ELSEVIER

Pharmaceutica Acta Helvetiae 71 (1996) 247–252

PHARMACEUTICA ACTA HELVETIAE

Synthesis of imidazo[2,1-b]thiazoles as herbicides

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Received 7 August 1995; revised 12 September 1995

Abstract

A series of imidazo[2,1-b]thiazoles bearing halogens or a sulfonylurea group or an imidazolidone group, were synthesized and subjected to pre- and post-emergence herbicidal tests. 5-Bromo-6-(3-pyridyl)-2,3-dihydroimidazo[2,1-b]thiazole (**4e**) and 6-(2,3,4-trichlorophenyl)-2,3-dihydroimidazo[2,1-b]thiazole-5-carboxylic acid (**8b**) showed moderate activity in the post-emergence herbicidal tests only.

Keywords: Imidazo[2,1-b]thiazoles; Halogeno derivatives; Sulfonylureas; Imidazolidones

1. Introduction

In connection with our previous papers on the synthesis of imidazo[2,1-b]thiazoles as agrochemicals (Andreani et al., 1989, 1991a,b) we wish now to report the synthesis of new derivatives prepared according to Scheme 1.

Compounds **4**, **6–8** and **11** bear one or more halogens; compounds **4** and **11**, in particular, are related to a series of 5-haloimidazo[2,1-b]thiazoles we published a few years ago (Andreani et al., 1991a) and to a patent by Dupont (Selby and Stevenson, 1993).

Compounds **14** and **16** are examples of sulfonylureas, a well known class of herbicides (Snel, 1989): chlorsulfuron, a member of this family, is reported at the top right of Scheme 1. Sulfonylureas are now known even for their antineoplastic activity (Boder et al., 1992).

A paper dealing with imidazo[2,1-b]thiazole sulfonylurea herbicides has been published already (Ohta et al., 1993): in this series of compounds, sulfur is connected at the 5 position of the imidazothiazole system which, therefore, replaces the 2-chlorobenzene ring of chlorsulfuron; on the contrary, in compounds **14** and **16** sulfur is connected to the 2-chlorobenzene ring, i.e., the imidazothiazole system replaces the triazine ring.

Finally, compounds **19** bear an imidazolidone group and are related to a series of indoles recently prepared (Andreani et al., 1995). The imidazolinone herbicides are a class of potent compounds, discovered (Shaner et al., 1982) and developed (Guaciaro et al., 1992) by American Cyanamid, which act as uncompetitive inhibitors of acetohydroxyacid synthase (Shaner et al., 1984).

A Shell team (Pilgram et al., 1987) prepared numerous imidazolidones (whose general formula is reported in Scheme 1) in order to study the effect of the linkage on the biological activity. We selected a linkage which produced active compounds (azomethine) and replaced the phenyl ring with the imidazothiazole moiety: the result was a series of 5-(2-oxo-1-imidazolidinyliminomethyl)-imidazo[2,1-b]thiazoles **19a–c** and thiazolines **19d–f**.

2. Chemistry

2-Aminothiazole **1a** and 2-amino-2-thiazoline **1b** were treated with the bromoacetyl pyridines **2a–c** to yield the

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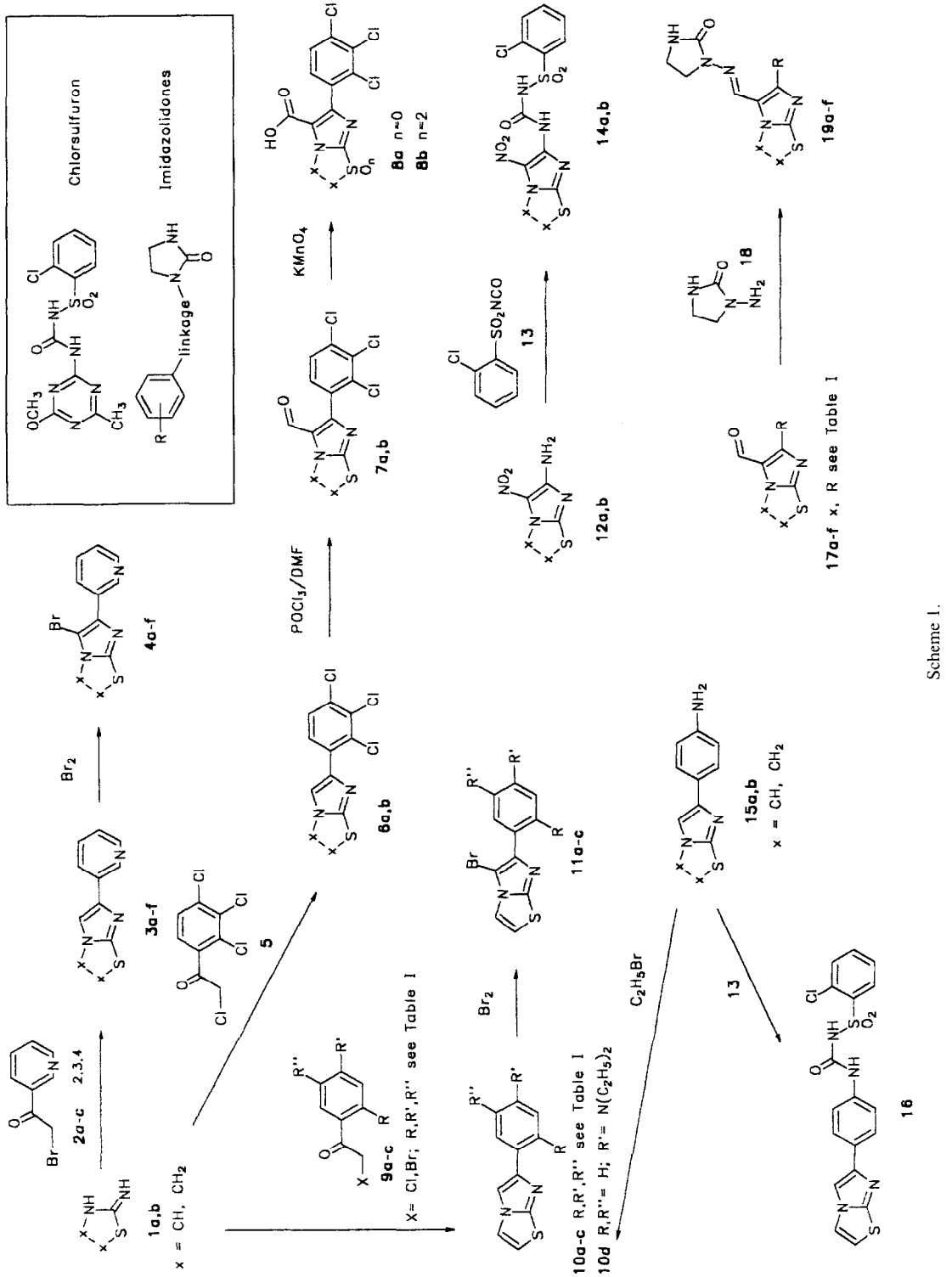
PII S0031-6865(96)00021-0


Chlorsulfuron
Imidazolidones
linkage
1a,b
x = CH, CH2
2a-c 2,3,4
3a-f
4a-f
Br2
5
6a,b
POCl3/DMF
7a,b
KMnO4
8a n=0
8b n=2
9a-c
X= Cl,Br; R,R',R'' see Table 1
11a-c
10a-c R,R',R'' see Table 1
10d R,R''= H; R'= N(C2H5)2
C2H5Br
12a,b
13
14a,b
15a,b
x = CH, CH2
18
17a-f x, R see Table 1
19a-f
16

Scheme 1.

6-pyridylimidazo[2,1-b]thiazoles **3a–f** which, in turn, were the starting material for the 5-bromo analogues **4a–f**.

Similar reaction was repeated for the synthesis of the 5-bromo derivatives **11a–c**: under the usual experimental conditions 6-(4-diethylaminophenyl)imidazo[2,1-b]thiazole **10d** (prepared in turn from **15a**) did not give the corresponding 5-bromo derivative.

With the same procedure, the 6-(2,3,4-trichlorophenyl)imidazo[2,1-b]thiazoles **6a–b** were prepared from **5** and subjected to the Vilsmeier reaction to give the aldehydes **7a–b** which, in turn, were oxidized to the corresponding acids **8a–b**. The spectroscopic data of compounds **4**, **8** and **11** are in agreement with the assigned structures.

As far as the sulfonylureas are concerned, we planned the synthesis of two series of derivatives, the first one arising from the 6-amino group and the second one from the 6-(4-aminophenyl) group. In both cases the imidazo[2,1-b]thiazoles **12a** and **15a** showed a behaviour different from the 2,3-dihydro analogues (**12b, 15b**). In fact compounds **12a** and **15a**, treated with 2-chlorobenzenesulfonyl isocyanate **13** gave the expected sulfonylureas **14a** and **16**. On the contrary, under the same experimental conditions, the 2,3-dihydro derivatives **12b** and **15b** yielded mixtures containing only small amounts of the expected sulfonylureas which were not separated: in the case of compound **14b**, its ^{1}H-NMR could be extrapolated from the spectrum of the mixture (see Experimental).

Compounds **19a–f** were prepared by reaction of the appropriate imidazo[2,1-b]thiazole-5-carboxaldeydes **17a–f** with 1-amino-2-imidazolidone **18**. In the ^{1}H-NMR spectra, recorded in CF_3COOD, the thiazole protons show the typical aromatic (**19a–c**) or aliphatic (**19d–f**) pattern, while the methine group falls in the range 7.5–7.8 ppm and the imidazolidone protons at 4 ppm ca; the NH group is evident only in the spectrum recorded in $(CD_3)_2SO$ (**19e**). In the MS, the molecular ion peak is always prominent and in one case (**19d**) is the base peak. Signals from loss of 2-imidazolidinone (M-86) or its deprotonated form (M-85) are evident in all the compounds.

3. Biological results

Compounds **4a–f, 6a,b–8a,b, 11a–c, 14a, 16** and **19a–f** were subjected to pre- and post-emergence herbicidal tests (see Experimental).

None of our compounds showed activity as pre-emergence herbicides. In contrast, some compounds showed activity in the contact tests: among the 5-bromo derivatives, compound **4e** was active (rating = 5) against *Setaria, Sinapis* and *Stellaria*. Compound **8b** showed weak activity (rating = 6) against the above mentioned species. The inactivity of the sulfonylureas suggests that the substituted triazine is essential for the herbicidal activity. Even the imidazolidones **19a–f** were inactive.

In these pre- and post-emergence screening tests, commercial products like chlorsulfuron show activities in the 1 to 3 rating range against *Setaria, Sinapis* and *Stellaria*.

4. Experimental

4.1. Chemistry

The melting points are uncorrected. Analyses (C, H, N) were within $\pm 0.4\%$ of the theoretical values. Bakerflex plates (silica gel IB2-F) were used for TLC and Kieselgel 60 (Merck) for column chromatography: the eluent was a mixture of petroleum ether/acetone in various proportions. The IR spectra were recorded in nujol on a Perkin–Elmer 298; ν_{max} is expressed in cm $^{-1}$. The ^{1}H-NMR spectra were recorded in $(CD_3)_2SO$ (unless otherwise reported) on a Varian EM-390 (90 MHz) or on a Varian Gemini (300 MHz) using TMS as the internal standard; the chemical shift is expressed in δ (ppm) and J in Hz, with the following abbreviations: ar = aromatic, im = imidazole, py = pyridine, th = thiazole, thn = thiazoline. The EI–MS were recorded on a VG 7070E at 70 eV; the positive ion is reported as m/z (in brackets the relative abundance in %). See also Table 1.

Table 1
New imidazo[2,1-b]thiazoles reported in Scheme 1

Comp	x	N	R	R'	R''	Formula (MW)	Mp (°C)
4a	CH	2	-	-	-	$C_{10}H_6BrN_3S$ (280.1)	111-113
4b	CH	3	-	-	-	$C_{10}H_6BrN_3S$ (280.1)	167-170
4c	CH	4	-	-	-	$C_{10}H_6BrN_3S$ (280.1)	183-185
4d	CH_2	2	-	-	-	$C_{10}H_8BrN_3S$ (282.2)	135-139
4e	CH_2	3	-	-	-	$C_{10}H_8BrN_3S$ (282.2)	145-148
4f	CH_2	4	-	-	-	$C_{10}H_8BrN_3S$ (282.2)	183-187 dec
8a	CH	-	-	-	-	$C_{12}H_5Cl_3N_2O_2S$ (347.6)	185-190 dec
8b	CH_2	-	-	-	-	$C_{12}H_7Cl_3N_2O_4S$ (381.6)	261-263 dec
10b	-	-	H	t-Bu	H	$C_{15}H_{16}N_2S$ (256.4)	164-168
10c	-	-	Cl	Cl	NO_2	$C_{11}H_5Cl_2N_3O_2S$ (314.1)	232-236
10d	-	-	H	NEt_2	H	$C_{15}H_{17}N_3S$ (271.4)	193-198 dec
11a	-	-	H	CH_3	H	$C_{12}H_9BrN_2S$ (293.2)	127-130
11b	-	-	H	t-Bu	H	$C_{15}H_{15}BrN_2S$ (335.3)	146-148
11c	-	-	Cl	Cl	NO_2	$C_{11}H_4BrCl_2N_3O_2S$ (393.0)	204-208
14a	CH	-	-	-	-	$C_{12}H_8ClN_5O_5S_2$ (401.8)	220-225 dec
16	-	-	-	-	-	$C_{18}H_{13}ClN_4O_3S_2$ (432.9)	139-143 dec
19a	CH	-	Cl	-	-	$C_9H_8ClN_5OS$ (269.7)	302-305 dec
19b	CH	-	CH_3	-	-	$C_{10}H_{11}N_5OS$ (249.3)	299-303 dec
19c	CH	-	C_6H_5	-	-	$C_{15}H_{13}N_5OS$ (311.4)	262-265 dec
19d	CH_2	-	Cl	-	-	$C_9H_{10}ClN_5OS$ (271.7)	271-274 dec
19e	CH_2	-	CH_3	-	-	$C_{10}H_{13}N_5OS$ (251.3)	263-265 dec
19f	CH_2	-	C_6H_5	-	-	$C_{15}H_{15}N_5OS$ (313.4)	298-300 dec

*4.1.1. 5-Bromoimidazo[2,1-b]thiazoles **4,11***

*4.1.1.1. Starting materials **3,10***

The 6-pyridylimidazo[2,1-b]thiazoles and thiazolines **3** (Andreani et al., 1985) were prepared by reaction of **1a** and **1b** with the appropriate bromoacetyl pyridine **2**.

The 6-phenylimidazo[2,1-b]thiazoles **10** arise from the reaction of the aminothiazole **1a** with the appropriate 2-haloacetophenone **9**. 6-(4-Tolyl)imidazo[2,1-b]thiazole **10a** (R, R'' = H; R' = CH_3) from **9a** is already known (Buu-Hoi et al., 1966) whereas the other compounds were prepared as follows:

*6-(4-t-butylphenyl)imidazo[2,1-b]thiazole **10b*** 2-Aminothiazole **1a** (27 mmol) was dissolved in 80 ml of acetone and treated with the equivalent of 2-bromo-4′-*t*-butyl-acetophenone **9b** (Nickl et al., 1970). The reaction mixture was refluxed under stirring for 20 min and, after cooling, the resulting precipitate was collected and refluxed for 1 h with 250 ml of 1 M HBr. The still warm solution thus obtained was cautiously made basic with 10% NH_4OH. The resulting precipitate was collected and crystallized from ethanol with a yield of 80%.

IR: 1540, 1190, 845, 715, 645 ^{1}H-NMR: 1.29 (9H, s, CH_3); 7.24 (1H, d, th, J = 4.4); 7.40 (2H, d, ar, J = 8.5); 7.75 (2H, d, ar, J = 8.5); 7.91 (1H, d, th, J = 4.4); 8.16 (1H, s, im)

*6-(2,4-Dichloro-5-nitrophenyl)imidazo[2,1-b]thiazole **10c*** 2-Aminothiazole **1a** (20 mmol) was dissolved in 100 ml of ethanol and treated with the equivalent of 2,4-dichloro-5-nitrophenacyl chloride **9c** (Luthardt et al., 1984). The reaction mixture was refluxed for 8 h and the precipitate thus formed was collected and crystallized from ethanol with a yield of 30%.

IR: 1520, 1300, 1070, 740 ^{1}H-NMR: 7.38 (1H, d, th, J = 4.4); 7.97 (1H, d, th, J = 4.4); 8.08 (1H, s, ar); 8.60 (1H, s, im); 8.80 (1H, s, ar)

*6-(4-Diethylaminophenyl)imidazo[2,1-b]thiazole **10d*** 6-(4-Aminophenyl)imidazo[2,1-b]thiazole **15a** (Matsukawa and Ban, 1951) (2 mmol) was dissolved in 10 ml of anhydrous DMF and treated portionwise with 3 mmol of NaH. The reaction mixture was stirred at room temperature for 20 min and treated with 5 mmol of bromoethane. After 5 h under stirring at room temperature, the mixture was poured onto ice and the resulting precipitate was collected and purified by column chromatography. Final crystallization from ethanol gave 35% of compound **10d**.

IR: 1610, 1540, 1260, 1190 ^{1}H-NMR: 1.09 (6H, t, CH_3, J = 7); 3.34 (4H, q, CH_2, J = 7); 6.67 (2H, d, ar, J = 9); 7.18 (1H, d, th, J = 4.4); 7.60 (2H, d, ar, J = 9); 7.86 (1H, d, th, J = 4.4); 7.95 (1H, s, im)

*4.1.1.2. General procedure of bromination (**4,11**)*

The appropriate imidazothiazole (**3, 10**) (5 mmol) was dissolved in $CHCl_3$ (40 ml) and treated dropwise, under cooling and stirring, with bromine (5.5 mmol) dissolved in $CHCl_3$ (10 ml). The reaction mixture was stirred at room temperature for 2 h and the resulting precipitate (**4, 11** · HBr) was collected. The free base was separated (NH_4OH) and crystallized from ethanol with a yield of 60–70%. Under this experimental procedure **10d** did not give the expected 5-bromo derivative.

4a IR: 1585, 1150, 990, 780, 670 ^{1}H-NMR: 7.40 (1H, m, py); 7.55 (1H, d, th, J = 4.5); 7.98 (1H, d, th, J = 4.5); 8.05 (2H, m, py); 8.70 (1H, m, py) MS: 279 (M^+, 100); 200 (M–Br, 23); 174 (6); 156 (7)

4b IR: 1590, 1540, 1320, 1240, 850 ^{1}H-NMR: 7.47 (1H, d, th, J = 4.5); 7.50 (1H, m, py); 7.95 (1H, d, th, J = 4.5); 8.30 (1H, m, py); 8.68 (1H, m, py); 9.20 (1H, m, py) MS: 279 (M^+, 100); 200 (M–Br, 70); 173 (11)

4c IR: 1595, 1315, 1250, 1225 ^{1}H-NMR: 7.49 (1H, d, th, J = 4.5); 7.94 (3H: 1H, d, th, J = 4.5 + 2H, d, py, J = 5.5); 8.63 (2H, d, py, J = 5.5) MS: 279 (M^+, 100); 200 (M–Br, 25); 173 (9)

4d IR: 1585, 1145, 990, 780 ^{1}H-NMR: 3.94 (2H, m, thn); 4.25 (2H, m, thn); 7.27 (1H, m, py); 7.86 (2H, m, py); 8.61 (1H, m, py) MS: 281 (M^+, 100); 202 (M–Br, 6); 174 (40)

4e IR: 1565, 1110, 970, 800, 700 ^{1}H-NMR: 3.96 (2H, m, thn); 4.27 (2H, m, thn); 7.48 (1H, m, py); 8.21 (1H, m, py); 8.55 (1H, m, py); 9.11 (1H, m, py) MS: 281 (M^+, 45); 202 (M–Br, 15); 176 (100)

4f IR: 1600, 1120, 980, 820 ^{1}H-NMR: 3.95 (2H, m, thn); 4.25 (2H, m, thn); 7.85 (2H, d, py, J = 5.5); 8.64 (2H, d, py, J = 5.5) MS: 281 (M^+, 100); 202 (M–Br, 7); 174 (52)

11a IR: 1530, 1325, 1100, 970, 815 ^{1}H-NMR: 2.34 (3H, s, CH_3); 7.27 (2H, d, ar, J = 8); 7.43 (1H, d, th, J = 4.5); 7.85 (2H, d, ar, J = 8); 7.89 (1H, d, th, J = 4.5)

11b IR: 1540, 1330, 970, 835, 675 ^{1}H-NMR: 1.31 (9H, s, CH_3); 7.43 (1H, d, th, J = 4.5); 7.48 (2H, d, ar, J = 8); 7.87 (2H, d, ar, J = 8); 7.90 (1H, d, th, J = 4.5)

11c IR: 1525, 1360, 1000, 900, 650 ^{1}H-NMR: 7.52 (1H, d, th, J = 4.5); 7.98 (1H, d, th, J = 4.5); 8.20 (1H, s, ar); 8.27 (1H, s, ar).

*4.1.2. 6-(2,3,4-Trichlorophenyl)imidazo[2,1-b]thiazole-5-carboxylic acids **8***

The appropriate aldehyde **7** (Andreani et al., in press) (5 mmol) was dissolved in acetone (600 ml) and treated with a solution of $KMnO_4$ (40 mmol) in H_2O (100 ml). The

mixture was stirred at room temperature for 24 h, decoloured with 10% H_2O_2, filtered, evaporated and acidified with 2 M HCl. The resulting precipitate was crystallized from ethanol with a yield of 65–70%.

8a IR: 3400–2300, 1690, 1235, 1180, 1120 ^{1}H-NMR: 3.75 (1H, broad s, COOH); 7.51 (1H, d, ar, $J = 8$); 7.56 (1H, d, th, $J = 4.4$); 7.72 (1H, d, ar, $J = 8$); 8.22 (1H, d, th, $J = 4.4$)

8b (sulfone) IR: 3200–2200, 1720, 1330, 1240, 1130 ^{1}H-NMR: 3.35 (1H, broad s, COOH); 4.28 (2H, t, thn, $J = 6$); 4.84 (2H, t, thn, $J = 6$); 7.49 (1H, d, ar, $J = 8$); 7,75 (1H, d, ar, $J = 8$)

*4.1.3. Sulfonylureas **14,16***

The appropriate aminoimidazothiazole [**12** (Andreani et al., 1993), **15** (Matsukawa and Ban, 1951; Markova et al., 1965)] (2 mmol) was dissolved in THF (60 ml) and treated with 3 mmol of 2-chlorobenzenesulfonyl isocyanate **13**. The mixture was refluxed for 12 h, evaporated under reduced pressure and crystallized from ethanol with a yield of 55–65%.

14a IR: 3335, 3145, 3105, 1720, 1570, 1315, 1270, 1160 ^{1}H-NMR: 7.58 (1H, d, th, $J = 4.4$); 7.63 (1H, m, ar); 7.73 (2H, m, ar); 8.15 (1H, m, ar); 8.29 (1H, d, th, $J = 4.4$); 9.78 (1H, s, NH); 12.20 (1H, broad s, NH) MS: 401 (M^+, 1); 217 (35); 184 (56); 175 (43); 138 (20); 126 (50); 111 (100); 75 (65)

14b ^{1}H-NMR: 3.96 (2H, t, thn, $J = 7.5$); 4.54 (2H, t, thn, $J = 7.5$); 7.65 (3H, m, ar); 8.13 (1H, d, ar); 9.63 (1H, s, NH); 12.10 (1H, broad s, NH)

16 IR: 1725, 1620, 1545, 1155, 1040 ^{1}H-NMR: 7.24 (1H, d, th, $J = 4.4$); 7.35 (2H, d, ar, $J = 8.7$); 7.62 (2H, m, ar); 7.72 (3H: 1H, d, ar + 2H, d, ar, $J = 8.7$); 7.91 (1H, d, th, $J = 4.4$); 8.13 (1H, d, ar); 8.14 (1H, s, im); 8.83 (1H, s, NH); 10.10 (1H, broad s, NH)

*4.1.4. 5-(2-Oxo-1-imidazolidinylimino-methyl)imidazo[2,1-b]thiazoles **19***

The appropriate imidazo[2,1-b]thiazole-5-carboxaldeyde or 2,3-dihydroimidazo[2,1-b]thiazole-5-carboxaldehyde **17** (Andreani et al., 1982) (30 mmol) was dissolved in ethanol (100 ml) and treated with the equivalent of 1-amino-2-imidazolidone **18** (Michels and Gever, 1956). The mixture was refluxed for 1 h and concentrated under reduced pressure. The precipitate thus formed was collected by filtration and crystallized from ethanol with a yield of 75–80%.

The IR spectra show NH stretching bands at 3300–3100 cm^{-1}. The ^{1}H-NMR spectra of compounds **19a–d** and **19f** were registered in CF_3COOD.

19a IR: 1740, 1400, 1260, 1220 ^{1}H-NMR: 4.08 (4H, m, im); 7.71 (1H, d, th, $J = 4.4$); 7.80 (1H, s, CH=); 8.96 (1H, d, th, $J = 4.4$)MS: 269 (M^+, 45), 184 (41); 183 (34); 135 (49); 86 (100); 85 (88); 58 (88); 45 (54); 42 (45)

19b IR: 1725, 1410, 1265, 1240 ^{1}H-NMR: 2.68 (3H, s, CH_3); 4.02 (4H, m, im); 7.58 (1H, d, th, $J = 4.4$); 7.81 (1H, s, CH=); 8.88 (1H, d, th, $J = 4.4$) MS: 249 (M^+, 83); 164 (82); 163 (100); 86 (69); 85 (82); 58 (72)

19c IR: 1725, 1400, 1250, 1190 ^{1}H-NMR: 3.99 (4H, m, im); 7.65 (1H, d, th, $J = 4.4$); 7.72 (5H, s, ar); 7.86 (1H, s, CH=); 9.0 (1H, d, th, $J = 4.4$) MS: 311 (M^+, 55); 226 (49); 225 (100); 200 (39)

19d IR: 1730, 1390, 1250, 1230 ^{1}H-NMR: 3.99 (4H, m, im); 4.20 (2H, t, thn, $J = 7.5$); 4.99 (2H, t, thn, $J = 7.5$); 7.50 (1H, s, CH=)MS: 271 (M^+, 100); 186 (59); 185 (97); 86 (70); 85 (54)

19e IR: 1700, 1410, 1265, 1240 ^{1}H-NMR: 2.16 (3H, s, CH_3); 3.40 (2H, m, im); 3.70 (2H, m, im); 3.88 (2H, t, thn, $J = 7.5$); 4.35 (2H, t, thn, $J = 7.5$); 7.02 (1H, s, NH); 7.53 (1H, s, CH=) MS: 251 (M^+, 69); 166 (37); 165 (100); 86 (19); 85 (22)

19f IR: 1720, 1405, 1270, 1250 ^{1}H-NMR: 3.93 (4H, m, im); 4.29 (2H, t, thn, $J = 7.5$); 5.08 (2H, t, thn, $J = 7.5$); 7.65 (6H: 5H, s, ar + 1H, s, CH=) MS: 313 (M^+, 82); 228 (32); 227 (100); 103 (10)

4.2. Biology

4.2.1. Pre-emergence herbicidal activity

Monocotyledonous and dicotyledonous test species (*Avena, Setaria, Sinapis* and *Stellaria*) were seeded in plastic pots containing standard soil. Immediately after seeding, the pots were sprayed with an aqueous suspension of the test compounds at rates of 2000 g of active ingredient per hectare (500 l of water per hectare). The pots were then transferred to the greenhouse for germination/growth under optimal conditions. The evaluation took place after three weeks, whereby the rating scale of 1 (100%) to 9 (no herbicidal effect) was employed. Ratings of 1 to 4 indicate good to excellent activity.

4.2.2. Post-emergence herbicidal activity

Monocotyledonous and dicotyledonous test species (*Avena, Setaria, Sinapis* and *Stellaria*) were raised in plastic pots containing standard soil. At the 4–6 leaf stage, the plants were sprayed with an aqueous suspension of the test compounds at rates of 2000 g of active ingredient per hectare (500 l of water per hectare). The pots were then transferred to the greenhouse for further cultivation under optimal conditions. The evaluation took place after 18 days, whereby the rating scale of 1 (100%) to 9 (no herbicidal effect) was employed. Ratings of 1 to 4 indicate good to excellent activity.

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