JOURNAL OF AGRICULTURAL AND FOOD CHEMISTRY

Article

pubs.acs.org/JAFC

Highly Fluorinated 2,2′-Biphenols and Related Compounds: Relationship between Substitution Pattern and Herbicidal Activity

Robert Francke,[†,#] Rüdiger Reingruber,[§] Dieter Schollmeyer,[†] and Siegfried R. Waldvogel*,[†]

[†]Institute for Organic Chemistry, Mainz University, Duesbergweg 10-14, 55128 Mainz, Germany
[§]BASF SE, GVA/HC – A030, 67056 Ludwigshafen, Germany

ABSTRACT: A broad range of halogenated 2,2′-biphenols was tested for applicability as crop protection agents. The activity of these compounds toward four typical pest plants was observed after application by spraying of diluted solutions. Despite their rather simple structure, it was found that the studied compounds reveal a surprisingly high herbicidal impact. To gain a better understanding of the structure–activity relationship, specific sites of the molecule were chemically modified and the core structures thus gradually changed. The influence of the substitution pattern on the herbicidal properties is discussed, and conclusions on the active site of the biphenol structure are drawn. It was observed that type and position of the halogen substituents have a significant influence on the activity of the core structure. The hydroxy functionalities play a crucial role for the effectiveness of the tested compounds. Because the blocking of the hydroxy moiety leads to dramatically deteriorated performances, the presence of these functionalities on the aromatic ring seems to be indispensable.

KEYWORDS: *fluorinated compound, phenol, comparative biological activity, pesticide, crop protection*

INTRODUCTION

For a long time, synthetic postemergence herbicides have been frequently employed to selectively control weeds, as manual removal is time-consuming and expensive and often leads to damage of the crop or ornamental plant.[1] The use of highly effective chemical control of weeds not only has replaced manual and mechanical weed control, it also increased productivity and has enabled the development of larger farm sizes and an improved subsistence for farmers.[2] There is still a high demand for new products in this field, because only a few selective postemergence weed control agents for the sufficient supply of the constantly growing world population are available. One of their major properties has to be the maximization of the crop yield along with the quality of the crops.[1]

Particularly, fluorinated 2,2′-biphenols might be of interest for crop protection or pharmaceutical applications. Finger et al. studied the biological activity of a series of fluorinated aryl compounds.[3] Their promising results prompted us to perform biological tests of a set of fluorinated 2,2′-biphenols and some related compounds. In this context, a high herbicidal impact was found. Consequently, we performed several modifications of this structural motif to learn more about the correlation between substitution pattern and impact of the substances on several types of weeds. Generally, such fluorinated aromatic compounds are highly stable under extremely harsh conditions, as the C–F bond is of high strength and the electron-withdrawing properties can prevent aromatic rings from metabolic[4,5] or electrochemical oxidation.[6,7] As the spatial size of a fluorine atom is similar to a hydrogen atom, a replacement of one or more hydrogen atoms by fluorine does not lead to a steric distortion of a molecule. This can lead to an incorporation of the fluorinated compound into the life cycle of diverse organisms.[8] Moreover, the specific lipophilicity and metabolic stability of fluorinated structures lead to significant application in drug development and pharmaceutics.[5] Hence, the worldwide inventory of pesticides containing miscellaneously halogenated compounds as active material has grown steadily in the past decades.[9,10] The current trend indicates clearly that especially fluorinated products will become more and more important.

MATERIALS AND METHODS

Synthesis of the Tested Compounds. For the NMR measurements, chemical shifts (δ) are reported in parts per million relative to traces of $CHCl_3$, CD_3OD, or DMSO in the corresponding deuterated solvents and to CCl_3F as an external standard for ^{19}F NMR, respectively. Coupling constants (J) are presented in hertz. The supplementary crystallographic data for this paper can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif (CCDC 905686, compound **5c**). Halogenated 2,2′-biphenols and 2,2′-bisanisoles were prepared according to procedures reported in the literature.[11,12] The preparation of the modified compounds was performed as follows:

3,3′-Dichloro-5,5′-difluoro-2′-hydroxy-2-methoxybiphenyl (**5a**). 3,3′-Dichloro-5,5′-difluoro-2,2′-bisanisole[12] (1.70 g; 5.33 mmol) in 20 mL of dry dichloromethane was placed in a Schlenk flask under argon and cooled to −78 °C. To the mixture was added dropwise under stirring 0.89 g of BBr_3 (3.55 mmol) in 15 mL of dichloromethane. After 2 h, the solution was allowed to warm to room temperature and stirred overnight. The mixture was fractionated by addition of water and the aqueous layer extracted with dichloromethane (2 × 40 mL). The combined extracts were dried over $MgSO_4$ and concentrated under reduced pressure. The desired product was isolated by column chromatography (cyclohexane/ethyl acetate 95:5, R_F = 0.21, flash gel, 1.5 bar) in 39% yield (0.63 g, 2.06 mmol, colorless crystalline solid): mp 74 °C; ^1H NMR (300 MHz, $CDCl_3$) δ 7.20 (dd, J = 7.7, 3.1, 1H), 7.17 (dd, J = 7.7, 3.1, 1H), 6.95

Received: March 10, 2013
Revised: April 30, 2013
Accepted: May 4, 2013
Published: May 5, 2013

dx.doi.org/10.1021/jf401081g | *J. Agric. Food Chem.* 2013, 61, 4709–4714

(dd, *J* = 8.5, 3.1, 1H), 6.94 (dd, *J* = 8.5, 3.1, 1H), 6.44 (s, 1H), 3.61 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 158.4 (d, *J* = 247.4), 155.9 (d, *J* = 242.9), 149.1 (d, *J* = 3.4), 145.7 (d, *J* = 2.9), 132.8 (dd, *J* = 9.2, 1.6), 129.3 (d, *J* = 11.4), 125.9 (dd, *J* = 8.5, 2.2), 122.7 (d, *J* = 11.0), 117.8 (d, *J* = 25.4), 117.1 (d, *J* = 24.3), 116.9 (d, *J* = 24.5), 116.2 (d, *J* = 23.7), 61.7 (s); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −115.7 (m), −121.7 (m). HRMS calcd for $C_{13}H_9F_2Cl_2O_2$, 304.9948; found, 304.9955. Elemental analysis ($C_{13}H_8F_2Cl_2O_2$, M = 305.10) calcd, (%) C 51.18, H 2.64; found (%) C 51.05, H 2.53. Forty percent of the starting material was recovered (0.68 g, 2.13 mmol, R_F = 0.55) and the 2,2′-biphenol **4a** was obtained after elution with pure ethyl acetate (0.25 g, 0.86 mmol, 16%).

*3,3′,5,5′-Tetrafluoro-2′-hydroxy-2-methoxybiphenyl (**5b**).* To a mixture of 1.28 g (4.97 mmol) of 3,3′,5,5′-tetrafluoro-2,2′-biphenol (**4b**),[12] 0.75 g (5.46 mmol, 1.1 equiv) of K_2CO_3, and 15 mL of DMF was added dropwsie 0.70 g (4.97 mmol) of methyl iodide. After overnight stirring, ammonia solution (10% in water) was added, and the aqueous layer was extracted two times with 50 mL of *tert*-butyl methyl ether (TBME). The organic layer was washed three times with water and dried over $MgSO_4$. After removal of the solvent under reduced pressure, the product mixture was separated using column chromatography (cyclohexane/ethyl acetate 9:1, R_F = 0.20, flash gel, 1.5 bar). The desired product was yielded as a colorless crystalline solid (0.50 g, 1.84 mmol, 37%): mp 84 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.99−6.88 (m, 2H), 6.88−6.76 (m, 2H), 6.34 (s, 1H), 3.77 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 158.3 (dd, *J* = 246.4, 12.2), 157.3−150.4 (m), 140.6 (dd, *J* = 12.2, 3.9), 138.4 (dd, *J* = 13.3, 3.7), 132.1−132.3 (m), 126.6−126.7 (m), 113.1 (dd, *J* = 23.6, 3.5), 112.1 (dd, *J* = 23.4, 3.7), 105.3 (dd, *J* = 26.7, 23.2), 104.8 (dd, *J* = 26.6, 22.9), 62.5 (d, *J* = 4.4); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −114.5 (m), −120.4 (m), −125.6 (m), −131.0 (m). HRMS calcd for $C_{13}H_8F_4O_2Na$, 295.0358; found, 295.0357. Elemental analysis ($C_{13}H_8F_4O_2$, 272.20) calcd (%), C 57.36, H 2.96; found (%), C 57.19, H 2.70. Furthermore, 0.40 g (1.40 mmol, 28%) of the corresponding bisanisole was isolated after column chromatography (R_F = 0.57). Unreacted starting material was recovered by neutralization and 2-fold extraction of the aqueous layer (0.31 g, 1.20 mmol, 24%).

*5,5′-Difluoro-2′-hydroxy-3,3′-dimethyl-2-methoxybiphenyl (**5c**).* Methyl iodide (0.83 g; 5.83 mmol) was added dropwise at 0 °C to a mixture of 1.46 g (5.83 mmol) of 5,5′-difluoro-3,3′-dimethyl-2,2′-biphenol (**4c**),[12] 0.80 g (5.83 mmol) of K_2CO_3, and 20 mL of DMF. The mixture was allowed to warm to room temperature and stirred for 3 h. Then ammonia solution (10% in water) was added and the aqueous layer extracted two times with TBME (30 mL). The organic layer was washed three times with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The desired product was isolated using column chromatography (cyclohexane/toluene 1:1, flash gel, 1.5 bar, R_F = 0.46). After sublimation (10^{-3} mbar, 60 °C), 1.05 g of **5c** (3.97 mmol, 68%) was obtained as a colorless crystalline solid: mp 57 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 7.05 (s, 1H), 6.88−6.95 (m, 2H), 6.87−6.81 (m, 2H), 3.50 (s, 3H), 2.34 (s, 3H), 2.31 (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 159.2 (d, *J* = 243.8), 156.0 (d, *J* = 244.0), 150.3 (d, *J* = 2.7), 147.8 (d, *J* = 2.2), 133.5 (d, *J* = 8.5), 132.5 (d, *J* = 8.6), 129.1 (d, *J* = 8.0), 125.8 (d, *J* = 6.4), 117.4 (m), 116.0 (d, *J* = 23.3), 113.9 (d, *J* = 23.2), 61.3 (s), 16.9 (s), 16.3 (s); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −117.7 to −118.1 (m), −124.6 to −124.8 (dd, *J* = 9.0, 9.0). HRMS calcd for $C_{15}H_{15}F_2O_2$, 265.1040; found, 265.1041. Elemental analysis ($C_{15}H_{14}F_2O_2$, M = 264.27), calcd (%) C 68.17, H 5.34; found (%), C 67.77, H 5.39. Aside from **5c**, the corresponding 2,2′-bisanisole (0.16 g, 0.57 mmol, 10%, R_F = 0.34) and unreacted starting material (0.82 mmol, 14%, R_F = 0.05, eluted with ethyl acetate) were isolated after column chromatography.

*2′-Hydroxy-2-(tert-butyloxycarbonyl)methoxy-3,3′,5,5′-tetrafluorobiphenyl (**7a**).* A mixture of 3 g (11.61 mmol) of 3,3′,5,5′-tetrafluoro-2,2′-biphenol (**4b**),[12] 1.62 g (11.61 mmol) of K_2CO_3, 2.27 g (11.61 mmol) of *tert*-butyl-2-bromoacetate, and 20 mL of DMF was stirred for 24 h at room temperature. Then it was fractionated by addition of water and TBME and the aqueous layer extracted two times with TBME (2 × 100 mL). The combined organic layers were washed three times with water and dried over $MgSO_4$, and the solvent was removed under reduced pressure. The product mixture was separated with column chromatography (cyclohexane/ethyl acetate 95:5). **7a** was obtained in the first fraction as a light brown solid (R_F = 0.21), which was sublimated to afford 1.90 g (5.72 mmol, 44%) of the colorless crystalline product: mp 104 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6.91−6.94 (m, 1H), 6.85−6.88 (m, 1H), 6.83−6.79 (ddd, *J* = 8.4, 3.0, 1.7, 1H), 6.73−6.69 (ddd, *J* = 8.8, 3.1, 2.0, 1H), 4.60 (d, *J* = 2.8, 2H), 1.44 (s, 9H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 168.4 (s), 157.3 (dd, *J* = 245.8, 12.4), 155.5 (dd, *J* = 241.5, 11.3), 153.8 (dd, *J* = 248.2, 12.8), 152.4 (dd, *J* = 245.8, 12.7), 138.6−138.7 (m), 138.4−138.5 (m), 130.8−130.9 (m), 126.9−127.1 (m), 113.7 (dd, *J* = 23.5, 3.2), 112.1 (dd, *J* = 23.2, 3.7), 105.3 (dd, *J* = 26.7, 24.0), 104.6 (dd, *J* = 26.3, 22.9), 83.7 (s), 69.3 (d, *J* = 8.8), 27.9 (s); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −116.3 to −116.5 (m), −120.6 to −120.9(m), −127.3 to −127.5 (m), −130.8 to −130.9 (m). HRMS calcd for $C_{18}H_{16}F_4O_4Na$, 395.0882; found, 395.0893. Elemental analysis ($C_{18}H_{16}F_4O_4$, M = 372.21): calcd (%), C 58.07, H 4.33; found (%), C 57.96, H 4.30. In the second fraction, **7b** was contained, whereas unconverted biphenol **4b** was recovered in 31% yield in the third fraction (0.93 g, 3.60 mmol, R_F = 0) after elution with ethyl acetate.

*2,2′-Di((tert-butyloxycarbonyl)methoxy)-3,3′,5,5′-tetrafluorobiphenyl (**7b**).* **7b** was obtained in 20% yield as a colorless crystalline solid (1.15 g, 2.36 mmol) after conversion of **4b** with 1 equiv of *tert*-butyl-2-bromoacetate (R_F = 0.11, see above): mp 98 °C; ^{1}H NMR (300 MHz, $CDCl_3$) *δ* 6. 86 (ddd, *J* = 11.3, 8.2, 3.1, 2H), 6.8 (ddd, *J* = 8.4, 3.0, 1.7, 2H), 4.43 (s, 4H), 1.40 (s, 18H); ^{13}C NMR (75 MHz, $CDCl_3$) *δ* 167.4 (s), 157.4 (dd, *J* = 244.7, 12.0), 154.6 (dd, *J* = 249.0, 12.7), 140.3 (dd, *J* = 11.2, 4.1), 131.6−131.8 (m), 113.0 (dd, *J* = 23.3, 3.5), 104.9 (dd, *J* = 26.5, 23.4), 81.9 (s), 70.4 (d, *J* = 5.8), 27.9 (s); ^{19}F NMR (377 MHz, $CDCl_3$) *δ* −116.7 (ddd, *J* = 8.4, 8.4, 4.2), −125.8 to −126.0 (m). HRMS calcd for $C_{24}H_{26}F_4O_6Na$, 509.1563; found, 509.1549. Elemental analysis ($C_{24}H_{26}F_4O_6$, M = 486.45), calcd (%): C 59.26, H 5.39; found (%), C 59.12, H 5.01.

*2′-Hydroxy-2-carboxymethoxy-3,3′,5,5′-tetrafluorobiphenyl (**6a**).* One gram (2.69 mmol) of **7a** was dissolved 6 mL of TFA and stirred overnight. The precipitated product was filtered off, recrystallized from boiling water, and sublimated (10^{-3} mbar, 120 °C). The product was obtained as a colorless crystalline solid (0.77 g, 2.44 mmol, 91%): mp 155 °C; ^{1}H NMR (400 MHz, CD_3OD) *δ* 7.06 (ddd, *J* = 11.5, 8.4, 3.1, 1H), 6.98 (ddd, *J* = 11.1, 8.4, 3.1, 1H), 6.92−6.86 (m, 1H), 6.85−6.81 (m, 1H), 4.55 (s, 1H); ^{13}C NMR (101 MHz, CD_3OD) *δ* 170.8 (s), 157.7 (dd, *J* = 243.0, 12.3), 155.0 (dd, *J* = 247.7, 13.2), 154.7 (dd, *J* = 238.9, 11.7), 151.4 (dd, *J* = 242.0, 12.6), 140.2 (dd, *J* = 11.3, 3.9), 138.9 (dd, *J* = 15.2, 3.5), 132.6 (d, *J* = 9.6), 126.5 (d, *J* = 9.1), 112.7−112.9 (m), 112.2 (dd, *J* = 23.4, 3.5), 104.1 (dd, *J* = 27.2, 23.8), 103.3 (dd, *J* = 27.1, 23.4), 69.3 (s, *J* = 8.8); ^{19}F NMR (377 MHz, DMSO-d_6) *δ* −117.5 (m), −123.2 (dd, *J* = 9.4. 9.4), −126.0 (d, *J* = 11.9), −130.9 (d, *J* = 11.3). HRMS calcd for $C_{14}H_8F_4O_4Na$, 339.0256; found, 339.0258. Elemental analysis ($C_{14}H_8F_4O_4$, M = 316.20): calcd (%), C 53.18, H 2.55; found (%), C 52.88, H 2.53.

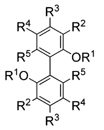
*2,2′-Di(carboxymethoxy)-3,3′,5,5′-tetrafluorobiphenyl (**6b**).* **7b** (0.80 g; 1.64 mmol) was dissolved in 5 mL of TFA and stirred overnight. The precipitated solid was filtered off, recrystallized from boiling THF, and dried overnight (10^{-3} mbar, 100 °C). The product was obtained as a colorless crystalline solid (0.58 g, 1.55 mmol, 94%): mp 253 °C; ^{1}H NMR (300 MHz, DMSO-d_6) *δ* 7.39 (ddd, *J* = 11.8, 8.8, 3.0, 2H), 7.10−7.02 (m, 2H), 4.51 (s, 4H); ^{13}C NMR (75 MHz, DMSO-d_6) *δ* 169.7 (s), 156.8 (dd, *J* = 242.1, 12.6), 154.2 (dd, *J* = 247.1, 13.6) 140.1 (dd, *J* = 11.2, 3.9), 131.3−131.5 (m), 113.4 (dd, *J* = 23.6, 3.3), 105.3 (dd, *J* = 27.0, 23.9), 69.56 (d, *J* = 5.6); ^{19}F NMR (377 MHz, DMSO-d_6) *δ* −117.2 (ddd, *J* = 8.8, 8.8, 4.0), −126.2 (dd, *J* = 12.0). HRMS calcd for $C_{16}H_{10}F_4O_6Na$, 397.0311; found, 397.0325. Elemental analysis ($C_{16}H_{10}F_4O_6$, M = 374.24) calcd (%), C 51.35, H 2.69; found (%), C 51.18, H 2.46.

Greenhouse Experiments. The culture containers used were plastic flowerpots containing loamy sand with approximately 3% of humus as the substrate. For the postemergence treatment, the test plants (see Table 1) were first grown separately, and several of the seedlings were transplanted into the test containers a few days prior to treatment. After they reached a height of 3−10 cm, depending on the

Table 1. Bayer Codes, Scientific Names, and English Names of the Tested Pest Plants

Bayer code	scientific name	English name
ABUTH	*Abutilon theophrasti*	velvetleaf
ALOMY	*Alopecurus myosuroides*	blackgrass
AVEFA	*Avena fatua*	wild oat
SETFA	*Setaria faberi*	giant foxtail

Table 2. Herbological Activities of Halogenated 2,2′-Biphenols; Variation of R^2

	Compound	R^1	R^2	R^3	R^4	R^5	ABUTH	ALOMY	AVEFA	SETFA	Ø
	4a	H	Cl	H	F	H	100	55	35	95	71
	4b	H	F	H	F	H	0	20	35	95	38
	4c	H	Me	H	F	H	0	15	25	100	35

plant, they were treated with the active ingredients (6 mg), which had been emulsified by addition of 2.4 mL of a 2:2:1 mixture of cyclohexanone, DMSO, and Wethol EM31 (a nonionic emulsifier produced by BASF SE, Ludwigshafen, Germany) and 1% DASH, diluted with deionized water to the corresponding spray volume and sprayed on the plants via a spray nozzle. DASH is a commercial adjuvant produced by BASF, especially developed for use with acidic agrochemicals. The mixture described above is frequently used as a standard preparation in greenhouse experiments and does not have an impact on the activity of the certain ingredient. The application rate corresponds to 2 kg/ha with an application volume of 750 L/ha.

The plants were kept at 20−35 °C. The test period extended over 21 days. During this time, the plants were tended, and their response to the individual treatments was visually evaluated. Evaluation was carried out using a scale from 0−100: 100 means complete destruction of at least the aerial moieties, and 0 means no damage or normal course of growth. The last column in Tables 2−4 indicates the average ratio of destruction over all applied species.

■ RESULTS AND DISCUSSION

Synthesis of the Tested Compounds. A reliable procedure to prepare the highly fluorinated biphenols **4** was developed in our laboratory (see Figure 1). An Ullmann-type coupling reaction with activated copper powder yielding the 2,2′-bisanisoles **3** is followed by a deprotection with BBr_3.[12] As starting material, the fluorinated iodoanisoles **2** are employed, which are readily accessible by a telescoped iodination/methylation sequence from commercially available fluorinated phenols **1**.[11] The iodination of **1** is performed with an I_2/I^- mixture under alkaline conditions. This sequence enables access to a broad range of 2,2′-biphenol derivatives and tolerates chloro, bromo, nitro, and methyl moieties.

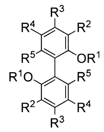
Biological Tests of 2,2′-Biphenols and 2,2′-Bisanisoles. The test series was conducted in pre- and postemergence with an application rate of 2 kg/ha. The results of the herbicidal activity tests are summarized in Tables 2−5, whereby 0 correlates with no damage to the test plant and 100 with total weed control. As test plants, *Abutilon theophrasti* (ABUTH) and *Setaria faberi* (SETFA), representing two key weeds in corn, as well as *Alopecurus myosuroides* (ALOMY) and *Avena fatua* (AVEFA), key weeds in cereals, have been selected.[13]

In contrast to the high activity toward weeds, no impact on insects was observed. Upon application of the 2,2′-biphenol samples at a dose rate of 2500 ppm on yellow fever mosquito (*Aedes aegypti*), boll weevil (*Anthonomus grandis*), Mediterranean fruit fly (*Ceratitis capitata*), tobacco budworm (*Heliothis virescens*), green peach aphid (*Myzus persicae*), and vetch aphid (*Megoura viciae*) no toxicity could be observed.

Whereas the pre-emergence impact of the fluorinated 2,2′-biphenols is rather moderate and in most cases no germination inhibition effect could be observed (results not shown), all of the studied 2,2′-biphenols (**4**) exhibit strong postemergence activity upon contact with the test plants (see Tables 2−5). Looking closer at the emerged symptoms, one could observe a rapid tissue necrosis that often appears when dealing with nonsystemic contact herbicides caused by uncoupler activity and ROS formation (reactive oxygen species).[1]

For 3,3′,5,5′-substituted 2,2′-biphenols the influence of a varying substitution pattern is shown in Tables 2−4. When the substituent in the *para*-position to the hydroxy group (R^2) is altered with R^4 = F, the activity increases in the following order: Cl > F > Me (see Table 2). When R^4 is varied while maintaining R^2 = F, the activity significantly decreases in the following order: Cl > F > Br (see Table 3). A comparison of

Table 3. Herbological activities of Halogenated 2,2′-Biphenols; Variation of R^4

	Compound	R^1	R^2	R^3	R^4	R^5	ABUTH	ALOMY	AVEFA	SETFA	Ø
	4d	H	F	H	Cl	H	75	20	25	75	49
	4b	H	F	H	F	H	0	20	35	95	38
	4e	H	F	H	Br	H	15	0	15	75	26

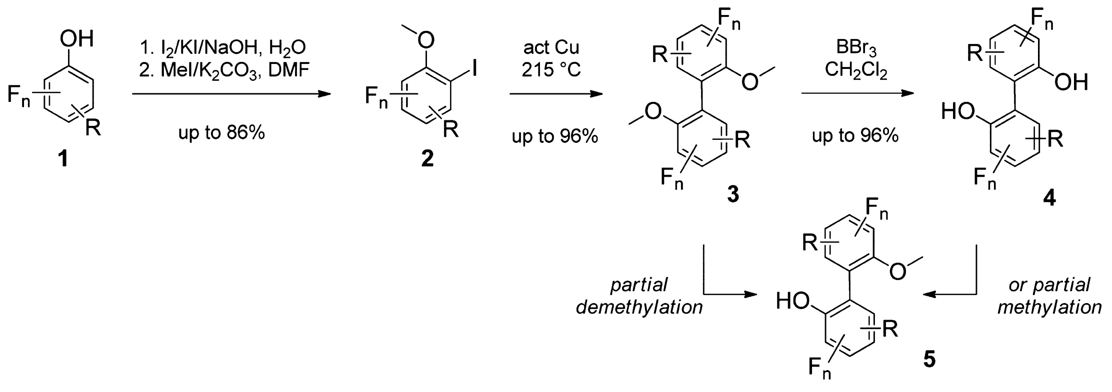
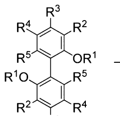


Figure 1. Preparation of halogenated 2,2′-bisanisoles and 2,2′-biphenols; R = Cl, Br, CH_3.

compounds which merely differ in the number and positions of fluorine substituents shows that fluorine in positions R^3 and R^4 is required for high activity, whereas additional fluorine in position R^2 seems to lower the performance significantly (see Table 4).

Table 4. Influence of the Substitution Pattern on the Biological Activity of Fluorinated 2,2′-Biphenols



Compound	R^1	R^2	R^3	R^4	R^5	ABUTH	ALOMY	AVEFA	SETFA	Ø
4f	H	H	F	F	H	100	0	15	100	54
4g	H	H	F	F	F	100	0	15	98	53
4b	H	F	H	F	H	0	20	35	95	38
4h	H	F	F	F	H	0	35	30	65	33

A comparison of the average herbicidal activity of halogenated 2,2′-biphenols shows that *Setaria faberi* exhibits the highest susceptibilities among the target plants with an average biphenol activity of 88 (see Figure 2). Whereas the impact on *Abutilon theophrasti* is still in a moderate range (average activity = 48). *Avena fatua* and *Alopecurus myosuroides* exhibit rather poor susceptibilities (24 and 18). This general trend can partly be explained by the sensitivity of the considered species, as *Avena fatua* and *Alopecurus myosuroides* (representing two very important key weeds in cereals) are usually very hard to control in an effective manner. In contrast to this, the intrinsic tolerance of the other species such as *Setaria faberi* is significantly lower, and as a result, the total vegetation control of the applied 2,2′-biphenols therefore is remarkably higher.

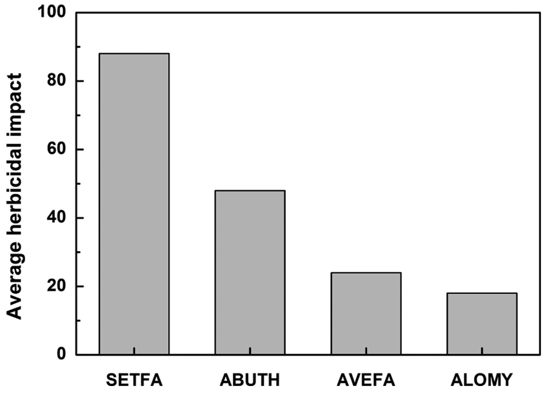
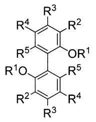


Figure 2. Susceptibility of the test plants toward the studied 2,2′-biphenols.

Modification of the Structures. As the results of the biological tests of halogenated 2,2′-biphenols appeared to be very promising, further steps were taken to gain a better understanding of the structure−activity relationship. Of particular interest is the influence of the hydroxy functionality on the activity of the studied compounds, as biological tests of the halogenated 2,2′-bisanisoles **3** according to the described procedure (Materials and Methods) revealed considerably lower biological activities compared to the corresponding 2,2′-biphenols **4** (results not shown). To determine the active site of the molecule, the partial modification of three active 2,2′-biphenol species **4a**, **4b**, and **4c** with a methyl group was performed, leading to compounds **5a**, **5b**, and **5c** (see Figure 1 and Table 5). The molecular structure of partially *O*-methylated **4b** was confirmed by X-ray analysis of a suitable single crystal (see Figure 3).

Table 5. Influence of Partial and Full *O*-Derivatization on the Herbological Activity of 2,2′-Biphenols; FG = $-CH_2COOH$, $-CH_2COOtBu$



Compound	R^1	R^2	R^3	R^4	R^5	ABUTH	ALOMY	AVEFA	SETFA
4a	H, H	Cl	H	F	H	100	55	35	95
5a	H, Me	Cl	H	F	H	0	0	0	0
4b	H, H	F	H	F	H	0	20	35	95
5b	H, Me	F	H	F	H	0	0	0	0
4c	H, H	Me	H	F	H	0	15	25	100
5c	H, Me	Me	H	F	H	0	0	0	0
6a, 7a	H, FG	F	H	F	H	0	0	0	0
6b, 7b	FG, FG	F	H	F	H	0	0	0	0

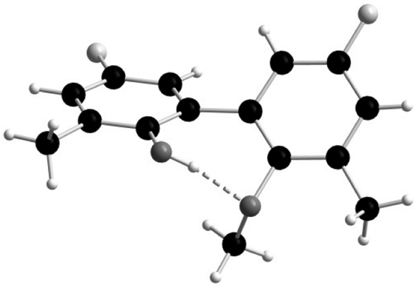
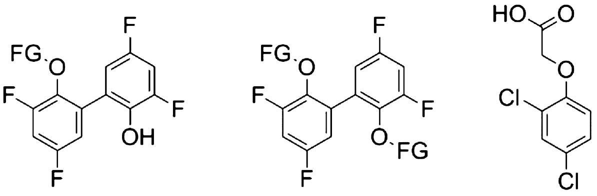


Figure 3. Molecular structure of **5c** obtained by X-ray analysis of a single crystal.

Furthermore, the carboxymethyl group as a typical feature of auxin-type herbicides[14,15] such as 2,4-dichlorophenoxyacetic acid (see Figure 4, right) was incorporated into the 2,2′-biphenol structure, leading to 1- and 2-fold substituted compounds **6a** and **6b** (see Figure 4, left and middle). This modification was performed to explore the possibility of a synergistic combination with auxin-type herbicidal property. **6a** and **6b** were obtained by conversion of 2,2′-biphenol **4b** with 2-bromoacetic acid *tert*-butyl ester under basic conditions and subsequent cleavage of ester **7a** and **7b**, respectively, with trifluoroacetic acid (see Figure 5).



6a: FG = $-CH_2COOH$
7a: FG = $-CH_2COOtBu$
6b: FG = $-CH_2COOH$
7b: FG = $-CH_2COOtBu$
2,4-D

Figure 4. Auxin-type substituted 2,2′-biphenols **6a**, **6b**, **7a**, and **7b** (left) and 2,4-dichlorophenoxyacetic acid (2,4-D) (right).

For the partially protected biphenols **5a**, **5b**, and **5c** a complete loss of weed control was observed (see Table 5). As the methylation of a single as well as of both OH groups (2,2′-bisanisoles **3**) leads to significantly deteriorated activities, a specific interaction between phenolic OH and active enzyme

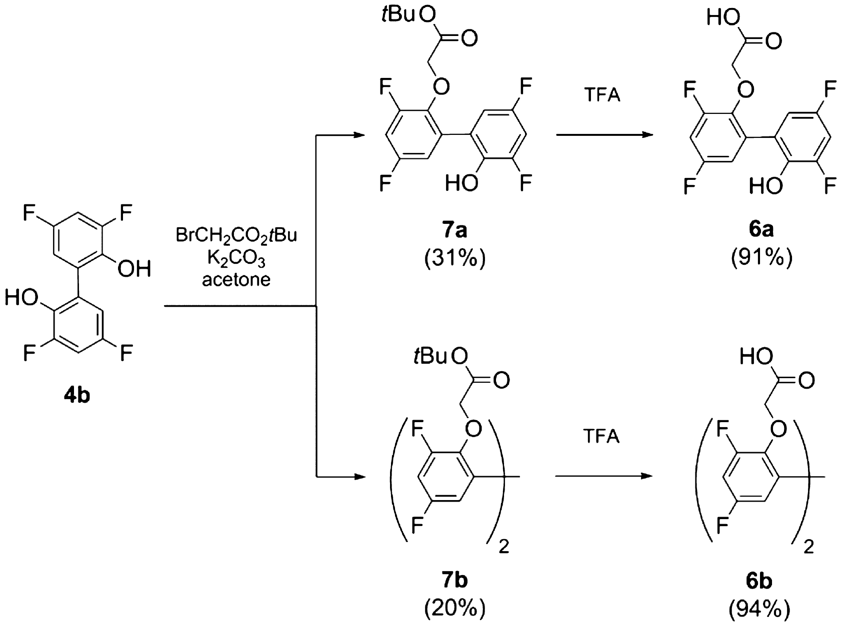


Figure 5. Preparation of auxin-type substituted 2,2′-biphenols **6a**, **6b**, **7a**, and **7b**.

sites in the plant metabolism is conceivable (e.g., hydrogen bonding). Another explanation for the reduced performance of the applied compounds together with the plants could also be their ADME properties (the term ADME is an acronym in pharmacokinetics and pharmacology for absorption, distribution, metabolism. and excretion, and in this case describes the disposition of an agricultural compound within the plant organism). By blocking the free hydroxy group with an alkyl moiety, the acidity of the compound is reduced dramatically and, therefore, the foliar uptake of the compound could also be decreased. Similarly, partial and full O-functionalization with the carboxymethyl group (compounds **6a** and **6b**) and the *tert*-butyloxycarbonylmethyl group (compounds **7a** and **7b**) leads to a full suppression of the performance. These results indicate that the whole biphenol unit is crucial for herbicidal impact.

The applicability of 2,2′-biphenols **4** for crop protection was studied, and high antipest plant activities were found in many cases. A clear correlation between structural elements and biological effect was found. The presence of hydroxy functionalities significantly enhances the activity toward weeds compared to methoxy groups. Specific interactions between these hydroxy functionalities and active enzyme sites (e.g., hydrogen bonding) seem to play an important role in the mode of action. Although the impact of these compounds is at an interesting level for a lead structure, an improvement in greenhouse activity by a factor of at least 10 will still be required to approach commercially acceptable level. In addition to that, one would also have to consider crop safety and evaluate the tolerance of the applied compounds against target crops such as wheat, corn, and rice, which was not performed within our studies. Within the range of tested compounds, 3-chloro-5-fluoro-2,2′-biphenol **4a** is the candidate with the most promising effectiveness. Among the target plants, *Setaria faberi* exhibits the highest susceptibilities.

To study the correlation between structure and biological impact, partially blocked 2,2′-biphenols **5a**, **5b**, and **5c** were synthesized. The test results clearly indicate that the whole 2,2′-biphenol unit is responsible for the activity, because partial blocking leads to a complete loss of activity. Moreover, it was found that the combination of structural motifs from auxin-type herbicides with the 2,2′-biphenol structure leads to a suppression of the weed control instead of a synergistically enhanced performance.

■ AUTHOR INFORMATION

Corresponding Author

*Phone: +49 6131 3926069. Fax: +49 6131 3926777. E-mail: waldvogel@uni-mainz.de.

Present Address

[#]Department of Chemistry and Biochemistry, University of California—Santa Barbara, Santa Barbara, CA 93106, United States.

Funding

S.R.W. and R.F. are grateful for financial support by Bundesministerium für Bildung und Forschung (HE-Lion, 03X4612J).

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

The collaboration with the Kompetenzzentrum der Integrierten Naturstoff-Forschung (University of Mainz) is highly appreciated.

■ REFERENCES

(1) Seitz, T.; Hoffmann, M. G.; Krähmer, H. Herbizide für die Landwirtschaft: Chemische Unkrautbekämpfung. *Chem. Unserer Zeit* **2003**, *37*, 112−116.

(2) Menne, H.; Köcher, H. HRAC classification of herbicides and resistance development. In *Modern Crop Protection Compounds*, 2nd ed.; Krämer, W., Schirmer, U., Jeschke, P., Witschel, M., Eds.; Wiley-VCH: Weinheim, Germany, 2012; Vol. *1*, pp 5−28.

(3) Finger, G. C.; Reed, F. H.; Tehon, L. R. Aromatic fluorine compounds as fungicides. *Illinois State Geol. Surv. Circ.* **1955**, *199*, 1−15.

(4) Kirsch, P. *Modern Fluoroorganic Chemistry*; Wiley-VCH: Weinheim, Germany, 2004.

(5) Mueller, K.; Faeh, C.; Diederich, F. Fluorine in pharmaceuticals: looking beyond intuition. *Science* **2007**, *317*, 1881−1886.

(6) Groult, H.; Nakajima, T. *Fluorinated Materials for Energy Conversion*; Elsevier: Oxford, UK, 2006.

(7) Francke, R.; Cericola, D.; Kötz, R.; Schnakenburg, G.; Waldvogel, S. R. Bis(2,2′-biphenoxy)borates for electrochemical double-layer capacitor electrolytes. *Chem.−Eur. J.* **2011**, *17*, 3082−3085.

(8) Pavlath, A. E. Theoretical considerations for the application of aromatic and heterocyclic fluorine compounds as pesticides. *Pestic. Sci.* **1986**, *17*, 412−417.

(9) Jeschke, P. The unique role of halogen substituents in the design of modern agrochemicals. *Pest Manag. Sci.* **2010**, *66*, 10−27.

(10) Jeschke, P. The unique role of fluorine in the design of active ingredients for modern crop protection. *ChemBioChem* **2004**, *5*, 570−589.

(11) Francke, R.; Schnakenburg, G.; Waldvogel, S. R. Efficient and reliable iodination and *O*-methylation of fluorinated phenols. *Eur. J. Org. Chem.* **2010**, 2357−2362.

(12) Francke, R.; Schnakenburg, G.; Waldvogel, S. R. Synthesis of highly fluorinated 2,2′-biphenols and 2,2′-bisanisoles. *Org. Lett.* **2010**, *12*, 4288−4291.

(13) Hock, B.; Fedke, C.; Schmidt, R. R. *Herbizide − Entwicklung, Anwendung, Wirkungen, Nebenwirkungen*; Thieme: Stuttgart, Germany, 1995.

(14) Grossmann, K. Auxin herbicides: current status of mechanism and mode of action. *Pest Manag. Sci.* **2010**, *66*, 113−120.

(15) Vanneste, S.; Friml, J. Auxin: a trigger for change in plant development. *Cell* **2009**, *136*, 1005−1016.