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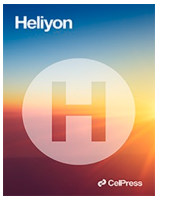

A new series of acylhydrazones derived from metribuzin with modulated herbicidal activity

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ABSTRACT

This paper reports the preparation and herbicidal evaluation of a small library of acylhydrazones based on the synthetic herbicide metribuzin. The hydrazone linkage easily obtained by reaction of metribuzin with aliphatic and aromatic aldehydes, masks efficiently the exocyclic amino group, thereby altering significantly H-bonding with the receptor and increasing the lipophilicity relative to the parent herbicide. The structures of all compounds, including key stereochemical issues on conformation and *E/Z* configuration around the C═N bond were thoroughly elucidated by spectroscopic methods, and unambiguously corroborated by X-ray diffraction analysis. The herbicidal assays using an aliphatic and an aromatic acylhydrazone were performed on tomato and rapeseed plants grown in greenhouse. Our results demonstrate, regardless of rate application, that such acylhydrazone formulations do not alter the selectivity of metribuzin. Moreover, the herbicide activity was even higher in the alkyl derivative than that achieved by commercial metribuzin, thus suggesting that this substance can be applied with no need of combination with chemical coadjuvants, unlike most formulations of commercially available herbicides. Therefore, the study shows the promising effect of chemical derivatization of a common herbicide as metribuzin, to improve the herbicide activity without compromising selectivity, and allowing the farmers its use in crop protection safely and effectively.

1. Introduction

The greening and safe use of pesticides and herbicides through synthetic modification and elaboration of environmentally benign formulations, constitute key concerns in sustainable agenda. As persistent pollutants, herbicides pose serious impacts on health and

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natural resources, especially groundwater [1–3]. The twelve principles of green chemistry should now be applied to the crop protection industry [4], which usually involve maximization of atom economy and mass efficiency, less hazardous syntheses, and molecular designs aimed at natural detoxification [5,6]. Among the approaches employed toward green herbicides, a few could be highlighted, such as the mimicry and modification of natural products [7], encapsulation in macromolecular hosts [8–13], adsorption on mineral nanoparticles/nanosheets [14,15], or the use of ionic liquids [16,17], which increase aqueous stability and reduce volatility. These strategies focus also on slow- or controlled-release of the active ingredient to induce prolonged effects, while minimizing bioaccumulation. A salient approach involves the use of enantiomeric formulations in the case of chiral herbicides, as single isomers often exhibit more potency and enhanced selectivity at lower doses than racemic mixtures [18–20].

Here we report on molecular redesign of metribuzin, a widely employed pre- and post-emergent herbicide with broad scope in a variety of crops, which inhibits photosynthetic pathways in plants by disrupting photosystem II [21]. Metribuzin, $C_8H_{14}N_4OS$, belongs to the triazinone family and compared with structurally related herbicides, it has high aqueous solubility and low lipophilicity ($\log P = 1.8$). Metribuzin can be classed as nonvolatile according to its Henry's law constant [22]. Sorption in soils is generally poor, although it increases in the presence of organic matter [23–25]. While acute toxicity has not been reported for metribuzin, this herbicide represents a source of water contamination with impact on aquatic life [26,27].

The chemical modification and full characterization described thoroughly takes advantage of the concept of *dynamic covalent bonds*, as metribuzin can be converted into a series of acylhydrazone derivatives bearing a labile imine linkage that enables reversible transformation. Acylhydrazones have been documented by numerous groups, particularly by Lehn and associates in supramolecular chemistry [28,29], and applied to the development of nanomachines and molecular switches. This versatility stems from the controlled isomerization of the C═N bond in opposite directions when running under thermal or photochemical conditions, which can also be induced by catalysis, ion complexation, along with variations in pH and redox potentials, all making acylhydrazones privileged scaffolds in systems chemistry [30–32]. The hydrazone moiety has also found broad applicability in drug discovery and biological screening, ranging from antimicrobial to fungicidal/herbicidal activity, among others [33–39]. Small-molecule libraries are usually available through combinatorial chemistry techniques [40,41].

A look at the chemical structure of metribuzin suggests that reversible bond formation could modulate its physicochemical properties, yet preserving or altering the herbicidal activity of the parent heterocycle. This could be achieved by reaction of the exocyclic amino group with aldehydes. Such a masking not only decreases the hydrophilic character of the amino functionality and its H-bonding ability, but would also lead to hydrophobic side chains with a better penetration through the leaf cuticle. The latter could

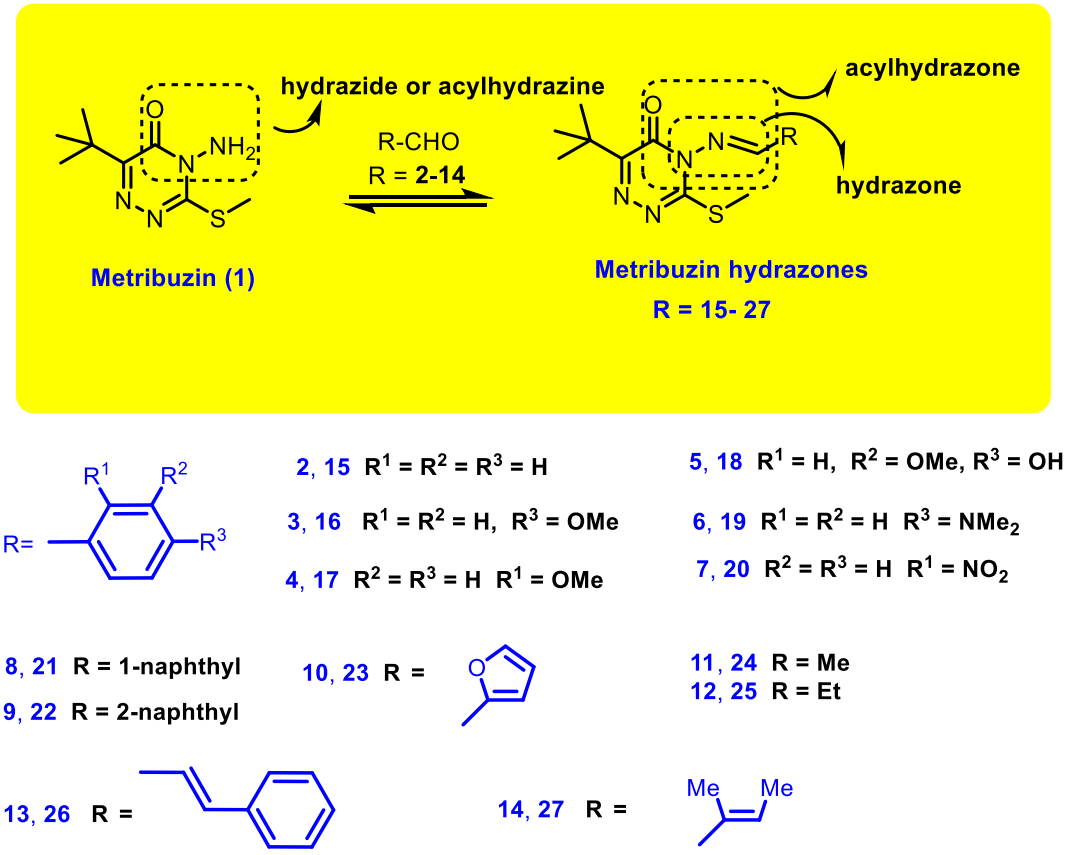

Fig. 1. Reaction of metribuzin with different aldehydes and target compounds.

likewise prevent the usual degradation routes of metribuzin, namely formation of deaminometribuzin, diketometribuzin, and deamino-diketometribuzin as main metabolites [42–45].

The present study represents a preliminary evaluation of *in-vivo* tests of metribuzin-based acylhydrazones on crops. There is no intention to accomplish a quantitative structure-activity relationship analysis. Accordingly, two compounds were selected on the basis of an aliphatic and an aromatic derivative as prototypical examples.

2. Results and discussion

2.1. Synthesis and structural characterization

The common route to hydrazones involves the condensation of hydrazines (or hydrazides) with carbonyl compounds (either aldehydes or ketones) in organic solvents [46,47]. Solution-based methods can also be replaced by other sustainable approaches like solvent-free reactions or mechanochemical activation [48,49].

We took advantage of the conventional reaction in solution, albeit simplifying the operational protocol using equimolar amounts of reactants whenever was possible, and antisolvents that caused the crystallization of reaction products. This resulted in a high-yielding synthesis of target compounds requiring little or no further purification. Thus, metribuzin was reacted with aromatic (**2**–**10**), aliphatic (**11**–**12**), and olefinic (**13**, **14**) aldehydes (Fig. 1). Reactions conducted in ethanol with benzaldehyde (**2**), *o*- and *p*-anisaldehydes (**3** and **4**), 2-naphthaldehyde (**9**), and cinnamaldehyde (**13**) were essentially complete after 48–72 h at 60 °C. Longer reaction times (4–7 days) at the same temperature were required for vanillin (**5**), *p*-dimethylaminobenzaldehyde (**6**), *o*-nitrobenzaldehyde (**7**), 1-naphthaldehyde (**8**), and furfural (**9**), as evidenced by TLC analyses.

For volatile aldehydes such as acetaldehyde (**11**) and propionaldehyde (**12**), molar excesses (3 equiv relative to metribuzin) were employed with reactions going to completion after 72 h and 96 h, respectively. The reaction with **11** in ethanol or methanol gave rise to a viscous oil, while in diethyl ether the resulting solid (**24**) crystallized in the refrigerator (~5 °C). The similar condensation with **12** afforded a crystalline solid either in ethanol or in diethyl ether, but a cleaner material was obtained in the former. The unsaturated aldehyde *trans*-2-methyl-2-butenal (**14**) was used in excess (2 equiv) as well, although the transformation occurred slowly in diethyl ether (*ca.* 5 days), yet yielding a crystalline solid (**27**) from the reaction mixture.

The chemical structures of the target acylhydrazones were characterized by spectrometric methods. Likewise, elemental microanalyses and/or HRMS spectra agree with their molecular formulas. ^{1}H NMR data show the resonances of the thiomethyl and *tert*-butyl groups at ~2.60 and 1.45 ppm, respectively. Also, ^{13}C NMR spectra show the distinctive resonances of the heterocyclic carbons linked to sulfur (162.8 ppm), *tert*-butyl (158.7 ppm), and carbonyl (148.5 ppm) groups (see Supplementary material). Further attention should be paid, however, to stereochemical aspects, namely configuration around the C=N bond as well as the conformation adopted by the heterocyclic ring with respect to the exocyclic hydrazone linkage. All acylhydrazones derived from aromatic aldehydes (**15**–**23**) and olefinic (**26** and **27**) display only one signal set in their NMR spectra. Conversely, **24** and **25** bearing alkyl substituents at the azomethine carbon show a second low-intensity signal set, especially in the case of compound **25**. The interconversion between *Z*- and *E*-isomers of acylhydrazones is well documented [28–31]. In some cases, the energy barriers can be high enough to detect both isomers at room temperature [46,50]. Fig. 2 depicts the four stereochemical possibilities featuring E/Z configurations and conformational arrangements involving the triazinone ring and the azomethine group.

Fortunately, suitable crystals for X-ray diffraction analyses could be obtained for compounds **17**, **25**, and **26**, which allowed us to elucidate the solid-state structures adopted by such acylhydrazones (Fig. 3). In all cases, the C=N bond of the hydrazone moiety

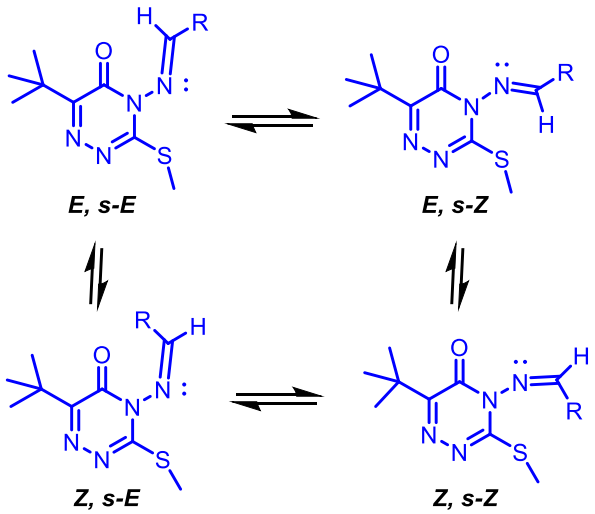

Fig. 2. Configurational and conformational equilibria for acylhydrazones derived from metribuzin.

exhibits *E*-configuration, as evidenced by the bond angle N–N═CH–C, 180° in **17** and **26**, and close to it for compound **25**. The conformation between the endocyclic and exocyclic nitrogen atoms is *s-E* in **17** with slight bond angle deviations of 25° and 44° in **24** and **26**, respectively. Moreover, hydrazone **25** shows *s-Z* disposition between the terminal methyl group and the N═C bond. It is noteworthy the almost complete co-planarity of rings and the double bond in the case of **17** (Fig. 3, Table 1).

Further insights into the structural behavior of metribuzin hydrazones in solution can be inferred from NMR data (Table 2). Thus, alkyl derivatives at the azomethine group such as **24** and **25** show less steric hindrance in both *E* and *Z* isomers with two signal sets attributable to both species. The *E*-configuration is assigned to the major stereoisomer, consistent with crystallographic data for **25**. The azomethine carbon proton is more deshielded (8.43 and 8.47 ppm for **24** and **25**, respectively), unlike the *Z*-isomers (8.10 and 7.93 ppm, respectively), due to the anisotropic effect caused by the carbonyl group of the amide function [51].

Likewise, *E*-configurations were assigned to the single isomer found in acylhydrazones derived from aromatic aldehydes (**15**–**23**), which show the azomethine proton more deshielded (9.93–8.85 ppm) than the aliphatic hydrazones. As mentioned above, this may reflect the deshielding effect from the amide group, but also the anisotropy caused by the aromatic ring. As inferred from the solid-state structure of **17**, the aforementioned proton, the carbonyl group, and both rings are essentially coplanar in the *E*-isomer detected. That proton (N═CH) in acylhydrazones conjugated with olefinic bonds (**26**, **27**) resonates at similar downfield (8.92 and 8.57 ppm, respectively) and agree with an *E*-configuration observed in the crystal structure of **26**. Other spectroscopic techniques also reveal the heterofunctionalization of metribuzin, such as UV–Vis spectra showing strong absorptions due to extended conjugation. FT-IR spectra (recorded in ATR mode) reveal in all cases the disappearance of the NH stretching band present in the starting herbicide, although an intense peak near 1670 cm^{-1}, indicative of the amide group, is still preserved (see Experimental data).

2.2. Evaluation of herbicidal activity

Three formulations were used in the present study involving an aqueous metribuzin solution (Sencor, 60 % w/v, S-code), together with an aromatic acylhydrazone (compound **15**, A15 code) and an aliphatic derivative (compound **24**, A24 code). The treatments used

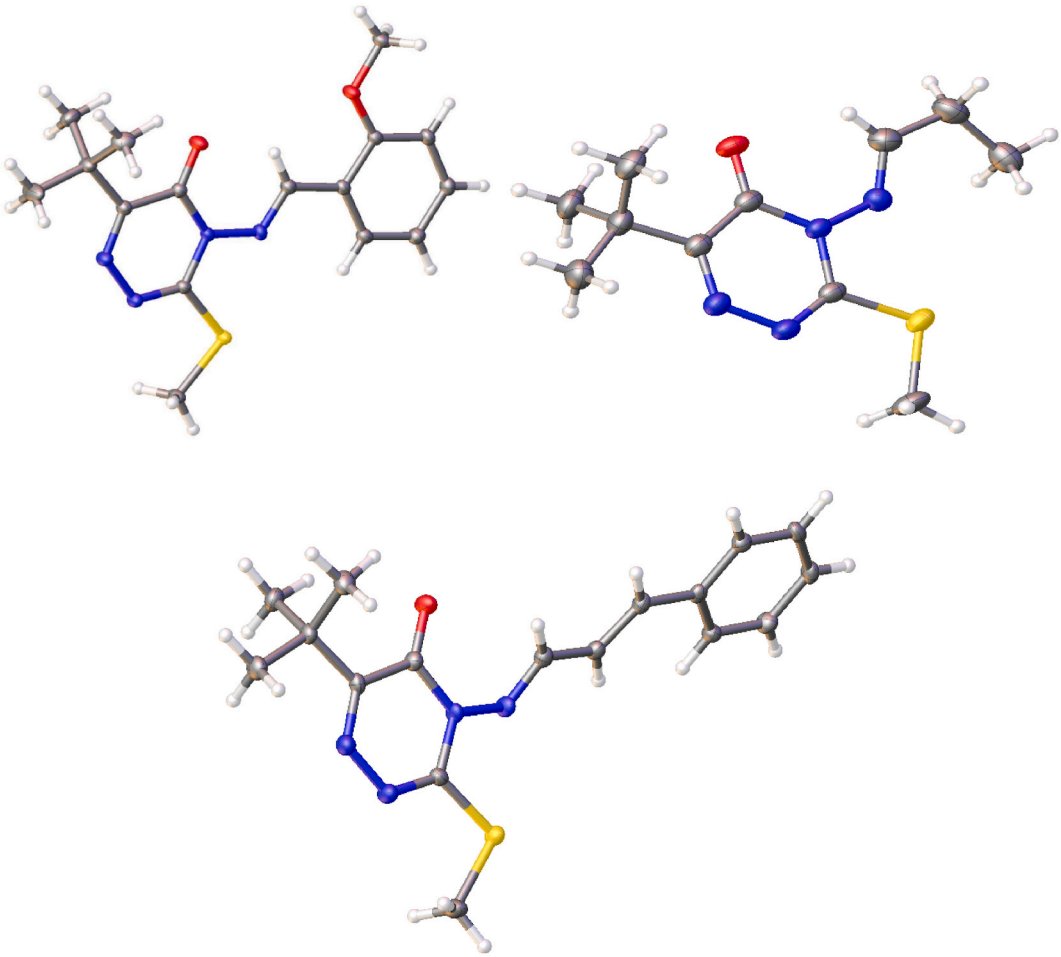

Fig. 3. Solid-state stereostructures for acylhydrazones **17** (top, left), **25** (top, right), and **26** (bottom). See Experimental for crystallographic details.

Table 1
Selected bond angles (degrees, crystal data) for acylhydrazones **17**, **25**, and **26**.

Compound	N–N═CH–C	SC-N-N═CH	OC-N-N═CH	N═CH–C8–C9	C═C–C10–C11
17	180.0	180.0	0.0	180.0	
25	176.7	−161.7	25.2	−2.0	
26	179.8	−147.3	44.4	−173.9	177.0

Table 2
Proton and carbon chemical shifts (δ, ppm) and isomerism around the N═CH-R group.

Compound[a]	*E*/*Z* steroisomer	δ, N═CH (ppm)	δ, N═CH (ppm)
15	*E*	9.28	166.1
16	*E*	9.06	166.3
17	*E*	9.48	163.6
18	*E*	8.85	170.2
19	*E*	8.77	167.5
20	*E*	9.93	162.0
21	*E*	9.78	167.1
22	*E*	9.44	165.9
23	*E*	9.14	153.6
24	*E* (88 %)	8.43	172.6
24	*Z* (12 %)	8.10	172.4
25	*E* (94 %)	8.47	176.2
25	*Z* (6 %)	7.93	–
26	*E*	8.92	168.7
27	*E*	8.57	171.7

[a] All spectra were recorded in $CDCl_3$, with the exception of **18** in DMSO-d_6.

in tomato plants (*Solanum lycopersicum* L.) and in rapeseed plants (*Brassica* spp) were as follow: Control (C) without herbicide application; Sencor (S-90) with a dose of 90 g of active ingredient (ai) per ha; Sencor (S-180) with a dose of 180 g ai ha^{-1}; the aromatic modification with doses of 90 g ha^{-1} (A15-90) and 180 g ha^{-1} (A15-180), and the aliphatic hydrazone with the same doses as above, 90 g ha^{-1} (A24-90) and 180 g ha^{-1} (A24-180). Ten replicates were arranged for each tomato treatment and 4 replicates for each rapeseed treatment (tomato for selectivity and rapeseed for herbicide activity) in a randomized block design (total: 98 pots). The first application of the herbicides took place 16 days after transplanting (DAT) for tomatoes and 25 DAT for rapeseed. It should be noted that the manufacturer of commercial metribuzin (Sencor Liquid) recommends a second application 5–15 days after the first treatment. Accordingly, we performed the 2nd application at 32 DAT and 30 DAT ranges for tomato crops and rapeseed, respectively. These protocols agree with literature data [52], which report the first application at 20 DAT for tomato followed by a second one 15 days after the first treatment. The application of herbicide doses through the different treatments was conducted using a Matabi E1 electric diffuser (1-L capacity at a flow rate of 0.25 L min^{-1}), amounting to a total volume of 500 L ha^{-1}. Once the herbicides were applied, water was poured into the soil surface to avoid the potential washing of such compounds from leaves. In order to assess other effects on

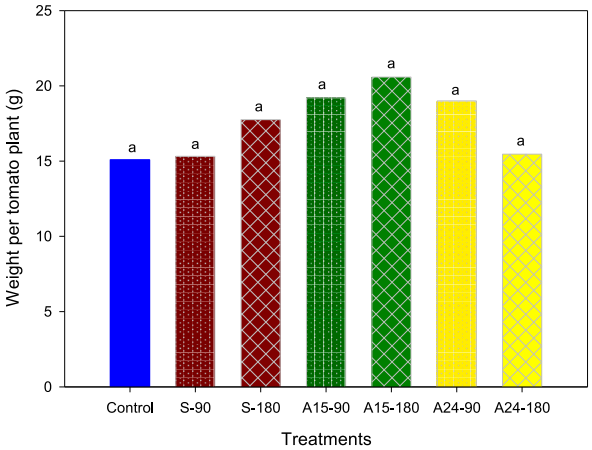

Fig. 4. Effect of different treatments on weight of tomato plants (*Solanum lycopersicum* L.). Bars with the same letter indicate no significant differences ($p < 0.05$) among treatments. S-90: Sencor with a dose of 90 g ai ha^{-1}; S-180: Sencor with a dose of 180 g ai ha^{-1}; A15-90: compound **15** with a dose of 90 g ha^{-1}; A15-180: compound **15** with a dose of 180 g ha^{-1}; A24-90: acylhydrazone **24** with a dose of 90 g ha^{-1}; A24-180: acylhydrazone **24** with a dose of 180 g ha^{-1}.

selectivity, potential injuries such as chlorosis, necrosis, and leaf deformation in tomato plants were examined visually. Moreover, after 47 DAT the tomato plants were harvested for fresh weight determination. In addition, to assess the effects of herbicidal action on rapeseed plants, their weights were measured after 53 DAT. The efficiency (E) of herbicide formulations was calculated according to E = (WC – WT)/WC, where WC is the weight of rapeseed in the control pots, while WT refers to the weight after treatment with herbicide.

Fig. 4 shows the effect of different treatments on biomass plant (g per plant) of tomato (*Solanum lycopersicum* L.) variety "Heinz 1015". Our results indicated that there were no significant differences between the treatments, with an average value of 17.4 g. Nevertheless, it is noteworthy that the treatments with different formulations provided values even above the control experiment.

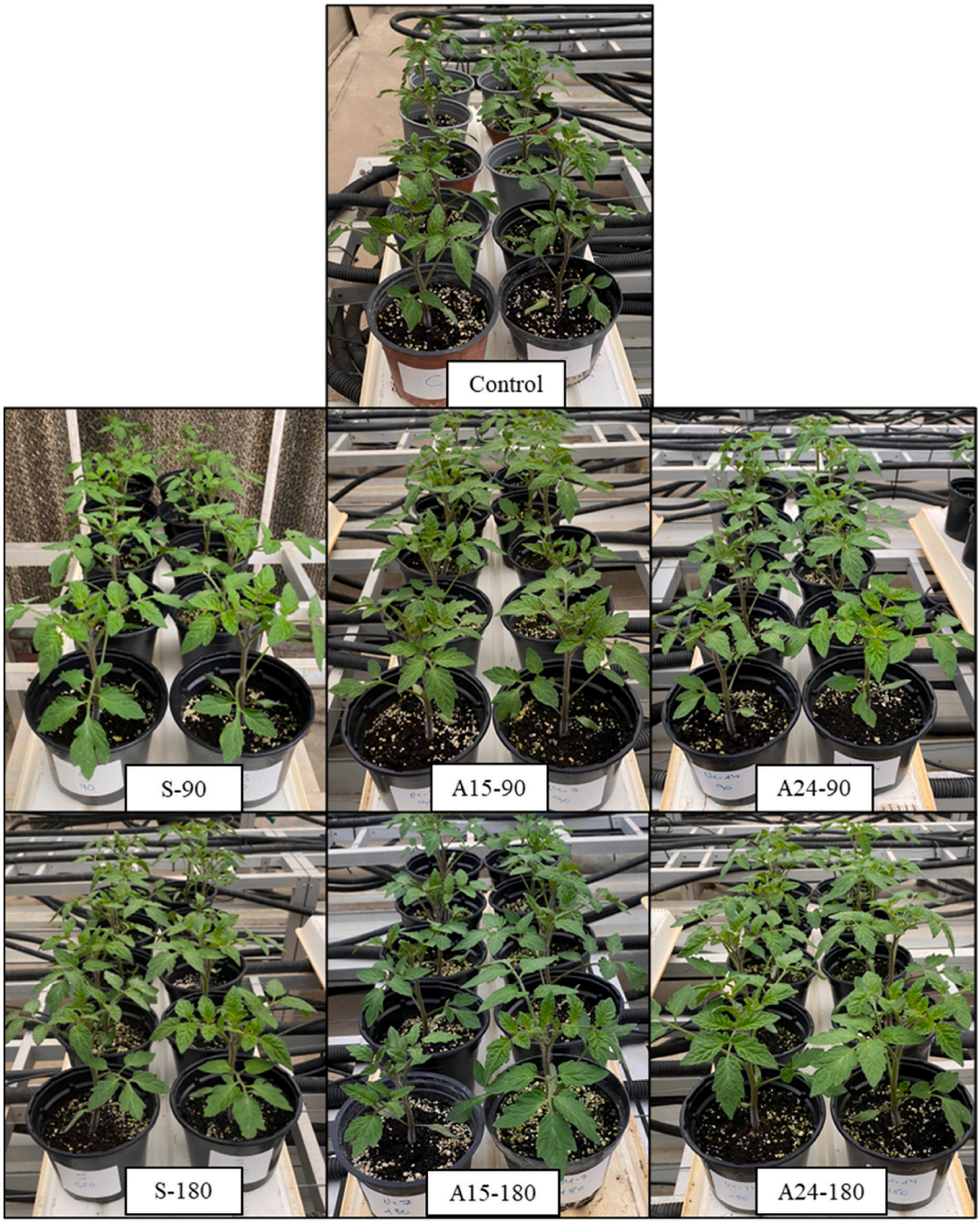

Fig. 5. Effect of the selectivity of metribuzin derivatives through different treatments on tomato plants. S-90: Sencor with a dose of 90 g ai ha^{-1}; S-180: Sencor with a dose of 180 g ai ha^{-1}; A15-90: compound **15** with a dose of 90 g ha^{-1}; A15-180: compound **15** with a dose of 180 g ha^{-1}; A24-90: compound **24** with a dose of 90 g ha^{-1}; A24-180: compound **24** with a dose of 180 g ha^{-1}.

Thus, the biomass data were lower in Control than with Sencor, A15, and A24 samples by factors of 1.11, 1.30 and 1.11, respectively. The highest values of plant biomass under A15 formulations, regardless of rates used (90 and 180 g ai ha^{-1}, Fig. 4), are probably associated with its lack of aqueous solubility, thus hindering its translocation inside the tomato plant.

These results are in line with visual inspection where no injury symptoms were observed on any formulations, regardless of the rate application (Fig. 5), thereby suggesting that the acylhydrazone formulations did not alter the selectivity of metribuzin. Accordingly, these acylhydrazones formulations (A15: acylhydrazone **15** and A24: acylhydrazone **24**) can be used safely by farmers in tomato growing, one of the most important crops where the use of metribuzin is approved.

Similar results have been observed under greenhouse conditions, in the fact that the post-emergence application of metribuzin caused less than 5 % of injury in tomatoes [53]. Likewise, other studies indicated that injury in tomatoes plants by metribuzin could be associated with the application rate, because 1 % of injury was observed when this herbicide was applied at 280 g ha^{-1} whereas 87 % of injury (100 % means plant death) was found with metribuzin applied at rate of 1120 g ha^{-1} [54].

Fig. 6 shows the effects of treatments on the weight of rapeseed weeds (*Brassica* spp). Results unveiled significant differences among the treatments. Thus, 4.60 g (per pot of rapeseed) was the mean value of the control experiment, whereas the application of Sencor (commercial format) at rates of 90 and 180 g ai ha^{-1} significantly reduced rapeseed biomass by factors of 1.75 and 3.56, respectively with respect to control treatment.

Therefore, an increase in herbicide concentration, from 90 to 180 g ai ha^{-1}, turned out to be more effective in eliminating the living tissue of rapeseed and showed substantial differences against the control treatment (Fig. 7).

Similarly, other authors have observed that the increase in metribuzin application rates (from 72 to 144 g ai ha^{-1}) led to the highest decrease in biomass of *Echinochloa* spp, from 70 to 100 %, respectively [55]. In the particular case of A15 formulations (acylhydrazone **15**), regardless of the application rate (A15–90 and A15-180), a reduction in biomass formation (3.48 g mean value) relative to control (4.60 g) was observed, although without significant differences ($p > 0.05$) between them. This effect caused by the application of A15–90 and A15-180 reduces the efficacy of hydrazone **15** by factors of 1.46 and 2.83 in reference to S-90 and S-180, respectively. Thus, formulations of this substance do not ensure the optimum weed control, at least at the application rates of 90 and 180 g ha^{-1} (Fig. 8). This result could be attributed to the lack of aqueous solubility shown by this aromatic acylhydrazone, which could hinder its translocation inside the weed. A related study dealing with the bioactivity of different herbicide microcapsules, including metribuzin, indicated that herbicidal activity increases with the herbicide solubility [56]. However, the application of A24 formulations (aliphatic acylhydrazone **24**) at both doses produced significant decreases in rapeseed biomass compared to the control treatment (Fig. 6), thus indicating that these formulations did not reduce the herbicide activity (Fig. 8).

Regarding the differences between the aromatic and aliphatic derivatives, i.e. A15 and A24 formulations, and irrespective of the application dose, the effectiveness of A24 was superior to that of A15 with increases of 40 % and 278 % at doses of 90 and 180 g ha^{-1}, respectively. Furthermore, although the differences are not significant, the results obtained through this study evidenced that A24 formulations, when compared to the commercial product (Sencor), gave rise to enhanced effectiveness by 13 % and 7 % using doses of 90 and 180 g ha^{-1}. Clearly, the aliphatic hydrazone (A24 formulations) did not reduce the efficacy of metribuzin, and the use of adjuvants (products that improve the efficacy of the herbicide) may not be required. It should finally be pointed out that there is an intense research activity under way to develop synthetic analogs of well-known herbicides, which can be employed as safeners, i.e. co-applied with herbicides to protect specific crops and without compromising weed control efficiency [57–60].

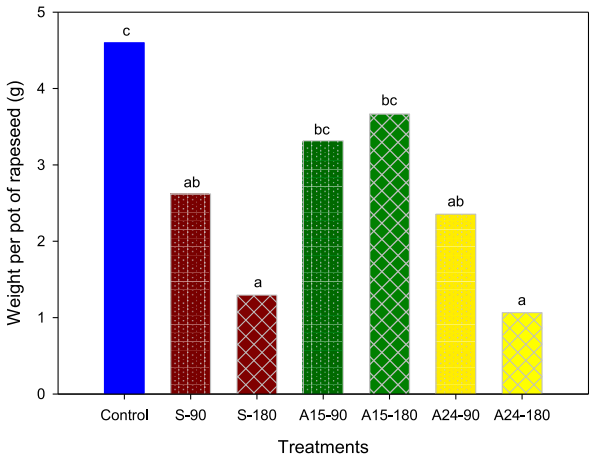

Fig. 6. Effect of different treatments on weight of rapeseed weeds (*Brassica* spp). Bars with different letters indicate significant differences ($p < 0.05$) among treatments. S-90: Sencor with a dose of 90 g ai ha^{-1}; S-180: Sencor with a dose of 180 g ai ha^{-1}; A15-90: compound **15** with a dose of 90 g ha^{-1}; A15-180: compound **15** with a dose of 180 g ha^{-1}; A24-90: acylhydrazone **24** with a dose of 90 g ha^{-1}; A24-180: acylhydrazone **24** with a dose of 180 g ha^{-1}.

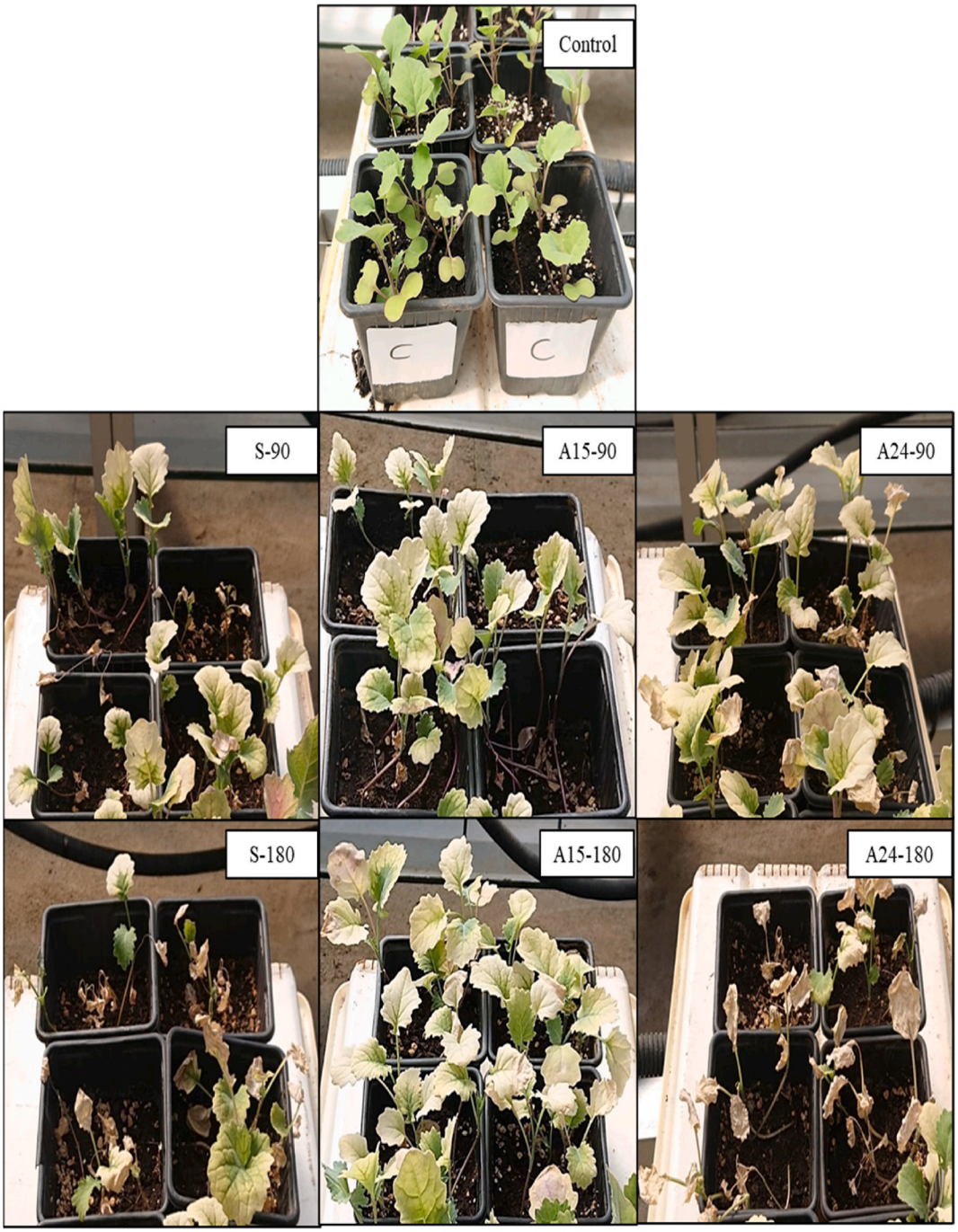

Fig. 7. Effect of the efficacy of metribuzin derivatives in different treatments on rapeseed plants. S-90: Sencor with a dose of 90 g ai ha^{-1}; S-180: Sencor with a dose of 180 g ai ha^{-1}; A15-90: compound **15** with a dose of 90 g ha^{-1}; A15-180: compound **15** with a dose of 180 g ha^{-1}; A24-90: compound **24** with a dose of 90 g ha^{-1}; A24-180: compound **24** with a dose of 180 g ha^{-1}.

3. Experimental procedures

3.1. Chemical methods

All reagents and solvents were obtained from commercial suppliers and used without further purification. Metribuzin was purchased from Henan Au Loddy Commerce (P.R. China) and used in subsequent syntheses as received. Reactions were monitored by thin layer chromatography (TLC) on silica gel 60 F_{254} plates (7 × 2 cm) using dichloromethane as eluent and UV–Vis detection. Melting

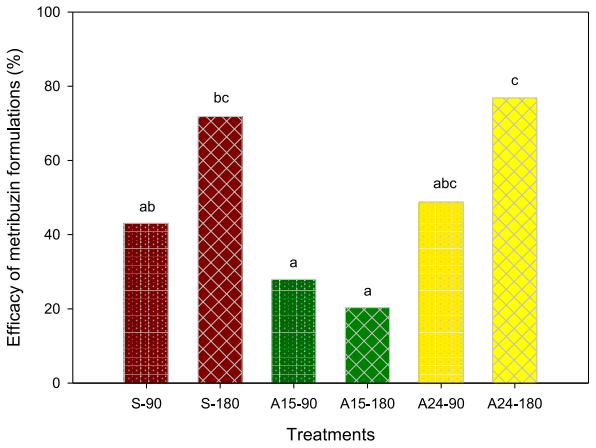

Fig. 8. Effect of different treatments on the efficacy of herbicidal formulations. Bars with different letters indicate significant differences ($p < 0.05$) among treatments. S-90: Sencor with a dose of 90 g ai ha^{-1}; S-180: Sencor with a dose of 180 g ai ha^{-1}; A15-90: acylhydrazone **15** with a dose of 90 g ha^{-1}; A15-180: acylhydrazone **15** with a dose of 180 g ha^{-1}; A24-90: acylhydrazone **24** with a dose of 90 g ha^{-1}; A24-180: acylhydrazone **24** with a dose of 180 g ha^{-1}.

points were determined with an Electrothermal IA9100 apparatus and are uncorrected. Fourier Transform Infrared (FT-IR) spectra were measured on an IR300 spectrophotometer (Thermo-Fisher) in the range 4000-500 cm^{-1}, using the attenuated total reflectance (ATR) device. UV–Vis spectra were obtained using a Thermo (Scientific Evolution 201 model) spectrophotometer in the wavelength range of 190 and 800 nm. Absorbances were measured in ethanol-water solutions. NMR spectra were recorded at 298 K in an Avance III 500 spectrometer (Bruker) equipped with Ultrashield™ 500 Plus magnet running at 500 MHz and 125 MHz for ^{1}H and ^{13}C nuclei, respectively. Samples were dissolved in $CDCl_3$ or DMSO-d_6, using tetramethylsilane (TMS) as internal reference ($\delta = 0.00$ ppm). The apparent coupling constants (in Hz) were measured on spectra as recorded. Interpretation and assignment of ^{13}C NMR peaks was facilitated by the DEPT (*Distortionless Enhancement by Polarization Transfer*) technique. Proton and carbon assignments marked with an asterisk* may be interchanged. High-resolution mass spectra (HRMS) were determined on an Agilent instrument (6520 Accurate Mass LCQ-TOF). Molecular masses were obtained by electrospray ionization (ESI-MS) in positive mode, with *m/z* values referred to $[M+H]^+$ species.

3.2. Experimental synthetic procedures of target compounds

To a solution of metribuzin (5.0 g, 23.3 mmol) in ethanol (10 mL) was added the corresponding aldehyde (23.3 mmol) and the reaction mixture was heated at 60 °C until completion (TLC analysis, CH_2Cl_2 as eluent). A crystalline precipitate was obtained at room temperature after a given period (2–7 days). Further storage in the refrigerator increased the crystalline mass, which was then filtered, washed with cold ethanol, and dried under vacuum.

*3.2.1. (E)-4-(benzylidene)amino)-6-(tert-butyl)-3-(methylthio)-1,2,4-triazin 5(4H)-one (**15**).* In following the general procedure with benzaldehyde (**2**) for 48 h, the title compound was isolated as a white solid in 70 % yield. ***Procedure B***. To a solution of metribuzin (5.0 g, 23.3 mmol) in EtOH (25 mL) was added benzaldehyde (4 mL, 38.9 mmol), and the mixture was refluxed under stirring for 24 h. Compound **15** was isolated as above in 89 % yield. Recrystallized from ethanol it had m.p. 138–139 °C. UV (40 % aqueous EtOH): $\lambda_{max} = 271$ nm, $\varepsilon = 33948$ L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1673, 1596, 1572, 1466, 1276, 1045, 757. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.28 (s, 1H, N═CH), 7.88 (d, 2H, Ar, H-2, H-6, $J_{o,m} = 7.5$), 7.57 (t, 1H, Ar, H-4, $J_{p,m} = 7.5$), 7.50 (t, 2H, Ar, H-3, H-5, $J_{m,p} = 7.5$), 2.61 (s, 3H, S–Me), 1.47 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.1 (N═CH), 162.8 (**C**–S), 159.2 (**C**-*tert*), 149.2 (C═O), 132.2 (phenyl, C_1), 129.2, 129.0 (phenyl, C*$_2$, C*$_6$ and/or C*$_3$, C*$_5$), 133.1 (phenyl, C_4), 38.1 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 303.1280, found 303.1288. Anal. Calcd for $C_{15}H_{18}N_4OS$ C: 59.58 %, H: 6.00 %, N: 18.53 %, S: 10.60 %; found C: 59.80 %, H: 6.14 %, N: 18.50 %, S: 10.68 %.

*3.2.2. (E)-6-(tert-butyl)-4-[(4-methoxybenzylidene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one (**16**).* In following the general procedure with *p*-anisaldehyde (**3**) for 48 h, this substance was isolated as a white solid in 51 % yield. Recrystallized from CH_2Cl_2 it had m.p. 161.5–163 °C, UV (40 % aqueous EtOH): $\lambda_{max} = 227, 271, 309$ nm, $\varepsilon = 6984.8, 8031.7$ L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1671, 1612, 1591, 1475, 1261, 1163, 1016, 826.^{1}H NMR (500 MHz, $CDCl_3$) δ 9.06 (s, 1H, N═CH), 7.84* (d, 2H, Ar, H-2, H-6, $J_{o,m} = 8.5$), 6.99* (d, 2H, Ar, H-3, H-5, $J_{m,o} = 8.5$), 3.89 (s, 3H, OMe), 2.60 (s, 3H, SMe), 1.46 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 166.3 (N═CH), 162.7 (**C**–S or aryl, C_4), 159.1 (**C**-*tert*), 148.7 (C═O), 124.9 (phenyl, C_1), 131.2* (phenyl, C_2 and C_6), 114.5* (phenyl, C_3, C_5), 163.7 (phenyl, C_4 or **C**–S), 55.5 (O–Me), 38.0 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.5 (S**Me**). HRMS $[M+H]^+$ calcd 333.1385, found 333.1380. Anal. Calcd for $C_{16}H_{20}N_4O_2S$ C: 57.81 %, H: 6.06 %, N: 16.85 %, S: 9.65 %, found C: 57.80 %, H: 6.18 %, N: 16.91 %, S: 9.63 %.

*3.2.3. (E)-6-(tert-butyl)-4-[(2-methoxybenzylidene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one (**17**).* In following the general procedure with *o*-anisaldehyde (**4**) for 48, this compound was isolated as a yellowish solid in 85 % yield. Recrystallized from EtOH it had m.p. 198–199.5 °C, UV (40 % aqueous EtOH): $\lambda_{max} = 271, 332$ nm, $\varepsilon = 9412.4, 8555.8$ L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1680,

1601, 1570, 1463, 751. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1H, N═CH), 8.12 (dd, 1H, Ar, H-6, $J_{6,5} = 8.0$, $J_{6,4} = 1.5$), 7.53 (dt, 1H, Ar, H-4, $J_{4,5} = J_{4,3} = 8,3$, $J_{4,6} = 1.5$), 7.06 (t, 1H, Ar, H-5, $J_{5,4} = J_{5,6} = 7.5$), 6.97 (d, 1H, Ar, H-3, $J_{3,4} = 8.0$), 3.90 (s, 3H, OMe), 2.60 (s, 3H, SMe), 1.47 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 163.6 (N═CH), 162.8 (**C**–S), 159.9 (aryl, C_2), 159.1 (**C**-*tert*), 148.5 (C═O), 134.9, 127.6, 121.0, 111.3 (aryl, C*$_4$, C*$_6$, C*$_5$, C*$_3$), 120.5 (aryl, C_1), 55.7 (OMe), 38.0 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.5 (S**Me**). HRMS $[M+H]^+$ calcd 333.1385, found 333.1381. Anal. Calcd for $C_{16}H_{20}N_4O_2S$ C: 57.81 %, H: 6.06 %, N: 16.85 %, S: 9.65 %, found C: 58.10 %, H: 6.22 %, N: 16.70 %, S: 9.85 %.

3.2.4. (E)-6-(tert-butyl)-4-[(4-hydroxy-3-methoxybenzylidene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one ***(18)***. In following the general protocol with vainillin (**5**) for 96 h, the title compound was obtained as a yellowish solid in 45 % yield, which after recrystallization from EtOH had m.p. 186–187 °C, UV (40 % aqueous EtOH): $\lambda_{max} = 232$, 326 nm, $\varepsilon = 11410$, 10322 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3144, 1678, 1596, 1571, 1459, 1283, 826. ^{1}H NMR (500 MHz, DMSO-d_6) δ 10.20 (bs, 1H, OH), 8.85 (s, 1H, N═CH), 7.48 (s, 1H, Ar, H-2), 7.38 (d, 1H, Ar, H-6*, $J_{6,5} = 8,0$), 6.95 (d, 1H, Ar, H-5*, $J_{5,6} = 8,0$), 3.84 (s, 3H, OMe), 2.53 (s, 3H, SMe), 1.37 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, DMSO-d_6) δ 170.2 (N═CH), 161.3 (**C**–S), 157.5 (**C**-*tert*), 148.1 (C═O), 152.2, 147.4 (aryl, C*$_4$, C*$_3$), 122.7 (aryl, C_1), 124.9, 115.7, 110.8 (aryl, C*$_6$, C*$_5$, C*$_2$), 55.5 (OMe), 37.4 (**C**Me$_3$), 27.4 (C**Me**$_3$), 13.8 (S**Me**). HRMS $[M+H]^+$ calcd 349.1334, found 349.1333. Anal. Calcd for $C_{16}H_{17}N_4O_3S$ C: 55.16 %, H: 5.79 %, N: 16.08 %, S: 9.20 %, found C: 55.10 % H: 5.95 %, N: 16.30 %, S: 9.31 %.

3.2.5. (E)-6-(tert-butyl)-4-[(4-(dimethylamino)benzylidene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one ***(19)***. In following the general procedure with *p*-dimethylaminobenzaldehyde (**6**) in EtOH (20 mL) for 7 days, the title compound was obtained as a yellowish solid in 65 % yield. Recrystallized from EtOH it had m.p. 154–155.5 °C, UV (40 % aqueous EtOH): $\lambda_{max} = 313$, 380 nm, $\varepsilon = 9211$, 13256 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1665, 1608, 1569, 1531, 1458, 1287, 814, 792. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.77 (s, 1H, N═CH), 8.23* (d, 2H, Ar, H-2, H-6, $J = 9.0$), 6.69* (d, 2H, Ar, H-3, H-5, $J = 9.0$), 3.07 (s, 6H, NMe_2), 2.57 (s, 3H, SMe), 1.45 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.5 (N═CH), 162.4 (**C**–S), 159.1 (**C**-*tert*), 148.8 (C═O), 153.6, 119.0 (aryl, C*$_4$, C*$_1$), 131.2, 111.4 (aryl, C*$_2$, C*$_6$, C*3, C*$_5$), 40.0 (NMe_2), 37.9 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.5 (S**Me**). HRMS $[M+H]^+$ calcd 346.1686, found 346.1694. Anal. Calcd for $C_{17}H_{23}N_5OS$ C: 59.10 %, H: 6.71 %, N: 20.27 %, S: 9.28 %, found C: 59.10 %, H: 6.64 %, N: 20.20 %, S: 8.85 %.

3.2.6. (E)-6-(tert-butyl)-3-(methylthio)-4-[(2-nitrobenzylidene)amino]-1,2,4-triazin-5(4H)-one ***(20)***. In following the general protocol with *o*-nitrobenzaldehyde (**7**) in EtOH (20 mL) for 7 days, this compound was obtained in 72 % yield. Recrystallized from EtOH it had m.p. 184–185 °C, UV (40 % aqueous EtOH): $\lambda_{max} = 238$ nm, $\varepsilon = 17403$ L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3079, 1683, 1607, 1565, 1520, 1459, 1338, 744. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.93 (s, 1H, N═CH), 8.19 (d, 1H, Ar, H-3*, $J = 9.5$), 8.17 (d, 1H, Ar, H-6*, $J = 8.5$), 7.78 (t, 1H, Ar, H-5*, $J = 8,5$), 7.28 (t, 1H, Ar, H-4*, H-5*, $J = 7.5$), 2.61 (s, 3H, SMe), 1.45 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 162.0 (N═CH), 163.2 (**C**–S), 159.0 (**C**-*tert*), 148.8 (C═O), 148.5 (aryl, C_2), 127.7 (aryl, C_1), 134.0, 132.7, 129.8, 125.0 (aryl, C*$_5$, C*$_4$, C*$_6$, C*$_3$), 38.2 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 348.11304, found 348.1135. Anal. Calcd for $C_{15}H_{17}N_5O_3S$ C: 51.86 %, H: 4.93 %, N: 20.16 %, S: 9.23 %, found C: 52.10 %, H: 5.05 %, N: 19.90 %, S: 9.53 %.

3.2.7. (E)-6-(tert-butyl)-3-(methylthio)-4-[(naphthalen-1-yl-*methylene)amino]-1,2,4-triazin-5(4H)-one* ***(21)***. In following the general procedure with 1-naphthaldehyde (**8**) in EtOH (20 mL) for 5 days, the title compound was obtained as a yellowish solid in 75 % yield and had m.p. 164–165 °C (EtOH), UV (40 % aqueous EtOH): $\lambda_{max} = 329$ nm, $\varepsilon = 9375$ L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3050, 1665, 1597, 1564, 1519, 1462, 765. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.78 (s, 1H, N═CH), 8.82 (d, 1H, Ar, H-9*, $J = 9.0$), 8.05 (d, 2H, Ar, H-2*, H-4*, $J = 8.5$), 7.93 (d, 1H, Ar, H-6*, $J = 8.5$), 7.68 (t, 1H, Ar, H-3*, $J = 7.5$), 7.59 (t, 1H, Ar, H-7*, $J = 7.0$), 7.57 (t, 1H, Ar, H-8*, $J = 8.0$), 2.64 (s, 3H, SMe), 1.50 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.1 (N═CH), 162.9 (**C**–S), 159.0 (**C**-*tert*), 148.7 (C═O), 133.8, 131.2, 127.8 (aryl, C*$_1$, C*$_5$, C*$_{10}$), 134.0, 131.4, 128.9, 128.2, 126.6, 125.1, 124.5 (aryl, C*$_2$, C*$_3$, C*$_4$, C*$_6$, C*$_7$, C*$_8$, C*$_9$), 38.1 (**C**Me$_3$), 27.8 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 353.1436, found 353.1433. Anal. Calcd for $C_{19}H_{20}N_4OS$ C: 64.75 %, H: 5.72 %, N: 15.90 %, S: 9.10 %, found C: 64.80 %, H: 5.73 %, N: 15.57 %, S: 9.09 %.

3.2.8. (E)-6-(tert-butyl)-3-(methylthio)-4-[(naphthalen-2-yl-*methylene)amino]-1,2,4-triazin-5(4H)-one* ***(22)***. This compound was obtained according to the general procedure using 2-naphthaldehyde (**9**) in EtOH (20 mL) for 3 days. The resulting white solid (77 % yield) was recrystallized from CH_2Cl_2 and had m.p. 193.5–194.5 °C, UV (80 % aqueous ethanol): $\lambda_{max} = 240$ y 304 nm, $\varepsilon = 23712$, 14858 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3060, 1674, 1628, 1602, 1589, 1570, 1522, 1464, 755. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.44 (s, 1H, N═CH), 8.18 (s, 1H, Ar, H-1), 8.11 (d, 1H, Ar, H-3*, $J = 8.5$), 7.93 (d, 2H, Ar, H-6*, H-9*, $J = 8.5$), 7.90 (d, 1H, Ar, H-4*, $J = 8.5$), 7.62 (t, 1H, Ar, H-6, $J = 8.5$), 7.60 (t, 1H, Ar, H-7, $J = 8.5$), 2.63 (s, 3H, SMe), 1.49 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 165.9 (N═CH), 162.9 (**C**–S), 159.3 (**C**-*tert*), 148.8 (C═O), 135.6, 132.8, 129.9 (aryl, C*$_5$, C*$_{10}$, C*$_2$), 133.1, 129.1, 129.0, 128.5, 128.0, 127.0, 122.8 (aryl, C*$_4$, C*$_6$, C*$_9$, C*$_1$, C*$_3$, C*$_7$, C*$_8$), 38.1 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 353.1436, found 353.1431. Anal. Calcd for $C_{19}H_{20}N_4OS$ C: 64.75 %, H: 5.72 %, N: 15.90 %, S: 9.10 %, found C: 65.09 %, H: 5.60 %, N: 15.92 %, S: 9.22 %.

3.2.9. (E)-6-(tert-butyl)-4-[(furan-2-yl-*methylene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one* ***(23)***. In following the general procedure with furfural (**10**) in EtOH (20 mL) for 6 days, the title compound was obtained as a yellowish solid (44 % yield) which was recrystallized from EtOH and had m.p. 163–164 °C, UV (40 % aqueous ethanol): $\lambda_{max} = 227$, 303 nm, $\varepsilon = 10155$, 15232 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3116, 1680, 1586, 1528, 1465, 770. ^{1}H NMR (500 MHz, $CDCl_3$) δ 9.14 (s, 1H, N═CH), 7.72 (s, 1H, Ar, H-5), 7.11 (d, 1H, Ar, H-3, $J_{3,4} = 3.5$), 6.61 (dd, 1H, Ar, H-4, $J_{4,3} = 3.5$, $J_{4,5} = 1.5$), 2.60 (s, 3H, SMe), 1.45 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 153.6 (N═CH), 162.7 (**C**–S), 159.1 (**C**-*tert*), 148.8 (C═O), 148.7 (aryl, C_2), 147.6, 120.0, 112.8 (aryl, C*$_5$, C*$_3$, C*$_4$), 38.0 (**C**Me$_3$), 27.7 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 293.1057, found 293.1069. Anal. Calcd for $C_{13}H_{16}N_4O_2S$ C: 53.41 %, H: 5.53 %, N: 19.16 %, S: 10.97 %, found C: 53.50 %, H: 5.59 %, N: 18.82 % S: 11.00 %.

3.2.10. (E and Z)-6-(tert-butyl)-4-(ethylideneamino)-3-(methylthio)-1,2,4-triazin-5(4H)-one ***(24)***. To a solution of metribuzin (5.0 g, 23.3 mmol) in diethyl ether (10 mL) was added acetaldehyde (3.9 mL, 70.0 mmol) and the mixture was kept at room temperature for 72 h, and then stored in the refrigerator until the formation of a white solid, which was filtered, washed with cold ether, and dried

under vacuum (5.0 g, 90 %). It was recrystallized from diethyl ether and had m.p. 135–136 °C, UV (40 % aqueous ethanol): $\lambda_{max} = 217$, 301 nm, $\varepsilon = 14657$, 9828 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1670, 1630, 1514, 1453, 1288. ^{1}H NMR (500 MHz, $CDCl_3$), *E*-isomer δ 8.43 (q, 1H, N═CH, $J_{CH,Me} = 5.0$), 2.30 (d, 3H, Me, $J_{Me,CH} = 5.0$), 2.59 (s, 3H, SMe), 1.42 (s, 9H, *tert*-butyl), *Z*-isomer δ 8.10 (q, 1H, N═CH, $J_{CH,Me} = 5.5$), 1.88 (d, 3H, Me, $J_{Me,CH} = 5.5$), 2.62 (s, 3H, SMe), 1.44 (s, 9H, *tert*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$), *E*-isomer δ 172.6 (N═CH), 162.9 (**C**–S), 158.0 (**C**-*tert*), 148.0 (C═O), 38.0 (**C**Me_3), 27.6 (C**Me**$_3$), 19.8 (=CH–**Me**), 14.5 (S**Me**), *Z*-isomer δ 172.4 (N═CH), 37.9 (**C**Me_3), 27.52 (C**Me**$_3$), 19.2 (=CH–**Me**), 14.3 (S**Me**). HRMS $[M+H]^+$ calcd 241.1123, found 241.1129. Anal. Calcd for $C_{10}H_{16}N_4OS$ C: 49.98 %, H: 6.71 %, N: 23.31 %, S: 13.34 %, found C: 50.33 %, H: 6.68 %, N: 23.20 %, S: 13.50 %.

*3.2.11. (E and Z)-6-(tert-butyl)-3-(methylthio)-4-(propylideneamino)-1,2,4-triazin-5(4H)-one (**25**).* This compound was obtained as a white solid (44 % yield) by reacting metribuzin, according to the general method, with excess propanaldehyde (5 mL, 70 mmol) for 96 h. After recrystallization from EtOH, it had m.p. 107–108 °C, UV (40 % aqueous ethanol): $\lambda_{max} = 217$, 302 nm, $\varepsilon = 8818$, 5750 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 1677, 1627, 1517, 1450, 1290, 675. ^{1}H NMR (500 MHz, $CDCl_3$), *E*-isomer δ 8.47 (t, 1H, N═CH, $J_{CH,Me} = 4.5$), 2.62 (m, 2H, CH_2), 1.27 (t, 3H, Me, $J_{Me,CH2} = 7.5$), 2.59 (s, 3H, SMe), 1.43 (s, 9H, *tert*-butyl), *Z*-isomer δ 7.93 (t, 1H, N═CH, $J_{CH,CH2} = 5.5$). ^{13}C NMR (125 MHz, $CDCl_3$), *E*-isomer δ 176.2 (N═CH), 162.9 (**C**–S), 158.2 (**C**-*tert*), 148.0 (C═O), 38.0 (**C**Me_3), 27.6 (C**Me**$_3$), 14.4 (S**Me**), 27.2 (CH_2), 9.3 (CH_3). HRMS $[M+H]^+$ calcd 255.12796, found 255.1275. Anal. Calcd for $C_{11}H_{18}N_4OS$ C: 51.94 %, H: 7.13 %, N: 22.03 %, S: 12.61 %, found C: 52.29 %, H: 7.28 %, N: 21.70 %, S: 12.40 %.

*3.2.12. 6-(tert-butyl)-3-(methylthio)-4-[(E)-(E)-3-phenylallylidene)amino]-1,2,4-triazin-5(4H)-one (**26**).* In following the general procedure with *trans*-cinnamaldehyde (13) and after 72 h, the title compound was isolated as a yellowish solid in 52 % yield. After recrystallization from EtOH it had m.p. 134–135 °C, UV (40 % aqueous ethanol): $\lambda_{max} = 227$, 313 nm, $\varepsilon = 7849$, 13076 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3060, 3034, 1670, 1622, 1578, 1515, 1448, 1284, 749, 684. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.92 (d, 1H, N═CH, $J = 9.5$), 7.27 (d, 1H, CH═C**H**-Ph, $J_{trans} = 16.0$), 7.07 (dd, 1H, C**H**═CH-Ph, $J = 9.5$, $J_{trans} = 16.0$), 7.55 (m, 2H, Ph), 7.41 (m, 3H, Ph), 2.60 (s, 3H, SMe), 1.47 (s, 9H, *tery*-butyl). ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.7 (N═CH), 162.8 (**C**–S), 158.6 (**C**-*tert*), 148.5 (C═O), 148.1* (N═C–C═**C**), 130.6* (N═C–C═**C**), 134.7 (phenyl, C_1), 129.0, 128.0 (phenyl, C^*_3, C^*_5, C^*_2, C^*_6), 123.4 (phenyl, C^*_4), 38.0, (**C**Me_3), 27.7 (C**Me**$_3$), 14.6 (S**Me**). HRMS $[M+H]^+$ calcd 329.1436, found 329.1438. Anal. Calcd for $C_{17}H_{20}N_4OS$ C: 62.17 %, H: 6.14 %, N: 17.06 %, S: 9.76 %, found C: 62.42 %, H: 6.12 %, N: 16.98 %, S: 9.38 %.

*3.2.13. 6-(tert-butyl)-4-[(E)-(E)-2-methylbut-2-en-1-ylidene)amino]-3-(methylthio)-1,2,4-triazin-5(4H)-one (**27**).* To a solution of metribuzin (1.0 g, 4.7 mmol) in diethyl ether (5.0 mL) was added *trans*-2-methyl-2-butenal (0.7 mL, 9.3 mmol), and the reaction mixture was kept at room temperature for 5 days. The resulting crystalline solid was filtered, washed with cold ether, and dried under vacuum (0.74 g, 53 %). Recrystallized from diethyl ether, it had m.p. 99–100 °C, UV (40 % aqueous ethanol): $\lambda_{max} = 233$, 295 nm, $\varepsilon = 6439$, 11424 L/mol·cm. IR (ATR, $\nu_{max,}$ cm^{-1}): 3000, 1674, 1637, 1575, 1523, 1428, 1277. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.57 (s, 1H, N═CH), 6.35 (q, 1H, CMe = C**H**–Me, $J = 7.5$), 2.60 (s, 3H, SMe), 1.45 (s, 9H, *tert*-butyl), 1.97 (s, 3H, C**Me** = CHMe), 1.96 (d, 3H, CMe = CH**Me**, $J = 7.5$). ^{13}C NMR (125 MHz, $CDCl_3$) δ 171.7 (N═CH), 162.6 (**C**–S), 158.9 (**C**-*tert*), 148.3 (C═O), 134.2 (**C**Me = CHMe), 145.0 (CMe = **C**HMe), 38.0 (**C**Me_3), 27.8 (C**Me**$_3$), 14.9* (S**Me**), 14.5* (CMe = CH**Me**), 10.3* (C**Me** = CHMe). HRMS $[M+H]^+$ calcd 281.1436 ($C_{13}H_{21}N_4OS$), found 281.1422.

3.3. Crystallographic analyses

Single-crystal structure determinations of compounds **17**, **25**, and **26** were obtained from the corresponding substances by slow evaporation. Suitable crystals for X-ray diffraction were selected and mounted on a MITIGEN holder with silicon oil on a Rigaku AFC12 FRE-HF diffractometer. The crystal was kept at a steady temperature as stated (*vide infra*) during data collection. The structure was solved with the ShelXT solution program [61] using dual methods and by using OLEX2 1.5-alpha [62] as the graphical interface. The model was refined wih ShelXL [63] using full matrix least squares minimization on F^2. The crystallographic data were deposited at the Cambridge Crystallographic Data Centre (CCDC) with the following registry numbers: CCDC-2089415 (**17**), CCDC-2113384 (**25**), and CCDC-2093693 (**26**). These data are available at https://www.ccdc.cam.ac.uk/structures, and can be obtained free of charge on request to CCDC, 12 Union Road, Cambridge CB 1EZ, UK; e-mail: deposi@ccdc.cam.ac.uk.

*3.3.1. Crystallographic data for **17***: Molecular formula = $C_{16}H_{20}N_4O_2S$, $M_r = 332.42$, monoclinic, $P2_1/m$ (No. 11), $a = 10.3479(2)$ Å, $b = 6.78490(10)$ Å, $c = 11.9087(3)$ Å, $\beta = 104.788(2)^\circ$, $\alpha = \gamma = 90^\circ$, $V = 808.41(3)$ Å^3, $T = 120(2)$ K, $Z = 2$, $Z' = 0.5$, μ(Mo K_α) = 0.216, 13241 reflections measured, 2650 unique ($R_{int} = 0.0309$) which were used in all calculations. The final wR_2 was 0.0882 (all data) and R_1 was 0.0330 [$I \geq 2\ \sigma(I)$].

*3.3.2. Crystallographic data for **25***: Molecular formula = $C_{11}H_{18}N_4OS$, $M_r = 254.35$, monoclinic, $P2_1/n$ (No. 14), $a = 6.9016(2)$ Å, $b = 9.5934(3)$ Å, $c = 20.1889(5)$ Å, $\beta = 90.443(2)^\circ$, $\alpha = \gamma = 90^\circ$, $V = 1336.66(7)$ Å^3, $T = 100.00(10)$ K, $Z = 4$, $Z' = 1$, μ(Mo K_α) = 2.085, 13032 reflections measured, 2467 unique ($R_{int} = 0.0393$) which were used in all calculations. The final wR_2 was 0.1832 (all data) and R_1 was 0.0615 [$I \geq 2\ \sigma$ (I)].

*3.3.3. Crystallographic data for **26***: Molecular formula = $C_{17}H_{20}N_4OS$, $M_r = 328.43$, monoclinic, $P2_1/c$ (No. 14), $a = 20.4022(8)$ Å, $b = 9.7387(3)$ Å, $c = 8.3672(3)$ Å, $\alpha = 90.0^\circ$, $\beta = 91.769(3)^\circ$, $\gamma = 90.0^\circ$, $V = 1661.69(10)$ Å^3, $T = 130(2)$ K, $Z = 4$, $Z' = 1$, μ(Mo K_α) = 0.205, 5904 reflections measured, 5904 unique which were used in all calculations. The final wR_2 was 0.1358 (all data) and R_1 was 0.0503 [$I \geq 2\ \sigma$ (I)].

3.4. Greenhouse bioassays

All experiments were carried out in a greenhouse, located at the Agricultural Engineering School of the University of Extremadura (38°53′N, 6°58′W) in Badajoz, Spain, in the spring of 2022. The greenhouse was programmed not to exceed an ambient temperature of

30 °C, using a cooling system and irrigation water from the local municipality, having a pH value of 6.30 and electrical conductivity of 0.70 dS m^{-1}, which are suitable values for crop development. To determine the selectivity of the herbicidal formulation, industrial tomato (*Solanum lycopersicum* L.), variety "Heinz 1015″, was used because this genotype is widely employed by farmers in the study area. To check the herbicidal efficacy, rapeseed weeds (*Brassica* spp) were used. Each plastic pot (10-cm high, 13-cm diameter) was filled with a mixed culture substrate based on Sphagnum peat and Wood Fiber, whose properties were as follow: pH ($CaCl_2$) 5.8–6.2, apparent density 180 g m^{-3}, electrical conductivity 0.80 dS m^{-1}, humidity 40 %, and granulometry 0–20 mm, with a heavy metal content below the authorized limits for this product. In addition, to increase the moisture retention of the substrate, a light layer of expansive perlite, from volcanic rock, with a pH 7, electrical conductivity 0.09 dS m^{-1}, and granulometry of 0.1–6 mm, was incorporated into the pot surface. The tomatoes were transplanted into pots (one plant per pot) 30 days after sowing the seeds in the alveolar trays, when the plant had two true leaves. Regarding *Brassica* spp, it was germinated in trays with cotton and transplanted into pots (5 plants per pot) after 4 days. Irrigations were applied manually every day to maintain optimum plant growth. The herbicide used for control was commercially available metribuzin, Sencor Liquid (metribuzin 60 % w/v) purchased from Bayer CropScience.

3.5. Statistical analysis

Statistical analyses were performed with the SPSS 27 software. The resulting data were subjected to one-way ANOVA to evaluate statistical differences among the treatments employed. Whenever significant differences were obtained, a post hoc Duncan-test was used to further elucidate differences among means ($p \leq 0.05$). Data homogeneity in variance and normality was previously verified.

4. Conclusions

In this study, a series of acylhydrazones derived from metribuzin, a common herbicide chiefly employed in the treatment of tomato crops, have been synthesized and their structures were elucidated using UV, FT-IR, NMR, and HRMS (ESI, positive mode), and unambiguously corroborated by single-crystal X-ray analyses. The solid-state structures of three representative hydrazones (all in monoclinic space group), evidence the conformational disposition around the exocyclic C═N double bond, and the preferential (*E*)-configuration, which account for the greater thermodynamic stability of a *trans*-arrangement. Results show that the chemical derivatization of metribuzin did not affect its selectivity whereas the herbicidal activity was improved, especially with an aliphatic derivative, thus suggesting that this compound could be employed without adjuvants, unlike the commercially available formulations of metribuzin. This research opens the door to design alternative, stable, and easy to handle herbicides through synthetic derivatization.

Data availability statement

Data of the study has not been deposited into a publicly available repository. Data included in article/supp. material/referenced in article.

CRediT authorship contribution statement

David Peña: Conceptualization, Data curation, Formal analysis, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Antonio López-Piñeiro:** Conceptualization, Data curation, Formal analysis, Funding acquisition, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing. **Damian Fernández:** Data curation, Formal analysis, Investigation, Methodology. **Mark E. Light:** Conceptualization, Data curation, Investigation, Methodology, Validation, Writing – original draft, Writing – review & editing. **Juan Manuel Prieto:** Data curation, Formal analysis, Investigation, Methodology. **Lucía Santisteban:** Data curation, Formal analysis, Investigation, Methodology. **Richardo Xhavier Valladares:** Data curation, Formal analysis, Investigation, Methodology. **Pedro Cintas:** Conceptualization, Data curation, Investigation, Methodology, Supervision, Validation, Writing – original draft, Writing – review & editing. **Reyes Babiano:** Conceptualization, Data curation, Funding acquisition, Investigation, Supervision, Validation, Writing – original draft, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.heliyon.2023.e21313.

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