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Aryldiones incorporating a [1,4,5]oxadiazepane ring. Part I: Discovery of the novel cereal herbicide pinoxaden ☆

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ABSTRACT

Derivatives of the new class of 3-hydroxy-4-phenyl-5-oxo-pyrazolines were optimized towards both herbicidal activity on key annual grass weed species and selectivity in small grain cereal crops. The generic structure can be separated into three parts for the analysis of the structure–activity relationships, namely the aryl, the dione with its prodrug forms and the hydrazine moiety. Each area appears to play distinct and different roles in overall expression of biological performance which is further beneficially influenced by adjuvant response and safener action. Pinoxaden **6**, a novel graminicide for use in wheat and barley incorporating a [1,4,5]oxadiazepane ring, eventually emerged as a development candidate from the discovery and optimization process.

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1. Introduction

2-Aryl-1,3-diones (ADs) and their enol derivatives have emerged as a new class of acetyl-coenzyme A carboxylase (ACCase, EC 6.4.1.2) inhibitors over the last couple of years.[1] Depending on the structural nature of both aryl substitution and L–M–P bridge (Fig. 1), ADs were found to be highly effective as either insecticides/acaricides[2] or herbicides.[3] Union Carbide reported on the acaricidal activity of 2-aryl-1,3-indandiones[4] in 1973, and further on the preparation of 2-aryl-1,3-cyclohexanedione and 2-aryl-1,3-cyclopentanedione compounds[5] with miticidal and herbicidal properties in the early 1980s. A decade later, fused 3-aryl-pyrrolidine-2,4-diones[6] were discovered at Bayer, who aggressively published about 200 patents covering several diverse AD subclasses. In particular the tetrahydro-indolizinedione derivative **1** was shown by Babczinski and Fischer to inhibit plant ACCase using isolated corn enzyme.[7] Shortly thereafter, the herbicidal activity of 4-mesityl-pyrazolidine-3,5-dione **2** (CGA 271312) was almost simultaneously claimed by Cederbaum[8] (Ciba-Geigy, now Syngenta) and Krueger[9] (Bayer, now Bayer CropScience).

A few ADs discovered in the late 1990s are currently in development. Research in the field of this novel class has thus been fruitful in delivering active ingredients ready to enter the market in different agrochemical indications. Bayer already commercialized the two tetronic acids spirodiclofen **3**[10] and spiromesifen **4**,[11] while a third keto-enol from the tetramic acid subclass named spirotetramat **5**[12] is under development. All three actives find applications as acaricides and insecticides.

Inspired by some of this public domain background, we intended conceptually to differentiate from competitor structures like **1** by stepping into the class of 4-aryl-pyrazolidine-3,5-diones where the AD bridge L–M–P thereby represents a simple N–N bond, thus involving a hydrazine building block.[8,13] Elaborating on the confirmed herbicidal activity of lead CGA 271312 (**2**), a more specific interest in cyclic hydrazine L–M–P motives emerged quickly (Fig. 2).

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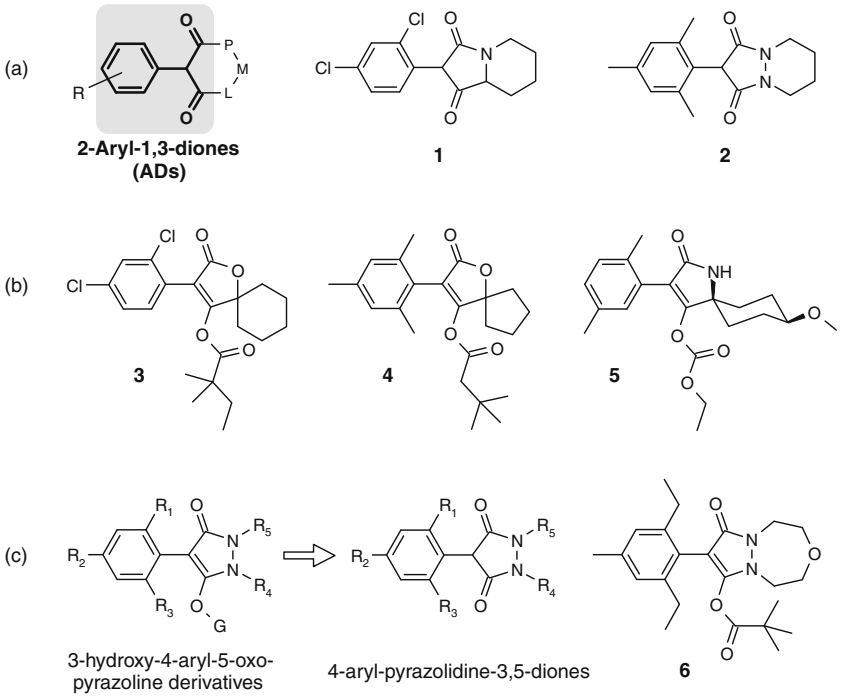


Figure 1. General structure of aryldiones (ADs) and representative herbicidal lead structures **1** and **2** (a), insecticidal/acaricidal development candidates **3**–**5** (b) and herbicidal chemical class of the novel cereal graminicide pinoxaden **6** (c).

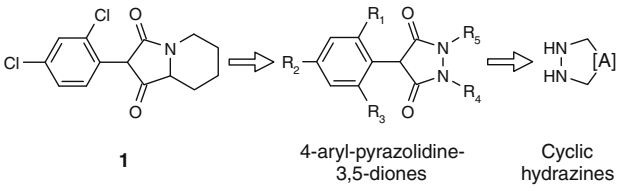
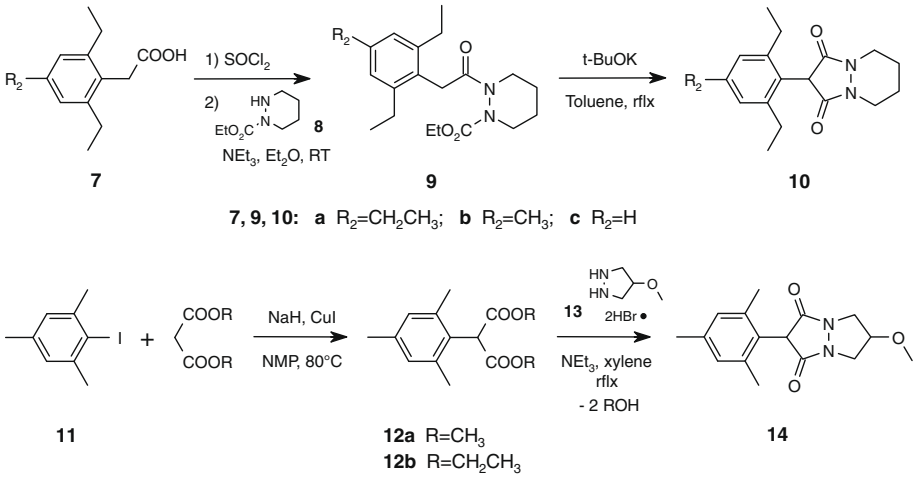


Figure 2. Design of new herbicidal ADs containing cyclic hydrazine derivatives.

Cyclic hydrazines represent a common template found in a number of bioactive compounds, both in the area of medicinal[14] and crop protection[15,16] chemistry. Three main synthetic methods towards simple carbocyclic hydrazine reagents and derivatives have been reported:[17] (i) N,N′-alkylation of a symmetrically or orthogonally protected form of hydrazine[18] applicable for 5- to 7-membered systems and hence useful to prepare optionally substituted pyrazolidines (Fig. 2, [A] = $-CH_2-$), hexahydro-pyridazines ([A] = $-(CH_2)_2-$) and [1,2]diazepanes ([A] = $-(CH_2)_3-$), (ii) hetero Diels–Alder[19] cycloaddition between azodicarboxylates and dienes to access optionally functionalized 6-membered cyclic hydrazine skeletons and (iii) the more recent involvement of ring-closing metathesis[20] enabling the formation of medium-size cyclic hydrazines.

Focussing on a potential crop protection use in the herbicide domain, we wish to report on how careful optimization of both hydrazine R-groups and aryl substitution in the generic structure of the 4-aryl-pyrazolidine-3,5-diones impacted decisively biological features like herbicidal potency and crop tolerance. Satisfyingly, this effort ultimately led to the discovery[21] and market introduc-



Scheme 1. General access to 4-aryl-pyrazolidine-3,5-diones via either a cyclization sequence (**10**) or a condensation route (**14**).

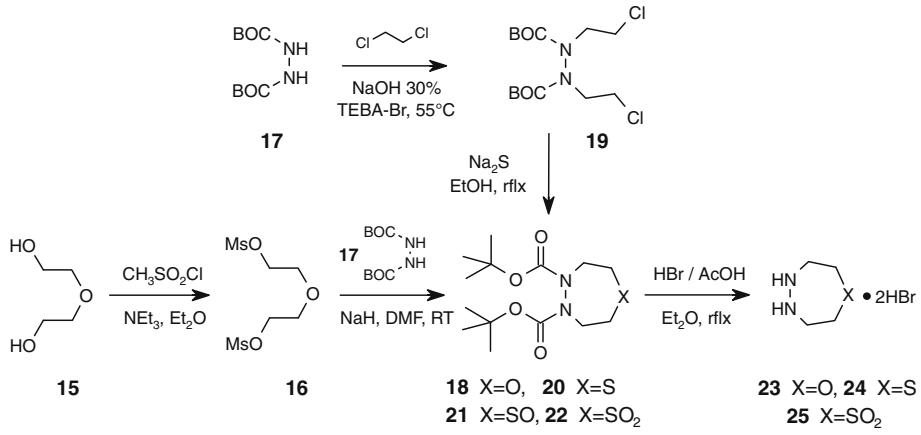
tion of the cereal herbicide pinoxaden **6** (Fig. 1), a novel AD incorporating a [1,4,5]oxadiazepane ring ([A] = $-CH_2-O-CH_2-$).

2. Chemistry

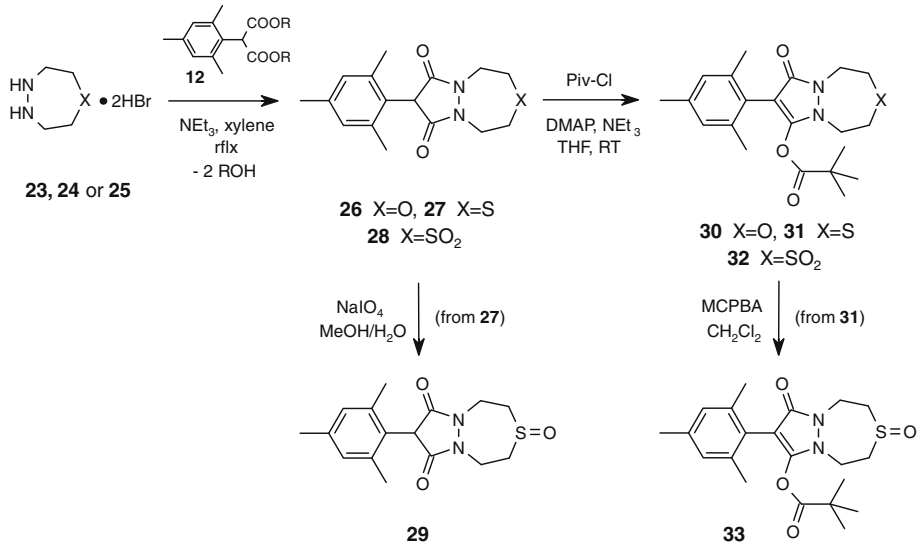
Synthetic routes for the preparation of 2-aryl-1,3-diones are outlined in Schemes 1, 3, 4 and 6, whereas synthesis of the required hydrazine intermediates and aryl acetic acid or aryl malonate building blocks in Schemes 2 and 5.

Aryl-pyrazolidine-3,5-diones were primarily prepared via a thermal condensation reaction between hydrazines and aryl malonates or by involving aryl acetic acid derivatives and hydrazine monoesters in a cyclization sequence.[22] Thus, coupling of the activated form of acids **7**[23] with tetrahydro-pyridazine monoester **8**[19c] under standard conditions and cyclization of intermediates **9** through exposure to base gave the AD products **10** (Scheme 1). Alternatively, thermal condensation of mesityl malonate **12**, conveniently obtained through Cu(I)-mediated malonate arylation[24] using iodide **11**, with carbocyclic hydrazine **13**[15b] while distilling off the alcohol formed delivered dione **14**. A number of analogs incorporating 5- to 7-membered carbocyclic hydrazines were prepared by using any of these two routes (Table 1).[8,13]

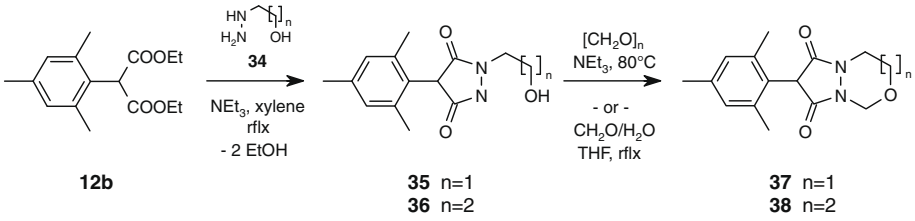
Aiming to study the influence of the hydrazine moiety on biological activity, our attention was captured by the preparation of



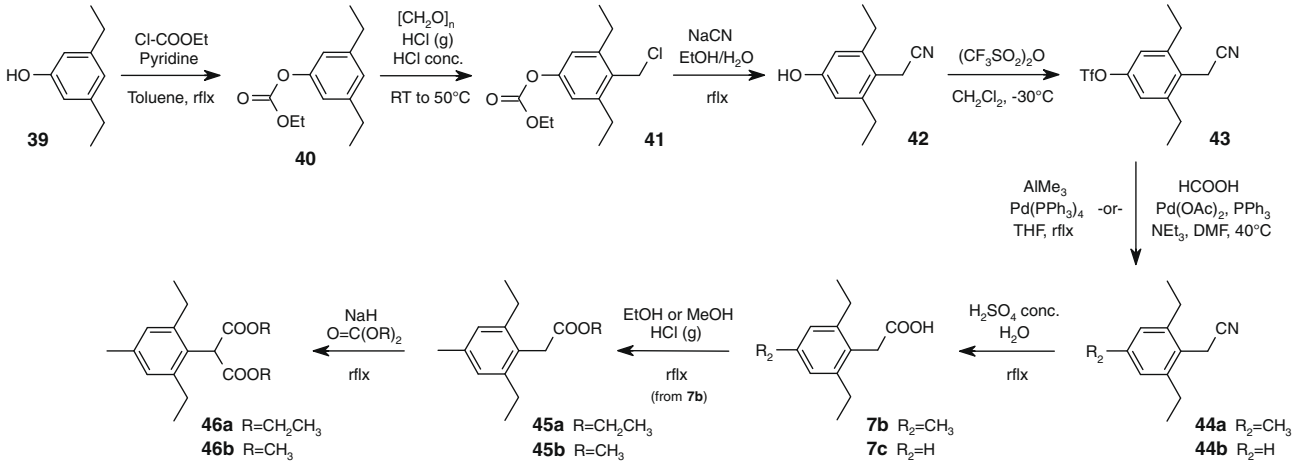
Scheme 2. Preparation of [1,4,5]oxadiazepane **23** and its thio analogs, [1,4,5]thiadiazepane **24** and [1,4,5]thiadiazepane 1,1-dioxide **25**.



Scheme 3. Methods for the preparation of [1,4,5]oxa(thia)diazepane containing ADs **26**–**29** and their enol pivaloyl esters **30**–**33**.



Scheme 4. Synthetic approach to [1,3,4]oxadiazinane **37** and [1,3,4]oxadiazepane **38** containing ADs.



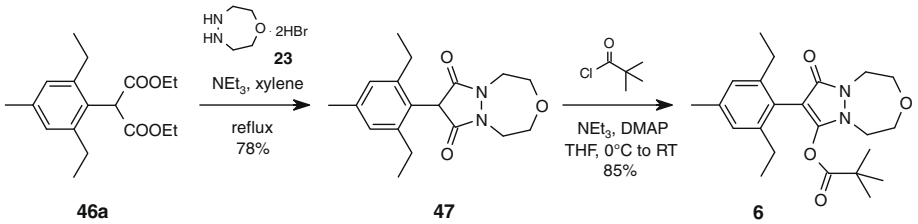
Scheme 5. First generation synthesis of aryl acetic acids **7**, esters **45** and malonates **46** with a 2,6-diethyl substitution.

ADs incorporating a [1,4,5]oxadiazepane ring (also named hexahydro-1,4,5-oxadiazepine) or one of its thio ring analogs. Little was known in the literature about these ring systems at the outset of this study. Akopyan and Paronikyan[25] reported this motive in some crown ethers containing a pyridazine ring and possessing antimutagenic activity. Researchers at Konica Co. claimed for example *N*-cyanoethyl-[1,4,5]oxadiazepane as a photofading preventative substance for color photographic materials.[26] Bicyclic thiadiazepines obtained via Michael-type addition of cyclic hydrazides to divinyl sulfones have been detailed by Zinner[27] and exploited by Pissiotas[28] to prepare herbicides. And finally Kotelko, Glinka and others[29] described *N*-mono- and *N*,*N*′-bis-alkylated or acylated [1,4,5]oxadiazepanes with pharmacological activity on the central nervous system in a few papers and specific polish patents. However, both [1,4,5]oxa- and [1,4,5]thiadiazepane (**23**, **24**) to be used as reagents/reactants had no literature precedent to the best of our knowledge. The 7-membered cyclic hydrazine reagents **23**–**25** were easily prepared in multigram quantities and good overall yields starting from cheap raw materials (Scheme 2). Double deprotonation of 1,2-bis-Boc-hydrazine **17** with sodium hydride and reaction with the bis-mesylate **16** of diethylene glycol **15** afforded smoothly the bis-protected hydrazine cycle **18** in good yield. Deprotection of the Boc groups using hydrogen bromide/acetic acid in diethyl ether generated the hydrobromide salt of [1,4,5]oxadiazepane **23** as a white, hygroscopic but easy to handle solid. The sulfur interrupted 7-membered cyclic hydrazine equivalents were approached by starting with a bis-alkylation of **17** using concentrated sodium hydroxide, tetrabutylammonium bromide and 1,2-dichloroethane under phase transfer catalysis conditions. Cyclization of the resulting 1,2-bis(2-chloroethyl) derivative **19** with sodium sulfide in ethanol gave the bis-Boc-protected cyclic sulfide **20**, from which sulfoxide **21** and sulfone **22** were obtainable by treatment with MCPBA under standard conditions. Similar Boc-deprotection as above delivered the hydrobromide salts of [1,4,5]thiadiazepane **24** and its sulfone analog **25**.

Engaging the newly generated 7-membered, heteroatom-interrupted cyclic hydrazine reagents **23**–**25** in a thermal coupling with mesityl malonate **12** permitted the preparation of the unprecedented [1,4,5]oxa- and [1,4,5]thiadiazepane containing ADs **26**–**28**, from which the corresponding enol pivaloyl esters **30**–**32** were easily derived by treatment with pivaloyl chloride and base (Scheme 3).[21] Adjustment of the sulfur-oxidation state was also achievable directly on the AD sulfide products **27**/**31** ($NaIO_4$ or MCPBA) as illustrated with the preparation of the corresponding sulfoxides **29** and **33**.

[1,3,4]Oxadiazinane and [1,3,4]oxadiazepane containing ADs **37** and **38** were best synthesized from their pyrazolidine-dione precursors **35**/**36**, themselves obtained by condensation of mesityl malonate **12b** with either (2-hydroxyethyl)hydrazine ($n = 1$) or (3-hydroxypropyl)hydrazine ($n = 2$) **34**. Ring closure of the hydrazido-alcohols **35**/**36** was achieved by exposure to either paraformaldehyde in triethylamine or aqueous formaldehyde in tetrahydrofuran (Scheme 4).[30]

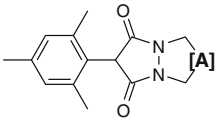
As the triethyl-phenyl analog **10a** displayed enhanced herbicidal potency over its mesityl analog **2** (Table 4), we became interested in varying more carefully the 2,4,6-aryl motive. Scheme 5

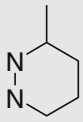
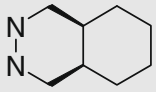
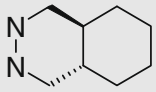


Melting point	189-191°C			122-123°C	
pK_a	3.82			----	
	pH 7.4	pH 5			
H_2O Solubility	380	5.2	g/L	0.2	g/L
Log P_{ow}	-1.1	0.6		3.2	

Scheme 6. First synthesis of pinoxaden **6** and key physicochemical properties.

Table 1
Effects of substitution and ring size in the carbocyclic hydrazine series[a] on crop tolerance[b] and herbicidal grass[c] activity



Entry	Compound	[A]	Adjuvant[d]	HORVX	TRZAW	ALOMY	AVEFA	LOLPE	SETFA	Ref.
1[e]	**48**			20	10	40	40	50	**80**	8
2	**49**	$-CH_2-$		40	0	40	20	**80**	40	8,9
3	**50**	$-CH(CH_3)-$	X-77	50	40	50	**90**	60	50	
4	**14**	$-CH(OCH_3)-$	X-77	0	0	20	20	20	60	
5	**51**	$-C(CH_3)_2-$		90	60	**100**	**90**	**90**	**90**	9
6	**2**	$-CH_2CH_2-$		90	60	60	**90**	**90**	NT[f]	8,9
7[e]	**52**			80	20	40	**90**	**90**	40	8
8	**53**	$-CH(CH_3)CH_2-$		90	50	**90**	**90**	**90**	50	
9	**54**	$-CH(CH_3)CH(CH_3)-$		60	20	**80**	**80**	**80**	60	8
10[e]	**55**		X-77	60	50	60	**80**	**90**	60	
11[e]	**56**		X-77	50	50	60	50	60	**80**	
12	**57**	$-CH_2CH_2CH_2-$	X-77	40	20	50	**90**	50	60	9
13	**58**	$-CH_2CH(CH_3)CH_2-$		60	20	**90**	**90**	**80**	60	

[a] Post-emergence crop damage and grass control (%) at 500 g ai ha^{-1} on whole plants of compounds formulated as WP25.
[b] HORVX = barley, TRZAW = wheat.
[c] ALOMY = *Alopecurus myosuroides*, AVEFA = *Avena fatua*, LOLPE = *Lolium perenne*, SETFA = *Setaria faberi*.
[d] If applicable adjuvant concentration is 0.2% X-77 (v/v).
[e] In this entry [A] denotes the complete structure of the hydrazine moiety.
[f] NT = not tested.

outlines our first generation pathway aimed at introducing substitution in position-4 of the phenyl ring while retaining both *ortho*-ethyl groups. Key aryl triflate intermediate **43** was synthesized from 3,5-diethyl phenol[31] **39** over four steps in analogy to a published protocol.[32] Palladium-catalyzed cross-coupling of **43** with trimethyl aluminum[33] as methyl group donor was highly effective in forming the 4-methyl-phenyl-acetonitrile derivative **44a**, in contrary to first unsuccessful attempts utilizing either higher order mixed cuprate addition (MeLi, CuCN, THF)[34] or tetramethyl tin cross-coupling under various conditions (Me_4Sn, $Pd(PPh_3)_4$, LiCl, dioxane;[35a] Me_4Sn, $Pd_2(dba)_3$, LiCl, $AsPh_3$, NMP[35b]). On the other hand, palladium-catalyzed reduction of triflate **43** to the analog **44b** was achieved using triethylammonium formate as hydrogen donor.[36] Substituted phenyl-acetonitriles **44** were further converted under conventional conditions into their corresponding phenyl acetic acids **7**, esters **45** and aryl malonates **46**.

Availability of the specific phenyl-malonic ester **46a** allowed its cyclocondensation with [1,4,5]oxadiazepane **23** under concomitant off-distillation of ethanol to form the aryl-pyrazolidine-dione NOA 407854 **47** efficiently. Final esterification with pivaloyl chloride delivered pinoxaden **6** (NOA 407855)[21] without problems (Scheme 6). Relevant physicochemical parameters for both AD **47** and pinoxaden **6** are given in Scheme 6.

Essentially all ADs described herein were present in the unique diketo tautomeric form when recording the proton NMR in $CDCl_3$. Two *ortho*-ethyl groups on the phenyl ring will result in noticeable hindered rotation along the bond between the aryl and the dione functionalities, rendering sets of nuclei anisochronous. For example, two significant different chemical shifts for each of the CH_2 of the ethyl groups were observed for AD **47** (quartets at 2.26 ppm and 2.69 ppm). Likewise two sets of chemical shifts were obtained for the CH_3 signal of the ethyl groups (triplets at 1.18 ppm and 1.24 ppm) and for the aromatic protons (singlets at 6.90 ppm and 6.93 ppm).

The structure of pinoxaden **6** was confirmed by a single crystal X-ray structure determination. Crystals suitable for diffraction experiments were obtained from hot *tert*-butyl methyl ether. Pinoxaden **6** crystallizes in the triclinic space group $P\bar{1}$ with two independent molecules in the asymmetric unit which slightly differ in their conformation (Fig. 3): in molecule I the dihedral angle between the phenyl moiety and the 5-membered planar 3-hydroxy-5-oxo-pyrazoline ring is 83.0(1)°, in molecule II it is 70.2(1)°. This (in both cases) nearly orthogonal geometry can be explained

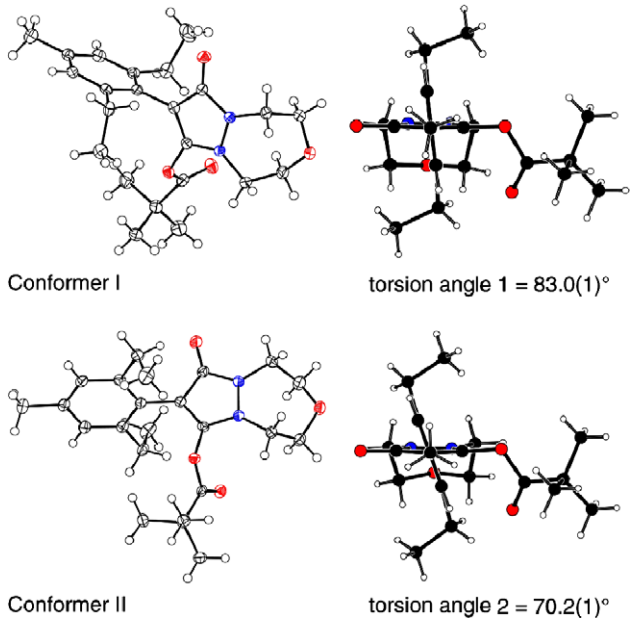


Figure 3. Structure of pinoxaden **6** in the crystal. Anisotropic displacement on the left, ball-and-stick model on the right.

by the steric repulsion between the two *ortho*-ethyl groups on the phenyl ring and the two oxygen functionalities on the 5-membered pyrazoline ring. The [1,4,5]oxadiazepane ring of both conformers adopts a chair-like conformation,[37] only slightly distorted due to the N,N′-annelated unsymmetrical 5-membered pyrazoline ring. Bond lengths and angles within the planar 5-membered 3-hydroxy-5-oxo-pyrazoline ring are close to the expected values.[27a]

3. Results and discussion

3.1. Herbicidal activity and crop tolerance

Post-emergence herbicidal activity of ADs was evaluated using standard in vivo greenhouse screening conditions. Tables 1–6 describe both degree of injury on two major cereal crops (wheat and barley) and weed control efficacy on four key grasses (*Alopecurus myosuroides*, *Avena fatua*, *Lolium perenne*, *Setaria faberi*) after foliar application of a spray solution derived from a formulation of the test compounds and in dependency of various structural modifications.

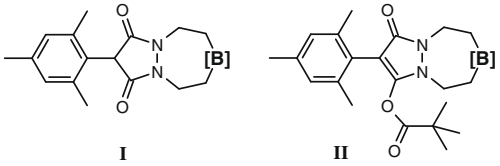
Herbicidal activity at 500 g ai ha^{-1} in the carbocyclic hydrazine series fixing the aromatic part to a 2,4,6-trimethyl (mesityl) pattern is summarized in Table 1. The simple acyclic analog **48**[8] was used as an internal reference compound. Ring size of the carbocyclic hydrazine was not necessarily of primary significance as 5-membered (entries 2–5), 6-membered (entries 6–11) and even 7-membered (entries 12 and 13) analogs displayed decent levels of grass control. Substitution as simple as small alkyls can play a role for a slight activity increase, in instances generating compounds (e.g., **51**, entry 5) superior to the standard **48**. However, cereal tolerance of these first generation compounds was clearly insufficient. Noticeably the degree of barley damage was consistently higher than phytotoxicity on wheat. Small plot field validation trials (data not shown) with a number of these early lead structures essentially confirmed post-emergence grass activity, and identified crop selectivity, spectrum reliability and use rates as the major critical issues.

Three main areas of the 4-aryl-pyrazolidine-3,5-dione scaffold were modified during the optimization phase towards graminicidal activity and selectivity in small grain cereals: the cyclic hydrazine moiety, the aryl part and the dione area which serves as an anchor for prodrug formation.

3.1.1. Structure–activity relationships for the cyclic hydrazine moiety

Table 2 outlines investigations on ADs incorporating a 7-membered cyclic hydrazine (mesityl series), especially studying the influence of the heteroatom which interrupts the cycle. Efficacy against target grasses is given for the actual active ingredient (aryldione structure I) and for its enol pivaloyl prodrug (structure II) at application rates of 2000 and 500 g ai ha^{-1}. The oxygenated representatives **26**/**30** (entry 2) clearly demonstrated enhanced activity on grasses compared to the purely carbocyclic hydrazine standards **57**/**59**, or to the sulfur analogs **27**/

Table 2
Herbicidal activity of 7-membered cyclic hydrazine containing analogs, influence of the heteroatom[a]

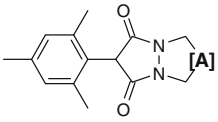


I II

Entry	Compound I/II	[B]	Use rate (g ai ha^{-1})	AVEFA	LOLPE	SETFA
1	**57**/**59**	–CH_2–	2000	**90**/**90**[b]	**90**/**100**	**90**/**90**
			500	50/60	60/**80**	**90**/**90**
2	**26**/**30**	–O–	2000	**100**/**100**	**100**/**90**	**100**/**100**
			500	**80**/**90**	**90**/**90**	**80**/**90**
3	**27**/**31**	–S–	2000	**90**/**90**	**90**/**80**	**100**/**100**
			500	60/50	50/40	**90**/60
4	**28**/**32**	–SO_2–	2000	**80**/**80**	60/50	60/50
			500	60/20	20/10	20/10
5	**29**/**33**	–S(O)–	2000	**80**/**80**	**80**/50	**90**/**80**
			500	40/20	40/20	60/40
6	**60**/—	–$N(CH_3)$–	2000	10/NT[c]	60/NT	**90**/NT
			500	0/NT	10/NT	40/NT

[a] Post-emergence grass control (%) at 2000 and 500 g ai ha^{-1} on whole plants of compounds formulated as IF50.
[b] xx/yy denotes herbicidal activity (%) of structures **I** and **II**, respectively.
[c] NT = not tested.

Table 3
Effects of oxadiazinane and oxadiazepane containing analogs on crop selectivity and herbicidal grass activity[a]



Entry	Compound	[A]	HORVX	TRZAW	ALOMY	AVEFA	LOLPE	SETFA
1	**37**	$-OCH_2-$	0	20	40	**90**	**90**	**90**
2	**38**	$-OCH_2CH_2-$	10	10	0	0	20	50
3	**26**	$-CH_2OCH_2-$	20	50	**80**	**90**	**90**	**90**

[a] Post-emergence crop damage and grass control (%) at 250 g ai ha^{-1} on whole plants of compounds formulated as WP25 with 1% adjuvant Merge® (v/v).

31 (entry 3). Adjusting the sulfur oxidation state (entries 4 and 5) resulted in activity loss, whereas the NMe analog **60** (entry 6) displayed the weakest performance.

Subsequent SAR studies with oxadiazinane and oxadiazepane scaffolds (Table 3; use rate 250 g ai ha^{-1}) permitted to gain a more detailed picture about the influence of an oxygen interrupted hydrazine moiety on activity/tolerance. The 6-membered [1,3,4]oxadiazinane derivative **37** proved interesting, but exhibited a clear gap on ALOMY. The corresponding 7-membered [1,3,4]oxadiazepane analog **38** was disappointingly weak, a result which can be explained by stability issues of the N-acyl hemiaminal moiety towards hydrolysis. In contrary, aryldione **26** incorporating a [1,4,5]oxadiazepane ring expressed good levels of activity over all weed species and particularly noteworthy demonstrated a trend to reduce cereal phytotoxicity, especially dramatically improving tolerance in barley (compare with Table 1).

Field validation trials conducted with ADs **26**/**30** confirmed this trend and moreover revealed that safener action[38] (cloquintocet-mexyl[39]) on **30** reduced crop phytotoxicity in both wheat and barley with only slight activity loss, allowing for a selective control of *Apera spica-venti* and *Lolium multiflorum* at 125 g ai ha^{-1}, and of *Alopecurus myosuroides* and *Avena fatua* at $\geqslant$250 g ai ha^{-1}. While still weaker than market standards, the potential use of [1,4,5]oxadiazepane containing analogs for grass weed control in barley as an innovation value began to emerge.

3.1.2. Structure–activity relationships for the aromatic part

A breakthrough with regard to the level of herbicidal activity was achieved by systematic manipulation of the aromatic region and a 2,4,6-substitution pattern proved beneficial in this respect. The hexahydro-pyridazine series was used to probe substitution in position-4 of the phenyl ring while retaining two *ortho*-ethyl groups (Table 4; use rate 125 g ai ha^{-1}). 2,4,6-Triethyl-phenyl derivative **10a** ($R_2 = CH_2CH_3$, entry 2), easily accessible by synthesis, showed to be more potent than its mesityl equivalent **2**. Sensitivity of the *para*-position was illustrated with the preparation of **10c** ($R_2 = H$, entry 3) presenting inconsistent spectrum control. Surprisingly however, a simple methyl group ($R_2 = CH_3$, entry 4) at the 4-position (**10b**) boosted the graminicidal activity decisively, despite of showing severe cereal damage.

3.1.3. Adjuvant effect, fragment combination and pro-herbicide preparation

Some of the test compounds were shown to also have a significant bioefficacy enhancement by addition of certain adjuvants, a well known feature when dealing with foliar-applied agrochemicals.[40] Such an improvement in uptake was for example demonstrated with hexahydro-pyridazine derivative **10b** when evaluated either in combination with adjuvant X-77[c] or Merge[d] under otherwise identical greenhouse screening conditions (Table 5, entries 1 and 2). Use of the more appropriate adjuvant Merge, triggering better bioavailability within leaves and plant tissues, allowed to lower the application rate to 30 g ai ha^{-1}, however at the moment still with acute loss of cereal tolerance.

Active ingredients **10b**, **26** and **47**[39a] (entries 2–4, Merge only) are actually demonstrating and summarizing how judicious fragment combination was key to activity level against grass weed species (aryl moiety) and tolerance in cereal crops (hydrazine moiety). Complementary contributions of adjuvant effect and preferred 2,6-diethyl-4-methyl aromatic substitution pattern improved drastically herbicidal potency against grasses. Crop injury reduction by incorporation of the [1,4,5]oxadiazepane ring nicely topped this upshot, revealing AD **47** (NOA 407854) as an exciting new selective herbicide.

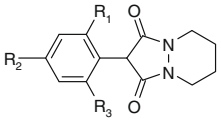
With a pK_a of about 3.8 (vinylogous acid), the dione area of **47** is well suited for prodrug formation with the aim to further increase leaf penetration. Various pro-herbicides have been synthesized (Table 6), most enol carbamates, ethers or *N*,*N*′-dialkylsulfamate esters (entries 3, 5, 7) were weakly active reflecting lack of hydrolysis under plant physiological conditions. Conversely, most enol esters (e.g., **6**; hydrolysis half-life [pH 7] at 50 °C: t_{50} = 20.6 h), sulfonates (**65**; t_{50} = 3.0 h) and carbonates (**61**) were found to hydrolyze easily *in planta* releasing the active principle AD **47**, which is responsible for the target site activity. Enol pivaloate **6** (NOA 407855, pinoxaden, entry 1) was finally selected as a candidate for development following intensive screening in field trials.

3.2. Pinoxaden–safener combination

As described in Table 5, minimization of crop injury by AD **47** and pinoxaden **6** in wheat and barley has been obtained through chemical optimization essentially via incorporation of the [1,4,5]oxadiazepane ring into the AD template. To ensure excellent crop tolerance and secure substantial selectivity margin under agronomical relevant application conditions, the herbicides **47** and **6** have been evaluated in combination with the proprietary safener cloquintocet-mexyl.[39] A comparative greenhouse study of **47** or **6** applied either alone or each in combination with the safener revealed two key aspects regarding crop safety and herbicidal efficacy (Table 7). The herbicide–safener mixture, in combination with the adjuvant Merge, eliminated early crop phytotoxicity (assessed 12 days after application) at a use rate of 60 g

[c] X-77 is a mixture of alkyl aryl polyoxyethylene glycols and free fatty acids in isopropanol; a product from Loveland Industries.
[d] Merge® is a mixture of surfactant blends (ca. 10%) and hydrocarbon solvents and oils (ca. 90%); a registered trademark of BASF Canada Inc.

Table 4
Influence of the *ortho*- and *para*-alkyl substitution on crop tolerance and herbicidal activity[a] of 2-phenyl-tetrahydro-pyrazolo[1,2-*a*]pyridazine-1,3-diones



Entry	Compound	R_1	R_2	R_3	HORVX	TRZAW	ALOMY	AVEFA	LOLPE	SETFA
1[b]	**2**	CH_3	CH_3	CH_3	40	0	40	50	40	NT[c]
2	**10a**	CH_2CH_3	CH_2CH_3	CH_2CH_3	40	40	**90**	**100**	60	50
3	**10c**	CH_2CH_3	H	CH_2CH_3	0	0	60	**80**	40	40
4	**10b**	CH_2CH_3	CH_3	CH_2CH_3	90	80	**90**	**100**	**90**	**80**

[a] Post-emergence crop damage and grass control (%) at 125 g ai ha^{-1} on whole plants of compounds formulated as WP25 with 0.2% adjuvant X-77 (v/v).
[b] No adjuvant.
[c] NT = not tested.

ai ha^{-1} in different cereal varieties of wheat and barley, but importantly did not impair herbicidal efficacy on grass weeds at 30 g ai ha^{-1} which was evaluated conventionally 20 days after treatment.

4. Conclusions

A series of chemical investigations in the AD area of 4-aryl-pyrazolidine-3,5-diones and analysis of the structure–activity relationship information allowed to identify key structural factors influencing both weed control efficacy against grasses and crop tolerance in cereals. Interruption of the alkylene fragment in the cyclic hydrazine derivatives with heteroatoms, oxygen in particular, resulted in the discovery of oxadiazinane and oxadiazepane analogs with reduced crop injury. Worth mentioning are ADs incorporating a [1,4,5]oxadiazepane ring with improved tolerance in wheat and especially barley allowing for a single active ingredient application in these two major cereal markets. Their preparation was made easily possible through the use of the cyclic hydrazine building block [1,4,5]oxadiazepane (**23**), a simple reagent/reactant with no precedent in the chemical literature. Adjusting the aryl 2,4,6-substitution pattern to the specific 2,6-diethyl-4-methyl-phenyl motive permitted to lower use rates decisively and to secure broad spectrum grass control. Key fragment combination and pro-herbicide preparation finally unveiled AD **47** and pinoxaden **6** as exciting herbicides. The first generation synthetic sequence towards **6** disclosed herein, rather lengthy with some steps suffering from low yields and poor practicality, could nevertheless be successfully upscaled to satisfy first amount demands for field trials. The drug discovery of **47** and **6** was complemented by two further capital findings leading to the development of pinoxaden **6**: adjuvant response and safener action. The understanding of beneficial structural requirements to herbicidal activity and crop tolerance gathered during the chemical optimization process was further positively impacted by these two effects.

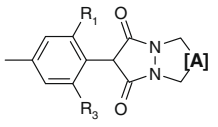
In summary, pinoxaden **6** is a new graminicide for cereal crops, an enol pivaloyl AD prodrug from the chemical class of the 3-hydroxy-4-phenyl-5-oxo-pyrazolines (often just simply called phenylpyrazolines). Its active principle at the ACCase target site is AD **47**, a novel member of the 4-aryl-pyrazolidine-3,5-dione family incorporating a [1,4,5]oxadiazepane ring. Pinoxaden **6** has been launched by Syngenta in 2006 under the tradename Axial® for worldwide use in both wheat and barley.[41] Axial® is applied post-emergence at low use rates and offers outstanding levels of herbicidal activity against key annual grass weed species together with unrivaled cereal crop safety.

5. Experimental

5.1. Chemical synthesis

All new compounds were characterized by standard spectroscopical and analytical methods. ^1H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 100 MHz) spectra were recorded on Bruker Avance spectrometers, using $CDCl_3$, $(CD_3)_2SO$ or CD_3OD as solvents and tetramethylsilane as internal standard. Chemical shifts are reported in ppm downfield from the standard (δ = 0.00). Mass spectra were obtained on Waters ZQ (LC-MS; HP 1100 HPLC from Agilent), Finnigan MAT 90 and Micromass QTOF mass spectrometers. IR spectra were taken on a Bruker FT-IR IFS48 and recorded as KBr pellets. Melting points were determined in open-end capillary tubes on a Büchi 530 melting point apparatus and are uncorrected. Analytical thin-layer chromatography (TLC) was performed using Silica Gel 60 F_{254} precoated plates. Preparative flash chromatography was performed using Silica Gel

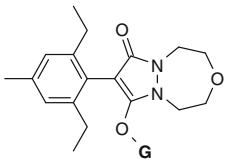
Table 5
Summary of the aryl-pyrazolidine-dione optimization demonstrating key fragment contributions to activity level against grass weed species (aryl moiety) and tolerance in cereal crops (hydrazine moiety)[a]



Entry	Compound	R_1	R_3	[A]	HORVX	TRZAW	ALOMY	AVEFA	LOLPE	SETFA
1[b]	**10b**	CH_2CH_3	CH_2CH_3	$-CH_2CH_2-$	10	40	**80**	**90**	50	40
2	**10b**	CH_2CH_3	CH_2CH_3	$-CH_2CH_2-$	80	80	**100**	**100**	**80**	**90**
3	**26**	CH_3	CH_3	$-CH_2OCH_2-$	0	0	10	60	**80**	50
4	**47**	CH_2CH_3	CH_2CH_3	$-CH_2OCH_2-$	0	10	**100**	**100**	**90**	**90**

[a] Post-emergence crop damage and grass control (%) at 30 g ai ha^{-1} on whole plants of compounds formulated as WP25 with 1% adjuvant Merge® (v/v).
[b] Adjuvant is 0.2% X-77 (v/v).

Table 6
Crop tolerance and herbicidal grass activity of AD **47** in various prodrug forms[a]



Entry	Compound	G	Formulation	HORVX	TRZAW	ALOMY	AVEFA	LOLPE	SETFA
1	**6**	$C(O)C(CH_3)_3$	WP25	0	10	**100**	**100**	**100**	**90**
2	**61**	$C(O)OCH(CH_3)_2$	WP25	0	0	**80**	**90**	**100**	**100**
3	**62**	$C(O)N(CH_2CH_3)_2$	WP25	0	0	0	0	0	0
4	**63**	$CH_2OC(O)C(CH_3)_3$	WP10	0	10	60	**100**	**100**	**90**
5	**64**	CH_2CH_3	WP10	0	0	0	0	20	0
6	**65**	$SO_2(CH_2)_7CH_3$	IF50	0	20	**80**	**100**	**100**	**90**
7	**66**	$SO_2N(CH_3)_2$	IF50	0	0	0	10	50	20

[a] Post-emergence crop damage and grass control (%) at 30 g ai ha^{-1} on whole plants of compounds formulated as WP10, WP25 or IF50 with 1% adjuvant Merge® (v/v).

60 (40–63 μm, E. Merck). All reactions were carried out under anhydrous conditions in an inert atmosphere (nitrogen or argon) with dry solvents. All reagents were purchased from commercial suppliers and used without further purification. Representative procedures are given below; the yields were not optimized.

5.1.1. 2-(2,4,6-Trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*a*]pyridazine-1,3-dione (2, CGA 271312)

Prepared according to WO 1992/16510.[8] Yield: 47% as a white solid, mp 244–246 °C. ^{1}H NMR ($CDCl_3$): δ 1.79 (m, 4H), 2.02 (s, 3H), 2.24 (s, 3H), 2.38 (s, 3H), 3.65 (m, 4H), 4.64 (s, 1H), 6.82 (s, 1H), 6.91 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.0, 20.8, 20.9, 22.4, 43.2, 48.7, 126.0, 129.3, 129.9, 136.0, 137.9, 138.3, 169.5. MS (ES+) *m/z*: 273 $(C_{16}H_{20}N_2O_2 + H)^+$.

5.1.2. 2-[2-(2,4,6-Triethyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic acid ethyl ester (9a)

To a solution of tetrahydro-pyridazine-1-carboxylic acid ethyl ester **8**[19c] (8.2 g, 51.7 mmol), triethylamine (7.9 ml, 5.75 g, 56.8 mmol) and a catalytic amount of 4-dimethylaminopyridine in tetrahydrofuran (120 ml) at 0–5 °C was added a solution of the acid chloride of (2,4,6-triethyl-phenyl)-acetic acid **7a**[23] (12.32 g, 51.7 mmol, prepared using thionyl chloride and a catalytic amount of DMF) dropwise. The suspension was stirred at room temperature overnight, then poured on ice-water and ethyl acetate. The layers were separated, the aqueous phase extracted with ethyl acetate, the combined organic layers washed twice with water and brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:9). Yield: 14.82 g (80%) as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 6H), 1.22 (t, 3H), 1.32 (t, 3H), 1.60–1.80 (m, 4H), 2.50–2.63 (m, 6H), 2.72 (m, 1H), 2.97 (m, 1H), 3.7 (q, 2H), 4.20–4.35 (m, 3H), 4.55 (m, 1H), 6.90 (s, 2H).

5.1.3. 2-[2-(2,6-Diethyl-4-methyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic acid ethyl ester (9b)

Obtained from the acid chloride of (2,6-diethyl-4-methyl-phenyl)-acetic acid **7b** and tetrahydro-pyridazine-1-carboxylic acid ethyl ester **8** according to procedure 5.1.2. Yield: 73% as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 6H), 1.32 (t, 3H), 1.72 (m, 4H), 2.30 (s, 3H), 2.55 (q, 4H), 2.74 (m, 1H), 2.97 (m, 1H), 3.62 (d, J_{AB} = 17 Hz, 1H), 3.76 (d, J_{AB} = 17 Hz, 1H), 4.19–4.37 (m, 3H), 4.55 (m, 1H), 6.88 (s, 2H).

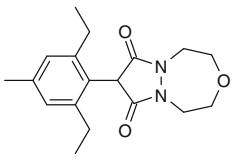
5.1.4. 2-[2-(2,6-Diethyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic acid ethyl ester (9c)

Obtained from the acid chloride of (2,6-diethyl-phenyl)-acetic acid **7c** and tetrahydro-pyridazine-1-carboxylic acid ethyl ester **8** according to procedure 5.1.2 (reaction run in diethyl ether). Yield: 77% as a viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.20 (t, 6H), 1.33 (t, 3H), 1.68–1.80 (m, 4H), 2.60 (q, 4H), 2.78 (m, 1H), 2.98 (m, 1H), 3.72 (q, 2H), 4.22–4.38 (m, 3H), 4.58 (m, 1H), 7.03–7.20 (m, 3H).

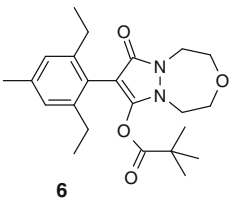
5.1.5. 2-(2,4,6-Triethyl-phenyl)-tetrahydro-pyrazolo[1,2-*a*]pyridazine-1,3-dione (10a)

To a solution of potassium *tert*-butoxide (5.0 g, 45 mmol) in toluene (70 ml) at reflux was added a solution of 2-[2-(2,4,6-triethyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic

Table 7
Herbicidal grass activity and crop tolerance of AD **47** and pinoxaden **6** (H) applied either alone or in combination with the safener (S) cloquintocet-mexyl[a]



47



6
Pinoxaden

Compound	Winter barley (*cv Fanfare*)		Winter wheat (*cv Arina*)		Summer wheat (*cv Remia*)		*Avena fatua*		*Lolium rigidum*	
	H	H + S	H	H + S	H	H + S	H	H + S	H	H + S
47	40	0	20	0	50	0	90	90	90	90
6	20	0	30	0	30	0	90	90	90	95

[a] Post-emergence crop damage and weed control (%) at 30 g ai ha^{-1} on grasses (evaluation 20 DAT) and at 60 g ai ha^{-1} on barley and wheat varieties (evaluation 12 DAT) of compounds formulated as EC200 with 1% adjuvant Merge® (v/v), with and without cloquintocet-mexyl (EC100 formulation) added at 25% the rate of the herbicide.

acid ethyl ester **9a** (10.8 g, 30 mmol) in toluene (30 ml) dropwise. The mixture was stirred at reflux for 1 h. To the cooled reaction mixture was added ice-water, the organic layer separated and discarded after being reextracted twice with 1 N aqueous sodium hydroxide. The combined aqueous alkaline phases were acidified with cooling to pH 2–3 by addition of a 4 N HCl solution, the resulting precipitate was filtered off and recrystallized from hot ethyl acetate. Yield: 6.4 g (69%) as a white solid, mp 189–191 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H), 1.21 (t, 3H), 1.25 (t, 3H), 1.81 (m, 4H), 2.25 (q, 2H), 2.59 (q, 2H), 2.70 (q, 2H), 3.67 (m, 4H), 4.64 (s, 1H), 6.92 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.3, 15.3, 16.0, 22.5, 25.6, 28.2, 28.6, 43.4, 48.1, 124.8, 126.4, 126.7, 142.2, 144.4, 144.6, 170.2. MS (ES+) *m/z*: 315 $(C_{19}H_{26}N_2O_2 + H)^+$.

5.1.6. 2-(2,6-Diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-*a*]pyridazine-1,3-dione (10b)

Method (a): Obtained from 2-[2-(2,6-diethyl-4-methyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic acid ethyl ester **9b** (6.8 g, 19.6 mmol) and potassium *tert*-butoxide (3.83 g, 34.1 mmol) in toluene (70 ml) according to procedure 5.1.5. Yield: 28% as a white solid, mp 175–177 °C. ^{1}H NMR ($CDCl_3$): δ 1.17 (t, 3H), 1.24 (t, 3H), 1.81 (m, 4H), 2.24 (q, 2H), 2.29 (s, 3H), 2.68 (q, 2H), 3.67 (m, 4H), 4.63 (s, 1H), 6.90 (s, 1H), 6.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.2, 16.0, 21.2, 22.5, 25.5, 28.1, 43.4, 48.1, 124.6, 127.6, 127.9, 138.3, 142.2, 144.6, 170.2. MS (ES+) *m/z*: 301 $(C_{18}H_{24}N_2O_2 + H)^+$.

Method (b): A solution of 2-(2,6-diethyl-4-methyl-phenyl)-malonic acid dimethyl ester **46b** (4.18 g, 15.0 mmol) in xylene (100 ml) was treated with hexahydro-pyridazine (1.57 g, 18.2 mmol). The reaction mixture was flushed with argon and stirred under argon atmosphere. The flask was placed in a preheated oil bath at 150 °C and the mixture heated for 4.5 h, while ethanol was distilled off. The cooled reaction mixture was treated with a 2 N aqueous sodium hydroxide solution (~15 ml) and the aqueous layer extracted with diethyl ether. The aqueous alkaline phase was acidified with cooling by careful addition of a 1 N HCl solution and the product extracted with dichloromethane. The chlorinated organic phase was dried over sodium sulfate, evaporated and the residue purified by chromatography on silica gel. Yield: 3.49 g (77%) as yellowish crystals, mp 174–176 °C. The spectral data were identical to those reported above under *method (a)*.

5.1.7. 2-(2,6-Diethyl-phenyl)-tetrahydro-pyrazolo[1,2-*a*]pyridazine-1,3-dione (10c)

Obtained from 2-[2-(2,6-diethyl-phenyl)-acetyl]-tetrahydro-pyridazine-1-carboxylic acid ethyl ester **9c** according to procedure 5.1.5. Yield: 33% as a white solid. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H), 1.25 (t, 3H), 1.80 (m, 4H), 2.27 (q, 2H), 2.72 (q, 2H), 3.66 (m, 4H), 4.68 (s, 1H), 7.09 (d, J = 7.7 Hz, 1H), 7.10 (d, J = 7.7 Hz, 1H), 7.22 (t, J = 7.7 Hz, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 15.9, 22.4, 25.5, 28.1, 43.4, 48.3, 126.6, 126.9, 127.7, 128.7, 142.4, 144.8, 169.9. MS (ES+) *m/z*: 287 $(C_{17}H_{22}N_2O_2 + H)^+$.

5.1.8. 2-(2,4,6-Trimethyl-phenyl)-malonic acid dimethyl ester (12a)

To a stirred suspension of sodium hydride (18.3 g, 60% w/w dispersion in mineral oil, 0.46 mol) in 1-methyl-2-pyrrolidone (NMP, 300 ml) at 0–5 °C was added malonic acid dimethyl ester (55.4 g, 0.42 mol) dropwise over 3 h. The mixture was stirred at room temperature overnight. After further addition of 2-iodo-1,3,5-trimethyl-benzene **11** (51.7 g, 0.21 mol) and copper(I) iodide (80 g, 0.42 mol), the reaction mixture was heated at 80–85 °C for 5 h, cooled and poured on a cold solution of 1 N HCl (800 ml) and ethyl acetate (500 ml) followed by vigorous stirring. The copper salts were filtered off, the layers of the filtrate separated, the aqueous phase extracted twice with ethyl acetate, the combined organic layers washed with water and brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:5). Yield: 34.0 g (65%) as a white solid, mp 75–77 °C. ^{1}H NMR ($CDCl_3$): δ 2.25 (s, 3H), 2.31 (s, 6H), 3.74 (s, 6H), 5.02 (s, 1H), 6.88 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 20.6, 20.8, 52.5, 52.6, 127.9, 129.9, 137.5, 137.6, 169.0. MS (ES+) *m/z*: 251 $(C_{14}H_{18}O_4 + H)^+$, 273 $(C_{14}H_{18}O_4 + Na)^+$.

5.1.9. 2-(2,4,6-Trimethyl-phenyl)-malonic acid diethyl ester (12b)

Obtained from malonic acid diethyl ester, 2-iodo-1,3,5-trimethyl-benzene and copper(I) iodide according to procedure 5.1.8. Yield: 57% as an off-white solid, mp 48–49 °C. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H), 2.23 (s, 3H), 2.32 (s, 6H), 4.22 (q, 4H), 4.98 (s, 1H), 6.87 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.1, 20.7, 20.9, 53.0, 61.6, 128.1, 129.8, 137.4, 137.6, 168.7. MS (ES+) *m/z*: 279 $(C_{16}H_{22}O_4 + H)^+$, 301 $(C_{14}H_{18}O_4 + Na)^+$.

5.1.10. 6-Methoxy-2-(2,4,6-trimethyl-phenyl)-dihydro-pyrazolo[1,2-*a*]pyrazole-1,3-dione (14)

Obtained from 4-methoxy-pyrazolidine dihydrobromide **13**[15b] and 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** according to procedure 5.1.19. Yield: 55% as a white solid, mp 147–149 °C. ^{1}H NMR ($CDCl_3$): δ 1.99 (s, 3H, isomer A + B), 2.24 (s, 3H, isomer A + B), 2.36 (s, 3H, isomer A + B), 3.28 (s, 2.4H, isomer A), 3.38 (s, 0.6H, isomer B), 3.39 (dd, J = 12.4 Hz, 3.7 Hz, 1.6H, isomer A), 3.78 (dd, J = 11.7 Hz, 3.3 Hz, 0.4H, isomer B), 3.90 (dd, J = 11.7 Hz, 5.3 Hz, 0.4H, isomer B), 4.18 (t, J = 3.7 Hz, 0.8H, isomer A), 4.27 (m, 0.2H, isomer B), 4.29 (d, J = 12.4 Hz, 1.6H, isomer A), 4.86 (s, 0.2H, isomer B), 4.96 (s, 0.8H, isomer A), 6.83 (s, 1H, isomer A + B), 6.89 (s, 1H, isomer A + B). ^{13}C NMR ($CDCl_3$): δ 20.1 (isomer A + B), 20.8 (isomer A + B), 48.2 (isomer B), 48.9 (isomer A), 51.1 (isomer A), 51.6 (isomer B), 56.0 (isomer A), 57.3 (isomer B), 79.3 (isomer B), 79.6 (isomer A), 124.8 (isomer A), 125.7 (isomer B), 129.0 (isomer A + B), 129.8 (isomer A + B), 137.4 (isomer A + B), 138.0 (isomer A + B), 168.8 (isomer B), 170.1 (isomer A) (two diketo-form isomers in a ratio A/B = 4:1). MS (ES+) *m/z*: 289 $(C_{16}H_{20}N_2O_3 + H)^+$.

5.1.11. Diethylene glycol dimethanesulfonate (16)

Diethylene glycol **15** was bis-mesylated in nearly quantitative yield under standard conditions.[21] White solid, mp 51–52 °C (from ethyl acetate/toluene 4:3). ^{1}H NMR ($CDCl_3$): δ 3.07 (s, 6H), 3.80 (t, 4H), 4.38 (t, 4H).

5.1.12. 4,5-Bis-*tert*-butyloxycarbonyl-[1,4,5]oxadiazepane (18)

A solution of 1,2-bis-Boc-hydrazine **17** (174.5 g, 0.75 mol) in 350 ml of dimethylformamide was added dropwise over 2 h to a stirred suspension of sodium hydride (60.6 g, 60% w/w dispersion in mineral oil, 1.52 mol) in dimethylformamide (1270 ml) at 0–5 °C. The mixture was allowed to warm to room temperature and subsequently heated to 30 °C for 15 min to bring hydrogen evolution to completion (caution!). A solution of diethylene glycol dimethanesulfonate **16** (203 g, 0.77 mol) in 210 ml of dimethylformamide was then added dropwise over 1.5 h at 0–5 °C. The reaction mixture was stirred overnight at room temperature and poured on a mixture of ice, saturated aqueous ammonium chloride and *tert*-butyl methyl ether. The layers were separated, the aqueous phase extracted with *tert*-butyl methyl ether (4 × 500 ml), the combined organic layers washed with water (4 × 500 ml) and brine, dried over sodium sulfate, evaporated and the residue dried at 40 °C under reduced pressure. Yield: 216 g (95%) as an oil, this material was used without further purification. An analytical sample of **18** was obtained through purification by chromatography on silica gel (*tert*-butyl methyl ether/

hexane 1:1). White solid, mp 67–69 °C. ^{1}H NMR ($CDCl_3$): δ 1.48 (appar t, 18H), 3.12–4.17 (m, 8H). ^{13}C NMR ($CDCl_3$): δ 28.3, 49.9, 69.4, 80.8, 154.4 (mixture of rotamers/conformers, major isomer reported).

5.1.13. 1,2-Bis-Boc-1,2-bis-(2-chloroethyl)-hydrazine (19)

A mixture of 1,2-bis-Boc-hydrazine **17** (23.2 g, 0.1 mol), 30% aqueous sodium hydroxide (100 ml) and a catalytic amount of tetrabutylammonium bromide (1 g) in 1,2-dichloroethane (200 ml, 2.54 mol) was heated 5 h at 55 °C. The layers were separated upon cooling, the aqueous phase extracted with dichloromethane, the combined organic layers washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:12 to 1:8). Yield: 27.8 g (78%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.49 (appar t, 18H), 3.53–3.97 (m, 8H).

5.1.14. 4,5-Bis-*tert*-butyloxycarbonyl-[1,4,5]thiadiazepane (20)

A solution of 1,2-bis-Boc-1,2-bis-(2-chloroethyl)-hydrazine **19** (22 g, 61.6 mmol) and sodium sulfide (8.8 g, $Na_2S{\cdot}xH_2O$ 60%, 67.7 mmol) in ethanol (1000 ml) was heated at reflux for 20 h. The reaction mixture was evaporated, diluted with *tert*-butyl methyl ether and the resulting precipitate removed by filtration. The filtrate was evaporated and the residue purified by chromatography on silica gel (ethyl acetate/hexane 1:9). Yield: 12.4 g (63%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.47 (appar t, 18H), 2.45–2.61 (m, 2H), 2.73–2.89 (m, 2H), 3.23–3.56 (m, 2H), 3.92–4.37 (m, 2H).

5.1.15. 4,5-Bis-*tert*-butyloxycarbonyl-1,1-dioxo-1λ^6-[1,4,5]thiadiazepane (22) and 4,5-bis-*tert*-butyloxycarbonyl-1-oxo-1λ^4-[1,4,5]thiadiazepane (21)

To a solution of 4,5-bis-*tert*-butyloxycarbonyl-[1,4,5]thiadiazepane **20** (8.3 g, 26.1 mmol) in dichloromethane (20 ml) was added *m*-chloroperbenzoic acid (10.9 g, MCPBA ~70%, 44.2 mmol) in dichloromethane (50 ml) at 0–5 °C dropwise. The mixture was stirred at room temperature overnight, then poured on 0.5 N aqueous sodium hydroxide and the layers separated. The aqueous phase was extracted with dichloromethane, the combined organic layers washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:2) to first afford the sulfone **22**. Yield: 5.73 g (63%) as white solid. ^{1}H NMR ($CDCl_3$): δ 1.48 (appar t, 18H), 3.07–3.63 (m, 6H), 4.01–4.39 (m, 2H).

Further elution delivered the sulfoxide **21**. Yield: 1.7 g (20%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.46 (appar t, 18H), 2.82–3.29 (m, 4H), 3.31–3.80 (m, 2H), 4.07–4.48 (m, 2H).

5.1.16. [1,4,5]Oxadiazepane dihydrobromide (23)

To a solution of 4,5-bis-*tert*-butyloxycarbonyl-[1,4,5]oxadiazepane **18** (216 g, 0.71 mol) in 2800 ml of diethyl ether cooled at 0–5 °C under nitrogen was added a solution of hydrogen bromide in acetic acid (376 ml, HBr 33% w/w in glacial acetic acid, 5.7 M, 2.14 mol) dropwise over 1.5 h. The reaction mixture was stirred overnight at room temperature, and further 20 h at reflux. In between the mixture was diluted with another 200 ml of diethyl ether and treated with additional hydrogen bromide in acetic acid (30 ml, 0.17 mol). The resulting suspension was cooled to room temperature, filtered under nitrogen and the white solid washed with diethyl ether. The solid was dried over phosphorus pentoxide under vacuum at 50 °C. Yield: 131.9 g (70%) as a white hygroscopic solid, mp 138–141 °C (dec). ^{1}H NMR (DMSO-d_6): δ 3.22 (t, 4H), 3.79 (t, 4H), 8.3 (br s, 4H). ^{13}C NMR (DMSO-d_6): δ 49.8, 67.5. Differential scanning calorimetry (DSC): energy of exothermic decomposition = 0.61 kJ·g^{-1} (peak at 140 °C, peak width ± ~22 °C) measured in the range 50–460 °C, 4 °C min^{-1}.

5.1.17. [1,4,5]Thiadiazepane dihydrobromide (24)

Obtained from 4,5-bis-*tert*-butyloxycarbonyl-[1,4,5]thiadiazepane **20** (4.1 g, 12.9 mmol) and hydrogen bromide in acetic acid (11.9 ml, 4.1 M, 48.8 mmol) in diethyl ether (80 ml) according to procedure 5.1.16. Yield: 85% as a white solid. ^{1}H NMR (DMSO-d_6): δ 2.84 (t, 4H), 3.28 (t, 4H), 8.5 (br s, 4H).

5.1.18. 1,1-Dioxo-1λ^6- [1,4,5]thiadiazepane dihydrobromide (25)

Obtained from 4,5-bis-*tert*-butyloxycarbonyl-1,1-dioxo-1λ^6-[1,4,5]thiadiazepane **22** (5.73 g, 16.4 mmol) and hydrogen bromide in acetic acid (10.5 ml, 5.7 M, 59.9 mmol) in diethyl ether (80 ml) and dichloromethane (20 ml) according to procedure 5.1.16. Yield: 73% as a white solid. ^{1}H NMR (DMSO-d_6): δ 3.39 (m, 4H), 3.52 (m, 4H), 9.2 (br s, 4H).

5.1.19. 8-(2,4,6-Trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione (26)

A degassed suspension of [1,4,5]oxadiazepane dihydrobromide **23** (40 g, 151.5 mmol) and triethylamine (99 ml, 71.8 g, 710 mmol) in 1000 ml of xylene was stirred under argon at 60 °C for 3 h. After further addition of 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** (42.5 g, 152.7 mmol), the reaction mixture was heated to 150 °C (oil bath temperature) while distilling off the formed ethanol and part of the excess triethylamine. The cooled reaction mixture was poured on ice-water (500 ml), the pH made alkaline by addition of 1 N aqueous sodium hydroxide (~100 ml) and the aqueous layer extracted twice with ethyl acetate. The combined organic layers were discarded after being reextracted twice with 1 N aqueous sodium hydroxide. The combined aqueous alkaline phases were acidified with cooling to pH 2–3 by addition of a 4 N HCl solution. The resulting precipitate was filtered off, washed with water and hexane, and the solid dried over phosphorus pentoxide under vacuum at 60 °C overnight. Yield: 34.6 g (79%) as a slight tan solid, mp 242–244 °C (dec). ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 3H), 2.25 (s, 3H), 2.39 (s, 3H), 3.81 (ddd, 2H), 3.92–4.02 (m, 4H), 4.22 (ddd, 2H), 4.72 (s, 1H), 6.83 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.0, 20.9, 21.0, 46.1, 48.3, 70.5, 125.9, 129.5, 130.0, 136.1, 138.2, 138.4, 165.5. MS (ES+) *m*/*z*: 289 ($C_{16}H_{20}N_2O_3$ + H)$^+$.

5.1.20. 8-(2,4,6-Trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione (27)

Obtained from [1,4,5]thiadiazepane dihydrobromide **24** (3.55 g, 12.7 mmol), 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** (3.98 g, 14.3 mmol) and triethylamine (8 ml, 5.8 g, 57.4 mmol) in xylene (150 ml) according to procedure 5.1.19. Yield: 80% as an off-white solid, mp 225 °C (dec). ^{1}H NMR ($CDCl_3$): δ 2.03 (s, 3H), 2.25 (s, 3H), 2.39 (s, 3H), 2.81–2.95 (m, 4H), 4.20 (ddd, 2H), 4.44 (ddd, 2H), 4.69 (s, 1H), 6.83 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.1, 20.9, 21.0, 31.8, 47.7, 48.2, 125.9, 129.5, 130.0, 136.0, 138.1, 138.4, 166.1. MS (ES+) *m*/*z*: 305 ($C_{16}H_{20}N_2O_2S$ + H)$^+$. Anal. Calcd for $C_{16}H_{20}N_2O_2S$: C, 63.13; H, 6.62; N, 9.20; O, 10.51; S, 10.53. Found: C, 62.43; H, 6.71; N, 9.13; O, 10.84; S, 10.32.

5.1.21. 3,3-Dioxo-8-(2,4,6-trimethyl-phenyl)-tetrahydro-3λ^6-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione (28)

Obtained from 1,1-dioxo-1λ^6-[1,4,5]thiadiazepane dihydrobromide **25** (3.72 g, 11.9 mmol), 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** (3.32 g, 11.9 mmol) and triethylamine (6.7 ml, 4.9 g, 48.1 mmol) in xylene (120 ml) according to procedure 5.1.19. Yield: 90% as an off-white solid, mp >250 °C. ^{1}H NMR ($CDCl_3$): δ 2.01 (s, 3H), 2.26 (s, 3H), 2.39 (s, 3H), 3.29–3.43 (m, 4H), 4.35–4.49 (m, 4H), 4.71 (s, 1H), 6.85 (s, 1H), 6.95 (s, 1H). MS (ES+) *m*/*z*: 337 ($C_{16}H_{20}N_2O_4S$ + H)$^+$.

5.1.22. 3-Oxo-8-(2,4,6-trimethyl-phenyl)-tetrahydro-3λ⁴-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione (29)

A solution of sodium periodate (720 mg, 3.37 mmol) in methanol (3 ml) and water (3 ml) was added dropwise to a solution of 8-(2,4,6-trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione **27** (500 mg, 1.64 mmol) in methanol (20 ml) at 0–5 °C. The reaction mixture was stirred 2 h at 5 °C and 6 h at room temperature, then poured on saturated aqueous sodium chloride and extracted three times with tetrahydrofuran. The aqueous phase was acidified to pH 3–4 by addition of a 2 N HCl solution and further extracted with tetrahydrofuran. The combined organic layers were washed with saturated aqueous $Na_2S_2O_3$ and brine, dried over magnesium sulfate and evaporated. The residue was triturated with diethyl ether, filtered and dried. Yield: 530 mg (~100%) as a yellowish solid, mp 212 °C (dec). ^{1}H NMR ($CDCl_3$): δ 1.98 (s, 1.2H), 2.03 (s, 1.8 H), 2.25 (s, 3H), 2.39 (s, 3H), 2.61 (ddd, 0.8H), 2.75 (ddd, 1.2H), 3.30–3.39 (m, 2H), 4.10–4.21 (m, 2H), 4.64–4.78 (m, 3H), 6.84 (br s, 1H), 6.93 (br s, 1H) (two diketo-form isomers in a ratio 3:2). MS (ES+) *m*/*z*: 321 $(C_{16}H_{20}N_2O_3S + H)^+$.

5.1.23. 2,2-Dimethyl-propionic acid 9-oxo-8-(2,4,6-trimethyl-phenyl)-1,2,4,5-tetrahydro-9*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-yl ester (30)

To a solution of 8-(2,4,6-trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione **26** (3.0 g, 10.4 mmol) and triethylamine (2.2 ml, 1.60 g, 15.8 mmol) in tetrahydrofuran (100 ml) at 0–5 °C was added a catalytic amount of 4-dimethylaminopyridine (DMAP, ~5 mol %), followed by pivaloyl chloride (1.6 ml, 1.57 g, 13.0 mmol) dropwise. The reaction mixture was stirred at 0 °C for 30 min and at room temperature for 1 h, then poured on saturated aqueous sodium chloride and extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/methanol 19:1), and the crude product triturated with diethyl ether, filtered and dried. Yield: 2.94 g (76%) as a crystalline white solid, mp 135–136 °C. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H), 2.17 (s, 6H), 2.24 (s, 3H), 3.81–3.89 (m, 4H), 3.93 (m, 2H), 4.25 (m, 2H), 6.83 (s, 2H).

5.1.24. 2,2-Dimethyl-propionic acid 9-oxo-8-(2,4,6-trimethyl-phenyl)-1,2,4,5-tetrahydro-9*H*-pyrazolo[1,2-*d*][1,4,5]thiadiazepin-7-yl ester (31)

Obtained from 8-(2,4,6-trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione **27** (1.5 g, 4.93 mmol), pivaloyl chloride (0.62 ml, 0.60 g, 4.98 mmol), triethylamine (0.7 ml, 0.51 g, 5.02 mmol) and a catalytic amount of 4-dimethylaminopyridine in tetrahydrofuran (50 ml) according to procedure 5.1.23. Yield: 82% as a white solid, mp 173–174 °C. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H), 2.16 (s, 6H), 2.23 (s, 3H), 2.78 (m, 2H), 2.91 (m, 2H), 4.07 (m, 2H), 4.42 (m, 2H), 6.83 (s, 2H).

5.1.25. 2,2-Dimethyl-propionic acid 3,3,9-trioxo-8-(2,4,6-trimethyl-phenyl)-2,3,4,5-tetrahydro-1*H*,9*H*-3λ⁶-pyrazolo[1,2-*d*][1,4,5]thiadiazepin-7-yl ester (32)

Obtained from 3,3-dioxo-8-(2,4,6-trimethyl-phenyl)-tetrahydro-3λ⁶-pyrazolo[1,2-*d*][1,4,5]thiadiazepine-7,9-dione **28** (1.0 g, 2.97 mmol), pivaloyl chloride (0.37 ml, 0.36 g, 3.0 mmol), triethylamine (0.42 ml, 0.30 g, 3.01 mmol) and a catalytic amount of 4-dimethylaminopyridine in tetrahydrofuran (35 ml) according to procedure 5.1.23. Yield: 82% as a white solid, mp 186 °C. ^{1}H NMR ($CDCl_3$): δ 1.06 (s, 9H), 2.13 (s, 6H), 2.23 (s, 3H), 3.22 (m, 2H), 3.40 (m, 2H), 4.15 (m, 2H), 4.46 (m, 2H), 6.84 (s, 2H).

5.1.26. 2,2-Dimethyl-propionic acid 3,9-dioxo-8-(2,4,6-trimethyl-phenyl)-2,3,4,5-tetrahydro-1*H*,9*H*-3λ⁴-pyrazolo[1,2-*d*][1,4,5]thiadiazepin-7-yl ester (33)

To a solution of 2,2-dimethyl-propionic acid 9-oxo-8-(2,4,6-trimethyl-phenyl)-1,2,4,5-tetrahydro-9*H*-pyrazolo[1,2-*d*][1,4,5]thiadiazepin-7-yl ester **31** (500 mg, 1.29 mmol) in dichloromethane (3 ml) was added a solution of *m*-chloroperbenzoic acid (320 mg, MCPBA ~70%, 1.29 mmol) in dichloromethane (2 ml) at 0–5 °C dropwise. The mixture was stirred at this temperature for 1 h, then poured on 1 N aqueous sodium hydroxide and the layers separated. The aqueous phase was extracted with dichloromethane, the combined organic layers washed with water and brine, dried over magnesium sulfate and evaporated. Yield: 520 mg (~100%) as an off-white solid, mp 191 °C. ^{1}H NMR ($CDCl_3$): δ 1.07 (s, 9H), 2.13 (s, 6H), 2.23 (s, 3H), 2.69 (m, 2H), 3.21 (m, 2H), 3.80 (dd, 1H), 4.31 (dd, 1H), 4.58 (dd, 1H), 4.79 (m, 1H), 6.83 (s, 2H).

5.1.27. 1-(2-Hydroxy-ethyl)-4-(2,4,6-trimethyl-phenyl)-pyrazolidine-3,5-dione (35)

A solution of 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** (42.35 g, 0.151 mol) in xylene (300 ml) was treated with (2-hydroxyethyl)hydrazine (**34**, *n* = 1) (11.50 g, 0.151 mol). The reaction mixture was heated and stirred at 100 °C under nitrogen atmosphere. The progression of the reaction was checked by TLC analysis (methanol/ethyl acetate 3:7). After completion of the reaction, the resulting white suspension was filtered and the filter cake thoroughly washed with *n*-hexane, then recrystallized from ethyl acetate. Yield: 24.65 g (62%) as white crystals, mp 203–209 °C. ^{1}H NMR (MeOH-d_4): δ 2.15 (s, 6H), 2.24 (s, 3H), 3.76 (appar s, 4H), 6.88 (s, 2H). ^{13}C NMR (MeOH-d_4): δ 20.6, 21.2, 48.6, 60.9, 89.2, 127.1, 128.9, 138.0, 140.5, 163.4, 166.7. MS (ES+) *m*/*z*: 263 $(C_{14}H_{18}N_2O_3 + H)^+$.

5.1.28. 1-(3-Hydroxy-propyl)-4-(2,4,6-trimethyl-phenyl)-pyrazolidine-3,5-dione (36)

5.1.28.1. Step 1: (3-Hydroxypropyl)hydrazine (34, *n* = 2). To a solution of sodium hydroxide pellets (48.09 g, 1.2 mol) in hydrazine monohydrate (300 g, 6.0 mol) at 98 °C under nitrogen atmosphere was added 3-chloropropanol (113.1 g, 1.2 mol) dropwise while maintaining the temperature between 95 °C and 100 °C. The reaction mixture was concentrated under reduced pressure, the resulting suspension filtered and the filtrate submitted to distillation under reduced pressure. Yield: 61.6 g (43%) as a colorless liquid, bp 105 °C/0.08 mbar. ^{1}H NMR (MeOH-d_4): δ 1.72 (quint, 2H), 2.85 (t, 2H), 3.65 (t, 2H), 4.70–5.00 (br s, 4H). ^{13}C NMR (MeOH-d_4): δ 29.9, 51.8, 69.8.

5.1.28.2. Step 2: 1-(3-Hydroxy-propyl)-4-(2,4,6-trimethyl-phenyl)-pyrazolidine-3,5-dione (36). A solution of 2-(2,4,6-trimethyl-phenyl)-malonic acid diethyl ester **12b** (8.40 g, 30.2 mmol) in xylene (200 ml) was treated with (3-hydroxypropyl)hydrazine (**34**, *n* = 2) (2.70 g, 30.0 mmol). The reaction mixture was flushed with argon and stirred under argon atmosphere. The flask was placed in a preheated oil bath at 150 °C and the mixture heated for 35 min, while ethanol was distilled off. The cooled reaction mixture was poured on a 1 N aqueous sodium hydroxide solution (50 ml) and the aqueous layer extracted twice with dichloromethane. The aqueous alkaline phase was acidified with cooling by careful addition of a 1 N HCl solution and the product extracted with dichloromethane. The organic phase was dried over sodium sulfate and evaporated. Yield: 1.10 g (13%) as beige crystals. ^{1}H NMR (MeOH-d_4): δ 1.92 (quint, 2H), 2.13 (s, 6H), 2.26 (s, 3H), 3.59 (t, 2H), 3.92 (t, 2H), 6.93 (s, 2H). MS (ES+) *m*/*z*: 277 $(C_{15}H_{20}N_2O_3 + H)^+$.

5.1.29. 7-(2,4,6-Trimethyl-phenyl)-dihydro-pyrazolo[1,2-*c*][1,3,4]oxadiazine-6,8-dione (37)

A mixture of 1-(2-hydroxy-ethyl)-4-(2,4,6-trimethyl-phenyl)-pyrazolidine-3,5-dione **35** (500 mg, 1.91 mmol), paraformaldehyde (126 mg, 4.20 mmol CH_2O) and triethylamine (5 ml) was stirred at 80 °C. The reaction was followed by TLC analysis. After complete conversion, the reaction mixture was evaporated under reduced pressure and the residue subjected to column chromatography on silica gel (ethyl acetate/methanol 8:2). Yield: 320 mg (62%) as white crystals, mp 212–213 °C. ^{1}H NMR (MeOH-d_4): δ 2.16 (s, 6H), 2.27 (s, 3H), 3.65 (t, 2H), 4.05 (t, 2H), 5.10 (s, 2H), 6.93 (s, 2H). ^{1}H NMR ($CDCl_3$): δ 2.06 (s, 3H), 2.25 (s, 3H), 2.39 (s, 3H), 3.68 (ddd, 1H), 3.79 (ddd, 1H), 3.94 (m, 2H), 4.67 (s, 1H), 5.06 (d, J_{AB} = 9.2 Hz, 1H), 5.19 (d, J_{AB} = 9.2 Hz, 1H), 6.84 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.2, 20.9, 21.0, 43.6, 48.7, 65.0, 75.2, 125.4, 129.5, 130.0, 136.0, 138.3, 138.5, 166.9, 170.4. MS (ES+) *m/z*: 275 ($C_{15}H_{18}N_2O_3$ + H)$^+$.

5.1.30. 8-(2,4,6-Trimethyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,3,4]oxadiazepine-7,9-dione (38)

A suspension of 1-(3-hydroxy-propyl)-4-(2,4,6-trimethyl-phenyl)-pyrazolidine-3,5-dione **36** (1.0 g, 3.62 mmol) in tetrahydrofuran (10 ml) was treated with a 37% aqueous solution of formaldehyde (6.8 ml, 90.5 mmol) and heated at reflux for 1 h. The reaction mixture was poured on water and extracted with ethyl acetate. The organic phase was dried over sodium sulfate and evaporated. The residue was subjected to column chromatography on silica gel (ethyl acetate/hexane 1:1 to 100% ethyl acetate). Yield: 510 mg (49%) as white crystals, mp 223–227 °C. ^{1}H NMR ($CDCl_3$): δ 1.90–2.08 (m, 2H), 2.05 (s, 3H), 2.25 (s, 3H), 2.39 (s, 3H), 3.66–3.75 (m, 2H), 4.00–4.07 (ddd, 1H), 4.43–4.51 (ddd, 1H), 4.69 (s, 1H), 4.84 (d, J_{AB} = 12.5 Hz, 1H), 5.62 (d, J_{AB} = 12.5 Hz, 1H), 6.83 (s, 1H), 6.92 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 20.1, 20.9, 21.0, 31.2, 41.6, 48.4, 72.4, 73.5, 125.9, 129.4, 130.0, 136.5, 138.1, 138.3, 164.6, 166.3. MS (ES+) *m/z*: 289 ($C_{16}H_{20}N_2O_3$ + H)$^+$.

5.1.31. Carbonic acid 3,5-diethyl-phenyl ester ethyl ester (40)

To a solution of 3,5-diethyl-phenol **39**[31] (100.6 g, 0.67 mol) and pyridine (53 ml, 52 g, 0.66 mol) in toluene (300 ml) was added ethyl chloroformate (108 g, 1.0 mol) dropwise. The suspension was heated at reflux overnight. The reaction mixture was poured on water, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over magnesium sulfate and evaporated. Yield: 143.1 g (96%) as an oil, this material was used without further purification. ^{1}H NMR ($CDCl_3$): δ 1.21 (t, 6H), 1.37 (t, 3H), 2.62 (q, 4H), 4.30 (q, 2H), 6.82 (s, 2H), 6.91 (s, 1H).

5.1.32. Carbonic acid 4-chloromethyl-3,5-diethyl-phenyl ester ethyl ester (41)

Through a milky solution of carbonic acid 3,5-diethyl-phenyl ester ethyl ester **40** (27.4 g, 123.3 mmol) and paraformaldehyde (3.7 g, 123.2 mmol CH_2O) in concentrated HCl (170 ml) at −5 °C was bubbled gaseous hydrogen chloride slowly over 1.5 h. The reaction mixture was stirred at room temperature overnight. Over the next three days, the mixture was further treated with paraformaldehyde (2 × 5 g, 1 × 2 g) and gaseous hydrogen chloride, and stirring continued at 50 °C until the reaction was judged complete by thin layer chromatography. The reaction mixture was flushed with argon, extracted twice with toluene, the combined organic phases washed twice with water and brine, dried over magnesium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:20). Yield: 16.98 g (51%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H), 1.38 (t, 3H), 2.78 (q, 4H), 4.31 (q, 2H), 4.66 (s, 2H), 6.91 (s, 2H).

5.1.33. (2,6-Diethyl-4-hydroxy-phenyl)-acetonitrile (42)

To a solution of sodium cyanide (5.38 g, 109.8 mmol) in ethanol (130 ml) and water (130 ml) was added a solution of carbonic acid 4-chloromethyl-3,5-diethyl-phenyl ester ethyl ester **41** (16.98 g, 62.7 mmol) in ethanol (40 ml) dropwise. The reaction mixture was heated to reflux for 17 h. The ethanol was evaporated, the residue diluted with ethyl acetate and poured on ice-water. The aqueous layer was extracted with ethyl acetate, the combined organic phases washed with brine, dried over magnesium sulfate and evaporated. Yield: 10.35 g (87%) as a solid, this material was used without further purification. An analytical sample of **42** was obtained through purification by chromatography on silica gel (ethyl acetate/hexane 1:4). White solid, mp 112 °C. ^{1}H NMR ($CDCl_3$): δ 1.22 (t, 6H), 2.63 (q, 4H), 3.61 (s, 2H), 5.69 (br s, 1H), 6.58 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.7, 16.1, 26.5, 113.5, 115.5, 118.3, 144.5, 155.6.

5.1.34. Trifluoromethanesulfonic acid 4-cyanomethyl-3,5-diethyl-phenyl ester (43)

To a solution of (2,6-diethyl-4-hydroxy-phenyl)-acetonitrile **42** (19.5 g, 103.0 mmol) and triethylamine (17.8 ml, 12.9 g, 127.7 mmol) in dichloromethane (215 ml) at −35 °C was added trifluoromethanesulfonic anhydride (19.1 ml, 32.8 g, 116.4 mmol) dropwise. The reaction mixture was stirred at −30 °C for 30 min, then allowed to warm to room temperature. The mixture was poured on cold saturated aqueous sodium hydrogen carbonate and extracted with dichloromethane. The combined organic layers were washed twice with saturated aqueous sodium hydrogen carbonate and brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl acetate/hexane 1:9). Yield: 27.0 g (82%) as an oil. ^{1}H NMR ($CDCl_3$): δ 1.29 (t, 6H), 2.77 (q, 4H), 3.69 (s, 2H), 7.02 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.2, 16.4, 26.4, 117.0, 118.7 (q, ^1J(C,F) = 321 Hz), 119.1, 126.8, 145.6, 149.5.

5.1.35. (2,6-Diethyl-4-methyl-phenyl)-acetonitrile (44a)

To a solution of trifluoromethanesulfonic acid 4-cyanomethyl-3,5-diethyl-phenyl ester **43** (27.0 g, 84.0 mmol) in tetrahydrofuran (70 ml) at room temperature was added tetrakis(triphenylphosphine)palladium(0) (430 mg, 0.37 mmol), followed by a 2 M trimethylaluminum solution in hexane (27.5 ml, 55.0 mmol) dropwise. The reaction mixture was heated at reflux for 4 h, treated with another portion of 2 M trimethylaluminum solution in hexane (3 ml, 6.0 mmol) and refluxed further for 1 h. The mixture was evaporated, the residue diluted with dichloromethane and the solution carefully treated with ice-water dropwise. The mixture was filtered through hyflo (calcined diatomaceous earth) to remove inorganic residues, the layers separated, the aqueous phase extracted with dichloromethane, the combined organic phases washed four times with water and brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (1% ethyl acetate in hexane). Yield: 12.77 g (81%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H), 2.31 (s, 3H), 2.69 (q, 4H), 3.64 (s, 2H), 6.92 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.9, 16.2, 21.0, 26.3, 118.2, 123.0, 127.5, 138.1, 142.4. MS (ES+) *m/z*: 188 ($C_{13}H_{17}N$ + H)$^+$.

5.1.36. (2,6-Diethyl-phenyl)-acetonitrile (44b)

To a solution of trifluoromethanesulfonic acid 4-cyanomethyl-3,5-diethyl-phenyl ester **43** (11.16 g, 35 mmol) in dimethylformamide (280 ml) at room temperature was added triethylamine (19.5 ml, 14.2 g, 140 mmol), formic acid (6.44 g, 140 mmol), triphenylphosphine (1.8 g, 6.9 mmol) and palladium acetate (390 mg, 1.74 mmol). The reaction mixture was heated to 40 °C and stirred for 17 h. After dilution with dichloromethane, the organic phase was washed twice with 1 N aqueous hydrogen chloride and brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (ethyl ace-

tate/hexane 1:9). Yield: 5.43 g (90%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.27 (t, 6H), 2.73 (q, 4H), 3.70 (s, 2H), 7.08–7.36 (m, 3H).

5.1.37. (2,6-Diethyl-4-methyl-phenyl)-acetic acid (7b)

To a cold solution of concentrated sulfuric acid (71 ml) in water (82 ml) was added (2,6-diethyl-4-methyl-phenyl)-acetonitrile **44a** (12.92 g, 69.0 mmol) and the mixture was heated at reflux until the reaction was judged complete by thin layer chromatography. The reaction mixture was diluted with water and ethyl acetate, the layers separated and the aqueous phase extracted with ethyl acetate. The combined organic layers were washed with water and brine, dried over sodium sulfate and evaporated. Yield: 13.86 g (97%) as an off-white solid, mp 123–125 °C. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 2.30 (s, 3H), 2.61 (q, 4H), 3.72 (s, 2H), 6.90 (s, 2H), 10.94 (br s, 1H). ^{13}C NMR ($CDCl_3$): δ 15.1, 21.2, 26.4, 33.5, 126.3, 127.2, 137.2, 143.0, 178.5. MS (ES−) *m/z*: 205 $(C_{13}H_{18}O_2–H)^-$.

5.1.38. (2,6-Diethyl-phenyl)-acetic acid (7c)

Obtained from (2,6-diethyl-phenyl)-acetonitrile **44b** (5.43 g, 31.3 mmol) in concentrated sulfuric acid (32 ml) and water (36 ml) according to procedure 5.1.37. Yield: 87% as a white solid, mp 71–73 °C. ^{1}H NMR ($CDCl_3$): δ 1.23 (t, 6H), 2.68 (q, 4H), 3.78 (s, 2H), 7.05–7.26 (m, 3H).

5.1.39. (2,6-Diethyl-4-methyl-phenyl)-acetic acid ethyl ester (45a)

Through a solution of (2,6-diethyl-4-methyl-phenyl)-acetic acid **7b** (19.31 g, 93.6 mmol) in ethanol (390 ml) was bubbled gaseous hydrogen chloride under cooling to keep the temperature below 35 °C. The reaction mixture was then heated at reflux for 5 h, allowed to cool, flushed with argon and evaporated. The residue was purified by chromatography on silica gel (2% ethyl acetate in hexane). Yield: 19.02 g (87%) as a colorless oil. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 1.24 (t, 3H), 2.30 (s, 3H), 2.62 (q, 4H), 3.68 (s, 2H), 4.14 (q, 2H), 6.89 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.2, 15.1, 21.2, 26.4, 33.9, 60.7, 127.1, 127.2, 136.8, 143.0, 172.0. MS (ES+) *m/z*: 235 $(C_{15}H_{22}O_2 + H)^+$, 257 $(C_{15}H_{22}O_2 + Na)^+$.

5.1.40. (2,6-Diethyl-4-methyl-phenyl)-acetic acid methyl ester (45b)

Data for the methyl ester of acid **7b**. Colorless oil, bp 95–98 °C/0.2 mbar. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 2.30 (s, 3H), 2.62 (q, 4H), 3.66 (s, 3H), 3.70 (s, 2H), 6.89 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 15.0, 21.1, 26.3, 33.7, 51.9, 126.9, 127.1, 136.8, 142.9, 172.4. MS (ES+) *m/z*: 221 $(C_{14}H_{20}O_2 + H)^+$, 243 $(C_{14}H_{20}O_2 + Na)^+$.

5.1.41. 2-(2,6-Diethyl-4-methyl-phenyl)-malonic acid diethyl ester (46a)

A solution of (2,6-diethyl-4-methyl-phenyl)-acetic acid ethyl ester **45a** (19.02 g, 81.2 mmol) in 50 ml of diethyl carbonate was added dropwise to a stirred suspension of sodium hydride (10.6 g, 55% w/w dispersion in mineral oil, 243 mmol) in diethyl carbonate (200 ml) at 100 °C (caution!). The mixture was heated at reflux overnight and quenched by slow addition of water dropwise under cooling. Upon destruction of the excess sodium hydride, the mixture was diluted with ethyl acetate and acidified to pH 1–2 by addition of a 1 N aqueous hydrogen chloride solution at 0–5 °C. The layers were separated, the aqueous phase extracted with ethyl acetate, the combined organic layers washed three times with water and twice with brine, dried over sodium sulfate and evaporated. The residue was purified by chromatography on silica gel (2% ethyl acetate in hexane). Yield: 18.32 g (73%) as a colorless viscous oil. ^{1}H NMR ($CDCl_3$): δ 1.19 (t, 6H), 1.27 (t, 6H), 2.30 (s, 3H), 2.65 (q, 4H), 4.22 (m, 4H), 5.02 (s, 1H), 6.92 (s, 2H).

5.1.42. 2-(2,6-Diethyl-4-methyl-phenyl)-malonic acid dimethyl ester (46b)

Data for the dimethyl malonate analog of **46a**. White solid, mp 54–55 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 6H), 2.30 (s, 3H), 2.64 (q, 4H), 3.73 (s, 6H), 5.06 (s, 1H), 6.93 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 15.2, 21.1, 26.6, 51.5, 52.6, 126.4, 127.9, 137.9, 143.6, 169.3. MS (ES+) *m/z*: 279 $(C_{16}H_{22}O_4 + H)^+$, 301 $(C_{16}H_{22}O_4 + Na)^+$.

5.1.43. 8-(2,6-Diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione (47, NOA 407854)

Obtained from [1,4,5]oxadiazepane dihydrobromide **23** (4.4 g, 16.6 mmol), 2-(2,6-diethyl-4-methyl-phenyl)-malonic acid diethyl ester **46a** (5.07 g, 16.5 mmol) and triethylamine (10.6 ml, 7.7 g, 76.1 mmol) in xylene (174 ml) according to procedure 5.1.19. Yield: 4.08 g (78%) as an off-white solid, mp 189–191 °C. ^{1}H NMR ($CDCl_3$): δ 1.18 (t, 3H), 1.24 (t, 3H), 2.26 (q, 2H), 2.29 (s, 3H), 2.69 (q, 2H), 3.74 (ddd, J = 13.3 Hz, 8.0 Hz and 0.9 Hz, 2H), 3.92 (ddd, J = 15.3 Hz, 8.0 Hz and 0.9 Hz, 2H), 3.96 (ddd, J = 13.3 Hz, 6.3 Hz and 0.9 Hz, 2H), 4.25 (ddd, J = 15.3 Hz, 6.3 Hz and 0.9 Hz, 2H), 4.70 (s, 1H), 6.90 (s, 1H), 6.93 (s, 1H). ^{13}C NMR ($CDCl_3$): δ 14.1, 15.9, 21.0, 25.5, 28.0, 45.9, 47.4, 70.3, 124.5, 127.5, 127.9, 138.3, 142.1, 144.5, 165.9. MS (ES+) *m/z*: 317 $(C_{18}H_{24}N_2O_3 + H)^+$. HRMS (EI+) *m/z*: Calcd for $(C_{18}H_{24}N_2O_3)^+$: 316.1787; Found: 316.1783. IR (KBr): ν 3418, 2963m, 1739, 1692, 1550, 1453, 1277, 1129, 1000 cm^{-1}.

5.1.44. 2,2-Dimethyl-propionic acid 8-(2,6-diethyl-4-methyl-phenyl)-9-oxo-1,2,4,5-tetrahydro-9*H*-pyrazolo[1,2-*d*][1,4,5]oxadiazepin-7-yl ester (6, NOA 407855, pinoxaden)

Obtained from 8-(2,6-diethyl-4-methyl-phenyl)-tetrahydro-pyrazolo[1,2-*d*][1,4,5]oxadiazepine-7,9-dione **47** (NOA 407854, 1.0 g, 3.16 mmol), pivaloyl chloride (0.5 ml, 0.49 g, 4.06 mmol), triethylamine (0.9 ml, 0.65 g, 6.46 mmol) and a catalytic amount of 4-dimethylaminopyridine (DMAP, ~3 mol %) in tetrahydrofuran (30 ml) according to procedure 5.1.23. The crude product obtained after extractive workup was purified by chromatography on silica gel (ethyl acetate/methanol 20:1). Yield: 1.07 g (85%) as a crystalline white solid, mp 122–123 °C. ^{1}H NMR ($CDCl_3$): δ 1.03 (s, 9H), 1.12 (t, 6H), 2.29 (s, 3H), 2.35–2.63 (m, 4H), 3.81–3.90 (m, 4H), 3.93 (m, 2H), 4.26 (m, 2H), 6.88 (s, 2H). ^{13}C NMR ($CDCl_3$): δ 14.7, 21.3, 26.3, 26.4, 39.1, 45.6, 49.5, 69.4, 70.6, 97.3, 122.7, 126.0, 137.7, 144.3, 149.1, 162.0, 174.1. FD-MS *m/z*: 400 $(C_{23}H_{32}N_2O_4)^+$. HRMS (EI+) *m/z*: Calcd for $(C_{23}H_{32}N_2O_4)^+$: 400.2362; Found: 400.2361. IR (KBr): ν 2968m, 1778, 1639, 1603, 1473m, 1389, 1330m, 1275, 1122, 1077, 1013 cm^{-1}.

5.2. Crystal structure determination

Pinoxaden **6** was dissolved in hot *tert*-butyl methyl ether, filtered through a cotton-wool plug, and the resulting colorless solution allowed to cool to room temperature to obtain needle-like crystals. A colorless single crystal of dimensions 280 × 80 × 70 μm^3 was used to carry out the structure determination. Diffraction data were collected at 100 K with a Bruker AXS SMART 6000 CCD detector on a three-circle platform goniometer with graphite monochromatized Cu(Kα) radiation from a sealed tube generator. A semi-empirical absorption correction was applied, based on the intensities of symmetry-related reflections measured at different angular settings (Sheldrick, G. M. SADABS, University of Göttingen, Göttingen, Germany). The structure was solved and refined on F^2 with the SHELXTL suite of programs (Sheldrick, G. M. SHELXTL, Bruker AXS Inc. Madison, Wisconsin, USA). The asymmetric unit contains two crystallographically independent molecules. All non-hydrogen atoms were refined with anisotropic displacement parameters, hydrogen atoms were located in a Difference Fourier map and refined in idealized positions using a riding model.

Final crystallographic data and structure refinement parameters for pinoxaden **6**: $C_{23}H_{32}N_2O_4$, $M_r = 400.51$, triclinic, space group $P\bar{1}$ with $a = 9.450(3)$, $b = 14.759(4)$, $c = 17.368(5)$ Å, $\alpha = 69.935(14)°$, $\beta = 75.975(13)°$, $\gamma = 86.187(17)°$, $V = 2207.1(11)$ Å^3, $Z = 4$, $D_c = 1.205$ g cm^{-3}, 26327 reflections measured, 7600 independent, $2.79° < \theta < 66.61°$, $T = 100(2)$ K, 535 parameters, no restraints, $R_1 = 0.0388$, $wR_2 = 0.0979$ for 6583 reflections with $I > 2\sigma(I)$, $R_1 = 0.0456$, $wR_2 = 0.1062$ for all 7600 data, GoF = 1.065, res. el. dens. = +0.41/−0.29 e Å^3.

Crystallographic data (excluding structure factors) for **6** have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication number CCDC 706870. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1 EZ, UK (fax: +44-(0)1223-336033 or e-mail: deposit@ccdc.cam.ac.uk).

5.3. Biological greenhouse tests

5.3.1. Test plants

The following crops and weed species have been used to evaluate the herbicidal activity: *Hordeum vulgare* L. (HORVX, barley), *Triticum aestivum* L. (TRZAW, winter wheat), *Alopecurus myosuroides* (ALOMY, blackgrass), *Avena fatua* (AVEFA, wild oat), *Lolium perenne* (LOLPE, perennial ryegrass), *Setaria faberi* (SETFA, foxtail).

5.3.2. Evaluation of post-emergence herbicidal activity

Plant cultivation, herbicide application and damage evaluation were conducted as follows: Monocotyledonous test plants were sown in plastic pots filled with standard soil. After cultivation under controlled glasshouse conditions, the plants were sprayed at the 3- to 6-leaf stage with an aqueous spray solution (500 L ha^{-1} carrier volume) prepared by diluting appropriately a formulation of the technical active ingredient with water and with optional addition of either the adjuvant X-77 (0.2%, v/v) (Registry number 11097-66-8) or Merge® (1%, v/v) (Registry number 147230-14-6). Application rates were between 2000 and 30 g ai ha^{-1}. Formulations used in this study included either wettable powders (WP10 or WP25) or instant formulations (IF50) obtained by dissolving an acetone solution of the test compound into a blank formulation containing 10.6% Emulsogen EL (Registry number 61791-12-6), 42.2% *N*-methyl pyrrolidone, 42.2% dipropylene glycol monomethyl ether (Registry number 34590-94-8) and 0.2% X-77. After further cultivation in the greenhouse under optimum conditions for 21 days, visual assessment of weed control and crop damage was made using a 0–100% rating scale (100% = total damage to test plant; 0% = no damage to test plant).

5.3.3. Safener effect on herbicidal activity

For the comparative study of NOA 407854 **47** and pinoxaden **6** applied alone or in combination with the safener cloquintocet-mexyl[39] (Registry number 99607-70-2) (Table 7), the above protocol 5.3.2 was slightly modified. Test plants sown in plastic pots filled with sandy clay loam and grown under controlled glasshouse conditions were sprayed at the 3- to 6-leaf stage with an aqueous spray solution (500 L ha^{-1}) derived either from an EC200 formulation of the herbicides **47** or **6** alone, or from a mixture of an EC200 formulation of each herbicide (H) with an EC100 formulation of the safener (S) cloquintocet-mexyl at a ratio H/S of 4:1. Merge® (0.7%, v/v) was incorporated to the spray solution as adjuvant. Visual assessment of weed control and crop damage upon treatments with and without safener was made using a 0–100% rating scale (100% = total damage to test plant; 0% = no damage to test plant). Crop injury 12 days after treatment (DAT) on winter barley (*cv Manitou*), winter wheat (*cv Arina*) and summer wheat (*cv Lona*) was assessed at a use rate of 60 g ha^{-1} **47** or **6**, whereas grass control on AVEFA and LOLRI was evaluated 20 DAT at 30 g ha^{-1} **47** or **6**.

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