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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-mesylate **4** under standard conditions. *N,N′*-alkylation of the 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 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 proherbicides[8] **15**.[9]

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

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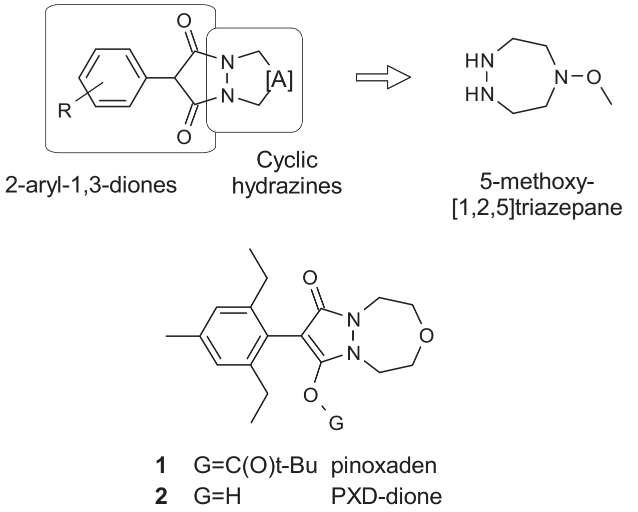
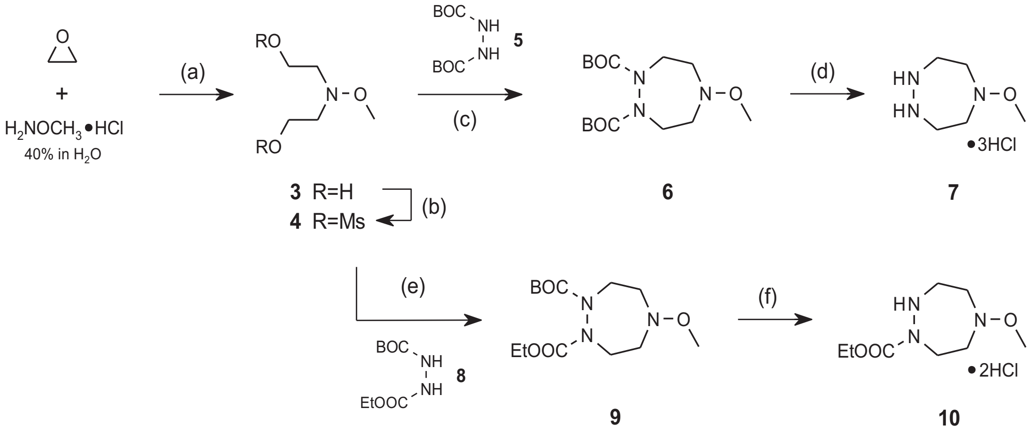


Fig. 1. The class of herbicidal ADs containing cyclic hydrazines illustrated with pinoxaden (PXD) **1** and its active principle AD **2**.

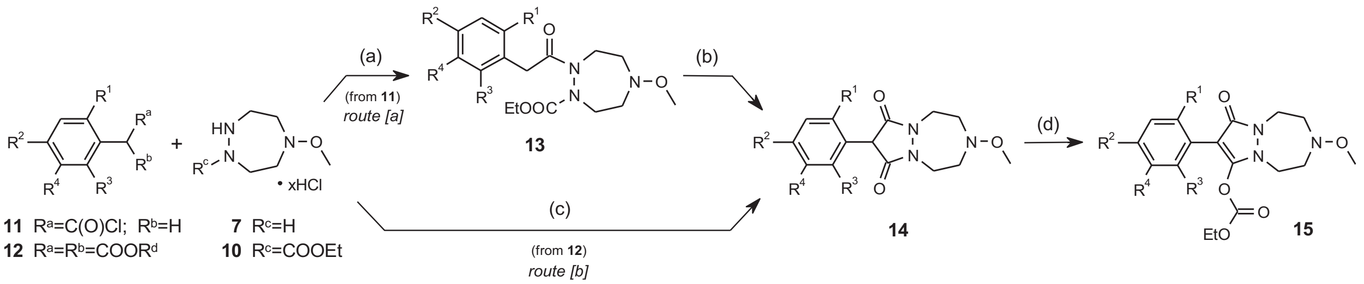
winter wheat shoots grown from seeds treated with the safener cloquintocet-mexyl (TRZAW-CQC), when compared to the unsafened control (TRZAW), permitted to estimate the potential for crop injury reduction (safener[10] action). The herbicidal potency/selectivity data of pinoxaden **1** is included for 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 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)



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, 0–65 °C; or alternatively **5**, bis-mesylate **4**, 30% NaOH w/w in H_2O, Bu_4NBr cat., toluene, reflux; (d) 2 M HCl in Et_2O, Et_2O, 0 °C–RT, isolate precipitate; then 4 M HCl in dioxane, EtOAc, 90 °C; (e) BOCNHNHCOOEt **8**, NaH, DMF, 0–65 °C; (f) 2 M HCl in Et_2O, Et_2O, RT; optional aqueous basic workup.



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) Arylacetyl 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.