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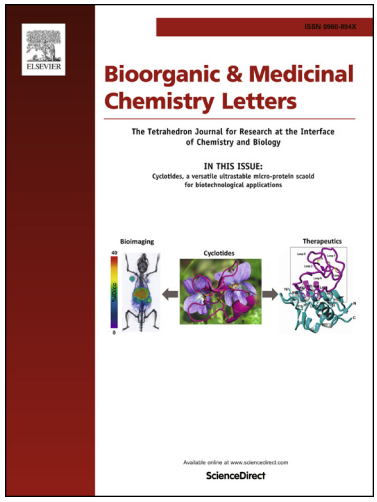

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Herbicidal aryldiones incorporating a 5-methoxy-[1,2,5]triazepane ring

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ABSTRACT

Novel 2-aryl-cyclic-1,3-diones containing a 5-methoxy-[1,2,5]triazepane unit were explored towards an effective and wheat safe control of grass weeds. Their preparation builds on the ease of synthetic access to 7-membered heterocyclic [1,2,5]triazepane building blocks. Substitution and pattern hopping in the phenyl moiety revealed structure-activity relationships in good agreement with previously disclosed observations amongst the pinoxaden family of acetyl-CoA carboxylase inhibitors. In light of basic physicochemical, enzyme inhibitory and binding site properties, the *N*-methoxy functionality effectively acts as a bioisostere of the ether group in the seven-membered hydrazine ring.

Diverse 2-aryl-cyclic-1,3-dione derivatives (ADs) reported in recent years have demonstrated weed control effects against monocotyledonous plant species.[1,2] They interfere with lipid biosynthesis in sensitive grass weeds by inhibiting the carboxyl transferase (CT) domain of homomeric acetyl-coenzyme A carboxylase (ACCase) located in the chloroplasts. Research work in the particular 4-aryl-pyrazolidine-3,5-dione subclass that features 5- to 7-membered cyclic hydrazines, optionally interrupted by heteroatoms such as oxygen or sulfur, led to the discovery[3] and commercialization of the cereal herbicide pinoxaden **1** (PXD, Fig. 1). The pivaloyl functionality G acts as a cleavable group *in planta* resulting in release of the active principle PXD-dione **2**, which is responsible for the ACCase target site activity.[4]

We intend herein to describe chemistry and biology of aza-PXD analogs (pinazadens), more specifically ADs incorporating a 5-methoxy-[1,2,5]triazepane ring ([A]= -CH_2-N(OCH_3)-CH_2-). Their preparation relies on the use of corresponding 7-membered heterocyclic [1,2,5]triazepane building blocks unprecedented in the chemical literature.

The 7-membered cyclic hydrazine building blocks **7** and **10** were prepared in multigram quantities from readily available starting materials (Scheme 1). Thus, oxirane was condensed twice with *O*-methyl-hydroxylamine and the resulting bis-hydroxyethylamine **3**[5] further converted into the corresponding ~~bis-mesy~~late **4** under standard conditions. *N,N'*-alkylation of the

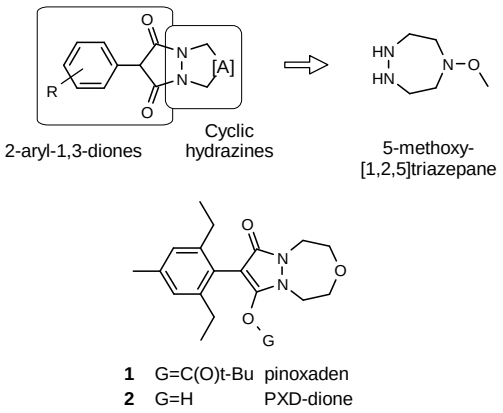

Figure 1. The class of herbicidal ADs containing cyclic hydrazines illustrated with pinoxaden (PXD) **1** and its active principle AD **2**.

bisanion of 1,2-bis-BOC protected hydrazine **5** with **4**, followed by BOC-deprotection of **6** using hydrochloric acid delivered the 5-methoxy-[1,2,5]triazepane hydrochloride salt **7** smoothly. Alternatively the triazepane ring formation could also be achieved under phase transfer catalysis conditions.[6] Bis-alkylation of the orthogonally protected hydrazine **8**[6b] with mesylate **4** similarly afforded the 5-methoxy-[1,2,5]triazepane

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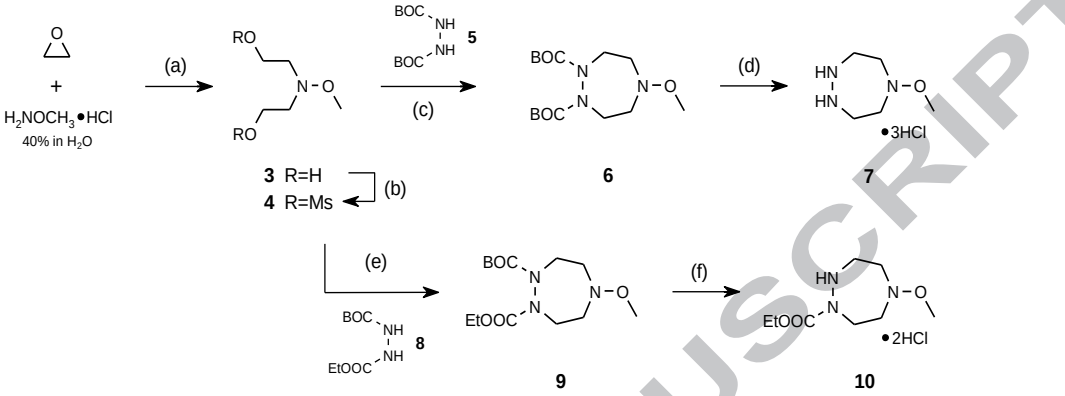
monoester **10** after deprotection, isolated either as a free base or as a hydrochloride salt.[7]

Aryl-pyrazolidine-3,5-diones **14** were mainly prepared by base-mediated cyclization[3] of intermediates **13**, themselves available by coupling activated aryl acetic acid derivatives **11** with the novel cyclic hydrazine monoester **10** (Scheme 2, route [a]). When handling substrates **13** with bulky substitution in the *ortho*-position of the phenyl ring, the ring closure reaction had to be performed at elevated temperature. Conversely, thermal condensation reactions between appropriately substituted aryl malonic acid esters **12** and the methoxy-triazepane building block **7** were also possible, *albeit* delivering **14** in low yields (route [b]). Nearly all dione active principles **14** were derivatized as enol ethyl carbonate pro-herbicides[8] **15**.[9]

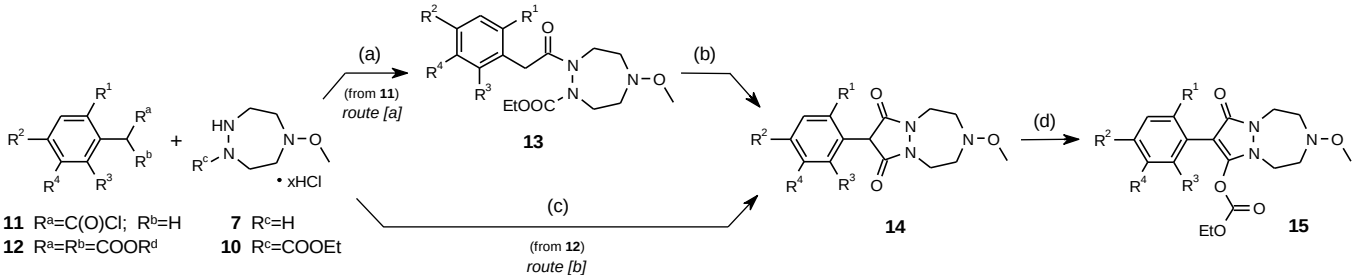


Scheme 1. Preparation of the 5-methoxy-[1,2,5]triazepane building blocks **7** and **10**.
Reagents and conditions: (a) Oxirane, *O*-methyl-hydroxylamine hydrochloride (40% w/w in H_2O), NaOH, 0°C; (b) CH_3SO_2Cl, NEt_3, THF, 0°C-RT; (c) BOCNHNHBOC **5**, NaH, DMF, 0 to 65°C; or alternatively **5**, bis-mesylate **4**, 30% NaOH w/w in H_2O, Bu_4NBr cat., toluene, reflux; (d) 2M HCl in Et_2O, Et_2O, 0°C-RT, isolate precipitate; then 4M HCl in dioxane, EtOAc, 90°C; (e) BOCNHNHCOOEt **8**, NaH, DMF, 0 to 65°C; (f) 2M HCl in Et_2O, Et_2O, RT; optional aqueous basic workup.

Phenyl substitution impact of pinazaden compounds **15** on weed control efficacy (four key grasses: *Alopecurus myosuroides*, *Avena fatua*, *Echinochloa crus-galli*, *Lolium perenne*) and on crop tolerance (wheat and rice) is presented in Table 1 for post-emergence applications at a use rate of 62.5 g ai ha^{-1} under standard screening conditions (see Supporting Information). Tolerance data on winter wheat shoots grown from seeds treated with the safener cloquintocet-mexyl (TRZAW-CQC), when compared to the unsafened control (TRZAW), permitted to estimate the potential for crop injury reduction (safener[10] action). The herbicidal potency/selectivity data of pinoxaden **1** is included for comparison.

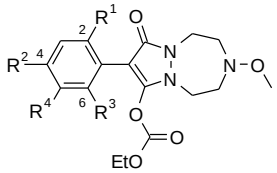
Probing a 2,5-dimethyl (**15a**) or 2,4,5-trimethyl (**15b**) substitution on the phenyl ring resulted in very weak active analogs at best. In contrast, a 2,4,6-trimethyl substitution (**15c**) returned decent potency against grasses. That phenyl pattern further tolerated a number of bulkier substituents in the *ortho*-position, such as bromo, ethyl, ethynyl or methoxy (**15d**, **15j**, **15m**, **15n**), usually associated with an improved herbicidal activity impact. However, phenyl in this *ortho*-position was detrimental (**15p**). Combining chloro and ethyl in the 2,6-positions unveiled an interestingly active compound (**15o**), but the extent of crop damage was too severe. Conversely, the *para*-position (R^2) was found sensitive to the substituent type, halogens or ethynyl (**15e**, **15f**, **15g**, **15l**) led to weakened control of the monocotyledonous species. A 4-methyl substituent (**15d**, **15j**, **15k**, **16**, **15o**) appeared satisfactory, if not optimal, with respect to performance against the targeted grassy weeds, but even bulkier groups were tolerated (4-F-Ph, **15r**). The latest however exhibited a gap on LOLPE, whilst also showing borderline cereal selectivity. Owing to observations that substituted phenyl rings at R^4 were indulged[1], we also explored 2-methyl-5-halophenyl derivatives (**15q**, **15s**). The 2,5-disubstituted analog **15q** displayed acceptable levels of grass control, but phytotoxicity to wheat may be of some concern. Adding a further methyl group in the *ortho*-position (2,5,6-trisubstituted **15s**) surprisingly resulted in significant diminished herbicidal activity at the rate tested.

Interesting herbicidal activity of the 4-halophenyl derivative **15r** prompted to further explore *para*-substituted analogs (Table 2, activity/selectivity data of dione active principles **14**). A 4-propynyl substituent (**14t**) already demonstrated improved graminicidal activity over its ethynyl equivalent **14l**. Noticeably



Scheme 2. Preparation of 5-methoxy-[1,2,5]triazepane containing ADs **14** and their corresponding enol ethyl carbonate pro-herbicides **15**.
Reagents and conditions: (a) Aryl-acetyl chloride **11**, methoxy-triazepane **10**, NEt_3, DMAP cat., THF, 0°C-RT; (b) NaOMe, DMF, 10°C-RT (and up to 80°C, depending on bulkiness of *ortho*-aryl substitution); (c) Aryl malonate **12** (R^d = Me or Et), methoxy-triazepane **7**, NEt_3, xylene, reflux; (d) EtOC(O)Cl, NEt_3, DMAP cat., THF, 0-5°C.

Table 1
Influence of the phenyl substitution of carbonic acid ethyl ester 3-methoxy-9-oxo-8-phenyl-2,3,4,5-tetrahydro-1H,9H-pyrazolo[1,2-a][1,2,5]triazepin-7-yl esters on crop selectivity and herbicidal grass activity[a]



15

Compound	R^1	R^2	R^3	R^4	TRZAW-CQC	TRZAW	ORYSA	ALOMY	AVEFA	ECHCG	LOLPE
15a	CH_3	H	H	CH_3	**0**	**0**	**0**	0	0	0	0
15b	CH_3	CH_3	H	CH_3	**0**	**0**	**10**	0	0	30	20
15c	CH_3	CH_3	CH_3	H	**0**	20	70	60	80	80	70
15d	CH_3	CH_3	Br	H	**0**	60	100	**100**	**90**	**90**	**90**
15e	CH_3	Br	CH_3	H	**10**	40	30	50	10	10	60
15f	CH_3	Cl	CH_3	H	**0**	30	**10**	60	30	40	60
15g	CH_3	Cl	Br	H	**0**	20	40	40	20	10	40
15h	Cl	CH_3	Br	H	**0**	30	70	60	50	20	70
15i	CH_3	CH_3	$-CH=CH_2$	H	**0**	**0**	**0**	50	10	0	20
15j	CH_3	CH_3	CH_2CH_3	H	40	90	100	**100**	**100**	**100**	**100**
15k	CH_2CH_3	CH_3	CH_2CH_3	H	**0**	70	100	**90**	**100**	**100**	**90**
16[b]	CH_2CH_3	CH_3	CH_2CH_3	H	**0**	60	100	**100**	**100**	**100**	**100**
15l	CH_3	$-C\equiv CH$	CH_3	H	**0**	**0**	20	10	10	30	30
15m	CH_3	CH_3	$-C\equiv CH$	H	20	80	80	**90**	**90**	**90**	80
15n	CH_3	CH_3	OCH_3	H	60	70	70	70	70	80	70
15o	Cl	CH_3	OCH_3	H	50	90	100	**100**	**90**	**100**	**90**
15p	CH_3	CH_3	Ph	H	**0**	20	30	30	10	0	10
15q	CH_3	H	H	4-Cl-Ph	40	80	20	70	**90**	80	50
15r	CH_3	4-F-Ph	CH_3	H	**10**	50	100	80	80	**100**	50
15s	CH_3	H	CH_3	4-F-Ph	**0**	**0**	**0**	0	0	0	0
PXD **1**[c]	CH_2CH_3	CH_3	CH_2CH_3	H	**5**	40	90	**90**	**100**	**100**	**100**

[a] Post-emergence crop damage and grass control (%) at 62.5 g ai ha^{-1} on whole plants of formulated compounds **15** with 0.5% adjuvant Tween 20 (v/v). Crops: TRZAW-CQC = wheat with a cloquintocet-mexyl seed treatment applied at a rate of 0.5g ai kg^{-1} seeds, TRZAW = wheat, ORYSA = rice; Grass weeds: ALOMY = *Alopecurus myosuroides*, AVEFA = *Avena fatua*, ECHCG = *Echinochloa crus-galli*, LOLPE = *Lolium perenne*.

[b] Enol pivaloyl pro-herbicide of active principle **14k**, which was prepared in analogy to published procedures.[3]

[c] Results for PXD are representative of several independent experiments (project standard) and show arithmetic means (n=65).

haloheteroaryl derivatives **14u-x** revealed good to excellent post-emergence grass weed control, wherein pyridyl (**14w**) and pyrimidinyl (**14x**) analogs overcame the LOLPE gap observed amongst other halo(het)aryl variants (**14r**, **14u**). Remarkably the binding site appears able to accommodate such bulky groups at the 4-position located deepest in the ACCase dimer interface (see discussion Fig. 2 below). As a major drawback however, those attractive compounds clearly lacked crop selectivity.

Potent pinazaden compounds **15** on the cereal grass weed spectrum (*Alopecurus myosuroides*, *Avena fatua*, *Lolium perenne*) were also controlling the rice weed *Echinochloa crus-galli* efficiently. Noticeably though the degree of rice damage was almost consistently higher than phytotoxicity on wheat. Lack of intrinsic rice tolerance as an insufficient attribute of this AD class represents therefore a serious challenge for a post-emergence application in rice.

Proherbicides **15k** and **16** incorporating a 5-methoxy-[1,2,5]triazepane ring and featuring a 2,6-diethyl-4-methyl-phenyl moiety expressed excellent activity levels over the cereal weed spectrum and particularly noteworthy demonstrated a clear trend to reduce wheat crop injury in combination with a safener exertion. Their common active principle *N*-methoxy triazepane dione **14k** moreover exhibits a very similar biological profile in comparison to the PXD-dione **2** (Table 3). Indeed, an essentially equipotent performance (both activity levels and wheat crop selectivity) was obtained at 15.6 g ai ha^{-1} to achieve roughly 80-90% grass weed control with low wheat damage which can be fully cleared through the cloquintocet safener treatment. In contrast, the mesityl active principle analog **14c** is biologically much less attractive.

The observed herbicidal activity similarity between derivatives incorporating either a 5-methoxy-[1,2,5]triazepane (**14c**, **14k**) or a [1,4,5]oxadiazepane (**17**, **2**) ring may be in part rationally explained when looking at basic molecular properties (Table 4). Weak acid character of the cyclic-1,3-dione unit, water solubility and lipophilicity are all in close range within pairs.

Those physicochemical properties importantly drive translocation properties *in planta*, movement which was demonstrated to happen bi-directionally (two-way systemicity or ambimobility).[4] Of further particular note, the maize chloroplastic ACCase activity also turned out to be of the same order of magnitude when measuring matched pairs indicating similar receptor affinities.

Equally important are facts taken from the binding mode of those inhibitors in the ACCase active site. By analogy to PXD-dione **2**, AD **14k** is likely bound to the carboxyl transferase (CT) domain at its dimer interface. Figure 2 summarizes key anchoring points of interaction,[11] such as the enolate hydrogen-bonding to the main chain amides of Ala1627 and Ile1735 (oxyanion site), the hydrogen bond between the other oxygen of the central pyrazoline ring and the amide of Gly1998', one of the ethyl substituents that points in the direction of a hydrophobic pocket that containing residue Leu1705 or pi-stacking of the phenyl ring to flat amide fragments. Importantly, the 5-methoxy-[1,2,5]triazepane ring is largely solvent exposed without relevant

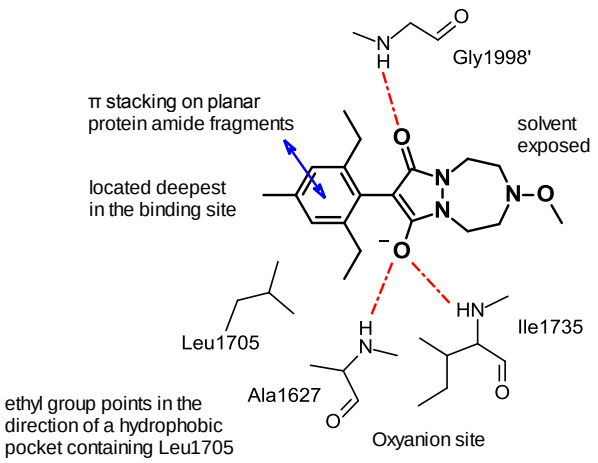
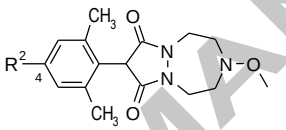


Figure 2. Schematic drawing of the anchoring points of interaction between AD **14k** and the yeast CT domain active site (adapted from Tong et al. [11]).

Table 2
Influence of selected alkynyl and halo(het)aryl substitution in the 4-position of 8-(2,6-dimethylphenyl)-3-methoxy-1,2,4,5-tetrahydropyrazolo[1,2-a][1,2,5]triazepine-7,9-dione on crop selectivity and herbicidal grass activity[a]



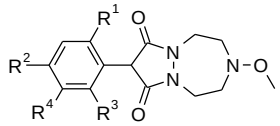
14

Compound	R^2	TRZAW-CQC	TRZAW	ORYSA	ALOMY	AVEFA	ECHCG	LOLPE
14l	-C≡CH	**0**	**0**	30	20	10	40	40
14t	-C≡CCH$_3$	30	60	NT[b]	70	60	80	60
14r	4-F-Ph	**10**	70	90	80	80	**100**	30
14u	4-chloropyrazol-1-yl	20	70	80	80	70	**90**	30
14v	5-chloro-2-pyridyl	60	70	70	70	70	70	70
14w	5-chloro-3-fluoro-2-pyridyl	60	80	100	**90**	**90**	**100**	**90**
14x	5-chloropyrimidin-2-yl	70	70	90	80	**90**	**90**	80

[a] Post-emergence crop damage and grass control (%) at 62.5 g ai ha^{-1} on whole plants of formulated compounds **14** with 0.5% adjuvant Tween 20 (v/v). Crops: TRZAW-CQC = wheat with a cloquintocet-mexyl seed treatment applied at a rate of 0.5g ai kg^{-1} seeds, TRZAW = wheat, ORYSA = rice; Grass weeds: ALOMY = *Alopecurus myosuroides*, AVEFA = *Avena fatua*, ECHCG = *Echinochloa crus-galli*, LOLPE = *Lolium perenne*.

[b] NT = not tested.

Table 3
Crop selectivity and herbicidal grass activity[a] of *N*-methoxy triazepane derivative **14k** in comparison to PXD-dione **2**.

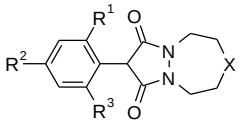


14

Compound	R^1	R^2	R^3	R^4	TRZAW-CQC	TRZAW	ORYSA	ALOMY	AVEFA	ECHCG	LOLPE
14c	CH_3	CH_3	CH_3	H	**0**	**0**	30	50	20	40	50
14k	CH_2CH_3	CH_3	CH_2CH_3	H	**0**	20	80	80	**90**	**90**	**90**
PXD-dione **2**	CH_2CH_3	CH_3	CH_2CH_3	H	**0**	**10**	80	**90**	80	**90**	70

[a] Post-emergence crop damage and grass control (%) at 15.6 g ai ha^{-1} on whole plants of formulated compounds **14** and **2** with 0.5% adjuvant Tween 20 (v/v). Crops: TRZAW-CQC = wheat with a cloquintocet-mexyl seed treatment applied at a rate of 0.5g ai kg^{-1} seeds, TRZAW = wheat, ORYSA = rice; Grass weeds: ALOMY = *Alopecurus myosuroides*, AVEFA = *Avena fatua*, ECHCG = *Echinochloa crus-galli*, LOLPE = *Lolium perenne*.

Table 4
Key physicochemical properties and maize chloroplastic ACCase inhibition of *N*-methoxy triazepanes **14c** and **14k** in comparison to PXD-dione analogs **17** and **2**.



Compound	R^1	R^2	R^3	X	pKa	log P	log D	Solubility[b] (ppm)		ACCase[c]
						neutral	pH 6[a]	neutral	pH 6[a]	IC_{50} (μM)
14c	CH_3	CH_3	CH_3	$NOCH_3$	3.98	1.6	-0.5	499	52702	4.78 ± 1.21
14k	CH_2CH_3	CH_3	CH_2CH_3	$NOCH_3$	3.78	2.2	-0.1	121	20277	0.10 ± 0.02
17[d]	CH_3	CH_3	CH_3	O	3.91	1.2	-0.9	435	53975	5.44 ± 0.96
PXD-dione **2**	CH_2CH_3	CH_3	CH_2CH_3	O	3.84	1.8	-0.3	248	36057	0.34 ± 0.10

[a] LogD and solubility at pH 6 are calculated.
[b] Water solubility expressed as parts per million (ppm).
[c] Inhibition of the maize chloroplastic isoform of ACCase (colourimetric assay): arithmetic mean and standard deviation based on 4 replicates.
[d] Preparation of compound **17** was disclosed previously.[3]

interactions with the enzyme. Hence, the *N*-methoxy surface region of the 7-membered ring derivative **14k** is likely to predominantly impact participation in polar interactions with water, as is the oxygen functionality of its ether counterpart **2**. Hereby, the basicity of the *N*-methoxy nitrogen plays a minor role as hydroxylamines are known to be considerably less basic than amines.[12]

Above molecular properties and target site binding data highlight the *N*-methoxy group within the [1,2,5]triazepane as a surrogate for the in-ring oxygen of the [1,4,5]oxadiazepane moiety. Owing the low nitrogen basicity (the aqueous basicity of Me_2NOMe [3.65] is more than 6 pK units weaker[12a] than NMe_3 [9.80]), and hence the unlikely role of the hydroxylamine nitrogen to act as a hydrogen bond acceptor, this in-ring ether is formally isosterically substituted with an on-ring methoxy functionality. Overall, this effective bioisosteric replacement[13] elicits very similar herbicidal effects, as both grass weed control and wheat tolerance of ADs **15k**/**16** and **14k** are on par with their pinoxaden analogues **1** and **2**.[14] Other ring ether isosteric replacements explored thus far, such as classical bivalent methylene, sulfur (in all oxidation states) or *N*-methyl groups,[3] indeed also resulted in bioactive inhibitors, though with (much) diminished graminicide potency levels. By contrast, a simple alcohol group on the seven-membered carbocyclic hydrazine ring investigated previously[4] was identified as a potent on-ring oxygenated isostere variant, *albeit* with a too severe extent of crop damage.

In summary, we conducted herein a series of chemical and biological investigations in the 4-aryl-pyrazolidine-3,5-dione class of compounds incorporating a 5-methoxy-[1,2,5]triazepane ring. Such 7-membered heterocyclic AD derivatives were easily prepared in few steps and through the key involvement of versatile cyclic hydrazine [1,2,5]triazepane building blocks **7** and **10**. Modulation of the aryl substitution (both pattern and substituent type) revealed derivatives with significant post-emergence herbicidal action against grass weeds and attractive tolerance to wheat, particularly in combination with a cloquintocet safener treatment. Those structure-activity relationship observations follow earlier described trends[3,4] in the PXD **1** class and unveil here the pinazaden family **14**/**15** of ACCase inhibitors. Linking this SAR parallelism between [1,4,5]oxadiazepane and 5-methoxy-[1,2,5]triazepane containing graminicides to similarities of the physicochemical properties, the receptor affinities and the key interactions at the binding site suggest a bioisosteric relation wherein oxygen can be replaced by *N*-methoxy in the seven-membered hydrazine ring.

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References and notes

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9. Detailed experimental and analytical data for compounds **3**, **4**, **6**, **7**, **9** and **10**, as well as representative procedures for the preparation of aryldiones **14** and their corresponding enol ethyl carbonate pro-herbicides **15** incorporating a 5-methoxy-[1,2,5]triazepane ring can be found in the Supplementary Material. Data for key compounds: *Carbonic acid 8-(2,6-diethyl-4-methyl-phenyl)-3-methoxy-9-oxo-2,3,4,5-tetrahydro-1H,9H-pyrazolo[1,2-a][1,2,5]triazepin-7-yl ester ethyl ester* (**15k**): ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.13 (t, *J* = 7.6 Hz, 6H), 1.21 (t, *J* = 7.1 Hz, 3H), 2.31 (s, 3H), 2.39-2.60 (m, 4H), 3.20 (m, 2H), 3.25 (m, 2H), 3.54 (s, 3H), 3.96 (br s, 2H), 4.15 (q, *J* = 7.1 Hz, 2H), 4.25 (br s, 2H), 6.92 (s, 2H) ppm; LC/MS (ES+): 418 $(M+H)^+$, R_t = 1.57 min.
8-(2,6-Diethyl-4-methyl-phenyl)-3-methoxy-tetrahydro-pyrazolo[1,2-a][1,2,5]triazepine-7,9-dione (**14k**): mp 240 °C (dec); ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.17 (t, *J* = 7.6 Hz, 3H), 1.24 (t, *J* = 7.6 Hz, 3H), 2.22 (q, *J* = 7.6 Hz, 2H), 2.29 (s, 3H), 2.68 (q, *J* = 7.6 Hz, 2H), 3.07-3.13 (m, 2H), 3.36-3.41 (m, 2H), 3.55 (s, 3H), 3.92-4.05 (m, 2H), 4.20-4.31 (m, 2H), 4.67 (s, 1H), 6.90 (s, 1H), 6.92 (s, 1H) ppm; LC/MS (ES+): 346 $(M+H)^+$ and (ES-): 344 $(M-H)^-$, R_t = 1.40 min.

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14. The development of resistance to ACCase inhibitors in several agronomically important grass weeds[1,14a] and involved resistance mechanisms[11a,14b] were extensively documented over the past several years, see in particular:
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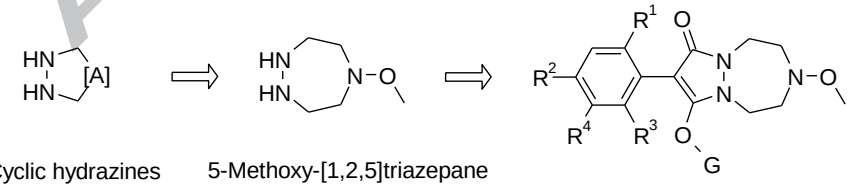
(b) Zhu XL, Yang GF. A comparative study of drug resistance mechanism associated with active site and non-active site mutations: I388N and D425G mutants of acetyl-coenzyme-A carboxylase. *Curr Comput Aided Drug Des*. 2012;8:62-69 and references cited therein. The potent and wheat safe AD **15k**/**16**-safener combination reported herein does not provide breakthrough solutions for the control of resistant biotypes.

Supplementary Material

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.xxx.

Graphical abstract



Cyclic hydrazines 5-Methoxy-[1,2,5]triazepane