_{90} values for warm-climate grass and broad-leaved weed control—see text for description)



Compound no.	R^1	R^2	R^3	R^4	R^5	ED_{90} grass weeds (g ha^{-1})	ED_{90} broad-leaved weeds (g ha^{-1})
10	H	H	H	H	H	>4000	$\gg$4000
11	OCH_3	H	H	H	H	1450	>4000
12	CH_3	H	H	H	H	727	1718
13	OCF_3	H	H	H	H	815	3199
14	$OCHF_2$	H	H	H	H	264	989
15	CF_3	H	H	H	H	317	1799
16	NO_2	H	H	H	H	69	582
17	NO_2	OCH_3	H	H	H	3359	2912
18	Cl	OC_2H_5	H	H	H	1307	$\gg$4000
19	NO_2	Cl	H	H	H	557	840
20	NO_2	H	Cl	H	H	60	197
21	NO_2	H	CN	H	H	126	254
8	NO_2	H	CF_3	H	H	36	133
22	NO_2	H	CH_3	H	H	1323	452
23	NO_2	H	OCH_3	H	H	200	684
24	CN	H	OCH_3	H	H	2893	2541
25	CF_3	H	CF_3	H	H	317	495
26	Cl	H	Cl	H	H	205	343
27	Cl	H	I	H	H	107	1496
28	Cl	H	CN	H	H	96	462
29	Cl	H	OCH_3	H	H	1292	>4000
30	CH_3	H	OCH_3	H	H	3399	2851
31	CH_3	H	CN	H	H	35	108
32	OCH_3	H	NO_2	H	H	340	3199
33	Cl	H	H	Cl	H	3063	1638
34	Cl	H	H	H	Cl	>4000	>4000

plantaginea, Echinochloa crus-galli, Setaria faberi, Setaria viridis and *Sorghum halepense*); these are the application rates in g ha^{-1} required to give an average of 90% control of each set of relevant weeds in a pre-emergence dose–response test. It should be borne in mind that many of the active compounds also show good post-emergence activity.

A 2-substituent is an absolute requirement for good herbicidal activity, with a preference for this being an electron-withdrawing group when this is the only substituent (compounds **10**–**16**). The monosubstituted analogues **11**–**16** show a bias towards grass control, with 2-nitrobenzoyl syncarpic acid **16** clearly being the most active compound. Combining an electron-withdrawing group at the 2-position with an electron-releasing alkoxy group at the 3-position gives rise to very poor activity (compounds **17** and **18**). In contrast, modest activity is seen for the 2-nitro-3-chloro analogue **19**. Combining the 2-nitro substituent with an electron-withdrawing group at the 4-position gives rise to highly active compounds (**20**, **21** and **8**) which show good potency on both grass and broad-leaved weeds; compounds containing electron-releasing groups at the 4-position (**22** and **23**) are less potent, though the methoxy compound (**23**) shows reasonable activity. In marked contrast to the nitro group, 2-cyano-substituted compounds show poor activity, as illustrated by compound **24**. 2,4-Bis-(trifluoromethyl)benzoyl syncarpic acid **25** shows an activity similar to that of the 2,4-dichloro analogue **26**. A trend similar to that seen with the 2-nitro-4-substituted compounds (**19**–**23**) is observed for 2-chloro-4-substituted analogues (**26**–**29**), in that the best activity is seen when the 4-substituent is an electron-releasing group (though the 4-iodo compound **27** is unusually weak against broad-leaved weeds). As might be expected, the 2-methyl-4-methoxy compound (**30**) shows poor activity, though combining a 2-methyl substituent with a powerfully electron-withdrawing 4-cyano substituent gives rise to potent herbicidal activity (compound **31**). However, the 2-methoxy-4-nitro analogue (**32**) showed only modest activity against grass weeds, performing poorly against the broad-leaved weeds. Finally, both the 2,5-dichloro- and 2,6-dichloro analogues (**33** and **34**, respectively) are weak herbicides compared to the 2,4-dichloro analogue (**26**).

Although excellent herbicidal activity was observed for many of these compounds (some were progressed to advanced field trials), other factors prevented their development as commercial herbicides. Firstly, whilst the spectrum of weed control was ideal for the US maize market, none of the compounds showed sufficient selectivity to maize to be used in that crop. Secondly, many of the compounds (particularly the more potent ones) were very persistent in soil, which could have given rise to environmental concerns.

In an attempt to overcome these issues empirically, some limited structural modifications were made to the syncarpic acid moiety. Firstly, the effective removal of one of the methyl groups was achieved via a modification of the syncarpic acid synthesis in which only 3 equiv of methyl iodide was used in the methylation step, allowing acetyl methylfilicinic acid **35** to be isolated in ca. 40% yield.[7] This was then converted to target compounds **36** as illustrated in Scheme 2.

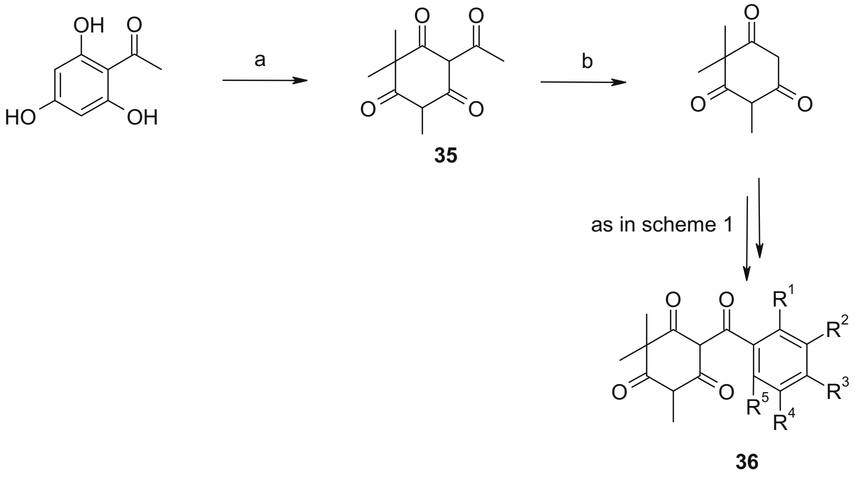
The benzoyl methylfilicinic acids **36** thus prepared were virtually devoid of herbicidal activity; subsequent work on the X-ray crystal structures of a diverse set of triketone herbicides bound to plant-derived HPPD indicates that the dienolic form of these compounds may make unfavourable interactions at the herbicide binding site, which might explain the lack of activity of these compounds.[9] Intriguingly, ring ethylation of the benzoyl methylfilicinic acids **36** afforded 1-carbon-extended homologues that were significantly less active than the parent syncarpic acids.[10] The benzoyl methylfilicinic acids **36** could be ring brominated adjacent to the isolated methyl substituent, and these bromo derivatives could then be converted to the corresponding methoxy analogues using the methods described by Balwe et al.[11] Again, these bromo and methoxy compounds showed virtually no herbicidal activity, most probably due to their general chemical instability.

3.2. 2-Substituted and 2,4-disubstituted benzoylcyclohexane-1,3-diones

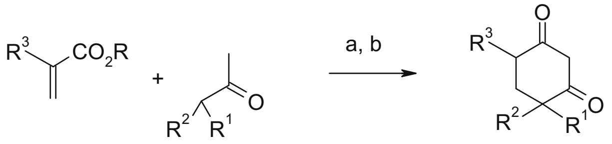
Comparison of the structures of two of the early lead compounds **6** (cyclohexane-1,3-dione) and **7** (syncarpic acid) led us to investigate a series of benzoyl cyclohexane-1,3-diones with differing levels of methylation on the cyclohexanedione ring. Initially, 2-substituted and 2,4-disubstituted benzoyl derivatives were considered, as benzoic acids with these substitution patterns were readily available and had already been shown to give rise to good herbicidal activity. Thus, 4-methyl-, 4,4-dimethyl, 4,6-dimethyl- and 4,4,6-trimethylcyclohexane-1,3-diones (**37**, **38**, **39 and 40,** respectively) were prepared by reaction of an acrylate or methacrylate ester with the appropriate methyl ketone in an apolar solvent (e.g., toluene) in the presence of a molar equivalent of a base (e.g., sodium ethoxide), as outlined in Scheme 3.[12] 4,4-6,6-Tetramethylcyclohexane-1,3-dione **41** was prepared from 4,4,6-trimethyl-cyclohexane-1,3-dione **40** via formation of the dianion with lithium di-isopropylamide followed by quenching with 1 equiv of methyl iodide (Scheme 4).[12]

These diones, together with cyclohexane-1,3-dione itself, were benzoylated with a range of 2-substituted and 2,4-disubstituted benzoyl chlorides using the O-acylation/rearrangement sequence outlined in Scheme 1, to provide a range of dione-methylated benzoyl cyclohexane-1,3-diones for testing as herbicides. Cyclohexane-1,3-dione and all of the methylated diones **37**–**41** afforded active molecules, with the relative potencies of the benzoyl moieties largely paralleling the pattern observed for the benzoyl syncarpic acids described above. In fact, for structure–activity purposes the structures of these benzoyl cyclohexane-1,3-diones were found to be separated into two distinct parts: the benzoyl moiety and the dione (Fig. 4), with each part being found to play distinct, different and independent roles in the overall expression of herbicidal activity.[12] As such, the herbicidal activities of these compounds could be described by a Free-Wilson type summation of quantitative descriptors for the benzoyl and dione moieties.[13]

As mentioned previously, early structure–activity work had indicated a preference for one or both of the benzoyl 2- and 4-substituents to be electron-withdrawing groups. Based on this, an extensive study was conducted into the relationship between herbicidal activity and Hammett sigma value for these substituents for this set of triketones. A key finding from this work was that a nitro group at the benzoyl 4-position seemed to be an outlier, in that it appeared to be much less active than might have been expected.[5] This apparent loss of herbicidal activity was speculated to be due

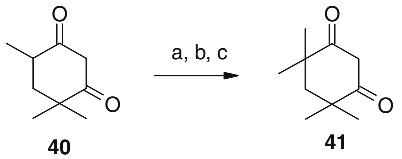


Scheme 2. Reagents and conditions: (a) NaOCH$_3$ (3 equiv), CH$_3$I (3 equiv), CH$_3$OH; (b) HCl (aq).



37: $R^1 = CH_3$, $R^2 = R^3 = H$
38: $R^1 = R^2 = CH_3$, $R^3 = H$
39: $R^1 = R^3 = CH_3$, $R^2 = H$
40: $R^1 = R^2 = R^3 = CH_3$

Scheme 3. Reagents and conditions: (a) $NaOCH_2CH_3$, $C_6H_5CH_3$; (b) HCl (aq).



Scheme 4. Reagents and conditions: (a) $LiN(CH(CH_3)_2)_2$ THF; (b) CH_3I; (c) HCl (aq).

to metabolic reduction, as work on other herbicides had previously demonstrated this group to be potentially metabolically labile in plants and/or soils,[14] so alternative 4-substituents with similar Hammett sigma values, but which might also be more stable to metabolism, were sought. One such replacement was the methanesulfonyl group, which has a sigma value of 0.72 cf. 0.78 for the nitro group. The one-pot synthetic route devised for the synthesis of 4-methanesulfonyl benzoic acids, which involved reduction of a sulfonyl chloride to the sulfinate salt, alkylation with chloroacetic acid and subsequent decarboxylation, is illustrated for 2-chloro-4-methanesulfonyl benzoic acid **42** in Scheme 5.[15] This chemistry is compatible with other 2-substituents such as nitro and alkyl. Longer chain alkylsulfones were similarly prepared by alkylation of the sulfinate with the appropriate α-halo alkanoic acid and subsequent decarboxylation. Satisfyingly, the 4-methanesulfonyl compounds thus prepared showed excellent herbicidal activity in glasshouse tests, restoring the trend between herbicidal activity and the Hammett sigma value; 4-ethanesulfonyl compounds also showed very good activity, though activity then began to tail off for longer chain or branched chain alkyl groups.[5]

A more up-to-date interpretation of the structure–activity relationships around the benzoyl group is simply that there is an overriding requirement for the aryl ring to be electron deficient, an observation that we can now rationalise, at least to some degree, through favourable interactions between the inhibitor and the enzyme binding site due to pi-stacking with two phenylalanine residues (residues 381 and 424 in HPPD from *Arabidopsis thaliana*), on the basis of X-ray crystallographic studies.[9] Although there is an absolute requirement for the aryl ring of the benzoyl group to be electron deficient, there are limits to the degree of electron deficiency that can be tolerated. If the ring is too electron deficient and contains a displaceable 2-substituent, then cyclisation to a fused dihydroxanthone occurs. Such 2-substituents that are readily displaced include fluoro, chloro, bromo, nitro and alkoxy groups.[5] This cyclisation is blocked by the introduction of a methyl group at the 2-position, and excellent activity can be maintained for these methyl compounds providing that the other substituents on the benzoyl group lead to the aryl ring being electron deficient.[1]

For this set of benzoyl cyclohexane-1,3-diones substituted at the benzoyl 2- and 4-positions, the effects of substitution on the benzoyl group are to modulate the overall herbicidal potency, but tend to have little effect on changing the spectrum of weeds controlled. In contrast, the substitution pattern on the dione moiety has a significant impact on the spectrum of weed control. This is illustrated in Table 3 for a series of dione-substituted 2-chloro-4-

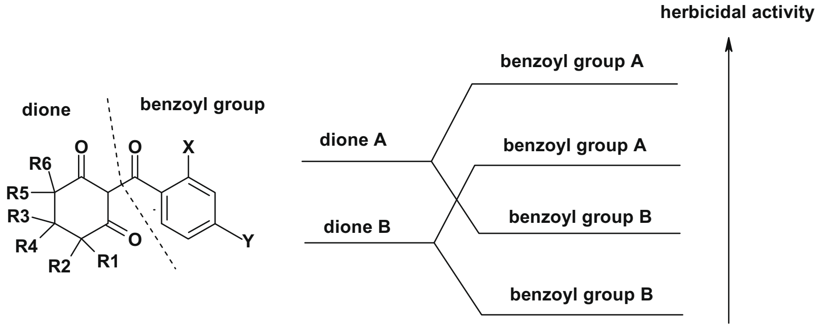
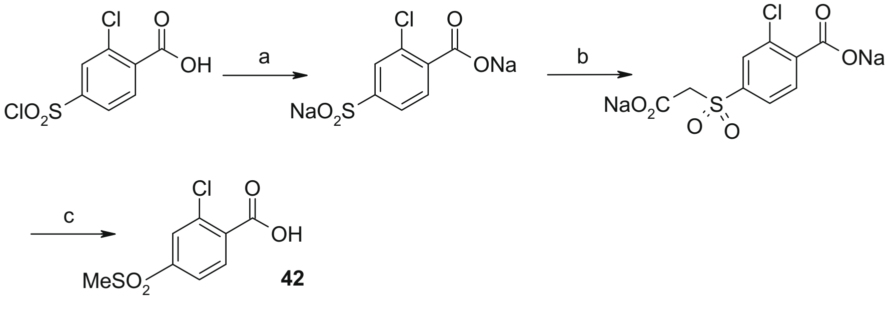


Figure 4. Segmentation of the SAR for the benzoylcyclohexanedione herbicides.



Scheme 5. Reagents and conditions: (a) Na_2SO_3, $NaHCO_3$, H_2O, 75 °C; (b) chloroacetic acid, NaOH, 105 °C; (c) 3 M HCl.

methanesulfonylbenzoyl cyclohexane-1,3-diones **43**–**47**, all of which have broadly comparable intrinsic binding constants to the target HPPD enzyme.

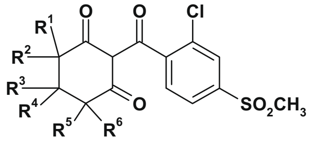
The functional effect of removing substituents from the dione is to open up potential sites for metabolism by plants. Studies using model compounds indicated that a principal route of metabolism by plants is hydroxylation at the 4-position of the cyclohexanedione moiety (if this position is blocked, then oxidation takes place at the chemically equivalent 6-position), and it was shown that placing two methyl groups at the 4-position of the cyclohexanedione slows down this process compared to the unsubstituted cyclohexanedione.[16] Thus, as substituents are removed, there is a greater potential for herbicidal activity to be reduced through *in planta* metabolism. This potentiation of herbicidal activity is more evident in grass weeds than in broad-leaved weeds; although herbicidal activity against broad-leaved weeds is effectively unchanged, activity against grass weeds is reduced significantly as substituents are sequentially removed (Table 3).[12,13]

Increasing the potential for metabolism of benzoyl cyclohexane-1,3-diones also has other consequences. Selectivity to maize is increased, and soil persistence is reduced. The overall effect is to shift from non-selective, broad-spectrum, persistent benzoyl syncarpic acids to benzoyl cyclohexane-1,3-diones which are maize selective, (predominantly) broad-leaved weed herbicides that have desirable short soil half-lives (DT_{50} values), and this is where the first commercial triketone herbicides emerged. The first benzoyl cyclohexane-1,3-dione to be commercialised was sulcotrione **47**, a selective herbicide used for the control of broad-leaved weeds in European maize markets. Sulcotrione was registered for use by Zeneca (now Syngenta) in 1993.[17]

Mesotrione **48** (Fig. 5) was subsequently launched by Syngenta in 2001 into the US and European maize markets, under the brand name CALLISTO®. When applied pre- and post-emergence, mesotrione provides control of all the important broad-leaved weeds in maize together with suppression/control of some of the annual grass weeds. Typical use rates for mesotrione range from 100 to 225 g ha^{-1} when applied pre-emergence, and 70–150 g ha^{-1} for post-emergence applications.[18] Oxidative metabolism of the dione was identified as a key factor contributing to the maize selectivity of mesotrione,[13,19] though two other factors were also found to play significant roles: mesotrione is intrinsically more potent against HPPD derived from dicotyledenous (broad-leaved) plant species than that derived from monocotyledenous (grass) plant species,[19] and the compound is taken up more slowly into maize foliage than into susceptible weeds following post-emergence application.[13]

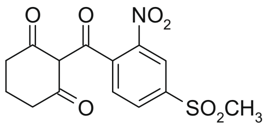
Table 3

Effects of dione substitution on pre-emergence herbicidal activity against grass weeds



Compound no.	R^1	R^2	R^3	R^4	R^5	R^6	ED_{50} grasses[a] (g ha^{-1})
43	CH_3	CH_3	CO		CH_3	CH_3	20
44	CH_3	CH_3	H	H	CH_3	CH_3	20
45	CH_3	CH_3	H	H	H	H	60
46	CH_3	CH_3	H	H	H	H	75
47	H	H	H	H	H	H	150

[a] Application rate required to provide an average control rating of 50% for *Digitaria sanguinalis*, *Echinochloa crus-galli*, *Setaria faberi*, *Setaria viridis* and *Sorghum halepense*.



48

Figure 5. Structure of mesotrione.

To complete the picture regarding structure–activity relationships of triketones derived from methylated cyclohexane-1,3-diones, benzoyl 5-methylcyclohexane-1,3-diones were investigated. 5-Methylcyclohexane-1,3-dione was prepared from acetone and ethyl 2-butenoate using the method illustrated in Scheme 3, and this was benzoylated using the O-acylation/rearrangement sequence (cf. Scheme 1). Although dimedone had been found to be a poor dione in the original discovery work, 5-methylcyclohexane-1,3-dione gave rise to compounds which often showed comparable herbicidal activity to those derived from cyclohexanedione itself.

2-Benzoyl cyclohexane-1,3-diones bearing longer alkyl chains were also investigated, using analogous chemistry to that described above. With the exception of 4-ethyl compounds, some of which showed reasonable herbicidal activity, these longer chain compounds were usually rather less active than the corresponding methylated derivatives. Other cyclohexanedione substitutions and further dione modifications are discussed in Section 3.3, below.

3.3. Alternative 2-benzoyl-1,3-diones

Triketones bearing methyl substituents on the cyclohexanedione ring were discussed in Section 3.2. A limited amount of further work was carried out in order to investigate the effects of introducing heteroatom-linked substituents. A series of compounds **49** (Fig. 6) bearing sulfur substituents at the 4-position of the cyclohexane-1,3-dione were prepared. The requisite 4-alkylthiocyclohexane-1,3-dione was obtained from an alpha-alkylthioketone and an appropriately substituted acrylate ester (cf. Scheme 3), and this was then benzoylated via O-acylation and cyanide-catalysed rearrangement. The alkylthio moiety could then be oxidised to the corresponding sulfone using 3-chloroperoxybenzoic acid.[20] In a variation of this chemistry, spirocyclic analogues **50** were prepared starting from cyclic methyl ketones **51** (Fig. 6).[21] Although many of these compounds showed reasonable herbicidal activity, they were not pursued further as they offered no advantages over less elaborate cyclohexane-1,3-diones.

A series of N-linked 5-amido-, carboxamido- and ureido derivatives **52** were obtained by Raney-Nickel-catalysed reduction of the appropriate amino-resorsinol derivative, followed by benzoylation (Scheme 6).[22] These compounds showed only moderate herbicidal activity, and were not pursued further.

Carbocyclic rings other than six-membered rings were also investigated. The standard O-acylation and cyanide-catalysed rearrangement procedure works equally well for cyclopentane-1,3-diones. Intriguingly, 2-benzoyl cyclopentane-1,3-diones **53** (Fig. 7) were invariably found to be significantly weaker herbicides than the corresponding cyclohexanediones, and were often completely inactive. The benzoylated squaric acid **54** was prepared from 3-isopropoxy-4-(tri-*n*-butylstannyl)cyclopropenedione and 2,4-dichlorobenzoyl chloride using the Pd–Cu-catalysed acylation method described by Liebeskind et al.[23] This compound showed no herbicidal activity.

Heteroatom-containing diones received a good deal of attention. A series of benzoylated mono- di-, tri- and tetra-methyl-substituted 2*H*-pyran-3,5-(4*H*,6*H*)-diones **55** (Fig. 8) were targeted, the latter as structural mimics of benzoyl syncarpic acids.

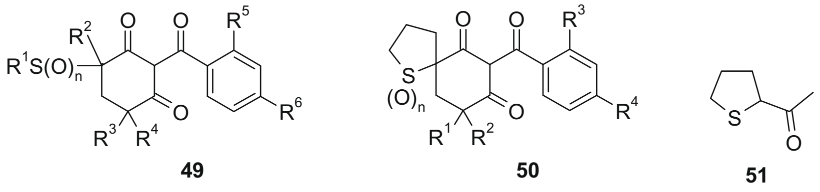
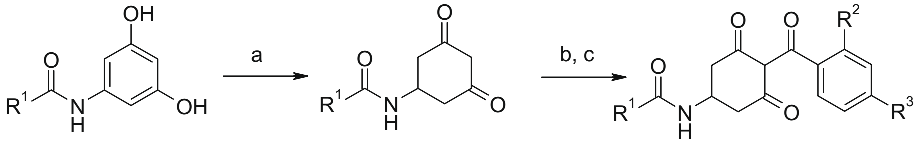

49 **50** **51**

Figure 6.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Scheme 6. Reagents and conditions: (a) Ra-Ni-H_2O, H_2, 1 M NaOH, 65 °C, 10 bar, 18 h; (b) ArCOCl, $(C_2H_5)_3N$, CH_2Cl_2, rt; (c) $(CH_3)_2C(OH)CN$ (5–10 mol %), $(C_2H_5)_3N$, CH_3CN, rt.

4-Methyl- and 4,4-dimethylpyran-3,5-(4*H*,6*H*)-dione were prepared by the method described by Morgan et al., which involves mercury-catalysed hydration of 3-carboxymethoxy-1-butyne and 3-carboxymethoxy-3-methyl-1-butyne, respectively, followed by Dieckman cyclisation to the dione.[24] The tri- and tetra-methyl pyrandiones were more conveniently prepared by reaction of 2,2,5-tri- and 2,2,5,5-tetramethyltetrahydrofuran-4,5-dione with ethyl diazoacetate, followed by ester hydrolysis and decarboxylation.[25] These diones were then benzoylated using the standard O-acylation/cyanide-catalysed rearrangement procedure.[26] Thiopyran anlogues **56** (Fig. 8) were also prepared. Mono- di-, tri- and tetra-methyl-substituted 2*H*-thiopyran-3,5-(4*H*,6*H*)-diones were prepared by base-catalysed cyclisation of the appropriately substituted acetylmercaptoacetic ester, and these were then benzoylated using the O-acylation/cyanide-catalysed rearrangement procedure.[26] Only a handful of 2-benzoyl piperidine-3,5-diones **57** were prepared; as for the thiopyrans, these were prepared by cyclisation of the appropriate acyclic keto-ester intermediate, followed by benzoylation.[26]

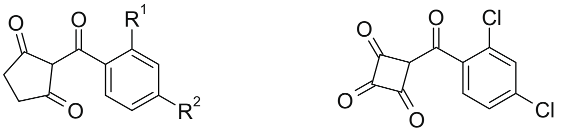
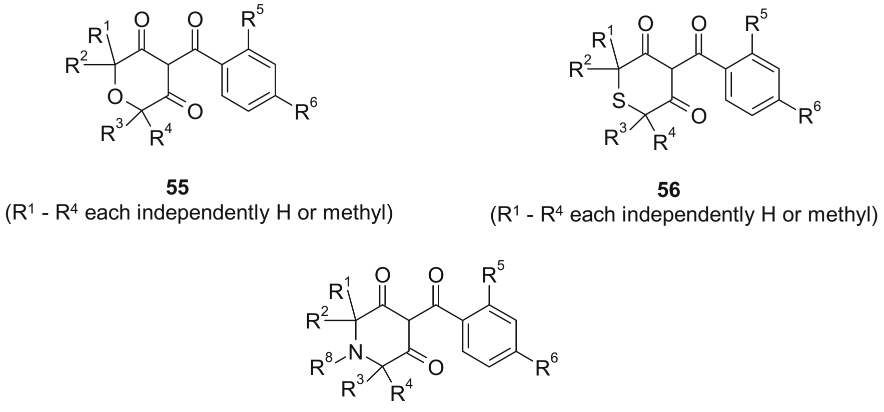

53 **54**

Figure 7.

The pyrandiones **55** generally showed good herbicidal activity, with potency and weed control spectrum increasing with the degree of methylation. Many of the tetramethyl compounds showed comparable broad-spectrum herbicidal activity to the corresponding syncarpic acids. However, these tetramethylpyrandiones also suffered from problems same as those of the syncarpic acids, namely no useful crop selectivity and potentially long half-lives (DT_{50} values) in soil. Interestingly, the trimethylpyrandiones also showed good activity, unlike the methylfilicinic acids described in Section 3.1. In contrast to the pyrandiones, thiopyrandiones **56** and piperidinediones **57** only showed weak herbicidal activity in glasshouse tests.

As the tetramethylpyrandiones showed good herbicidal activity, 4-benzoyl-2,6,6-trimethyl-2*H*-1,2-oxazine-3,5-diones **58** (Fig. 9) were investigated as potential isosteres, in which the weak N–O bond might offer some potential for metabolic degradation via reduction. The requisite trimethyloxazinedione was prepared by base-catalysed acylation of ethyl 2-methyl-2-(methylamino)oxypropionate by monoethyl malonyl chloride, followed by sodium


55
(R^1 - R^4 each independently H or methyl)

56
(R^1 - R^4 each independently H or methyl)

57
(R^1 - R^4 each independently H or methyl)

Figure 8.

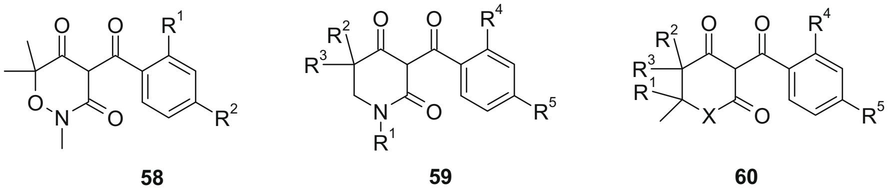


Figure 9.

methoxide-mediated cyclisation and ester hydrolysis and decarboxylation. Benzoylation using the standard conditions afforded the desired triketone analogues **58**.[27] A series of 3-benzoyl piperidine-2,4-diones **59** were also prepared. The starting diones were prepared via addition of the appropriate beta-amino acid to diketene, followed by sodium methoxide-mediated cyclisation and acid-catalysed de-acetylation, in an analogous fashion to that described by Lee et al. for the corresponding five-membered tetramic acids.[28] Both oxazinediones **58** and piperidinediones **59** showed promising herbicidal activity in early stage glasshouse tests, though this activity failed to hold up in more advanced tests.

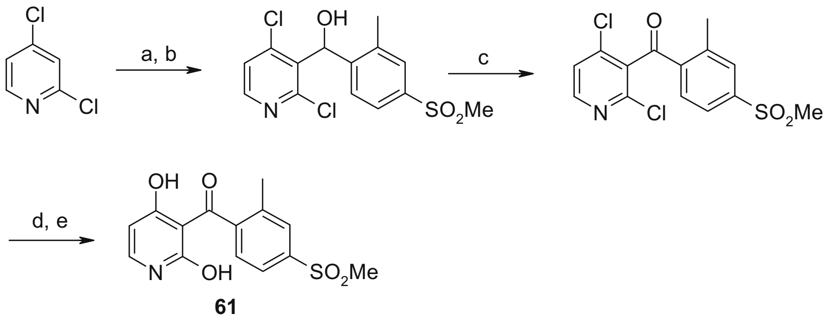
A series of benzoyl lactones (**60**; X = O) and thiolactones (**60**; X = S) were also prepared from available pyrandiones and thiopyrandiones, respectively.[29] These compounds showed only weak activity in glasshouse herbicide tests. 3-Benzoyl tetramic and tetronic acids (i.e., five-membered analogues of **59** and **60** (X = O)) were also prepared, and found to be devoid of herbicidal activity. Acyclic triones also showed no useful herbicidal activity.

Alpha-benzoyl hydroxy aromatics were also investigated as potential analogues of triketones. By far the most active compounds found were 3-benzoyl-2,4-dihydroxypyridines, for example, **61**, prepared as shown in Scheme 7.[30] However, these compounds were, at best, only moderately active as herbicides. Weak herbicidal activity was also found with some 2-benzoylphenols.

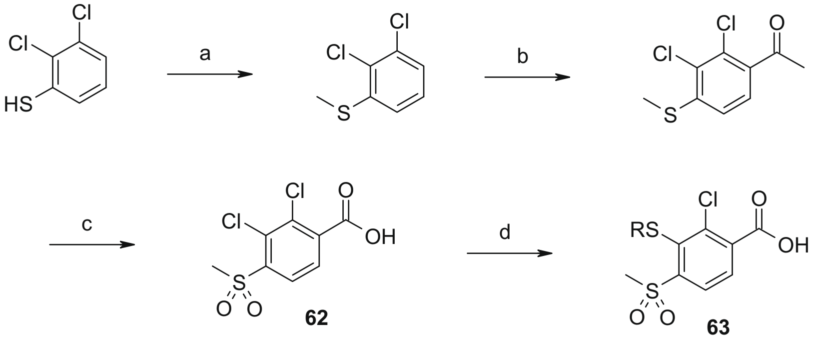
3.4. 2-(2,3,4-Trisubstituted) benzoylcyclohexane-1,3-diones

As a follow-up to the excellent activity against broad-leaved weeds seen for the 2-substituted-4-methanesulfonylbenzoyl cyclohexanediones (Section 3.2), attention turned to the preparation of analogues bearing more highly functionalised benzoyl groups. Given that the early structure–activity work had clearly shown that substitution at the 5- and 6-positions virtually eliminated activity, 2,3,4-trisubstituted compounds were specifically targeted. The initial focus of this work was around heteroatom-linked substituents, as it was reasoned that such compounds could be readily obtained via aromatic nucleophilic substitution of 2,3-dichloro-4-methanesulfonyl benzoic acid **62**.

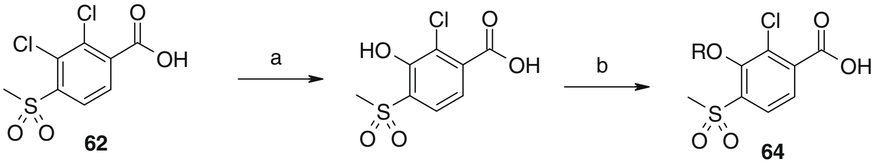
The synthesis of the starting benzoic acid **62** from 2,3-dichlorobenzenethiol in three steps is illustrated in Scheme 8. The 3-chloro substituent of this acid was found to be displaced by thiol nucleophiles to afford 3-S-linked substituted benzoic acids **63** directly (Scheme 8); some concomitant nucleophilic displacement of the 4-methanesulfonyl group was also observed.[31] These aryl sulfides could then be oxidised to sulfoxides and sulfones using standard conditions. The first method to be developed for the preparation of 3-O-linked substituted benzoic acids **64** was via displacement of chloride by hydroxide, followed by O-alkylation and subsequent de-esterification of the ester thus produced (Scheme 9).[31] Subse-



Scheme 7. Reagents and conditions: (a) $LiN(CH(CH_3)_2)_2$, THF, −70 °C, 45 min; (b) substituted benzaldehyde, THF, −70 °C, 1 h, (c) MnO_2, $C_6H_5CH_3$, 120 °C; (d) $NaOCH_2C_6H_5$ (3 equiv), THF, −20 °C to rt; (e) H_2, 10% Pd–C, dioxane, rt, 5 h.



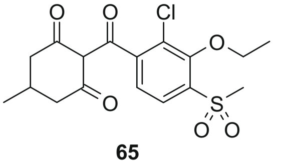
Scheme 8. Reagents and conditions: (a) CH_3I, K_2CO_3, CH_3CN, 80 °C; (b) CH_3COCl; $AlCl_3$, CH_2Cl_2, 5 °C; (c) NaOCl, dioxane, 80–100 °C; (d) alkyl sulfide, NaOH, H_2O, 100 °C, 24 h.



Scheme 9. Reagents and conditions: (a) 20% NaOH (aq), 100 °C, 7 h; (b) alkyl iodide, K_2CO_3, DMF, 90 °C, 7 h; (c) NaOH, C_2H_5OH, rt 16 h.

quent work showed that the 3-chloro substituent of 2,3-dichloro-4-methanesulfonyl benzoic esters could be directly displaced by alkoxides under reasonably forcing conditions.

Once obtained, these trisubstituted benzoic acids were coupled up to cyclohexane-1,3-dione using the O-acylation/cyanide rearrangement sequence, to afford the trisubstituted benzoyl cyclohexane-1,3-diones.[32] The herbicidal activities of compounds bearing a sulfur-linked substituent were generally disappointing; at best these compounds showed significantly reduced activity relative to the compound lacking the 3-substituent. However, simple 3-alkoxy derivatives were found to show potent herbicidal activity and—significantly—the pattern of activity observed was very different to that for the corresponding 3-unsubstituted compounds; the spectrum of weed control shifted more towards control of warm climate grass weeds rather than control of broad-leaved weeds, and the compounds were much more active when applied post-emergence rather than pre-emergence. Many of the compounds also showed good selectivity to maize.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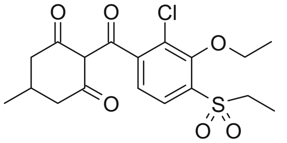
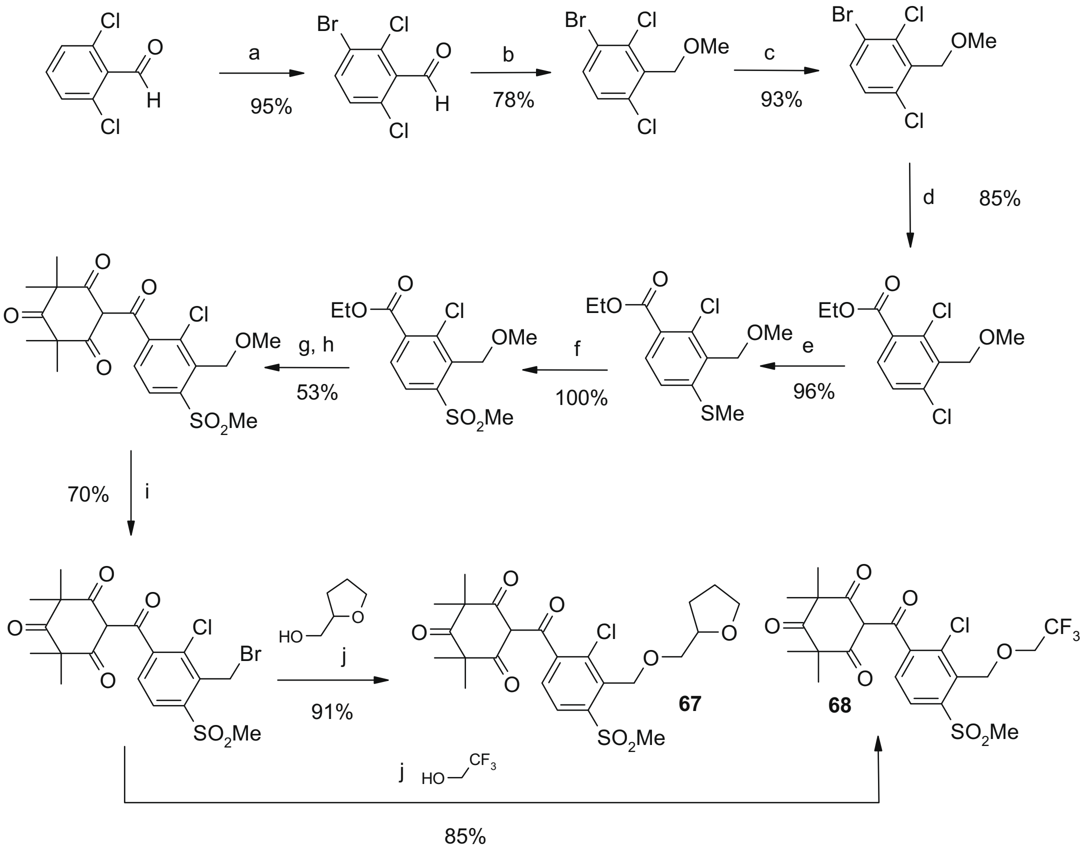
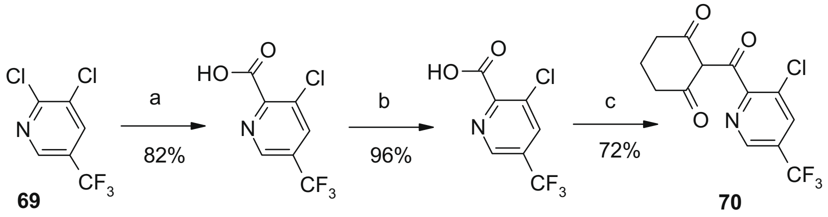

66

Figure 10.

The subsequent exploration of the detailed structure–activity relationships in this sub-series of triketones focussed on optimising the maize graminicide activity through variation of three parts of the molecule: the 3-alkoxy group; the length and nature of the alkyl group of the 4-alkanesulfonyl substituent and the cyclohexanedione moiety. In terms of structure–activity relationships, as far as the substituents on the benzoyl group are concerned the principal conclusions from this study were: there is a preference for short-chain alkyl groups on the 4-alkanesulfonyl substituent, with activity falling off markedly beyond ethyl or upon introducing branched alkyl groups; and there seems to be scope for introducing larger alkoxy groups (e.g., *n*-propoxy, *n*-butoxy and methoxyeth-



Scheme 10. Reagents and conditions: (a) $AlCl_3$, Br_2 rt; (b) $NaBH_4$, MeOH, THF, rt; (c) KOH/18-C-6 (cat.), THF, MeI, rt; (d) 100 °C under 50 bar CO in EtOH contg. Et_3N (3 equiv) and $(Ph_3P)_2PdCl_2$ (0.05 equiv); (e) NaSMe, DMF, rt; (f) $CH_3CO_3HCH_2Cl_2$, 0 °C; (g) LiOH, H_2O/MeOH, rt; (h) DCC, CH_3CN, rt, 1 h, then add Et_3N (2 equiv), acetonecyanohydrin (0.1 equiv); (i) BBr_3 ,CH_2Cl_2, 0 °C; (j) KOH/18-C-6 (cat.), THF, rt.



Scheme 11. Reagents and conditions. (a) 100 °C under 50 bar CO in EtOH contg. Et_3N (3 equiv) and $(Ph_3P)_2PdCl_2$ (0.05 equiv); (b) 2 N NaOH, rt; (c) DCC, CH_3CN, rt, 1 h, cyclohexanedione then add Et_3N (2 equiv).

oxy), although such compounds are no more active than simple methoxy or ethoxy analogues. With reference to the dione, excellent control of grass weeds was seen for many of the substituted diones, though in general the lesser-substituted ones were found to be preferred over more highly substituted ones; lesser-substituted diones also seemed to offer the most potential in terms of maize selectivity. In fact, following a significant amount of more advanced testing, two compounds emerged as having the best balance of grass control and crop selectivity: **65** and **66** (Fig. 10), both of which are 5-methylcyclohexanediones. Both compounds performed well in advanced field trials, though neither compound was ultimately selected for development as a commercial herbicide.

Once our initial patents appeared in this area, it rapidly became apparent across the agrochemical industry that a diverse range of substituents might be introduced at the benzoyl 3-position of triketone herbicides, and a multitude of analogues bearing novel substituents at this position started to appear in the patent literature.[1] Hoechst (now Bayer Crop Science) were especially active in this area, and one type of 3-substituent to emerge from their intensive research effort was an alkoxymethyl moiety.[33] We were also able to obtain intellectual property in this field by selecting highly substituted diones not covered by the earlier patent applications; the compounds targeted were syncarpic acids such as **67** and **68**, analogues of the Bayer development compounds tembotrione and tefuryltrione, which were prepared by the novel route shown in Scheme 10.[34] Although compounds of this type turned out to be highly active herbicides, extensive testing showed them to be inferior to the 3-alkoxy derivatives discussed above.

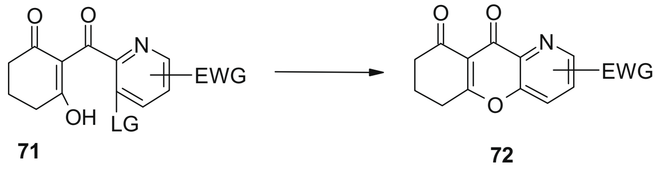


Figure 11. Deactivation of pyridyl triketone herbicides by cyclisation.

3.5. 2-Heteroaroyl cyclohexanediones

In the early mid-1980s Ciba Geigy,[35] ICI[36] and Stauffer[37] (all now Syngenta) had been interested in heterocyclic analogues of triketones, and each group had developed a specific emphasis on pyridines. In particular, chemists in Switzerland had developed access to such acids by selective carbonylation of the dichlorotrifluoromethyl pyridine intermediate **69** (Scheme 11). Subsequent conversion to the triketone **70** afforded a compound that showed reasonable post-emergence herbicidal activity against broadleaved weeds, albeit at relatively high rates (>500 g ha^{-1}).

As mentioned in Section 3.2, a problem with compounds of type **71** is that the pyridine *ortho*-substituent is a leaving group on an electron-deficient aromatic ring system, and thus intramolecular ring closure can occur leading to compounds **72** that are not active herbicides (Fig. 11). Nippon Soda solved this problem by utilising electron-deficient pyridines such as **73**, **74** and **75** (Fig 12), that contain an *ortho*-methyl substituent, which obviously cannot function as a leaving group.[38]

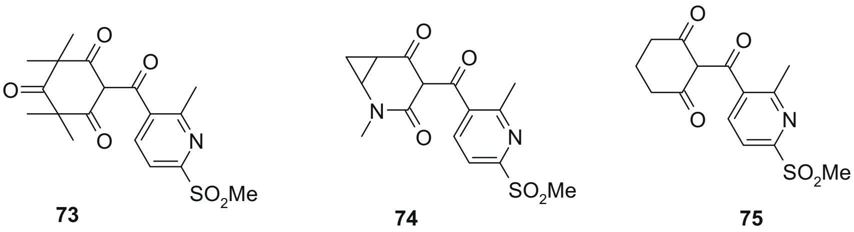
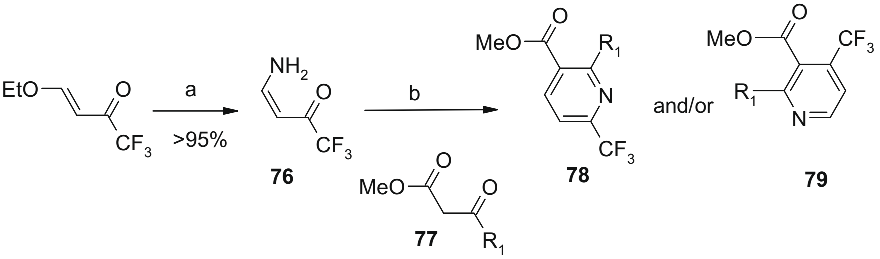


Figure 12.



Scheme 12. Reagents and conditions: (a) NH_3 (aq), CH_3CN, rt; (b) CF_3CO_2H (0.1 equiv), toluene, reflux.

Surprisingly, pyridyl triketones containing such an *ortho*-methyl substituent combined with a trifluoromethyl substituent—a substituent known to give rise to favourable herbicidal activity in the aryl series (cf. Section 3.2) - had hitherto not been explored. We investigated compounds of this general structural type by following up an observation by Okada et al., who had been trying to prepare 2,6-disubstituted trifluoromethyl nicotinoyl derivatives **79** by condensation of β-trifluoroacetylvinylamine **76** with active methylene compounds **77** (Scheme 12).[39]

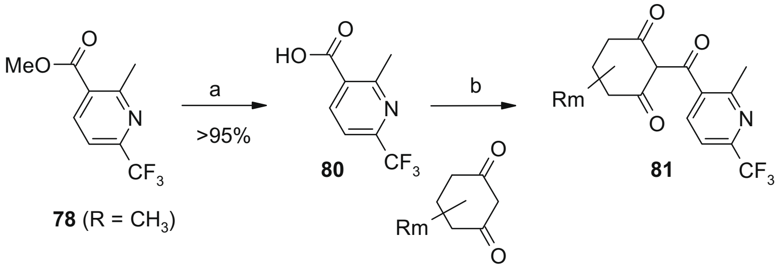
To their surprise, depending on the nature of the R^1 group, mixtures of the unexpected isomeric pyridine **78** as well as the expected isomer **79** were obtained. In the case of R^1 = methyl, the unexpected isomer **78**, in which the trifluoromethyl group attached to the carbon adjacent to the nitrogen in the starting material **77** is transposed from nitrogen by one carbon in the product **78**, was the only compound obtained. We recognised the favourable 2,4-substitution pattern of the pyridine, containing a small non-leaving group at the 2-position, as a potentially novel building block for triketone chemistry. The hitherto unknown nicotinic acid **80** was readily prepared by hydrolysis of the ester, and after coupling to diones by the standard methodology this acid afforded access to the first examples of the nicotinoyl subclass of triketone HPPD inhibitors bearing trifluoromethyl substituents (general structure **81**, Scheme 13).[40]

In glasshouse tests, the unsubstituted cyclohexanedione **82** (Fig. 13) showed very good post-emergence control of key broad-leaved weeds and suppression of some of the key grass weeds in maize and cereals, whilst remaining selective to both crops (Table 4). Pre-emergence herbicidal activity in maize (Table 5) was rather less impressive, which could at least in part be correlated to rapid degradation in soil (in model laboratory studies the compound had a measured half-life (DT_{50}) of 2 days). Initially, analogues in which the 2-methyl substituent was varied were obtained by the method outlined in Scheme 12, utilising different R^1 groups for β-ketoester **77**. After coupling to cyclohexane-1,3-dione, it was shown that a methyl substituent was superior to larger alkyl and phenyl substituents (i.e., Me > Et > *i*-Pr ≫ Ph/Heteroaryl). Having established methyl as a good 2-substituent, the effect of increasing methyl substitution on the cyclohexane dione ring was studied (compounds **83**, **84**, **85** and **86**; Fig. 13), as this was known to increase activity by blocking potential sites of metabolism (cf. Section 3.2). As can be seen from Tables 4 and 5, although post-emergence broad-leaved weed control in glasshouse tests was not greatly affected, pre-emergence activity against these weeds increased dramatically, along with pre- and post-emergence activities against grass weeds. However, phytotoxicity to maize also tended to increase with increasing substitution. Despite this, compound **83** was deemed to be sufficiently selective for it to be tested in advanced field trials as a potential pre-emergence grass herbicide for maize. The compound did not advance into further development as the pre-emergence weed control under field conditions proved insufficient, again most likely due to a relatively short soil half-life (DT_{50}) of only 8–10 days in model laboratory studies.

As a next step, the effect of the position of the nitrogen atom in the heterocyclic ring on herbicidal activity was investigated. The isomeric pyridine analogues **87** and **88** were prepared as shown in Schemes 14 and 15, respectively.

As can be seen from Table 4 (compare compounds **84**, **87** and **88**), the ranking of the relative herbicidal activities of these pyridyl isomers was as depicted in Figure 14.

At this stage, it was known that 2,3(*N*),4-substituted pyridyl (i.e., nicotinoyl) triketones were the most active isomers, and that



Scheme 13. Reagents and conditions: (a) LiOH, H_2O/MeOH, rt; (b) DCC, CH_3CN, rt, 1 h, then add Et_3N (2 equiv), acetonecyanohydrin (0.1 equiv).

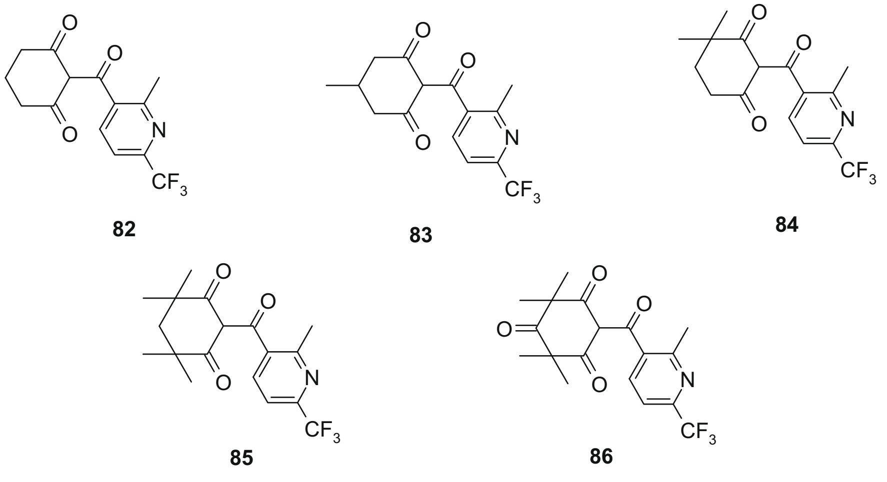


Figure 13.

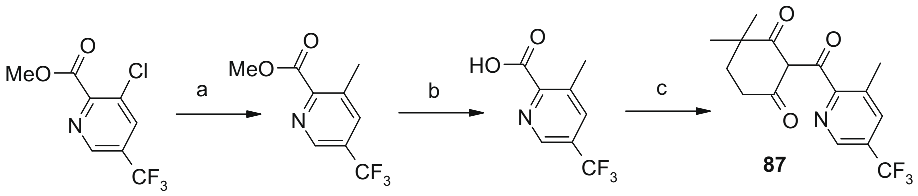
Table 4
Post-emergence herbicidal activity of compounds **82**–**88** against important broad-leaved and grass weeds in maize and cereals at 125 g ha^{-1} (score: 0 = no effect; 100 = complete kill)

Compound	Grass weeds in maize			Broad-leaved weeds in maize			Broad-leaved weeds in cereals		% Injury maize	% Injury cereals
	Setaria faberi	*Digitaria sanguinalis*	*Echinochloa crus-gatti*	*Abutilon theophrasti*	*Xanthiim strunarium*	*Amaranthus retroflexus*	*Chenopodium album*	*Sinapis arvensis*		
82	60	60	80	100	90	90	100	80	10	0
83	90	90	90	90	80	90	90	90	50	60
84	90	90	90	90	90	90	90	100	60	50
85	90	80	80	90	90	90	90	90	80	50
86	100	90	90	90	90	100	100	100	90	90
87	20	40	50	60	80	80	100	20	0	0
88	10	60	60	80	0	50	10	10	10	5

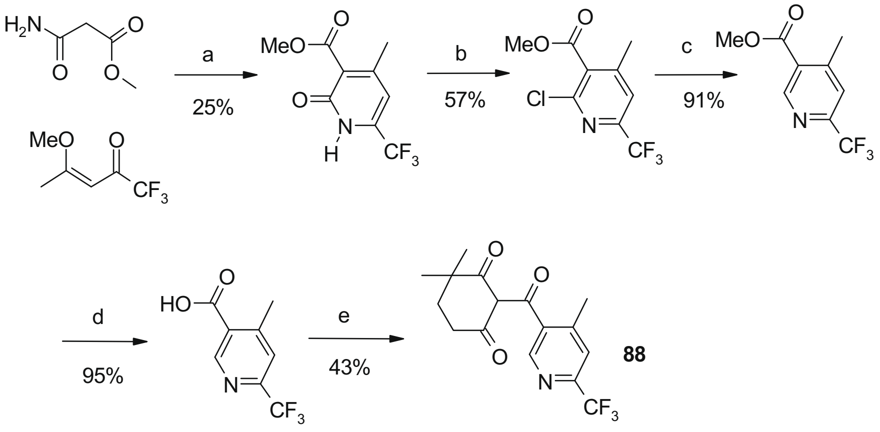
Table 5
Pre-emergence herbicidal activity of compounds **82**–**86** against important broad-leaved and grass weeds in maize at 125 g ha^{-1} (score: 0 = no effect; 100 = complete kill)

Compound	Grass weeds in maize			Broad-leaved weeds in maize			% Injury maize
	Setaria faberi	*Digitaria sanguinalis*	*Echinochloa crus-galli*	*Abutilon theophrasti*	*Xanthiim strunarium*	*Amaranthus retroflexus*	
82	20	60	10	60	20	20	0
83	100	100	100	90	80	60	40
84	90	100	100	100	80	60	50
85	80	100	90	100	80	90	20
86	100	100	100	100	80	100	60

herbicidal activity could be boosted by increasing methyl substitution in the dione ring, but that the activity of compounds with low soil half-lives (e.g., compound **83**) was insufficient when applied pre-emergence under field conditions. The syncarpic acid derivative **86** was very active in our glasshouse screens (Tables 4 and 5). However, the selectivity of this compound in both maize and cereals was found to be very low due to metabolic deactivation of the dione portion being completely blocked for the syncarpic acid moiety. Moreover, this compound was very persistent in soil, with a measured half-life (DT_{50}) of >100 days in model laboratory studies, this again likely being due to extremely slow metabolic breakdown of the highly substituted dione ring. It was therefore



Scheme 14. Reagents and conditions: (a) $PdCl_2[P(Ph)_3]_2$ (5%), K_2CO_3 (3 equiv), trimethylboraxine, dioxan, reflux; (b) LiOH, H_2O/MeOH, rt; (c) DCC, CH_3CN, 5,5-dimethylcyclohexane-1,3-dione (1 equiv) rt, 1 h, then add Et_3N (2 equiv), acetone cyanohydrin (0.1 equiv).



Scheme 15. Reagents and conditions: (a) $NaOCH_3$, CH_3OH, reflux; (b) $PhOP(O)Cl_2$, 170 °C; (c) $HC(O)O^-NH_4^+$, 10% Pd/C, MeOH, rt; (d) LiOH, H_2O/MeOH, rt; (e) DCC, CH_3CN, 5,5-dimethylcyclohexane-1,3-dione (1 equiv) rt, 1 h, then add Et_3N (2 equiv), acetone cyanohydrin (0.1 equiv).

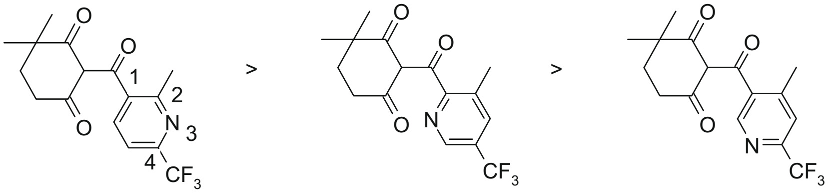


Figure 14. Relative herbicidal potencies of isomeric pyridyl triketones.

envisaged that it might be possible to improve crop selectivity and re-introduce some degree of soil degradation by introducing metabolic 'weak points' into the pyridyl moiety, enabling some metabolism to take place (Fig. 15).

The strategies devised for preparing nicotinoyl triketones functionalised at the 2-position (type **89**) are shown in Figure 16. It was not possible to prepare compounds of type **89** by derivatisation of a pre-formed triketone **92** as intramolecular cyclisation occurred when leaving groups were attached to the methyl group leading to cyclised products **93** and **94**. Therefore, the 2-chloromethyl acid **90**, which could be isolated as a stable, crystalline compound, was subjected to nucleophilic displacement with a range of O-, S- or N-centred nucleophiles, using specially developed reaction conditions (Scheme 16). The nicotinic acids prepared were then readily coupled with syncarpic acid to give a range of products with the generic structure **89**.[41]

The strategy employed to modify the trifluoromethyl substituent of the pyridine ring required preparation of the nicotinic ester **95** or pre-formed triketone **96** containing a difluorochloromethyl group. The chlorine atom could then be used as a handle to prepare derivatives of type **97** via single electron transfer or radical reaction chemistry, combined with standard chemical transformations (Fig. 17).[42]

Representative examples of single electron transfer chemistry[43] that was carried out on ester **95** are shown in Scheme 17. Each of the nicotinic esters prepared (**95**, **98**, **99**, **100**, **101** and **102**) were hydrolysed and coupled to syncarpic acid to give the required target molecules of type **97**. Examples of nicotinoyl syncarpic acids

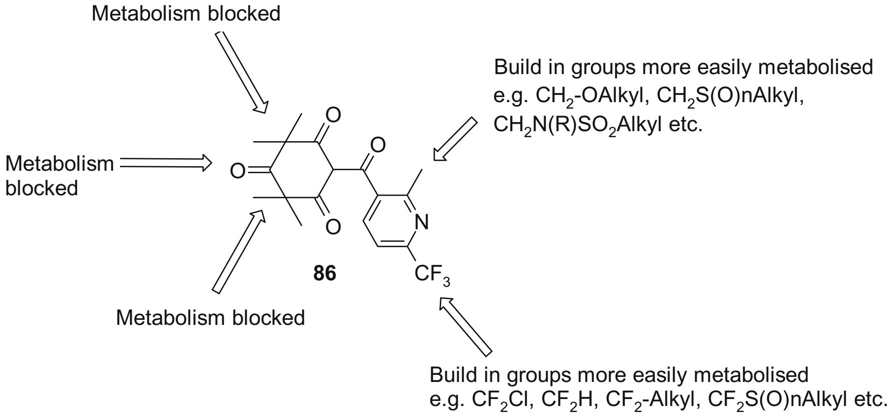


Figure 15. Strategies for improving crop selectivity of nicotinoyl syncarpic acid **86** through enhanced metabolic degradation.

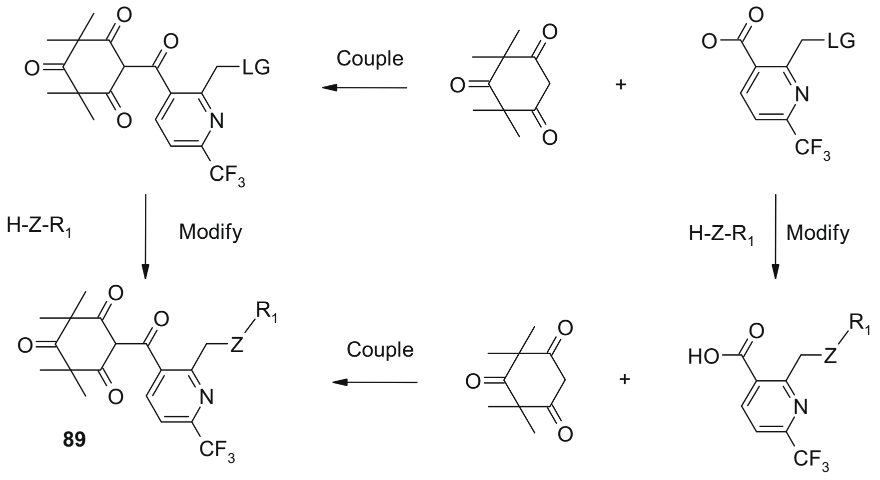
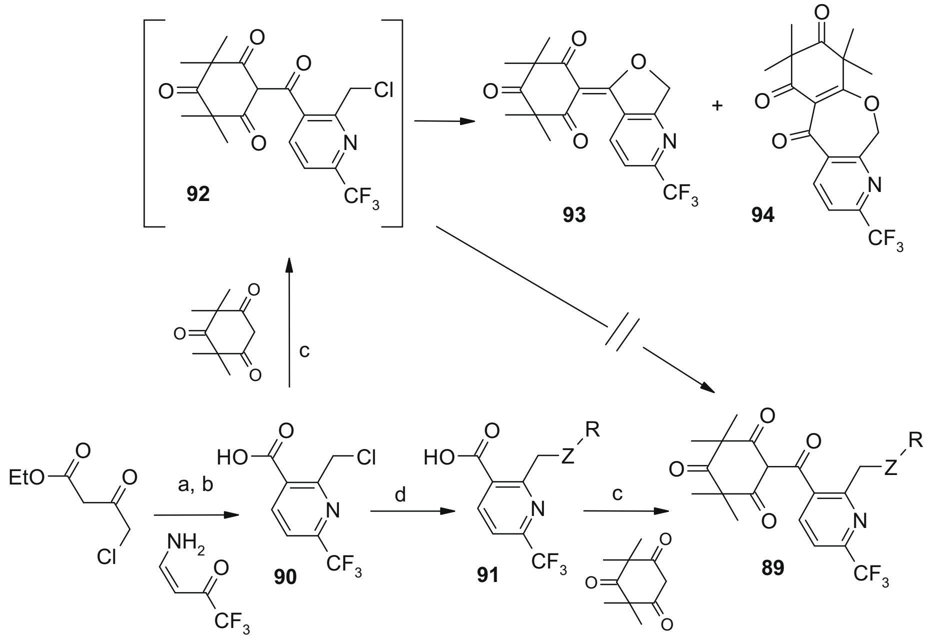


Figure 16. Chemical strategies for the preparation of functionalised nicotinoyl triketones **89**.



Scheme 16. Reagents and conditions: CF_3CO_2H (0.1 equiv), toluene, reflux; (b) LiOH, H_2O/MeOH, rt; (c) DCC, CH_3CN, syncarpic acid (1 equiv) rt, 1 h, then add Et_3N (2 equiv), acetonecyanohydrin (0.1 equiv); (d) KOH/18-C-6 (cat.), THF, R-ZH, rt.

prepared using free radical reactions as the key steps are shown in Scheme 18. Once again, the compounds **103**, **104**, **105** and **106** shown in Scheme 18 are representative examples; other derivatives were prepared through further chemical modification of the compounds shown.

The general conclusions around structure–activity relationships for these compounds are as follows. Substituents larger than hydrogen or fluorine on the CF_2 group at the nicotinic 6-position were found to be not well tolerated, giving rise to compounds that are significantly less active herbicides than the trifluoro- and difluoromethyl analogues. However, at the nicotinoyl 2-position, larger –CH_2–Z–R substituents were found to be much better tolerated, with herbicidal activity generally decreasing in the order –$CH_2OR > CH_2NR^1R^2 > CH_2SR$. Importantly, evidence that the principle of re-introducing crop selectivity through building metabolic 'weak points' into the non-selective lead compound **86** is a viable strategy, at least in part, is illustrated by two examples (Fig. 18). The pre- and post-emergence herbicidal activities of compound **86** and the 2-ethoxymethyl derivative **107** at 125 g ha^{-1} in maize are compared in Table 6. It can clearly be seen that the herbicidal activity against the weeds is comparable for the two compounds, but that compound **107** causes significantly less damage to maize than compound **86** (40% less damage in both pre- and post-emergence applications). Similarly, the post-emergence herbicidal activities of compound **86** and the difluoromethyl derivative **103** at an application rate of 30 g ha^{-1} in maize and cereals are compared in Table 7. Again, although weed control for the two compounds was comparable, an equally impressive reduction in

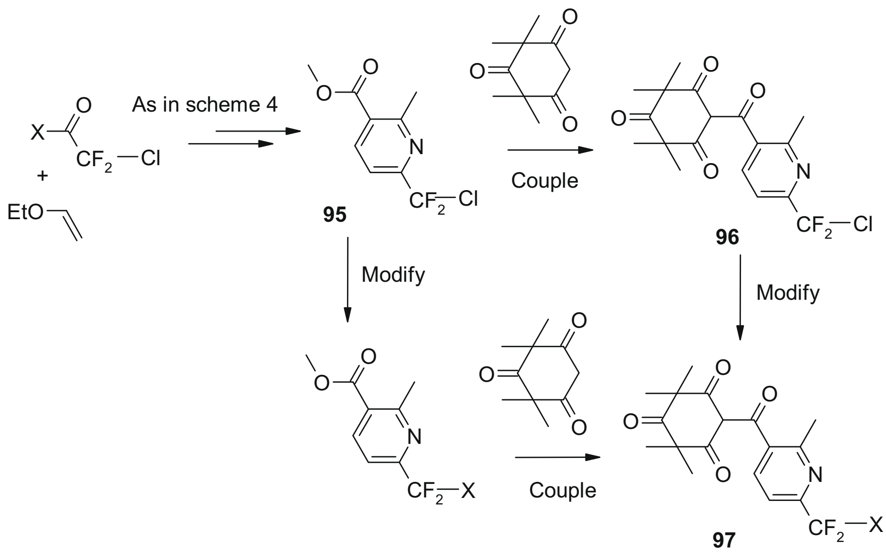
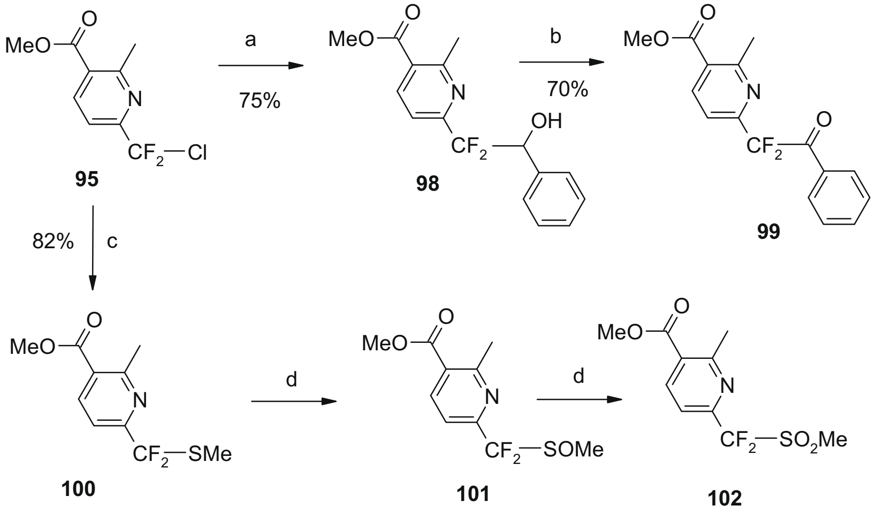


Figure 17. Strategies for the preparation of CF2X-substituted nicotinoyl triketones **97**.

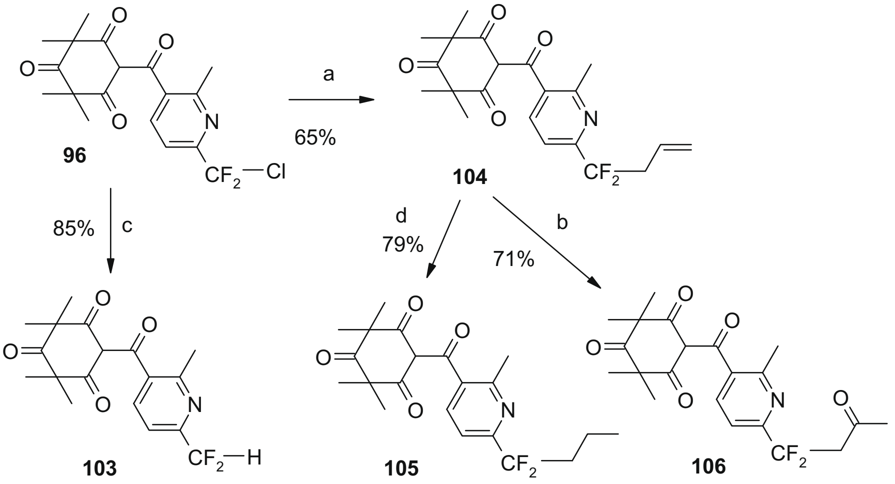


Scheme 17. Reagents and conditions. (a) tetrakis(dimethylamino)ethylene, PhCH=O, DMF, rt; (b) tetrapropylammoniumperuthate (0.05 equiv), *N*-methylmorpholineoxide, 4 Å MS, CH_2Cl_2, rt; (c) NaSMe, DMF, rt; (d) CH_3CO_3H (1 equiv), CH_2Cl_2, rt.

cereal crop damage (50%) is observed for compound **103** relative to compound **86**. Compound **103** was tested extensively in the field in cereal crops, but ultimately did not make it into further development. Thus, although neither compound **103** nor **107** were sufficiently selective to progress further towards development, these results clearly demonstrate that there is rich scope within the nicotinoyl class of triketone HPPD inhibitors to prepare highly active molecules that have the potential for commercialisation. This requires fine-tuning of substituents, not only on the nicotinoyl portion but also on the dione moiety, to give the optimal balance of herbicidal activity, crop selectivity and environmental safety.

4. Mode of action of the triketone herbicides

The triketone maize herbicide sulcotrione **47** was at first believed to act by inhibiting the phytoene desaturase (PDS) step in



Scheme 18. Reagents and conditions: (a) tributylallyltin, toluene, AIBN (cat), 80 °C; (b) $CuCl/PdCl_2$ (cat.), O_2, DMF/H_2O; (c) $(TMS)_3SiH$, toluene, AIBN (cat), 80 °C; (d) Pd/C (10%), H_2, 1 atm, MeOH.

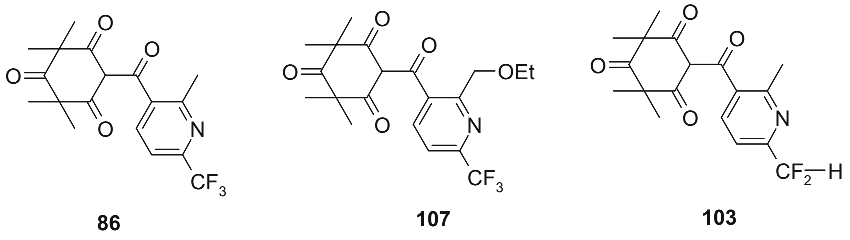


Figure 18.

Table 6
Pre- and post-emergence herbicidal activities at 125 g ha^{-1} of compounds **86** and **107** against important grass and broad-leaved weeds in maize (score: 0 = no effect; 100 = complete kill)

Application	Compound	Grass weeds in maize			Broad-leaved weeds in maize			% Injury maize
		Setaria faberi	*Digitaria sanguinalis*	*Echinochloa crus-galli*	*Abutilon theophrasti*	*Xanthium strumarium*	*Amaranthus retroflexus*	
Pre-em	**86**	100	100	100	100	80	100	60
	107	90	100	90	100	90	90	20
Post-em	**86**	100	90	90	90	90	100	90
	107	90	80	90	100	90	90	50

Table 7
Post-emergence herbicidal activity of compounds **86** and **103** against important grass and broad-leaved weeds in corn and cereals at 30 g ha^{-1} (score: 0 = no effect; 100 = complete kill)

Compound	Grass weeds			Broad-leaved weeds				% Injury maize	% Injury cereals
	Setaria faberi	*Digitaria sanguinalis*	*Echinochloa crus-galli*	*Abutilon theophrasti*	*Stellaria media*	*Amaranthus retroflexus*	*Chenopodium album*		
86	80	90	90	90	100	90	100	60	60
103	90	80	80	90	90	90	90	60	10

carotenoid biosynthesis.[44] Clues to the true mode of action came from toxicological studies indicating that rats fed with experimental triketone herbicides such as 2-(2-nitro-4-trifluoromethylbenzoyl)-cyclohexane-1,3-dione (NTBC; nitisinone) exhibit both increased levels of tyrosine in blood and also of *p*-hydroxyphenylpyruvate (HPP) in urine. This suggested a block in the catabolic degradation of tyrosine and further investigative work went on to show that nitisinone is a potent inhibitor of mammalian *p*-hydroxyphenylpyruvate dioxygenase (HPPD) which (Fig. 18) catalyses the oxidative decarboxylation and rearrangement of HPP to homogentisate (HGA), the first commited step in tyrosine degradation.[45,46] It was soon shown that triketone herbicides are also potent inhibitors of the HPPD enzyme in plants.[2,47] However whereas HPPD-dependent tyrosine degradation is a process common across aerobic organisms HPPD inhibitors are uniquely toxic to plants. In plants, the HGA product of the HPPD reaction is not only an intermediate in tyrosine degradation but also an essential intermediate in the pathways to the biosynthesis of tocopherols and plastoquinone (PQ).[48] Alternative prenyl transferase enzymes HGA solanesyltransferase (HST) or HGA phytyltransferase (HPT) located in the inner plastid envelope convert HGA to 2-methyl-6-solanyl-1,4-benzoquinone (MSBQ) or 2-methyl-6-phytyl-1,4-benzoquinone (MPBQ), respectively. These precursors are further methylated (by a single enzyme, MSBQ/MPBQ methyltransferase, common to both pathways) to yield, respectively, PQ or, in the case of the tocopherol pathway, 2,3-dimethyl-6-phytyl-1,4-benzoquinone which then gives rise to γ-and α-tocopherol (the dominant tocopherol in leaves) via further steps of cyclisation and methylation.[49] Tocopherols are important antioxidants and PQ serves not only as an essential electron transporter between photosystem II and photosystem I but is also a cofactor for the activity of PDS in carotenoid biosynthesis.[50] Not surprisingly therefore the herbicidal triketone inhibitors of HPPD cause stunting and bleaching effects on plants which appear visually very similar to the effects of PDS-inhibitor herbicides. It is clear however that HPPD is the unique site of action of triketone herbicides since (i) co-application of exogenous HGA to plants can prevent HPPD-inhibitor herbicide induced bleaching,[2,47] (ii) the phytoene accumulating Arabidopsis mutant, PDS1 maps to HPPD, exhibits a homozygous lethal bleaching phenotype and is also uniquely rescuable by addition of HGA[51] and (iii) expression of heterologous HPPDs in transgenic plants results in specific tolerance to 'HPPD-inhibitor' herbicides.[52] Whereas the downstream steps of the PQ and tocopherol biosynthesis pathways are localised in the plastid membranes Arabidopsis HPPD appears to be localised in the cytosol[53] and analysis of the single HPPD gene coding sequence of Arabidopsis by PSORT yields no conclusive prediction that it comprises a transit peptide leader sequence. Native HPPDs purified from maize seedlings[54] and also carrot cells[53] appear to be N-terminally proteolysed with, for example, the native maize HPPD having a 21-amino acid N-amino acid truncation relative to the coding sequence of the full length cDNA.

The herbicidal effects of HPPD-inhibitor triketones arise predominantly due to depletion of PQ. PQ is an essential electron acceptor in the PDS step of carotenoid biosynthesis and, accordingly, PQ levels are observed[55] to decrease in plants treated with HPPD herbicides ahead of the onset of bleaching and phytoene accumulation. The main role of carotenoids is in the light-harvesting antenna structures of photosynthetic tissue where they act to quench high energy triplet states of chlorophyll which would otherwise generate singlet oxygen. Herbicide-induced depletion of carotenoids is associated with light-dependent generation of singlet oxygen which damages lipids and proteins and causes disassembly of the photosynthetic complex and release of free chlorophyll. Free chlorophyll is photodynamically photodestructive and itself generates further singlet oxygen eventually leading to the destruction of all leaf pigments and the characteristic white bleaching. Direct inhibition of electron transport from PSII due to depletion of PQ may also have a bearing on the phytotoxic effects of HPPD inhibitors in mature tissues[56] and may possibly also underpin the observed synergy between PSII and HPPD inhibitor herbicides.[57] While tocopherol may have a role in protecting PSII reaction centres from singlet oxygen[58] it is clear that tocopherol depletion is not a major factor in triketone herbicide mode of action since various tocopherol-deficient mutants of Arabidopsis, vte2 (HPT), vte1 (tocopherol cyclase) and vte3-1 (an MSBQ/MPBQ point mutant deficient only in tocopherols) exhibit quite normal phenotypes.[49,59]

In recent years there has been rapid progress in understanding of both HPPD enzyme structure[54,60–62] and catalysis.[63–66] The reaction catalysed by HPPD (Fig. 19) involves oxidative decarboxylation, hydroxylation of the aromatic ring and a 1, 2 migration of the carboxymethylene group. The pyruvyl side chain is decarboxylated to a carboxymethylene group which then migrates to the adjacent carbon of the phenyl ring while the ring is hydroxylated on the carbon at the original point of side-chain attachment. Dur-

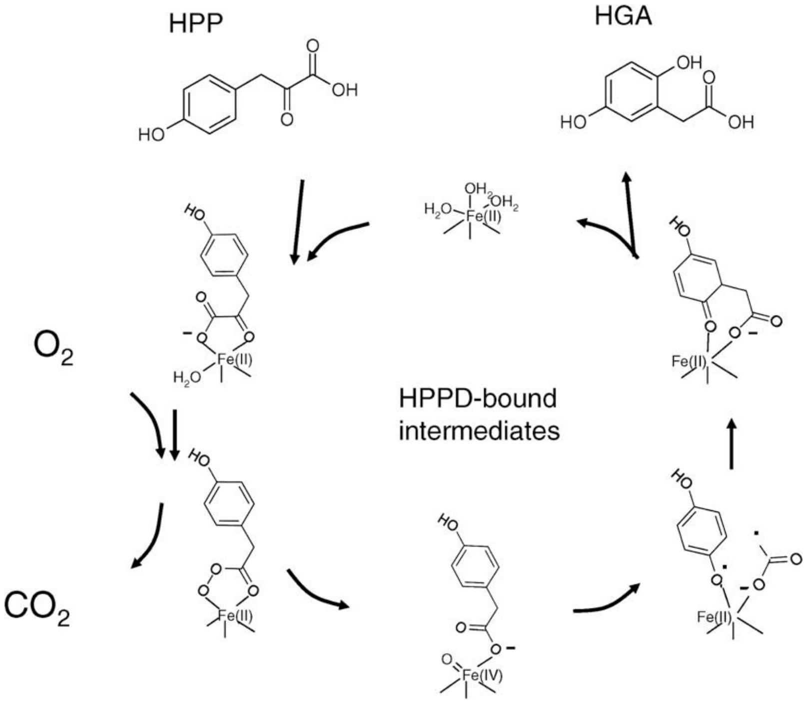


Figure 19. The HPPD reaction showing putative enzyme-bound intermediates.

ing the course of this reaction two electrons from oxidative decarboxylation of the pyruvyl side chain and two from the phenyl ring are used to reduce dioxygen**.**

HPPD is typically a tetramer in bacteria or, in eukaryotes, a dimer of Mr 40–50 kD polypeptide subunits. Conserved residues are found only in the C terminus and from recently solved X-ray structures (*P. fluorescens*, Arabidopsis thaliana, Zea mays, *S. avermitilis* and rat) it is clear that the Fe and its associated inhibitor/substrate-binding site are structurally well conserved and located within the C terminal part of the protein which folds as a discrete domain (cf. Fig. 20). At the primary sequence level, plant proteins appear somewhat distinct because they include a 15-amino acid insertion but, at a structural level, the core active site region remains similar to that in HPPDs from other phylla. As in all non-heme Fe(II) oxygenases this core comprises an active site Fe(II) coordinated by a triad of 2 histidine residues and one carboxylate.[63] In all HPPDs the Fe(II) is located at the centre of a cavity, between 8 and 14 Å in width, that is formed by an eight-stranded twisted half open β barrel. The three residues coordinating the Fe are located on three of these strands and the surrounding cavity environment is almost entirely conserved and dominated by hydrophobic amino acid residues within rigid secondary structural motifs.

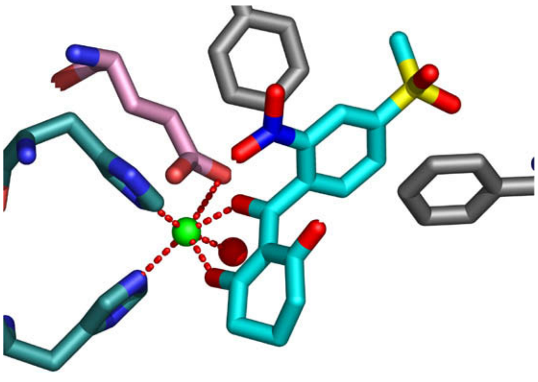


Figure 20. The immediate binding site around the Fe(II) from a crystal structure of mesotrione bound to Arabidopsis HPPD.

Insights into the catalytic mechanism have derived from structural, spectroscopic and pre-steady state kinetic data combined with theoretical chemical considerations and the scheme depicted in Figure 19 is an example based upon one such current view.[66] Steady state kinetic studies indicate that HPP binds first and that CO_2 is the first product released.[63] HPP associates with HPPD as a bidentate ligand of the Fe(II) to form an initial, enzyme—Fe(II)-HPP complex where the Fe is a mixture of 5 and 6 coordinates.[64] This complex is isolable under anaerobic conditions and inhibitors appear to bind in an analogous way,[62] for example, as depicted in Figure 18 (from a crystal structure of mesotrione **48** bound to Arabidopsis HPPD). In resting HPPD, the Fe(II) is relatively unreactive and, as is usual in dioxygenases, it appears that it is substrate coordination to the iron that primes reaction with dioxygen.[63] It is thought that a short-lived Fe(III)-O_2-species is formed wherein withdrawal of electrons into the Fe-bound dioxygen facilitates its nucleophilic attack on the α carbonyl carbon resulting in decarboxylation and the generation of a theoretical short-lived Fe(II)-peracid species that quickly heterolytically disproportionates to yield the oxo-Fe(IV) electrophile. The last key species has not been detected directly but its existence is inferred from the reaction chemistry and by analogy with similar enzymes. Proposals for the subsequent steps involve the oxo-Fe(IV) species either abstracting two electrons from the aromatic ring to generate an arenium cation or benzene oxide[63] or, alternatively,[66] a single electron to yield a radical sigma complex (that could potentially generate arene oxide via a non-productive side reactions). Figure 19 depicts one view of such a mechanism where this radical complex undergoes homolytic CC bond cleavage to yield a highly unstable biradical species which decays to form the new CC bond (corresponding with side-chain migration). In the final steps, re-aromatisation and tautomerisation then yield enzyme-bound HGA. The production of hydroxymandelate and oxepinone by certain mutated HPPDs[75] and the production of Hawkinsin in patients having a defective HPPD gene are all observations that argue for the generation of a benzene oxide in catalysis. From the isotope labelling and pre-steady state kinetic data it appears that release of HGA from the enzyme is likely rate limiting in the catalytic cycle.[65,67]

X-ray crystallography has provided detailed data on how triketones bind to HPPD (cf. Fig. 20). Nitisinone is a bidentate chelator of the Fe(II) in Streptomyces HPPD via its 5′ and 7′ oxygens and a water weakly occupies the sixth position.[62] Two phenylalanines sandwich the phenyl ring of the inhibitor in a π-stacking interaction; one of these provided by a C terminal helix shifts into position upon inhibitor binding. No other energetically significant interactions between inhibitor and enzyme surfaces are evident other than exclusion of water through space-filling Van der Waal contacts. Nitisinone, mesotrione and other HPPD inhibitors bind to the Fe(II) form of the enzyme[67–69] and the so-formed Fe(II) enzyme inhibitor complexes are highly stable, unreactive to oxygen and (similar to the anaerobic Fe(II) enzyme HPP complex) weakly coloured due to charge-transfer transitions. The relatively electron-deficient phenyl ring which is a common feature of potent inhibitors may mimic a reaction intermediate. Conceivably π-stacking stabilises the putative arenium cation[63] or, phenyl radical intermediate (Fig. 19). Whether this is true or not, tight binding of inhibitors as compared with substrate may be partly understood in terms of favourable interactions with electron-deficient aromatic rings.

In solution di and triketone inhibitors exist in solution as an equilibrium between a number of tautomers and, for nitisinone at least, the exocyclic enol(ate) predominates in solution at pH 7. On binding to enzyme, at least two substeps appear to precede final tight complex formation.[65,67] For example, in stopped-flow spectroscopic studies NTBC and mesotrione are seen to bind rapidly to anaerobic Fe(II) Arabidopsis HPPD to form a weak (Kd 0.6–0.9 mM) initial enzyme: inhibitor complex which at 4 °C isomerises fairly quickly (12–16 s^{-1}) to form a first charge-transfer complex which then more slowly (0.6 s^{-1}) isomerises to a second distinct chromophore. The finally formed enzyme inhibitor complexes appear highly stable with no loss of ferrous iron upon exposure to oxygen.

The effectiveness of triketone herbicides at low use rates is surely underpinned by their remarkable potency as HPPD inhibitors. Apparent second-order inhibitor binding rates in the range 1E4–3E5 $M^{-1} s^{-1}$ (which, in terms of pre-steady state binding likely reflects variations in the Kd values of initially formed weak enzyme: inhibitor complexes) to form enzyme/inhibitor complexes so stable that half-times for their dissociation need to be measured (e.g., by radiolabel exchange) over hours and days results in calculated Kd values in the pM range[70] and, indeed, triketones have been described as effectively irreversible inhibitors.[67] Furthermore, since the structure of the enzyme site around bound inhibitors appears to be very highly conserved it is not immediately obvious how inhibitor binding should significantly differ from one HPPD to another and thus it has reasonably been commented[67] that any biological selectivity of HPPD inhibitors must originate from differential bioprocessing rather than from any species-selective differences in HPPD binding. However this expectation is not borne out in detail and certain HPPD inhibitors do appear to exhibit big enough differences between the strength of their binding to HPPDs from different species to be biologically significant. Thus, an inhibitor of mammalian HPPD that was about three orders of magnitude less potent than an inhibitor of Arabidopsis HPPD was derived from an enzyme-screening campaign.[49] Similarly, the broad-leaved weed herbicide mesotrione **48** appears to be a much weaker inhibitor of HPPD from wheat and oats (Kd 7–11 nM) than it is of the Arabidopsis enzyme (Kd 0.015 nM).[19,70] On the other hand, **65** which, comparatively, is a much better grass herbicide than is mesotrione is also a much better inhibitor of the wheat and oat HPPDs (Kd 0.1–0.2 nM). Syncarpic-acid derived structures such as **20** also tend to be two or more orders of magnitude weaker as inhibitors of bacterial (*Pseudomonas fluorescens*) HPPD than of Arabidopsis HPPD (estimated Kd ~ 0.004 nM). These species differences in calculated inhibition constants originate mainly from differences in enzyme: inhibitor complex dissociation rates. Such two or more orders of magnitude differences in Kd value that may be significant biologically but quite modest energetically (~12 kJ mol^{-1}) must presumably originate from the sum of structural and orientation differences too subtle to discern from inspection of crystal structures of enzyme inhibitor complexes. Even given high quality structural information it remains challenging to understand the thermodynamics of inhibitor binding to a level of precision that is predictive for biology.

5. Pharmaceutical applications of triketones

HPPD catalyses an early step in a tyrosine degradation pathway[63,71] that is widely distributed in nature[72] and treatment of, for example, plants or animals with inhibitors causes significant accumulation of tyrosine.[44,45,47] HPP derived from transamination of tyrosine, is converted to HGA via HPPD, HGA is oxidised via HGA oxidase to 4-maleylacetoacetate which is further degraded via 4-maleylacetoacetate isomerase and 4-fumarylacetoacetate lyase to fumarate and acetoacetate. In microbes the pathway provides assimilable carbon from tyrosine and phenylalanine; in higher mammals defects cause hereditary diseases. Alkaptonuria that results from deficiency of homogentisate oxidase was first reported by Garrod in 1902 in his pioneering studies where this was the first disease to be interpreted as an autosomal recessive trait in humans. The disease that is associated with black urine, ochronosis and arthritis is caused by the accumulation of homogentisate and its oxidation products in body fluids.[71] Another hereditary disease associated with a defect in tyrosine catabolism is Hawkinsinurea wherein a single mutation in the N-terminal region of HPPD causes a specific dysfunction that uncouples decarboxylation from HGA formation towards an as yet unidentified, possibly epoxide-type product. This reacts with cysteine or glutathione to make Hawkinsin a substance which is released in large quantities in urine. Hawkinsinurea is a disease associated with metabolic acidosis and stunting. Most serious of the hereditary diseases of tyrosine degradation is Tyrosinaemia Type 1 wherein the functional deficiency lies in the last enzyme of the pathway, 4-fumarylacetoacetate lyase. With this deficiency, the precursors maleylacetoacetate and fumarylacetoacetate convert to succinylacetoacetate and succinyl acetone which are potent toxins which eventually cause liver failure, renal failure and a high rate of mortality from primary liver cancers. The triketone nitisinone that blocks HPPD and thereby prevents toxin accumulation[45] is now an FDA-approved treatment for Tyrosinaemia Type I and may also find use in ameliorating Alkaptonuria and Hawkinsinurea.[63,72]

Triketones have also been patented for the treatment of Parkinson's disease or other neurodegenerative diseases,[73] and for the treatment of depression and/or drug withdrawal symptoms.[74]

6. Summary

Triketones are potent herbicides that act by inhibition of HPPD. The spectrum of weeds controlled can be 'tuned' through careful selection of the substitution patterns around the cyclohexane-1,3-dione and benzoyl/heteroaroyl moieties; the effects of changes in substitution on each of these are largely independent of each other, and are roughly additive. Crop (maize) selectivity is due, in part, to selective oxidative metabolism by the crop plant. Persistence of triketone herbicides in soil, a key parameter for robust pre-emergence herbicidal activity under field conditions, is also dependent on the potential for metabolism.

Syngenta has a long history of research in triketone herbicides, from their original discovery in 1977 through to the present day. Although the area of chemistry has now been known for more than 25 years, we continue to believe that there are still exciting future prospects for novel triketones, through the exploitation of new chemical methodologies that allow access to hitherto inaccessible compounds targeted at new and emerging commercial opportunities presented by shifts in the global herbicide market place.

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