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Herbicidal activity of 2-substituted 1,3,4-(2*H*)-isoquinolinetriones

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Abstract

A series of 2-substituted 1,3,4-isoquinolinetriones (**B**) **1–15**, precursors of the phthalamic acids and of the 1,3-dihydro-1-hydroxy-3-oxo-1-isobenzofurancarboxamides (**F**), possessing root antigravitropic activities, were prepared and evaluated for herbicidal activity on weeds and crops. Among the compounds examined, several derivatives were very active against weeds, in many cases more active than the commercially available herbicides used as the reference standards. Phytotoxicities on crops, selectivity and persistence of herbicidal effect were observed.

Keywords: Herbicidal activity; Phytotoxicity; Isoquinolinetriones

1. Introduction

The herbicidal activity of a series of 2-arylsubstituted 1,3-(2*H*,4*H*)-isoquinolinediones (Scheme 1, **A**, R = aryl) has been investigated by us in a previous paper [1]. According to Smith and Kan [2] and to Gardner and Semple [3], these compounds, via oxidation to isoquinolinetriones (**B**), transform by benzylic rearrangement into 2,3-dihydro-1-hydroxy-3-oxo-(1*H*)-isoindole-1-carboxylic acids (**C**) and 1,3-(2*H*)-isoindolediones (**D**). The compounds (**C**) (R = aryl), arising along this pathway, were reported by us for their antigravitropic activity, of the same order as that of the 2-naphthylphthalamic acid [4] (NPA); the compounds (**D**) (R = aryl) are the well-known plant growth regulators phthalimides, precursors of phthalamic acids [5]. Moreover, the isoquinolinetriones (**B**) may yield by some enzyme mediated hydrolytic process, via a different ring opening, 2-arylamino-(1,2-dioxoethyl)benzoic acids (**E**), the dicarbonylic tautomeric form of the 1,3-dihydro-1-hydroxy-3-oxo-1-isobenzofurancarboxamides (**F**, R = aryl, aralkyl), described in our previous paper as plant growth regulators [6].

Being related to several classes of plant growth regulators, 1,3,4-(2*H*)-isoquinolinetriones (**B**) may be postulated as a class of precursors for active compounds of structure (**C**, **D**) and (**E**, **F**). Moreover, they are expected to cross the plant cell walls more easily than their derivatives (**C**) and (**E**, **F**), owing to their different polarities. In particular, we focused our attention on the 2-arylsubstituted isoquinolinetriones, whose activity is very scarcely documented in the literature (only for R = ethyl) [6].

For our purpose, we prepared a series of derivatives (**B**), variously substituted in the 2-position, bearing substituents with different electrophilic and lipophilic properties.

All compounds were subjected to a herbicidal assay against some common weeds; compounds possessing the highest activities were then tested on a wider range of weeds and common crops. The herbicidal activity was evaluated in comparison with that of commercially available products, used as reference standards.

2. Experimental

2.1. Chemistry

The 2-substituted 1,3,4-(2*H*)-isoquinolinetriones (**B**) were prepared as described by Petersen and Heitzer [7], by treatment of 2-substituted 1,3-(2*H*,4*H*)-isoquinolinediones with 4-nitroso-*N*,*N*-dimethylbenzenamine, in DMF, followed by acid hydrolysis of the dark violet mass obtained on cooling. The product, formerly crys-

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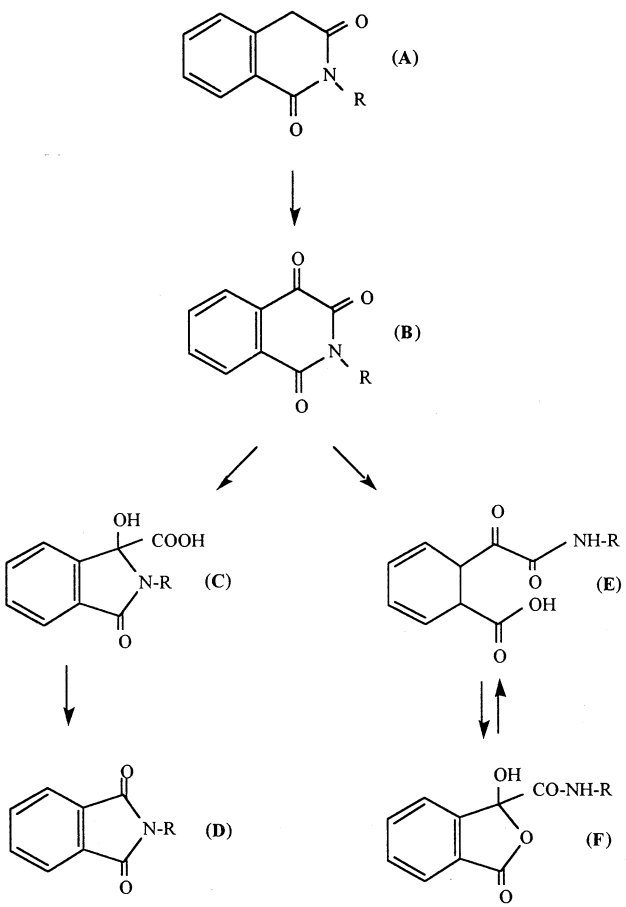

Scheme 1.

tallized by aqueous acetic acid was dried and recrystallized from suitable solvents. Reaction yields were high. All the 2-substituted 1,3-(2*H*,4*H*)-isoquinolinediones (**A**) used in the reaction were reported in the literature. The 2-substituted 1,3,4-(2*H*)-isoquinolinetriones are listed in Table 1; analytical data are referred for substances not yet reported in the literature.

Analyses for C, H, N were within $\pm 0.3\%$ of the theoretical values. Melting points were uncorrected. ^{1}H NMR spectra were recorded on Hitachi R1200 instrument (60 MHz), chemical shifts are reported as δ (ppm) relative to TMS.

2.2. Herbicidal assay[1]

For this assay 15 cm diameter flowerpots were filled with soil of the following composition: 78.5% sand, 16% silt, 4% clay and 1.5% organic matter. Weeds and crops were seeded at a depth of 5 cm.

A total of 10–40 μm powder of the test compound was dispersed in a suitable amount of 0.05% aqueous solution of sodium lignin sulfonate, and 40 ml/m^2 of this suspension were distributed by the De Vilbiss spray equipment [TeeJet nozzle 80015 VS: strainer screen size (100 mesh)].

The assay was performed following three different procedures. For pre-seeding application, the soil was sprayed and the upper 2–3 cm of the layer was thoroughly stirred before seeding. For pre-emergence application, the surface of soil was sprayed the day after seeding. For post-emergence application, seedlings were sprayed when the same was at the two to four leaf stage.

Every assay was performed in triplicate, on three to six pots, which were placed in a greenhouse under controlled climatic conditions. Herbicidal activity in each assay was evaluated at three different times, in

[1] Herbicidal assay was performed by Sipcam, Milan.

Table 1
Analytical data of 2-substituted 1,3,4-(2*H*)-isoquinolinetriones (**B**)

Comp.	Ar	M.p. (°C) (crystallization solvent or Ref.)	Molecular formula	Analyses
1	3-Cl-phenyl	182–184 (CCl_4)	$C_{15}H_8ClNO_3$	C, H, N
2	3-CF_3-phenyl	175–176 (EtOH)	$C_{16}H_8F_3NO_3$	C, H, N
3	4-EtOCO-phenyl	276–278 (AcOH)	$C_{18}H_{13}NO_5$	C, H, N
4	2,3-Me_2-phenyl	255–257 (EtOH)	$C_{17}H_{13}NO_3$	C, H, N
5	2,3-Cl_2-phenyl	250–252 (AcOH)	$C_{15}H_7Cl_2NO_3$	C, H, N
6	3,4-Cl_2-phenyl	255–256 (AcOH)	$C_{15}H_7Cl_2NO_3$	C, H, N NMR [a]
7	3,5-Cl_2-phenyl	216–217 (AcOH)	$C_{15}H_7Cl_2NO_3$	C, H, N
8	3-Cl-2-Me-phenyl	225–227 (EtOH)	$C_{16}H_{10}ClNO_3$	C, H, N
9	3-Cl-4-Me-phenyl	212–213 (*i*-PrOH)	$C_{16}H_{10}ClNO_3$	C, H, N
10	4-Br-3-Cl-phenyl	268 (AcOH)	$C_{15}H_7BrClNO_3$	C, H, N
11	1-Naphthyl	[8]		
12	2-Naphthyl	[8]		
13	3-Pyridyl·HCl	208 (H_2O)	$C_{14}H_9ClN_2O_3$	C, H, N
14	3,4-Cl_2-phenylmethyl	165–166 (EtOH)	$C_{16}H_9Cl_2NO_3$	C, H, N
15	Cyclohexyl	[9]		

[a] ^{1}H NMR (DMSO-d_6) δ: 7.2–8.3 (m, H aromatics).

Table 2
Herbicidal activities of compounds **1–15** [a]

Weed	Application	Dose (kg ha^{-1})	Active compounds and their activities relative to the standards		
			Higher	Same	Lower
Monocotyledons					
A. plantago-aquatica	post-em.	0.8			**9**, **10**
A. myosuroides	p.s.	8			**6**, **7**, **12**
		0.8			**10**
	pre-em.	8			**5**, **6**, **12**
		0.2	**7**		
	post-em.	8			**6**, **7**, **12**
A. ludoviciana	p.s.	8		**7**	**6**, **12**
		0.8			**10**
	pre-em.	8			**12**
		0.8	**6**, **7**, **10**		
	post-em.	8			**6**, **7**, **12**
		0.8			**10**
D. sanguinalis	p.s.	0.8			**6**, **7**, **10**, **12**
	pre-em.	1.6			**7**, **12**
		0.8			**6**, **10**
E. crus-galli	p.s.	8		**7**, **11**	**5**, **6**, **12**
		0.8			**10**
	pre-em.	8			**5**, **11**
		0.8	**6**, **7**, **12**		**10**
	post-em.	8			**6**, **7**, **12**
		0.8			**10**
H. limosa	post-em.	0.8			**9**, **10**
S. viridis	p.s.	0.2			**6**, **7**, **10**, **12**
	pre-em.	0.8			**6**, **7**, **10**, **12**
S. mucronatus	post-em.	0.8			**9**
Dicotyledons					
A. theophrasti	p.s.	0.8			**10**
		0.2		**6**, **7**	
	pre-em.	0.8			**6**, **10**
		0.2	**7**		
	post-em.	0.2	**6**, **10**		
A. retroflexus	p.s.	8			**5**, **8**
		3.2		**2**	**1**, **13**, **14**, **15**
		0.8			**4**, **11**
		0.2	**9**, **12**		
		0.05		**6**, **7**, **12**	
	pre-em.	8			**4**, **8**, **11**
		3.2			**1**, **2**, **14**, **15**
		0.8		**5**, **9**	
		0.2		**6**, **7**, **10**, **12**	
	post-em.	8			**8**
		3.2			**1**, **2**, **13**, **14**, **15**
		0.8			**4**, **11**
		0.2	**5**, **10**, **12**	**6**, **7**, **9**	
A. majus	p.s.	0.05	**6**, **7**, **10**		
	pre-em.	0.2	**12**		
		0.05	**6**, **7**, **10**		
	post-em.	0.05	**6**, **7**, **10**		
C. bursa-pastoris	p.s.	8			**4**, **11**
		0.2	**8**, **9**	**5**	
		0.05	**6**, **7**, **10**, **12**		
	pre-em.	8		**8**	**4**
		0.8		**9**, **11**	
		0.2	**6**, **7**	**5**, **10**, **12**	
	post-em.	8			**4**, **8**
		0.8		**12**	
		0.2	**5**, **6**, **9**, **11**		
		0.05	**7**, **10**		
C. album	p.s.	8			**5**, **8**
		3.2		**2**	**1**, **13**, **15**
		0.8			**4**, **11**
		0.05	**7**	**6**, **9**, **10**, **12**	
	pre-em.	8			**5**, **8**, **11**
		3.2		**2**	**1**

(continued)

Table 2 (Continued)

Weed	Application	Dose (kg ha^{-1})	Active compounds and their activities relative to the standards		
			Higher	Same	Lower
		0.8			**4**, **9**, **13**, **14**
		0.05	**7**	**6**, **10**, **12**	
	post-em.	8			**5**, **8**
		3.2		**2**	**1**, **13**, **14**, **15**
		0.8		**10**	**3**
		0.2	**6**, **7**, **9**, **12**		
G. aparine	p.s.	3.2		**2**	**1**, **13**
		0.8	**5**		**4**, **8**
		0.2	**9**		**11**
		0.05	**6**, **7**, **10**, **12**		
	pre-em.	3.2			**1**, **2**, **15**
		0.2	**4**, **5**, **9**		
		0.05	**12**, **14**	**6**, **7**, **10**	
	post-em.	3.2			**1**, **2**, **9**, **13**, **15**, **16**
		0.2	**5**, **12**		
		0.05	**6**, **7**, **10**, **14**		
M. chamomilla	p.s.	8			**4**
		0.2	**5**, **8**, **9**, **11**		
		0.05	**6**, **7**, **10**, **12**, **14**		
	pre-em.	8			**5**, **11**
		0.8		**6**, **12**	**8**
		0.2	**10**	**4**, **7**, **9**, **14**	
	post-em.	8			**5**, **6**
		0.2	**7**, **9**, **10**, **12**, **14**		
P. rhoeas	p.s.	0.05	**6**, **7**, **10**, **14**	**12**	
	pre-em.	0.8		**6**, **7**	**10**, **12**
		0.05		**14**	
	post-em.	0.8			**6**, **7**, **10**, **14**
P. persicaria	p.s.	0.8		**7**, **10**, **12**	**14**
		0.05	**6**		
	pre-em.	0.8			**6**
		0.2	**7**		
		0.05	**10**, **14**		
S. nigrum	p.s.	0.8			**4**, **5**, **8**, **11**
		0.2	**9**		
		0.05	**6**, **7**, **10**, **14**		
	pre-em.	0.8		**9**, **11**, **12**	**4**, **5**, **8**
		0.05	**10**, **14**	**6**, **7**	
	post-em.	0.8			**4**, **8**, **9**, **11**, **12**, **14**
		0.2	**6**, **7**, **10**		
S. media	p.s.	8			**5**, **8**, **11**
		0.8		**7**	
		0.05	**6**, **7**, **10**, **12**, **14**		
	pre-em.	8			**4**, **5**, **6**, **7**, **12**
		0.2	**14**	**7**	**10**
	post-em.	8	**6**		**4**, **5**, **12**
		0.05	**10**, **14**	**7**	
V. buxbaumii	p.s.	3.2		**2**	**1**, **13**, **15**, **16**
		0.8			**14**
		0.2	**6**, **9**, **12**	**7**, **10**	
	pre-em.	3.2			**1**, **2**, **13**, **15**
		0.8		**9**	**16**
		0.05	**6**, **7**, **10**, **12**, **14**		
	post-em.	3.2			**1**, **2**, **6**, **7**, **9**, **10**, **12**, **13**, **14**, **15**
		0.8			**3**
V. tricolor	p.s.	3.2			**1**, **13**, **14**
		0.8	**2**		**16**
		0.05	**6**, **7**, **10**, **12**, **14**	**9**	
	pre-em.	3.2			**1**, **2**, **13**, **14**
		0.8	**6**	**9**	
		0.05	**7**	**10**, **12**	
	post-em.	3.2			**1**, **2**, **6**, **9**, **10**, **12**, **13**, **15**
		0.2		**7**	

[a] p.s., pre-seeding; pre-em., pre-emergence; post-em., post-emergence.

Table 3
Phytotoxicities on crops of compounds **1–15** [a]

Crop	Application	Dose (kg ha^{-1})	Phytotoxic compounds and their evaluation relative to the standards	
			Higher	Same
B. vulgaris spp. *saccharifera*	p.s.	3.2		**6**, **12**
		0.8		**7**
		0.05	**10**	
	pre-em.	0.2		**6**, **7**
	post-em.	0.05	**6**	
B. napus	p.s.	0.2	**7**	
	pre-em.	0.8		**10**, **12**
G. hirsutum	p.s.	0.8	**2**, **9**	**10**
		0.2	**6**, **7**	
	pre-em.	0.8	**10**	
		0.2	**7**	
H. annuus	p.s.	0.2	**6**, **10**	
		0.05	**7**	
	pre-em.	0.2	**10**	
		0.05	**7**	**6**
H. vulgare	pre-em.	0.2	**7**, **10**, **12**	
O. sativa	pre-em.	0.8	**10**	
		0.05	**7**	
S. lycopersicum	p.s.	0.05	**7**	**6**, **10**, **12**
	pre-em.	0.05	**7**	**6**, **10**, **12**
G. max	p.s.	0.8	**2**, **6**, **9**	**10**
		0.2	**7**	
	pre-em.	0.8	**6**, **7**	**10**, **12**
	post-em.	0.2	**6**	
		0.05	**7**	
T. aestivum	p.s.	3.2	**6**	
		0.8	**2**, **7**	
	pre-em.	3.2		**14**
		0.8	**9**	**7**
Z. mais	p.s.	0.2	**6**, **7**	
	pre-em.	0.8	**6**, **10**	
		0.2	**7**, **9**	**12**
	post-em.	0.2	**6**	

[a] p.s., pre-seeding; pre-em., pre-emergence; post-em., post-emergence.

order to evaluate the persistence of herbicidal effect. Herbicidal activity for weeds and phytotoxicity for crops were expressed as per cent reduction of the development of the treated weed or crop in comparison with untreated controls grown under identical conditions, following European Weed Science Society specifications (unreported data). Statistical analysis of the results was performed according to Duncan's test.

The following monocotyledonous weeds were used for testing compounds reported within brackets: *Alisma plantago-aquatica* (common water plantain) (**4**, **6**–**11**), *Alopecurus myosuroides* (blackgrass) (**4**–**8**, **10**–**12**), *Avena ludoviciana* (fly oat) (**4**–**8**, **10**–**12**), *Digitaria sanguinalis* (large crabgrass) (**5**–**7**, **10**, **12**), *Echinochloa crus-galli* (barnyardgrass) (**4**–**8**, **10**–**12**), *Heteranthera limosa* and *reniformis* (duck salad) (**4**, **6**–**11**), *Panicum dichotomiflorum* (fall panicum) (**5**–**7**, **9**, **12**), *Setaria viridis* (green fox-tail) (**6**, **7**, **10**, **12**) and *Scirpus mucronatus* (roughseed bulrush) (**4**, **6**–**11**).

The following dicotyledonous weeds were used for testing compounds reported within brackets: *Abutilon theophrasti* (velvet leaf) (**6**, **7**, **10**, **12**), *Amaranthus retroflexus* (redrood pigweed) (**2**–**15**), *Ammi majus* (greater ammi) (**6**, **7**, **10**, **12**), *Capsella bursa-pastoris* (shepherdspurse) (**4**–**8**, **10**–**12**), *Chenopodium album* (common lambsquarters) (**1**–**15**), *Galium aparine* (cleavers) (**1**–**15**), *Matricaria chamomilla* (wild chamomile) (**4**–**12**), *Papaver rhoeas* (corn poppy) (**6**, **7**, **10**, **12**), *Polygonum persicaria* (lady's thumb) (**6**, **7**, **9**, **10**, **12**), *Portulaca oleracea* (common purslane) (**5**–**7**, **9**, **12**), *Solanum nigrum* (black nightshade) (**4**–**12**), *Stellaria media* (common chickweed) (**4**–**8**, **10**–**12**), *Veronica buxbaumii* (Buxbaum's speedweel) (**1**–**3**, **6**, **7**, **9**, **10**, **12**–**15**), *Viola tricolor* (wild pansy) (**1**–**3**, **6**, **7**, **9**, **10**, **12**–**15**).

The following crops were used for testing compounds reported within brackets: *Beta vulgaris* spp. *saccharifera* (sugar beet) (**5**–**7**, **9**, **10**, **12**), *Brassica napus* (rape) (**6**, **7**,

10, **12**), *Citrullus vulgaris* (water melon) (**6**, **7**, **12**), *Cucumis melo* (melon) (**5**, **9**), *Fragaria chiloensis* (strawberry) (**5**, **9**), *Gossypium hirsutum* (cotton) (**1**–**3**, **6**, **7**, **9**, **10**, **12**–**15**), *Heliantus annuus* (sunflower) (**6**, **7**, **10**, **12**), *Hordeum vulgare* (barley) (**6**, **7**, **10**, **12**), *Oryza sativa* (rice) (**1**, **2**, **4**, **6**–**15**), *Pisum sativum* (pea) (**6**, **7**, **12**), *Solanum lycopersicum* (tomato) (**6**, **7**, **10**, **12**), *Glycine max* (soybean) (**1**–**15**), *Sorghum* (sorghum) (**6**, **7**, **12**), *Triticum aestivum* (wheat) (**1**–**15**), *Vigna unguiculata* (green dwarf bean) (**6**, **7**, **12**) and *Zea mais* (maize) (**4**–**12**).

The herbicidal activities were evaluated in comparison with those of the commercially available products used as the reference standards: Trifluralin or Pendimethalin for pre-seeding application, Linuron for pre-emergence application and Glyphosate for post-emergence application.

The results of the herbicidal activity and of the phytotoxicity are not reported. The activities of the compounds (see Tables 2 and 3) are expressed in a simplified approach, in terms of compounds which were more active or phytotoxic, as active or phytotoxic as, or less active than the standards against each weed or crop and the dose of each assay. Compounds that were completely inactive or non-phytotoxic in each assay are not reported.

3. Results

3.1. Monocotyledons

Monocotyledonous weeds generally show little sensitivity to the compounds under examination. Only *A. myosuroides*, *A. ludoviciana* and *E. crus-galli* are affected, as shown by their growth in the pre-emergence assay. The most active compounds are the 3,4-Cl_2-phenyl (**6**), 3,5-Cl_2-phenyl (**7**), 3-Br-4-Cl-phenyl (**10**) and 2-naphthyl (**12**) derivatives. In pre-seeding assays, at the highest dose, compounds **7** and **11** were as active as the reference standard against *A. ludoviciana* and *E. crus-galli*.

3.2. Dicotyledons

Dicotyledonous weeds are generally much more affected in their growth than monocotyledonous ones by the compounds under examination.

3.2.1. Pre-seeding assay

Compounds **6**, **7**, **10**, **12**, as well as the 3-Cl-4-Me-phenyl (**9**) and 3,4-Cl_2-phenylmethyl (**14**) derivatives, showed herbicidal activities higher or of the same order as the reference standard against any weeds at the minimal dose of the assay. At higher doses the 3-CF_3-phenyl **2**, 2,3-Cl_2-phenyl (**5**), 3-Cl-2-Me-phenyl (**8**) and (**11**) derivatives were active against *A. retroflexus*, *C. bursa-pastoris*, *M. chamomilla* and *V. tricolor*.

3.2.2. Pre-emergence assay

The **6**, **7**, **10**, **12**, **14** derivatives at the lowest dose of the assay showed activities higher or of the same order as the reference standard against most weeds; *A. theophrasti*, *A. retroflexus*, *C. bursa-pastoris*, *M. chamomilla* and *S. media* were sensitive to the same compounds at higher doses. Moreover, the **2**, 2,3-Me_2-phenyl **4**, **5**, **8**, **9** and **11** derivatives at the highest doses of the assay were active against *A. retroflexus*, *C. bursa-pastoris*, *C. album*, *G. aparine*, *M. chamomilla*, *S. nigrum* and *V. tricolor*.

3.2.3. Post-emergence assay

Derivatives **6**, **7**, **10** and **14** showed higher or similar activities as the reference standard at the lowest dose of the assay against *A. theophrasti*, *A. majus*, *C. bursa-pastoris*, *G. aparine*, *S. media*; moreover, the same derivatives, as well as compounds **2**, **5**, **9**, **11** and **12**, were effective at higher doses against *A. retroflexus*, *C. album*, *M. chamomilla*, *S. nigrum* and *V. tricolor*.

3.3. Crops

As far as phytotoxicity is concerned, results on the most sensitive crops, reported in Table 3, show that many compounds possessing herbicidal activity are also phytotoxic and, in many cases, the derivatives examined possess toxicities of the same order or higher than the reference standards. The derivatives **6**, **7**, **10** and **12** exhibited higher or the same phytotoxicity as the standards against most crops at low doses, except for *T. aestivum*. At higher doses, the same compounds, as well as the derivatives **2**, **9** and **14**, were phytotoxic. Some selectivity was shown by derivatives **6** and **12** against *G. herbaceum*, by **6**, **10** and **12** against *H. vulgare*, by **6**, **7**, **10**, **12** against *G. max* and by **6**, **10** and **12** against *T. aestivum* (unreported data).

Higher persistence of the herbicidal effect was observed for the more active compounds (halogenated **5**–**10** and naphthyl **11**, **12** derivatives) in greenhouse than in field tests.

4. Conclusions

The results reported in Tables 2 and 3 show that the class of 2-substituted 1,3,4-(2*H*)-isoquinolinetriones possesses remarkable herbicidal activity. The compounds examined may act by their intrinsic activity or as pro-drugs giving either compounds **C** and **D** or compounds **E** and **F** by a metabolic pathway.

The highest activities are related to the halogenated and naphthyl derivatives.

The herbicidal activity is particularly remarkable against dicotyledons, while monocotyledons are affected in a lesser extent by treatment in pre- and post-emergence. High sensitivity to the compounds tested was

shown particularly by *A. retroflexus*, *C. bursa-pastoris*, *C. album*, *G. aparine*, *M. chamomilla*, *S. nigrum*, *V. buxbaumii* and *V. tricolor*, and to a lesser extent by *P. rhoeas*, *P. persicaria*, and *S. media*. The herbicidal activity of the same compounds are higher than those of the reference standards against most weeds.

The phytotoxicity on crops is high, in several cases higher than that of the respective reference standard, and selectivity is seldomly observed. These data, in comparison with the results reported for their precursors 1,3-(2*H*,4*H*)-isoquinolinediones (**A**) [1], indicate that the most active compounds bear the same substituents in both classes; moreover, the growth regulating properties of the compounds of the class **B** may be due to the same mechanism of action as the classes **C**–**D**, and **E**–**F**.

All these results and observations are a further confirmation that, in some cases, a simple assay like that described for antigravitropic activity [5], may be useful for detecting growth-regulating activities and, in some cases, herbicidal activity.

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