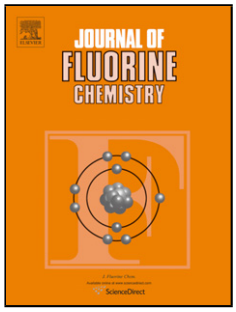

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PII: S0022-1139(17)30268-3
DOI: http://dx.doi.org/10.1016/j.jfluchem.2017.08.013
Reference: FLUOR 9039

To appear in: *FLUOR*

Received date: 11-6-2017
Revised date: 13-8-2017
Accepted date: 28-8-2017

Please cite this article as: Bogumiła Huras, Jerzy Zakrzewski, Anna Kiełczewska, Maria Krawczyk, Herbicidal and fungistatic properties of fluorine analogs of phenoxyacetic herbicides, Journal of Fluorine Chemistryhttp://dx.doi.org/10.1016/j.jfluchem.2017.08.013

Herbicidal and fungistatic properties of fluorine analogs of phenoxyacetic herbicides

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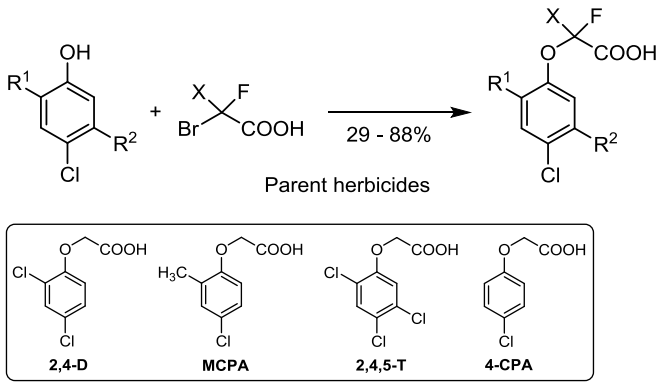
Graphical Abstract



Highlights

- Fluorine analogs of herbicides 2,4-D, MCPA, 2,4,5-T, and 4-CPA were synthesized.
- Fluorine derivatives of 2,4-D show herbicidal activity against three weed species.
- Parent herbicides and some monofluorine derivatives show fungistatic activity against *Phytophtora cactorum*.

Abstract. Aryloxy fluoroacetic acids **3a**-**3h** - fluorine analogs of phenoxyacetic herbicides 2,4-D, MCPA, 2,4,5-T, and 4-CPA were efficiently synthesized in 29 - 88% yield, using appropriate phenols and either bromodifluoro- or bromofluoroacetic acid in the presence of sodium hydride as a base and in either dioxane or THF as solvents. Fluorine derivatives of 2,4-D (**3a**, **3b**) show herbicidal activity against three weed species. Parent herbicides 2,4-D, MCPA, 2,4,5-T, 4-CPA, monofluorine derivatives of MCPA (**3d**) and 2,4,5-T (**3f**) show fungistatic activity against phytopatogenic fungi species *Phytophtora cactorum*.

Keywords: phenoxyacetic herbicides, fluorine analogs, herbicidal activity, fungistatic activity

1. Introduction

Fluorine atom can mimic a hydrogen atom without major deviation of geometry [1]. Close relation in structure and similar biological effects of two functional groups is known as bioisosterism. The replacement of hydrogen by fluorine is the most typical monovalent bioisosteric modification [2-4]. A comparison of analogous properties of compounds with or without fluorine is presented in reference [5]. Selective replacement of the hydrogen atom by the fluorine atom has been a very effective tool for modifying the reactivity of diverse organic compounds [6]. The steric factors [1-3,7], strong electron withdrawing inductive effect of the fluorine atom [1], as well as intermolecular hydrogen bonds between the fluorine atom and an acidic hydrogene atom [8] have been widely discussed. The comparison of biological activity of acetic acid vs monofluoroacetic acid is a good early example of the significant change of biological properties caused by the replacement of a hydrogen atom by a fluorine one [9,10].

From the beginning of the 1980s a significant increase of the commercially available pesticides (insecticides, acaricides, herbicides, fungicides, and plant growth regulators) containing halogen atoms (in particular, fluorine atoms) in the molecule, was observed [4,11-16]. Their description in the literature was closely related to their mode of action [4,11,13-16]. The structures and names [4,11-16] and the methods of synthesis [15] of the most important fluorinated pesticides were presented.

A number of compounds containing a fluorine atom have been tested as fungicides, herbicides, insecticides, and pheromones. The fungicidal activity of strobilurin derivatives with a trifluoromethyl moiety [17] and fluorine-containing stilbene derivatives of oxadiazole nucleus [18] were described. Fluorine derivatives of pyrazolo[3,4-d]pyrimidin-4-one [19] (a structural analog of purines [20-22]), and fluorinated derivatives of 2-phenyl-4H-3,1-benzoxazin-4-one (bentranil) [23] showed herbicidal activity. Insecticidal activity of *gem*-difluorovinyl terminated even-numbered long chain compounds [24], the SF_5 analogs of fipronil [25], as well as amidoflumet, metofluthrin, and a new fluorinated alfa-pyrone derivative [26] was observed. In contrast, fluorine derivatives of the controversial historical insecticide

DDT did not show any activity as insecticides [27]. The effect of the replacement of specific H atoms by F atoms in long chain insect sex pheromones was reviewed. In general, the activity of fluoro derivatives of pheromones seemed to be decreased with an increasing number of fluorine atoms in the chain [28].

Herein, we would like to present the synthesis and evaluation of herbicidal and fungistatic properties of fluorine analogs of the most popular phenoxyacetic herbicides: 2,4-D, MCPA, 2,4,5-T, and 4-CPA, which are known as selective herbicides that kill dicots without affecting monocots (Figure 1). They mimic a natural auxin at the molecular level.

2. Results and disscusion

The synthesis of aryloxyfluoroacetic acids has been reported as a reaction of phenols and either bromofluoroacetic acids or their esters in the presence of a base [29-33]. It is interesting to note that if Cs_2CO_3 as a base and an either Ir or Ru photocatalysts were used, the similar condensation with bromodifluoroacetic acid in visible-light led to decarboxylated products (terminated with a CF_2H moiety instead of CF_2COOH group) [34].

All methods were preliminary tested for two model compounds containing a linker CF_2 (**3a**) or CHF (**3d**), respectively (Scheme 1, Table1).

Finally, two methods were selected. The title fluorine analogs of phenoxyacetic herbicides **3a**-**3h** were synthesized from appropriate phenols **1** and either bromodifluoroacetic acid or bromofluoroacetic acid **2** in the presence of sodium hydride as a base. The fluorine analogs containing CF_2 linker, **3a**, **3c**, **3e**, **3g**, were efficiently synthesized using sodium hydride as a base in dioxane at 100 °C (method **A**). The fluorine analogs with CHF linker, **3b**, **3d**, **3f**, **3h**, were efficiently synthesized using sodium hydride as a base in THF at a room temperature (method **B**).

The synthesis of the fluorine analogs of phenoxyacetic herbicides 2,4-D, MCPA, 2,4,5-T, and 4-CPA **3a**-**3h** is presented in Scheme 2. The yields and melting points are presented in Table 2.

The compounds **3a**, **3c**, and **3e** obtained with method **A** and **3f** obtained with the method **B** (as well as all synthesized compounds **3** obtained with the preliminary tested methods, listed above), led to the corresponding products **3** in lower yields.

Significant amounts of side-products and copious amounts of the unreacted starting phenols were always detected by means of TLC in the reaction mixtures. The title fluorine analogs **3a**-**3h** were isolated and purified by column chromatography, however the presence of side-products as well as the presence of starting phenols make the isolation and purification of pure products **3** difficult.

The structures of fluorine-containing acids **3a-3h** were confirmed by the presence of the molecular peaks in MS, measurement of exact mass of the molecular peaks in HRMS, full compliance of ^{1}H and ^{13}C NMR spectra (CH_2 signals: DEPT 135°) and ^{19}F NMR with the structures, and by IR spectra. The spectra of fluorinated analogs **3a** - **3h** of phenoxyacetic herbicides see supplementary data.

The molecular ion peaks of **3a-3h** are present in EI MS. In the case of **3d** the molecular ion is the base peak, while the phenol fragment (**3a**, **3e** and **3g**), the aryloxy fragment (**3c**), and the aryl fragment (**3h**) are the base peaks in the respective compounds. The M-COOH fragment is a base peak in the case of **3b**, **3f**.

Doublets at ~ 5.92 - 5.98 ppm (J = 58 - 59 Hz) were observed for proton signals of CHF in ^{1}H NMR spectra of **3b**, **3d**, **3f**, **3h**. The correlated doublets at -130 - -131 ppm (J = 58 - 59 Hz) were observed for fluorine signals of CHF in ^{19}F NMR spectra of **3b**, **3d**, **3f**, **3h**. Singlets at -77 - -77.5 ppm were observed for fluorine signals of CF_2 in ^{19}F NMR spectra of **3a**, **3c**, **3e**, **3g**. Triplets at ~ 113.5 ppm (J = 270 - 275 Hz) were observed for carbon signals of CF_2 in ^{13}C NMR spectra of **3a**, **3c**, **3e**, **3g**. Doublets at ~ 102 ppm (J = 225 - 236 Hz) were observed for carbon signals of CHF in ^{13}C NMR spectra of **3b**, **3d**, **3f**, **3h**.

Carbonyl band at 1740 - 1770 cm^{-1} and another sharp peak at 1460 - 1490 were observed in the IR spectra of all compounds **3**.

Subsequently, herbicidal and fungistatic activities of the synthesized fluorine derivatives **3a**-**3h** were evaluated.

The herbicidal activity of **3a** - **3h** against ten weed species was examined in the pot experiments under greenhouse conditions. The results are presented in Table 3.

Tested fluorine derivatives of phenoxyacetic herbicides **3** showed lower herbicidal activity than the parent herbicides 2,4-D, MCPA, 2,4,5-T and 4-CPA. Both fluorine derivatives of 2,4-D, **3a** and **3b**, showed activity against three weed species. Other tested compounds **3c**-**3h** showed diverse, moderate activity.

The average activity of monofluorine compounds **3b**, **3d**, **3f**, and **3h** is slightly higher than the activity of the corresponding difluorine derivatives **3a**, **3c**, **3e**, and **3g**. The observed herbicidal activity of the fluorine derivatives **3** is only foliar. Phytotoxic symptoms were recognized for some tested fluorine compounds to some bioindicators (Table 3). Necrotic spots on leaves become visible within 24 hours after application of the compounds.

Because most herbicides are biologically active not only against weeds but also against non-target microorganisms, the fungistatic activity of **3a** - **3h** was evaluated. Fungicidal activity of herbicides is a known phenomenon, and has been described in many papers. Inhibition activity of herbicides against various plant pathogen fungi, was summarized in a review article [35]. Antifungal activity of herbicides: MCPA, simazine, linuron, tri-allate, paraquate [36] and herbicides 2,4-D, despedipham, clodinafop, diclofop-methyl, tralkoxydium [37], against either six [36], or twenty [37] soil fungi species were investigated. The herbicides under investigation showed antifungal activity, however the level of the activity was diverse. Inhibitory effect on the growth of *Fusarium oxysporum* fungus was investigated for the herbicides MCPA, 2,4-DB, flumetsulam, bentazon, and haloxyfop-methyl. Inhibitory effect was observed for the herbicides 2,4-DB and bentazon. However, it is worthy to note, that the herbicides flumetsulam and MCPA showed no effect, and surprisingly, haloxyfop-methyl showed a significant stimulant effect [38].
The antifungal activity of the fluoro analogues **3a** - **3h** and the parent phenoxyacetic herbicides 2,4-D, MCPA, 2,4,5-T and 4-CPA was tested against several representative pathogenic fungi: *Alternaria alternata, Botrytis cinerea, Fusarium culmorum, Phytophtora cactorum, Rhizoctonia solani, Blumeria graminis.* The results of fungistatic activity are presented in Table 4.

In general, the tested fluorine derivatives **3** showed fungistatic activity *in vitro* from low to moderate. The phenoxyacetic acid derivatives, which contain one fluorine atom reduced effectively linear growth of pathogenic fungus *Phytophtora cactorum* at concentration of 200 ppm (100% reduction for **3d** and **3f** and 64% and 56% reduction for **3b** and **3h**, respectively) and *Rhizoctonia solani* (74% reduction for **3d**). In contrast, the new tested derivatives with two fluorine atoms showed no significant fungistatic activity against tested phytopatogenic strains.

It is interesting to note that well known commercial herbicides: 2,4-D, MCPA, 2,4,5-T, 4-CPA themselves also reduced completely linear growth of pathogenic fungus *Phytophtora cactorum* at concentration of 200 ppm.

3. Conclusions

Fluorine derivatives **3** of the phenoxyacetic herbicides 2,4-D, MCPA, 2,4,5-T and 4-CPA, showed lower herbicidal activity compared to the parent herbicides 2,4-D, MCPA, 2,4,5-T and 4-CPA. Compounds **3** showed also the moderate fungistatic activity against several representative pathogenic fungi. Parent, commercial herbicides 2,4-D, MCPA, 2,4,5-T, 4-CPA were active against phytopathogenic fungus *Phytophtora cactorum*.

4. Experimental Part

4.1. General

Chlorophenols **1** were purchased from Aldrich. Both bromofluoroacetic acids **2** were purchased from Fluorochem. 2,4-D, MCPA, 2,4,5-T used as reference materials in biological assays, and acquired from the offer of standard materials manufactured and certified in IPO. 4-CPA was synthesized according to the method **A** described below (3 h, 100 ºC, yield 60.3%, m.p. 161-165 ºC (137-139 ºC [39], 159-161 ºC [40], 155-160 ºC [41])).

TLC was carried out on silica gel Merck Alurolle 5562 or Alufolien 5554; mobile phase: hexane:ethyl acetate (9:1); benzene: ethyl acetate (9:1); benzene:methanol (9:1). TLC visualization was achieved using UV 254 nm light and/or sprying with $AgNO_3$ (1% ethanolic solution), heating with IR irradiation) Column chromatography was performed on silica gel 0.040–0.063 mm, 230–400 mesh: Merck 1.09385.1000 or Zeochem 60 hyd. EI MS data (70 eV) were recorded on an AMD 604 and Agilent Technologies 5975 B mass spectrometers. HR EI MS data were recorded by using an AMD 604 mass spectrometer. ESI MS and HR ESI MS (methanol as a solvent) were recorded by using a Micromass LCT apparatus. IR spectra were recorded on an FT/IR Jasco 420 spectrophotometer. The ^{1}H, ^{13}C and ^{19}F NMR data were collected using a Varian UNITYplus 200 or 500 spectrophotometers (at 200 or 500 MHz, respectively). TMS (^{1}H and ^{13}C) and CCl_3F (^{19}F) were used as standards.

4.2 General Procedure A: NaH/dioxane/100 °C (3a, 3c, 3e, 3g)

An appropriate phenol (0.002 mol) and difluorobromoacetic acid **2a** (0.345 g, 0.002 mol) were dissolved in the anhydrous dioxane (5-6 mL). The solution was chilled to 0°C (ice/water bath). Sodium hydride (0.1 g, 0.0042 mol, 0.170 g of 60% mineral oil suspension) was added in portions under argon. The temperature of the reaction mixture rose to 40 °C. The reaction mixture was stirred at 100 °C for 3 h. The reaction mixture was allowed to cool to the room temperature. Then the reagents were poured to the 2 N HCl (12.5 mL). The reaction mixture was extracted with ethyl acetate. Organic layer was washed with water and then with sodium bicarbonate solution. Aqueous layers were acidified again with 2N HCl to pH 1 and extracted again with ethyl acetate. The organic layer was dried with the anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The appropriate crude difluorophenoxyacetic acids (**3a, 3c, 3e, 3g**) were obtained.

4.2.1 (2,4-Dichlorophenoxy)difluoroacetic acid (3a), $C_8H_4Cl_2F_2O_3$, M=257

The crude product was purified by multiple washings with with pentane to give (2,4-dichlorophenoxy)difluoroacetic acid; light cream solid, 0.208 g (40.6%), m.p. 65-68 °C; MS (EI, 70 eV, *m/z*, int [%]): 260 (6), 258 (36), 256 (55, M), 213 (7), 211 (10), 166 (16), 164(68), 163 (26), 162 (100, $Cl_2C_6H_3OH$), 161 (29, $Cl_2C_6H_3O$), 147 (20), 145 (30, $Cl_2C_6H_3$), 135 (20), 133 (31), 109 (21), 98 (10), 75 (13), 74 (13), 73 (13), 63 (22), 45 (10); MS (ESI, *m/z*, int [%]): 256 (10, M), 255 (15, M-1), 163 (70), 161 (100); HRMS (ESI, *m/z*): calcd for $C_8H_3Cl_2F_2O_3$ $[M-1]^+$: 254.9427, found, *m/z*: 254.9416; ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.23 - 7.34 (m, 2 H_{ar}), 7.48 (d, 1H, *J*=1.8 Hz, H_{ar}), 10.15 (s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$) δ 113.5 (t, *J*=274.0 Hz, CF_2), 124.3, 128.0, 128.7, 130.6, 132.8 , 143.9, 163.2 (t, *J*=41.8 Hz, COOH); ^{19}F NMR (282 MHz, $CDCl_3$): δ -77.04 (s, 2F); IR (ν, cm^{-1}, KBr): 3422, 1771, 1630, 1476, 1221, 1163, 1097, 806.

4.2.2 (4-Chloro-2-methylphenoxy)difluoroacetic acid (3c), $C_9H_7ClF_2O_3$, M=236.5

The crude product was purified by means of the crystallization from hexane to give (4-chloro-2-methylphenoxy)difluoroacetic acid; light cream solid, 0.190 g (40.3%), m.p. 39-42 °C; MS (EI, 70 eV, *m/z*, int [%]): 238 (35), 237 (11), 236 (98, M), 191 (10), 168 (15), 144 (22), 143 (41), 142 (66, $Cl(CH_3)C_6H_3OH$), 141 (100, $Cl(CH_3)C_6H_3O$), 127 (18), 125 (55, $Cl(CH_3)C_6H_3$), 113 (15), 107 (24), 99 (11), 89 (35), 78 (17), 77

(80), 63 (19), 51 (36), 50 (13), 45 (10); MS (ESI, *m/z*, int [%]): 493 (10, 2xM-1+Na), 237 (10), 235 (35, M-1), 191 (30), 141 (100); HRMS (ESI, *m/z*): calcd for $C_9H_6ClF_2O_3$ $[M-1]^+$: 234.9974, found, *m/z*: 234.9980; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.29 (s, 3H, CH_3), 7.16 (s, 2H, H_{ar}), 7.24 (s, 1H, H_{ar}), 9.38 (s, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 16.2 (CH_3), 113.7 (t, *J*=271.1 Hz, CF_2), 123.0, 126.9, 131.3, 131.9, 133.4, 146.1, 163.7 (t, *J*=42.0 Hz, COOH); ^{19}F NMR (282 MHz, $CDCl_3$): δ -76.68 (s, 2F); IR (ν, cm^{-1}, KBr): 3432, 2930, 1762, 1630, 1485, 1191, 809.

4.2.3 (2,4,5-Trichlorophenoxy)difluoroacetic acid (3e), $C_8H_3Cl_3F_2O_3$, M=291.5

The crude product was purified by the column chromatography (benzene; benzene:acetone 9:1, benzene:acetone 4:1) and crystallization from hexane to give (2,4,5-trichlorophenoxy)difluoroacetic acid; colorless solid, 0.215 g (36.9%), m.p. 60-62 °C; MS (EI, 70 eV, *m/z*, int [%]): 294 (16), 292 (50), 290 (52, M), 200 (33), 198 (97), 197 (20), 196 (100, $Cl_3C_6H_2OH$), 195 (14, $Cl_3C_6H_2O$), 181 (23), 179 (24, $Cl_3C_6H_2$), 169 (26), 167 (28), 143 (12), 109 (14), 97 (26), 74 (11), 62 (11), 45 (11); MS (ESI, *m/z*, int [%]): 195 (50), 199 (20), 289 (100, M-1), 293 (50, M+1), 579 (70, 2M-1), 581 (2M+1), 583 (60, 2M+2), 585 (20), 605 (2M+2+23); HR MS (ESI, *m/z*): calcd for $C_8H_2Cl_3F_2O_3$ $[M-1]^+$: 288.9031, found, *m/z*: 288.9038; ^{1}H NMR (500 MHz, $CDCl_3$): δ 6.49 (s, 3H, hydrate) (compare to [31]), 7.486 (s, 1H), 7.573 (s, 1H); ^{1}H NMR (500 MHz, DMSO): δ 7.721 (s, 1H), 8.058 (s, 1H), 12.73 (bs, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 113.6 (t, *J*=275.3 Hz, CF_2), 125.0, 126.9, 131.3, 131.5, 131.5, 144.0, 161.1 (t, *J*=40.0 Hz, COOH); ^{19}F NMR (470 MHz, $CDCl_3$): δ -77.30 (s, 2F); IR (ν, cm^{-1}, KBr): 3455, 1743, 1630, 1460, 1228, 1114, 1083, 767.

4.2.4 (4-Chlorophenoxy)difluoroacetic acid (3g), $C_8H_5ClF_2O_3$, M=222.5

The crude product was purified by washing off impurities with hexane to give (4-chlorophenoxy)difluoroacetic acid; light beige solid, 0.390 g (87.6%), m.p. 43-47 °C; MS (EI, 70 eV, *m/z*, int [%]): 224 (33), 223 (9), 222 (94, M), 179 (10), 177 (30), 130 (37), 129 (15), 128 (100, ClC_6H_4OH), 127 (24, ClC_6H_4O), 113 (31), 111 (92, ClC_6H_4), 101 (14), 99 (44), 75 (43), 73 (18), 63 (21), 51 (13), 50 (15); MS (ESI, *m/z*, int [%]): 127 (10), 177 (10), 221 (100, M-1), 223 (20, M+1); HR MS (ESI, *m/z*): calcd for $C_8H_4ClF_2O_3$ $[M-1]^+$: 220.9822, found, *m/z*: 220.9817; ^{1}H NMR (300 MHz, $CDCl_3$): δ 6.56 (s, 3H, hydrate) (compare to [31]), 7.17 (d, 2H, *J*=8.5), 7.33 (d, 2H, *J*=8.5); ^{13}C

NMR (75 MHz, $CDCl_3$): δ 113.8 (t, *J*=271.5 Hz, CF_2), 123.0, 129.7, 131.9, 147.8, 161.2 (t, *J*=40.6 Hz, COOH); ^{19}F NMR (282 MHz, $CDCl_3$): δ -77.28 (s, 2F); IR (ν, cm^{-1}, KBr): 3443, 1765, 1630, 1485, 1212, 1092, 1015, 745.

4.3 General Procedure B: NaH/THF, r.t. (3b, 3d, 3f, 3h)

An appropriate phenol (0.002 mol) was dissolved in the anhydrous THF (3 mL). The solution was chilled to 0 °C (ice/water bath). Sodium hydride (0.116 g, 0.0048 mol, 0.19 g of 60% mineral oil suspension) was added in portions under argon. The reagents were stirred for 15 min, then bromofluoroacetic acid **2b** (0.002 mol, 0.345 g) in the anhydrous THF (2 mL) at 0-5 °C was added dropwise. The reagents were stirred for 10 min. at 0-5 °C followed by 30 min at room temperature. After completion of the reaction, water (10 mL) was added to the reagents. Then the reaction mixture was acidified to pH 1 with 2N HCl and extracted with ethyl acetate. The organic layer was dried with the anhydrous magnesium sulphate, filtered and concentrated under reduced pressure. The crude product (oil) was triturated with hexane (10 - 15 mL), and then stored in a refrigerator. The product (**3b, 3d, 3f, 3h**) was filtered off as a light-creamy solid.

4.3.1 (2,4-Dichlorophenoxy)fluoroacetic acid (3b), $C_8H_5Cl2FO_3$, M=239.

Light cream solid, 0.30 g (63.0%), m.p. 83-86 °C; MS (EI, 70 eV, *m/z*, int [%]): 240 (55), 239 (8), 238 (85, M), 197 (11), 195 (65), 193 (100, M-COOH), 165 (14), 164 (39), 163 (36), 162 (61, $Cl_2C_6H_3OH$), 161 (49, $Cl_2C_6H_3O$), 149 (14), 147 (50), 145 (77,$Cl_2C_6H_3$), 135 (31), 133 (49), 111 (17), 110 (11), 109 (39), 98 (10), 75 (28), 74 (25), 73 (19), 63 (30), 62 (14), 49 (10); MS (ESI, *m/z*, int [%]): 239 (18), 237 (30, M-1), 163 (75), 161 (100).; HR MS (ESI, *m/z*): calcd for $C_8H_4Cl2FO_3$ $[M-1]^+$: 236.9522, found, *m/z*: 236.9523; ^1H NMR (300 MHz, $CDCl_3$): δ 5.94 (d, 1H, *J*=58.5 Hz, CHF), 7.19 (d, 1H, *J*=8.8 Hz, H_{ar}), 7.26 (dd, 1H, *J*=8.8 Hz *J*=2.4 Hz, H_{ar}), 7.46 (d, 1H, *J*=2.4 Hz, H_{ar}), 10.56 (bs, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.4 (d, *J*=235.26 Hz, CHF), 120.5, 126.2 (d, *J*=2.3 Hz), 128.2, 130.6, 131.0, 149.8 (d, *J*=2.6 Hz, C_{ar}), 167.8 (d, *J*=31.0 Hz, COOH); ^{19}F NMR (282 MHz, $CDCl_3$): δ -131.43 (d, 1F, J_{F-H}=58.4 Hz); IR (ν, cm^{-1}, KBr): 3432, 1759, 1630, 1481, 1238, 1129, 1034, 786.

4.3.2 (4-Chloro-2-methylphenoxy)fluoroacetic acid (3d), $C_9H_8ClFO_3$, M=218.5

Yellow solid, 0.287 g (65.9%), m.p. 90-93 °C.MS (EI, 70 eV, *m/z*, int [%]): 220 (33), 219 (10), 218 (100, M), 175 (14), 173 (42), 145 (14), 143 (34), 142 (23, $Cl(CH_3)C_6H_3OH$), 141 (98, $Cl(CH_3)C_6H_3O$), 127 (31), 125 (97, $Cl(CH_3)C_6H_3$), 113 (13), 107 (13), 99 (130, 90 (11), 89 (45), 78 (15), 77 (73), 63 (21), 51 (24); MS (ESI, *m/z*, int [%]): 217 (100, M-1), 219 (20); HR MS (ESI, *m/z*): calcd for $C_9H_7ClFO_3$ $[M-1]^+$: 217.0068, found, *m/z*: 217.0071; ^{1}H NMR (300 MHz, $CDCl_3$): δ 2.28 (s, 3H, CH_3), 5.92 (d, 1H, J_{H-F}=59.1 Hz, CHF), 7.04 (d, 1H, *J*=8.4 Hz, H_{ar}), 7.11-7.28 (m, 2H, H_{ar}), 11.30 (bs, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 15.9 (CH_3), 102.3 (d, *J*=226.5 Hz, CHF), 117.7, 127.1, 129.9, 130.8 (d, *J*=1.4 Hz), 131.2, 152.7 (d, *J*=2.8 Hz), 169.1 (d, *J*=32.4 Hz, COOH); ^{19}F NMR (470 MHz, $CDCl_3$): δ -129.41 (d, 1F, J_{F-H}=58.8 Hz); IR (ν, cm^{-1}, KBr): 3435, 1752, 1488, 1359, 1240, 1188, 1153, 1019, 809.

4.3.3 (2,4,5-Trichlorophenoxy)fluoroacetic acid (3f), $C_8H_4Cl_3FO_3$, M=273.5

Colorless solid, 0.158 g (29.2%), m.p. 120-122 °C; MS (EI, 70 eV, *m/z*, int [%]): 276 (25), 274 (78), 272 (81, M), 231 (32), 229 (96), 227 (100, M-COOH), 200 (24), 199 (17), 198 (73), 197 (33), 196 (74, $Cl_3C_6H_2OH$), 195 (29, $Cl_3C_6H_2O$), 183 (24), 181 (73), 179 (76, $Cl_3C_6H_2$), 171 (17), 169 (51), 167 (54), 145 (24), 143 (27), 109 (33), 97 (42), 74 (24), 62 (20); MS (ESI, *m/z*, int [%]):195 (100), 197 (88), 271 (20, M-1); HR MS (ESI, *m/z*): calcd for $C_8H_3Cl_3FO_3$ $[M-1]^+$: 270.9132, found, *m/z*: 270.9132; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.94 (d, 1H, J_{H-F}=58.2 Hz, CHF), 7.37 (s, 1H, H_{ar}), 7.55 (s, 1H, H_{ar}), 9.38 (bs, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.2 (d, *J*=236.5 Hz, CF), 121.0, 124.4 (d, *J*=2.0 Hz), 129.5, 131.5, 131.8, 149.9 (d, *J*=2.6 Hz, 167.08 (d, *J*=30.1 Hz, COOH); ^{19}F NMR (470 MHz, $CDCl_3$): δ -131.40 (d, 1F, J_{F-H}=58.4 Hz); IR (ν, cm^{-1}, KBr): 3437, 1762, 1463, 1347, 1244, 1128, 880.

4.3.4 (4-Chlorophenoxy)fluoroacetic acid (3h), $C_8H_6ClFO_3$, M=204.5

Light cream solid, 0.295 g (72.1%), m.p. 87-90 °C; MS (EI, 70 eV, *m/z*, int [%]): 206 (27), 205 (7), 204 (77, M), 161 (29), 159 (86), 131 (20), 128 (18, ClC_6H_4OH), 127 (14, ClC_6H_4O), 113 (34), 112 (9), 111 (100, ClC_6H_4), 101 (9), 99 (28), 75 (39), 73 (13), 63 (15), 50 (12); MS (ESI, *m/z*, int [%]): 203 (100, M-1), 205 (20), 429 (2M-2+23); HR MS (ESI, *m/z*): calcd for $C_8H_5ClFO_3$ $[M-1]^+$: 202.9911, found, *m/z*: 202.9909; ^{1}H NMR (300 MHz, $CDCl_3$): δ 5.98 (d, 1H, J_{H-F}=59.1 Hz, CHF), 7.08 (d, 2H, *J*=8.9), 7.33 (d, 2H, *J*=8.9), 10.47 (bs, 1H, COOH); ^{13}C NMR (75 MHz, $CDCl_3$): δ 102.1 (dd, *J*=4.0 Hz, *J*=233.0 Hz, CHF), 119.0 (d, *J*=1.2 Hz, C_{ar}), 129.9, 130.2,

154.0, (d, *J*=2.8 Hz), 168.5 (d, *J*=32.0 Hz, COOH). ^{19}F NMR (470 MHz, $CDCl_3$): δ -130.15 (d, 1F, J_{F-H}=59.3 Hz); IR (ν, cm^{-1}, KBr): 3432, 1744, 1492, 1218, 1094, 1030, 825.

4.4 Herbicidal Bioassay, Pre- and Post-Emergence Experiments

Herbicidal activity was evaluated using different weed species in pot experiments under controlled conditions. Polyethylene pots, 3.5 L capacity, were filled with 0.75 kg of soil (physicochemical characteristic: sandy clay, pH/KCl/ 6.7; organic matter 2.8%) and were wetted with water. Seeds of the weed species were planted into earth (0.5 cm depth). Plants were grown to the two-leaf stage under normal glasshouse propagation conditions (temperature, 20 ± 5 °C; lighting, 14 h photoperiod of daylight supplemented by lamps, 400 W). The pots were watered overhead. The test compounds were dissolved in an appropriate volume of acetone/water solution (1:3) with the addition of Tween 20 (0.05% v/v) to give the required dose of the tested substance. All treatments were applied as a pre-emergence or post-emergence spray at a volume rate of 300 L/ha using track laboratory sprayer (nozzle TeeJet60, pressure 0.2 MPa). There were three replicate pots per treatment arranged in a randomized block design. Pots after spraying were transferred to the growth chamber (temperature, day/night 20/15 °C; lighting, 16 h photoperiod, white fluorescent tubes giving 200 *μ*mol $m^{-2}s^{-2}$ PAR). A visual assessment of phytotoxicity separately for each species was made (18 days or 25 days after treatment for pre- and post-emergence experiments) as a percentage compared to the untreated plants. Results (degree [%] of a visual observation of a phytotoxicity weed damage for a weed species used against control) are expressed as a fraction: a numerator means a result [%] of a pre-emergence (via soil) treatment, a denominator means a result [%] of a post-emergence (on leaves) treatment.

4.5 Fungicidal Bioassay *in vitro*

Fungitoxicity of the tested compounds against phytopathogenic fungi was assessed in vitro using agar growth medium poison technique. PDA media in 100 mm Petri plates containing the acetone solutions of the tested compounds in the defined concentrations were infected with agar disks with thin mycelium of fungi cultures, and allowed the solvent to evaporate. Linear growth of each colony was determined

after 3-5 days. The effect of each compound on mycelial growth was assessed by calculating the percentage of growth reduction, where:
percentage of linear growth reduction = [(colony diameter of the control plate - colony diameter of the tested plate)/(colony diameter of the control plate)]*100.

Acknowledgment: This work was supported by the Polish Ministry of Science and Higher Education, 4180/E-142/S/2016.

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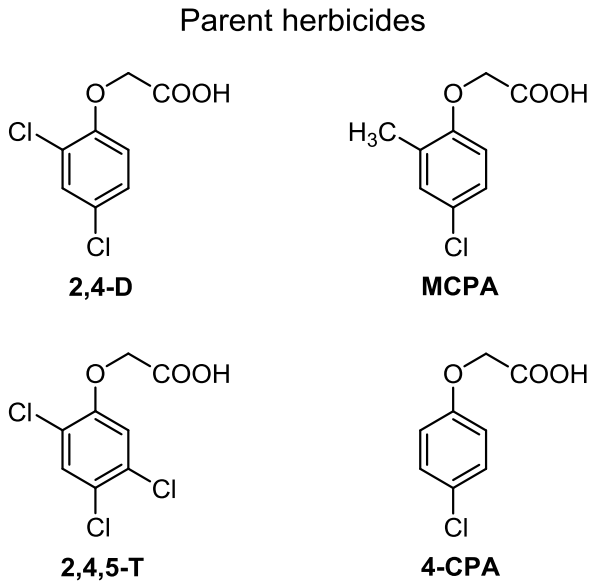
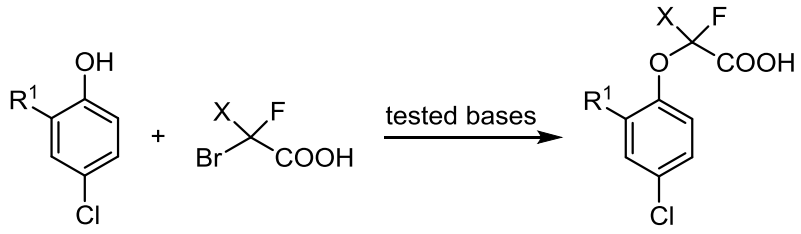
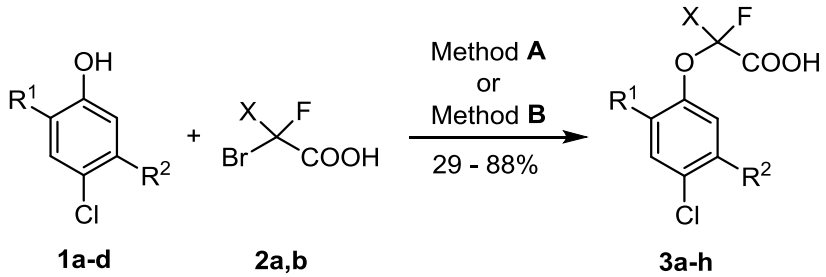


Figure 1: Parent herbicides



Scheme 1. Test reactions with phenols **1a**, **1b** to form products **3a** and **3d**.



Scheme 2. Synthesis of aryloxyfluoroacetic acids **3a**-**3h**

Table 1. The yields [%] of the products **3a** (CF_2 linker) and **3d** (CHF linker) for all condensation methods tested.

Base	Solvent	Temperature	Yield **3a** [%]	Yield **3d** [%]
NaH/method **A**	dioxane	100 °C	40.6	0[a)]
NaH/method **B**	THF	r.t.	0	65.9
NaH	THF	reflux	6.8	0
NaOH	H_2O	r.t.	0	41.3
NaOH	H_2O	reflux	9.8	0[a)]
NaOH	H_2O/benzene/ Aliquat 336	reflux	34.4	0
K_2CO_3	DMSO		0	0
Cs_2CO_3	CH_3CN		0	0

[a)] unidentified impurities were detected (TLC).

Table 2. Synthesized aryloxyfluoroacetic acids **3a**-**3h**; method **A**: NaH/Dioxan, 100°C; method **B**: NaH/THF, r.t.

Educt	R^1	R^2	Method	X	Product	Yield [%]	m.p. [°C]
1a	Cl	H	**A**	F	**3a**	40.6	65-68[a)]
1a	Cl	H	**B**	H	**3b**	63.0	83-86
1b	CH_3	H	**A**	F	**3c**	40.3	39-42
1b	CH_3	H	**B**	H	**3d**	65.9	90-93
1c	Cl	Cl	**A**	F	**3e**	36.9	60-62
1c	Cl	Cl	**B**	H	**3f**	29.2	120-122
1d	H	H	**A**	F	**3g**	87.6	43-47
1d	H	H	**B**	H	**3h**	72.1	87-90

[a)] moisture sensitive

Table 3. Herbicidal activity[a)] of fluorine derivatives **3a**-**3h**

Compound	R^1	R^2	X	Cleavers (*Galium aparine*)	Pale smartweed (Polygonum lapathifolium)	Common poppy (*Papaver rhoeas*)	Barnyard grass (*Echinochloa crusgali*)	Gallant soldier (*Galinsoga parviflora*)	Fathen (*Chenopodium album*)	Ribwort (*Plantago lanceolata*)	Black mustard (*Brassica nigra*)	Red-root amaranth (Amaranthus retroflexus)	Common chickweed (*Stellaria media*).	Average
3a	Cl	H	F	0/55[b)]	0/40	0/40	0/55[b)]	0/100	0/100	0/30	0/55	0/100	0/30	0/60.5
3b	Cl	H	H	0/70[b)]	0/55	0/40	0/40[b)]	0/100	0/100	0/40	0/70	0/100	0/40	0/65.5
2,4-D				0/40	0/100	0/100	0/70	0/100	0/100	0/90	0/100	0/100	0/90	0/89.0
Control				0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
3c	CH_3	H	F	0/40	0/30	0/70	0/55	0/55	0/40	0/40	0/40	0/40	0/40	0/45
3d	CH_3	H	H	0/70	0/40	0/70	0/61	0/55	0/90	0/40	0/61	0/70	0/55	0/61
MCPA				0/60	0/55	100/100	30/30	100/100	100/100	20/70	100/90	40/100	100/95	59/70
Control				0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
3e	Cl	Cl	F	0/61	0/40	0/70	0/61	0/61	0/70	0/40	0/55	0/70	0/70	0/60
3f	Cl	Cl	H	0/70	0/40	0/90	0/55	0/70	0/100	0/40	0/70	0/90	0/61	0/69
2,4,5-T				0/30	0/61	90/100	20/20	100/100	100/100	20/100	100/95	100/100	100/100	63/81
Control				0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0
3g	H	H	F	0/40	0/20	0/40	0/40	0/55	0/55	0/55	0/40	0/55	0/30	0/38
3h	H	H	H	0/55	0/40	0/40	0/30	0/40	0/70	0/30	0/55	0/55	0/40	0/46
4-CPA				0/30	0/70	70/100	20/55	40/100	40/100	70/70	100/100	70/100	100/90	51/81
Control				0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0	0/0

[a)] results (degree [%] of a visual observation of a phytotoxicity weed damage for a weed species used against control, dose 2 kg/ha) are expressed as a fraction: a numerator means a result [%] of a pre-emergence (via soil) treatment, a denominator means a result [%] of a post-emergence (on leaves) treatment.

[b)] phytotoxic symptoms: necrotic spots on leaves within 24 hours after application of **3a**, **3b**.

Table 4. Fungistatic activity of **3a** - **3h** and the herbicides 2,4-D, MCPA, 2,4,5-T, 4-CPA[a)]

Compound	R^1	R^2	X	*A.alternata*	*B.cinerea*	*F.culmorum*	*P.cactorum*	*R.solani*	*B.graminis*
3a	Cl	H	F	0	0	30	12	20	-
3b	Cl	H	H	0	10	26	64	20	-
2,4-D				18	28	0	100	10	-
3c	CH_3	H	F	0	0	0	0	0	2.1
3d	CH_3	H	H	16	48	0	100	74	0
MCPA				16	76	0	100	30	-
3e	Cl	Cl	F	0	0	0	12.2	0	1.05
3f	Cl	Cl	H	14	56	0	100	50	0
2,4,5-T				34	68	0	100	28	-
3g	H	H	F	0	0	0	15	0	2.1
3h	H	H	H	0	18	8.8	56	0	3.1
4-CPA				0	16	0	100	0	-

[a)] concentration: 200 mg/L; the results expressed as a percentage of linear growth reduction of a fungus colony;

percentage of linear growth reduction = [(colony diameter of a control plate - colony diameter of a tested plate)/(colony diameter of a control plate)]*100