J. Pestic. Sci. **42**(3), 84–92 (2017)
DOI: 10.1584/jpestics.D16-105

Original Article

Synthesis and fungicidal activity of phenylhydrazone derivatives containing two carbonic acid ester groups

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(Received December 21, 2016; Accepted March 19, 2017)

Substituted phenylhydrazone moieties and two carbonate groups were merged in one molecule scaffold to obtain 48 novel compounds. ^{1}H and ^{13}C NMR, MS, elemental analysis, and X-ray single-crystal diffraction were used to confirm their structures. Bioassay results revealed that some of the compounds have strong antifungal activities against *Botrytis cinerea*, *Rhizoctonia solani*, and *Colletotrichum capsici* (especially *Rhizoctonia solani*). Compound **5H$_1$** is the most promising of the tested compounds against *R. solani* with an EC_{50} value of 1.91 mg/L, which is comparable with the positive control fungicide drazoxolon (1.94 mg/L). The structure–activity relationships against *R. solani* formed three rules: 1) small carbonate groups may improve the antifungal activity of the title compounds; 2) electron-withdrawing groups at the phenyl ring of phenylhydrazone are preferable to their non-substituted counterparts; and 3) halogen at the *para* position is more beneficial than at the *ortho* or *meta* position.

Keywords: phenylhydrazone, carbonic acid ester, antifungal activity, structure-activity relationships.

Introduction

The widespread usage of synthetic pesticides has facilitated significant improvements in food production by protecting crops from weeds, pests, and pathogens. The emergence of pesticide resistance, pollution, unwanted residues, and the accumulation of agrochemicals in food and water have forced researchers to continuously develop new pesticides better suited to the needs of farms and consumers.[1–3] Plant diseases caused by fungi are considered a worldwide threat to crop safety and food security,[4] and the threat posed by such disease has only been heightened by farming practices and trade activities being used with increasing frequency.[4] Diseases caused by plant pathogenic fungi, such as *Botrytis cinerea*, *Rhizoctonia solani*, and *Colletotrichum capsici*, are very common and can cause serious economic losses.[5–8] New, broad-spectrum fungicides are urgently needed to control phytopathogenic fungi.

Hydrazones, a class of compounds characterized by -NHN=C- substructure, are usually prepared by the reaction of hydrazine with ketones or aldehydes. These compounds not only have potential application as insecticidal,[9] antimicrobial,[10] herbicidal,[11] antiviral,[12] and anticancer[13] agents but also feature simple preparation, high activity, and low toxicity, making them popular research subjects in agricultural and medicinal fields.[14,15] Hydrazone derivatives, such as drazoxolon[16] and ferimzone,[17] which are used for the control and prevention of phytopathogenic fungi, are abundant in agriculture and demotic life. Diflufenzopyr[11] is used to control weeds in cereal crops; hydramethylnon[18] is used to control pests.

Esters tend to have good liposolubility and can quickly and effectively penetrate the biomembrane into the cell to work.[19] To this effect, the introduction of ester groups into compounds is beneficial for many drugs. The esters in pesticides mainly include pyrethroid, carbamate, methoxyacrylate (strobilurin), and carbonate. Many commercial pesticides contain carbonate groups, such as spirotetramat,[20] dinobuton,[21] dinocap,[22] and meptyldinocap.[23]

On the basis of these considerations, 2,6-dihydroxyacetophenone was chosen as a staring material and reacted with substituted phenylhydrazines to create phenylhydrazones; these phenylhydrazone intermediates were reacted with various chloroformic esters to obtain carbonates, and the resulting series of phenylhydrazone derivatives were carefully compared. All of the title compounds were characterized by ^{1}H NMR, ^{13}C NMR, MS, and

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Published online May 23, 2017

elemental analysis and then evaluated for three kinds of common plant pathogenic fungi to investigate their broad-spectrum activity. The preliminary structure–activity relationships (SARs) were also determined, as discussed below.

Materials and Methods

1. Instruments and reagents

The melting points of the products were determined using a WRS-1B digital melting-point apparatus (Shanghai Precision and Scientific Instrument Co., China) and were not corrected. NMR was performed in a DMSO-d_6 solvent on a Bruker Avance III 400 NMR spectrometer at room temperature with TMS as an internal standard. Thin-layer chromatography (TLC) was performed on silica gel GF254 (Qingdao Marine Chemical Ltd., China). Electrospray ionization mass spectrometry was recorded on a QP-2010 GC-MS (Shimadzu, Japan). Crystallographic data was recorded on a Bruker Smart APEX II CCD (Bruker, Germany). All reagents were of pure analytical grade and used directly without further treatment unless otherwise noted.

2. Synthesis and purification

The reaction route is outlined in Fig. 1. In this study, eight substituted phenylhydrazines **2** and one substituted hypnone **3** were used to prepare hydrazones. Intermediates **2** were prepared *via* the same method described in previous studies,[24,25] starting from corresponding anilines through diazotization, reduction, and acidification. We used a cheap and common $NaHSO_3$-NaOH buffer solution in place of $SnCl_2$ in the reduction step. Compounds **4A**–**4H** were prepared according to the methods described by Yousefi *et al.*[26] and Rathelot *et al.*[27]

Take the synthesis of compound **4A** as an example: phenylhydrazine (0.02 mol, 2.16 g) and 2,6-hydroxyacetophenone (0.02 mol, 3.04 g) were dissolved in 30 mL of anhydrous ethanol, and a few drops of acetic acid were added as a catalyst. The mixture was stirred at 60°C for 10 hr until the reaction was completed, and it was continually monitored by TLC. The reaction solution was concentrated under reduced pressure to evaporate the ethanol. The residue was moved to a small beaker and placed in a 4°C refrigerator to stand overnight after small amounts of ether and petroleum ether were added. The formed solid was filtered and recrystallized from the mixture of petroleum ether and diethyl ether (v/v=4:1) to yield **4A** in a yellow powder form. Yield, 78.3%; mp, 118.1–119.7°C; IR (KBr, cm^{-1}) *v*: 3353, 3265, 3047, 1597, 1499, 1447, 1343, 1252, 1147, 1010, 779, 748, 714, 692; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.40 (s, 2H, 2×OH), 9.22 (s, 1H, NH), 7.23 (t, *J*=7.8 Hz, 2H, PhH), 7.06 (d, *J*=7.9 Hz, 2H, PhH), 6.95 (t, *J*=8.1 Hz, 1H, PhH), 6.78 (t, *J*=7.2 Hz, 1H, PhH), 6.35 (d, *J*=8.1 Hz, 2H, PhH), 2.32 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.18, 146.16, 146.04, 129.59, 119.68, 112.97, 112.41, 107.51, 18.34; EI-MS, *m*/*z* (%): 242 (M^+, 100), 225 (58), 150 (19), 93 (83), 77 (18), 65 (22); Anal. Calcd. for $C_{14}H_{14}N_2O_2$ (242.28): C, 69.41; H, 5.82; N, 11.56. Found: C, 69.42; H, 5.85; N, 11. 54.

The title compounds were prepared according to previously published methods, as well.[28,29] Six different chloroformic esters were reacted with intermediates **4** to obtain the target compounds. To prepare compound **5A$_1$**, for example, methyl chloroformate (0.021 mol, 0.16 mL) was added dropwise to a solution of 2-[1-(2-phenylhydrazono)ethyl]benzene-1,3-diol **4A** (0.02 mol, 0.5 g) and triethylamine (0.021 mol, 0.3 mL) in anhydrous diethyl ether (35 mL). The mixture was stirred at 0°C for 1 hr and then at room temperature for 3 hr; it was then washed with dilute hydrochloric acid, saturated sodium bicarbonate solution, and water successively. The organic layer was dried over $MgSO_4$ and concentrated under reduced pressure. The title compounds were obtained after purification by recrystallization (petroleum ether and diethyl ether, v/v=6:1). Other title compounds were synthesized similarly; the obtained crude products were purified by recrystallization or column chromatography. The numbers of title compounds and their corresponding substituents are detailed in Table 1.

Data for compound **5A$_1$**: Yellow powder; yield, 76.7%; mp, 136.8–138.1°C; IR (KBr, cm^{-1}) *v*: 3316, 3097, 3055, 2961, 1748, 1600, 1498, 1436, 1368, 1252, 1218, 952, 778, 743; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.27 (s, 1H, NH), 7.45 (d, *J*=7.9 Hz, 1H, PhH), 7.28 (d, *J*=8.2 Hz, 2H, PhH), 7.19 (t, *J*=7.9 Hz, 2H, PhH), 7.05 (d, *J*=7.7 Hz, 2H, PhH), 6.75 (s, 1H, PhH), 3.76 (s, 6H, 2×OCH_3), 2.08 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.81, 149.23, 146.09, 134.91, 129.25, 129.16, 127.60, 121.27, 119.70, 113.12, 56.08, 17.56; EI-MS, *m*/*z* (%): 358 (M^+, 100), 283(50), 223(27), 106(38), 91(43), 77(40), 59(37); Anal. Calcd. for $C_{18}H_{18}N_2O_6$ (358.35): C, 60.33; H, 5.06; N, 7.82. Found: C, 60.49; H, 5.11; N, 7.81.

Data for compound **5A$_2$**: Light yellow powder; yield, 80.3%; mp, 77.0–78.8°C; IR (KBr, cm^{-1}) *v*: 3337, 2983, 2942, 1740, 1600, 1497, 1460, 1367, 1251, 1215, 1002, 942, 744, 693; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H, NH), 7.46 (t, *J*=8.2 Hz, 1H, PhH), 7.27 (d, *J*=8.2 Hz, 2H, PhH), 7.18 (t, *J*=7.8 Hz,

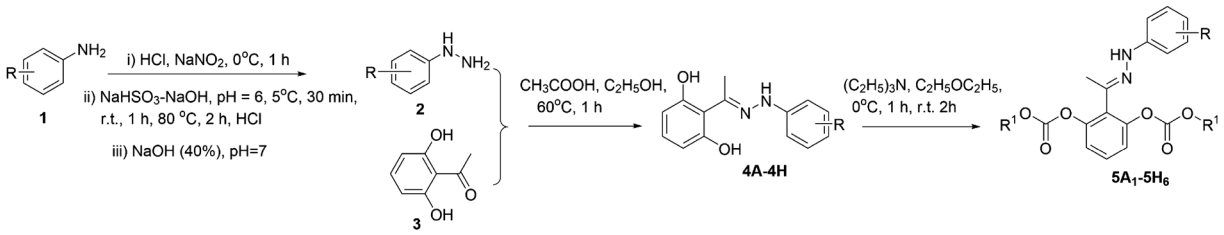

Fig. 1. Synthetic route to title compounds.

Table 1. The numbers of the compounds and their corresponding substituents

Comp.	R	R^1	Comp.	R	R^1	Comp.	R	R^1	Comp.	R	R^1
4A	H	—	$\mathbf{5B_1}$	2-F	Me	$\mathbf{5D_3}$	2-Cl	*n*-Pr	$\mathbf{5F_5}$	4-Cl	*i*-Bu
4B	2-F	—	$\mathbf{5B_2}$	2-F	Et	$\mathbf{5D_4}$	2-Cl	*i*-Pr	$\mathbf{5F_6}$	4-Cl	Ph
4C	4-F	—	$\mathbf{5B_3}$	2-F	*n*-Pr	$\mathbf{5D_5}$	2-Cl	*i*-Bu	$\mathbf{5G_1}$	2,4-Cl_2	Me
4D	2-Cl	—	$\mathbf{5B_4}$	2-F	*i*-Pr	$\mathbf{5D_6}$	2-Cl	Ph	$\mathbf{5G_2}$	2,4-Cl_2	Et
4E	3-Cl	—	$\mathbf{5B_5}$	2-F	*i*-Bu	$\mathbf{5E_1}$	3-Cl	Me	$\mathbf{5G_3}$	2,4-Cl_2	*n*-Pr
4F	4-Cl	—	$\mathbf{5B_6}$	2-F	Ph	$\mathbf{5E_2}$	3-Cl	Et	$\mathbf{5G_4}$	2,4-Cl_2	*i*-Pr
4G	2,4-Cl_2	—	$\mathbf{5C_1}$	4-F	Me	$\mathbf{5E_3}$	3-Cl	*n*-Pr	$\mathbf{5G_5}$	2,4-Cl_2	*i*-Bu
4H	4-Br	—	$\mathbf{5C_2}$	4-F	Et	$\mathbf{5E_4}$	3-Cl	*i*-Pr	$\mathbf{5G_6}$	2,4-Cl_2	Ph
$\mathbf{5A_1}$	H	Me	$\mathbf{5C_3}$	4-F	*n*-Pr	$\mathbf{5E_5}$	3-Cl	*i*-Bu	$\mathbf{5H_1}$	4-Br	Me
$\mathbf{5A_2}$	H	Et	$\mathbf{5C_4}$	4-F	*i*-Pr	$\mathbf{5E_6}$	3-Cl	Ph	$\mathbf{5H_2}$	4-Br	Et
$\mathbf{5A_3}$	H	*n*-Pr	$\mathbf{5C_5}$	4-F	*i*-Bu	$\mathbf{5F_1}$	4-Cl	Me	$\mathbf{5H_3}$	4-Br	*n*-Pr
$\mathbf{5A_4}$	H	*i*-Pr	$\mathbf{5C_6}$	4-F	Ph	$\mathbf{5F_2}$	4-Cl	Et	$\mathbf{5E_4}$	4-Br	*i*-Pr
$\mathbf{5A_5}$	H	*i*-Bu	$\mathbf{5D_1}$	2-Cl	Me	$\mathbf{5F_3}$	4-Cl	*n*-Pr	$\mathbf{5H_5}$	4-Br	*i*-Bu
$\mathbf{5A_6}$	H	Ph	$\mathbf{5D_2}$	2-Cl	Et	$\mathbf{5F_4}$	4-Cl	*i*-Pr	$\mathbf{5H_6}$	4-Br	Ph

2H, PhH), 7.06 (d, J=7.8 Hz, 2H, PhH), 6.75 (t, J=7.2 Hz, 1H, PhH), 4.18 (q, J=7.1 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.14 (t, J=7.1 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.16, 149.25, 146.11, 135.03, 129.17, 129.13, 127.68, 121.17, 119.67, 113.19, 65.28, 17.50, 14.29; EI-MS, m/z (%): 386 (M^+, 100), 314 (30), 297 (74), 224 (77), 106 (52), 93 (35), 77 (28); Anal. Calcd. for $C_{20}H_{22}N_2O_6$ (386.40): C, 62.17; H, 5.74; N,7.25. Found: C, 62.22; H, 5.75; N, 7.18.

Data for compound $\mathbf{5A_3}$: Light yellow powder; yield, 67.5%; mp, 75.4–77.2°C; IR (KBr, cm^{-1}) v: 3351, 3100, 2970, 2931, 2881, 1744, 1601, 1496, 1460, 1390, 1253, 1217, 931, 740, 694; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.29 (s, 1H, NH), 7.46 (t, 1H, PhH), 7.27 (d, J=8.2 Hz, 2H, PhH), 7.18 (t, J=7.8 Hz, 2H, PhH), 7.06 (d, J=7.7 Hz, 2H, PhH), 6.75 (t, J=7.2 Hz, 1H, PhH), 4.09 (t, J=6.6 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.60–1.46 (m, 4H, 2×CH_2), 0.80 (t, J=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.29, 149.24, 146.08, 134.78, 129.15, 127.73, 121.24, 119.63, 113.16, 70.63, 21.79, 17.50, 10.34; EI-MS, m/z (%): 414 (M^+, 25), 328 (84), 239 (32), 225 (100), 106 (34), 92 (43), 45 (32); Anal. Calcd. for $C_{22}H_{26}N_2O_6$ (414.46): C, 63.76; H, 6.32; N, 6.76. Found: C, 63.84; H, 6.32; N, 6.75.

Data for compound $\mathbf{5B_1}$: White powder; yield, 52.7%; mp, 61.4–62.3°C; IR (KBr, cm^{-1}) v: 3348, 3321, 2958, 1754, 1621, 1510, 1456, 1436, 1369, 1251, 1216, 1135, 956, 775, 736; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77 (s, 1H, NH), 7.42–7.54 (m, 1H, PhH), 7.31 (d, J=8.2 Hz, 2H, PhH), 7.26 (t, J=8.3 Hz, 1H, PhH), 7.14–7.19 (m, 1H, PhH), 7.08 (t, J=7.8 Hz, 1H, PhH), 6.77–6.86 (m, 1H, PhH), 3.76 (s, 6H, 2×OCH_3), 2.14 (d, J=9.7 Hz, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.77, 151.42, 149.17, 149.03, 139.49, 134.25, 129.52, 127.38, 125.10, 121.29, 120.33, 115.70, 115.43, 56.11, 17.53; EI-MS, m/z (%): 376 (M^+, 58), 318 (100), 301 (56), 242 (48), 124 (32), 111 (96), 83 (46); Anal. Calcd. for $C_{18}H_{17}N_2O_6F$ (376.34): C, 57.45; H, 4.55; N, 7.44. Found: C, 57.34; H, 4.57; N, 7.42.

Data for compound $\mathbf{5B_2}$: White powder; yield, 76.2%; mp, 54.6–55.2°C; IR (KBr, cm^{-1}) v: 3378, 2984, 1752, 1622, 1519, 1479, 1459, 1367, 1247, 1212, 1004, 941, 875, 754; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.77 (s, 1H, NH), 7.48 (t, J=8.2 Hz, 1H, PhH), 7.24–7.33 (m, 3H, PhH), 7.13–7.18 (m, 1H, PhH), 7.06 (t, J=7.7 Hz, 1H, PhH), 6.82 (d, J=6.1 Hz, 1H, PhH), 4.18 (q, J=7.1 Hz, 4H, 2×OCH_2), 2.14 (s, 3H, CH_3), 1.15 (t, J=7.1 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.13, 151.42, 149.18, 149.03, 139.48, 134.22, 129.48, 127.46, 125.03, 121.20, 120.31, 115.61, 115.45, 65.33, 17.46, 14.27 ; EI-MS, m/z (%): 404 (M^+, 100), 332 (24), 315 (37), 242 (91), 124 (57), 111 (45), 83 (21); Anal. Calcd. for $C_{20}H_{21}N_2O_6F$ (404.39): C, 59.40; H, 5.23; N, 6.93. Found: C, 59.28; H, 5.26; N, 6.91.

Data for compound $\mathbf{5B_3}$: White powder; yield, 73.1%; mp, 79.3–80.9°C; IR (KBr, cm^{-1}) v: 3371, 2970, 2942, 2881, 1756, 1620, 1515, 1459, 1369, 1213, 1142, 1037, 929, 771, 752; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.78 (s, 1H, NH), 7.48 (t, J=8.2 Hz, 1H, PhH), 7.28 (t, J=7.8 Hz, 3H, PhH), 7.12–7.17 (m, 1H, PhH), 7.06 (t, J=7.7 Hz, 1H, PhH), 6.76–6.89 (m, 1H, PhH), 4.09 (t, J=6.6 Hz, 4H, 2×OCH_2), 2.14 (s, 3H, CH_3), 1.47–1.61 (m, 4H, 2×CH_2), 0.80 (t, J=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.25, 151.43, 149.19, 149.04, 139.24, 134.21, 129.47, 127.52, 125.01, 121.24, 120.28, 115.62, 115.42, 70.67, 21.79, 17.43, 10.29; EI-MS, m/z (%): 432 (M^+, 100), 329 (28), 242 (89), 150 (46), 124 (53), 111 (57), 83 (36); Anal. Calcd. for $C_{22}H_{25}N_2O_6F$ (432.45): C, 61.10; H, 5.83; N, 6.48. Found: C, 61.05; H, 5.87; N, 6.43.

Data for compound $\mathbf{5C_1}$: White powder; yield, 56.2%; mp, 138.7–139.9°C; IR (KBr, cm^{-1}) v: 3311, 2967, 2848, 1746, 1615, 1510, 1435, 1367, 1251, 1213, 951, 924, 829, 746; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.31 (s, 1H, NH), 7.45–7.49 (m, 1H, PhH), 7.29 (d, J=8.1 Hz, 2H, PhH), 7.04–7.06 (m, 4H, PhH), 3.76 (s, 6H, 2×OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 157.82, 155.49, 153.79, 149.22, 142.76, 135.12, 129.20, 127.50, 121.25, 115.87, 115.65, 114.14, 114.07, 56.10, 17.57; EI-MS, m/z (%): 376 (M^+, 100), 318 (24), 301 (38), 242 (23), 150 (20), 124 (27), 111 (59), 83 (46); Anal. Calcd. for $C_{18}H_{17}N_2O_6F$ (376.34): C, 57.45; H, 4.55; N, 7.44. Found: C,

57.31; H, 4.59; N, 7.40.

Data for compound **5C$_2$**: Grey powder; yield, 76.6%; mp, 94.5–96.1°C; IR (KBr, cm^{-1}) *v*: 3338, 2983, 2936, 2961, 1765, 1736, 1611, 1511, 1460, 1367, 1252, 1216, 1001, 942, 832, 745; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.29 (s, 1H, NH), 7.46 (t, *J*=8.2 Hz, 1H, PhH), 7.26 (d, *J*=8.2 Hz, 2H, PhH), 7.04 (d, *J*=6.7 Hz, 4H, PhH), 4.18 (q, *J*=7.1 Hz, 4H, 2×OCH_2), 2.06 (s, 3H, CH_3), 1.15 (t, *J*=7.1 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 157.82, 155.49, 153.15, 149.25, 142.81, 135.23, 129.16, 127.59, 121.14, 115.78, 115.56, 114.22, 114.14, 65.29, 17.50, 14.29; EI-MS, *m*/*z* (%): 404 (M$^+$, 100), 315 (21), 242 (74), 150 (20), 124 (45), 111 (33), 83 (17); Anal. Calcd. for $C_{20}H_{21}N_2O_6F$ (404.39): C, 59.40; H, 5.23; N, 6.93. Found: C, 59.33; H, 5.27; N, 6.90.

Data for compound **5C$_3$**: Light yellow powder; yield, 78.4%; mp, 63.7–65.1°C; IR (KBr, cm^{-1}) *v*: 3332, 2973, 2876, 1765, 1741, 1610, 1510, 1460, 1393, 1256, 1217, 933, 831, 744; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.30 (s, 1H, NH), 7.46 (t, *J*=8.2 Hz, 1H, PhH), 7.27 (d, *J*=8.2 Hz, 2H, PhH), 7.04 (d, *J*=6.5 Hz, 4H, PhH), 4.09 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.06 (s, 3H, CH_3), 1.47–1.60 (m, 4H, 2×CH_2), 0.80 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 157.82, 155.49, 153.27, 149.26, 142.80, 135.00, 129.14, 127.67, 121.17, 115.73, 115.51, 114.21, 114.14, 70.63, 21.80, 17.46, 10.29. EI-MS, *m*/*z* (%): 432 (M$^+$, 100), 329 (15), 242 (62), 150 (19), 124 (37), 111 (29), 77 (4); Anal. Calcd. for $C_{22}H_{25}N_2O_6F$ (432.45): C, 61.10; H, 5.83; N, 6.48. Found: C, 60.94; H, 5.85; N, 6.46.

Data for compound **5D$_1$**: White powder; yield, 66.9%; mp, 64.8–66.1°C; IR (KBr, cm^{-1}) *v*: 3341, 2953, 2848, 1759, 1594, 1500, 1437, 1372, 1255, 1218, 1140, 957, 930, 744; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: Configuration A: 8.33 (s, 1H, NH), 7.49–7.53 (m, 1H, PhH), 7.46 –7.49 (m, 1H, PhH), 7.37–7.41 (m, 1H, PhH), 7.21–7.33 (m, 3H, PhH), 6.86 (t, *J*=7.4 Hz, 1H, PhH), 3.77 (s, 6H, 2×OCH_3), 2.18 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.77, 149.16, 141.54, 139.88, 129.77, 129.72, 128.38 127.05, 121.36, 121.22, 117.99, 114.90, 56.15, 17.04; Configuration B: 8.33 (s, 1H, NH), 7.69 (t, *J*=8.3 Hz, 1H, PhH), 7.46 –7.49 (m, 1H, PhH), 7.37–7.41 (m, 1H, PhH), 7.21–7.33 (m, 3H, PhH), 6.80 (t, *J*=7.6 Hz, 1H, PhH), 3.70 (s, 6H, 2×OCH_3), 2.14 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.42, 148.09, 140.72, 139.04, 132.10, 129.51, 128.59, 121.68, 121.53, 120.54, 116.71, 114.01, 56.40, 23.39; EI-MS, *m*/*z* (%): 392 (M$^+$, 100), 334 (25), 317 (44), 259 (16), 193 (40), 140 (18), 127 (52), 107 (37); Anal. Calcd. for $C_{18}H_{17}N_2O_6Cl$ (392.79): C, 55.04; H, 4.36; N, 7.13. Found: C, 55.14; H, 4.40; N, 7.07.

Data for compound **5D$_2$**: Light yellow powder; yield, 71.2%; mp, 56.8–58.1°C; IR (KBr, cm^{-1}) *v*: 3327, 2989, 2909, 1758, 1596, 1505, 1460, 1367, 1249, 1208, 1000, 880, 777, 748; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: Configuration A: 8.33 (s, 1H, NH), 7.44–7.52 (m, 2H, PhH), 7.37–7.41 (m, 1H, PhH), 7.22–7.31 (m, 3H, PhH), 6.86 (t, *J*=7.4 Hz, 1H, PhH), 4.18 (q, *J*=7.0 Hz, 4H, 2×OCH_2), 2.17 (s, 3H, CH_3), 1.15 (t, *J*=7.0 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.13, 149.18, 141.51, 139.87, 129.70, 128.31, 127.11, 121.26, 121.21, 117.98, 115.08, 65.37, 16.95, 14.27 ; Configuration B: 8.33 (s, 1H, NH), 7.68 (t, *J*=8.3 Hz, 1H, PhH), 7.44–7.52 (m, 1H, PhH), 7.37–7.41 (m, 1H, PhH), 7.22–7.31 (m, 3H, PhH), 6.79 (t, *J*=7.7 Hz, 1H, PhH), 4.06–4.14 (m, 4H, 2×OCH_2), 2.15 (s, 3H, CH_3), 1.12 (t, *J*=6.8 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 152.86, 148.13, 140.76, 139.06, 132.03, 129.49, 128.52, 121.68, 120.49, 116.71, 113.99, 65.73, 23.39, 14.18 ; EI-MS, *m*/*z* (%): 420 (M$^+$, 100), 348 (11), 331 (28), 258 (60), 150 (17), 140 (36), 127 (32), 107 (34), 77 (24); Anal. Calcd. for $C_{20}H_{21}N_2O_6Cl$ (420.85): C, 57.08; H, 5.03; N, 6.66. Found: C, 57.08; H, 5.04; N, 6.61.

Data for compound **5D$_3$**: White powder; yield, 43.7%; mp, 55.1–56.7°C; IR (KBr, cm^{-1}) *v*: 3363, 2969, 2939, 2878, 1757, 1594, 1502, 1459, 1392, 1211, 1144, 1032, 929, 752; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: Configuration A: 8.33 (s, 1H, NH), 7.44–7.52 (m, 2H, PhH), 7.37–7.40 (m, 1H, PhH), 7.22–7.31 (m, 3H, PhH), 6.86 (t, *J*=7.5 Hz, 1H, PhH), 4.09 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.17 (s, 3H, CH_3), 1.50–1.55 (m, 4H, 2×CH_2), 0.79 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.24, 149.21, 141.49, 139.63, 132.01, 129.65, 128.43, 127.19, 121.67, 121.26, 120.42, 117.98, 115.13, 70.70, 21.79, 16.87, 10.26 Configuration B: 8.33 (s, 1H, NH), 7.68 (t, *J*=8.3 Hz, 1H, PhH), 7.44–7.52 (m, 1H, PhH), 7.37–7.41 (m, 1H, PhH), 7.22–7.31 (m, 3H, PhH), 6.79 (t, *J*=7.6 Hz, 1H, PhH), 4.04 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.15 (s, 3H, CH_3), 1.50–1.55 (m, 4H, 2×CH_2), 0.79 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.01, 148.16, 141.49, 140.79, 138.87, 129.43, 128.43, 127.19, 121.73, 121.16, 120.42, 116.72, 113.98, 70.98, 23.35, 16.87, 10.21. EI-MS, *m*/*z* (%): 448 (M$^+$, 100), 362 (5), 345 (19), 258 (64), 150 (19), 140 (35), 127 (31), 107 (27), 77 (8); Anal. Calcd. for $C_{22}H_{25}N_2O_6Cl$ (448.90): C, 58.86; H, 5.61; N, 6.24. Found: C, 59.01; H, 5.64; N, 6.23.

Data for compound **5E$_1$**: Light yellow powder; yield, 67.3%; mp, 137.1–138.9°C; IR (KBr, cm^{-1}) *v*: 3325, 2953, 2848, 1742, 1597, 1514, 1473, 1436, 1366, 1256, 1220, 1143, 1068, 954, 856, 746; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.53 (s, 1H, NH), 7.49 (t, *J*=8.2 Hz, 1H, PhH), 7.30 (d, *J*=8.2 Hz, 2H, PhH), 7.21 (t, *J*=8.1 Hz, 1H, PhH), 7.08 (s, 1H, PhH), 6.99 (d, *J*=8.2 Hz, 1H, PhH), 6.78 (d, *J*=7.8 Hz, 1H, PhH), 3.78 (s, 6H, 2×OCH_3), 2.09 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.79, 149.17, 147.54, 136.60, 134.12, 130.91, 129.42, 127.28, 121.33, 119.13, 112.38, 111.89, 56.12, 17.71; EI-MS, *m*/*z* (%): 392 (M$^+$, 100), 334 (19), 317 (52), 258 (22), 193 (7), 140 (17), 127 (32), 77 (24); Anal. Calcd. for $C_{18}H_{17}N_2O_6Cl$ (392.79): C, 55.04; H, 4.36; N, 7.13. Found: C, 55.10; H, 4.40; N, 7.09.

Data for compound **5E$_2$**: White powder; yield, 82.7%; mp, 111.2–112.9°C; IR (KBr, cm^{-1}) *v*: 3323, 2982, 1739, 1597, 1519, 1470, 1458, 1368, 1251, 1213, 1144, 990, 875, 745; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.52 (s, 1H, NH), 7.44–7.52 (m, 1H, PhH), 7.28 (d, *J*=8.2 Hz, 2H, PhH), 7.20 (t, *J*=8.1 Hz, 1H, PhH), 7.09 (t, *J*=1.9 Hz, 1H, PhH), 6.96–7.02 (m, 1H, PhH), 6.78 (dd, *J*=7.8, 1.3 Hz, 1H, PhH), 4.20 (q, *J*=7.1 Hz, 4H, 2×OCH_2), 2.08 (s, 3H, CH_3), 1.15 (t, *J*=7.1 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.14, 149.19, 147.55, 136.72, 134.07, 130.84, 129.39 127.36, 121.24, 119.09, 112.44, 111.94,

65.32, 17.66, 14.28; EI-MS, *m*/*z* (%): 420 (M^+, 100), 331 (17), 258 (96), 140 (41), 127 (21), 107 (36), 77 (19); Anal. Calcd. for $C_{20}H_{21}N_2O_6Cl$ (420.85): C, 57.08; H, 5.03; N, 6.66. Found: C, 57.20; H, 5.08; N, 6.62.

Data for compound **5E$_3$**: Light yellow powder; yield, 71.6%; mp, 59.1–61.3°C; IR (KBr, cm^{-1}) *v*: 3325, 2970, 1742, 1595, 1458, 1437, 1368, 1251, 1214, 1144, 1068, 990, 857, 745; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.53 (s, 1H, NH), 7.48 (t, *J*=8.2 Hz, 1H, PhH), 7.29 (d, *J*=8.2 Hz, 2H, PhH), 7.20 (t, *J*=8.1 Hz, 1H, PhH), 7.09 (s, 1H, PhH), 6.99 (d, *J*=8.2 Hz, 1H, PhH), 6.78 (d, *J*=7.8 Hz, 1H, PhH), 4.11 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.08 (s, 3H, CH_3), 1.48–1.60 (m, 4H, 2×CH_2), 0.80 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.25, 149.22, 147.55, 136.50, 134.09, 130.77, 129.35, 127.44, 121.25, 119.05, 112.45, 111.95, 70.66, 21.81, 17.62, 10.28. EI-MS, *m*/*z* (%): 448 (M^+, 100), 345 (21), 258 (89), 140 (29), 127 (25), 107 (26), 77 (8); Anal. Calcd. for $C_{22}H_{25}N_2O_6Cl$ (448.90): C, 58.86; H, 5.61; N, 6.24. Found: C, 58.95; H, 5.62; N, 6.20.

Data for compound **5F$_1$**: White powder; yield, 59.7%; mp, 85.7–87.3°C; IR (KBr, cm^{-1}) *v*: 3314, 2967, 2848, 1742, 1599, 1489, 1435, 1366, 1252, 1217, 1086, 954, 823, 746; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.46 (s, 1H, NH), 7.49 (t, *J*=8.2 Hz, 1H, PhH), 7.30 (d, *J*=8.2 Hz, 2H, PhH), 7.24 (d, *J*=8.8 Hz, 2H, PhH), 7.05 (d, *J*=8.8 Hz, 2H, PhH), 3.76 (s, 6H, 2×OCH_3), 2.08 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.77, 149.19, 145.04, 136.01, 129.33, 129.10, 127.37, 123.06, 121.26, 114.55, 56.14, 17.67; EI-MS, *m*/*z* (%): 392 (M^+, 100), 317 (35), 258 (14), 140 (16), 127 (27), 77 (13), 59 (25); Anal. Calcd. for $C_{18}H_{17}N_2O_6Cl$ (392.79): C, 55.04; H, 4.36; N, 7.13. Found: C, 55.12; H, 4.39; N, 7.08.

Data for compound **5F$_2$**: Grey powder; yield, 77.9%; mp, 96.9–98.2°C; IR (KBr, cm^{-1}) *v*: 3333, 2978, 2909, 1762, 1737, 1600, 1506, 1460, 1366, 1251, 1219, 1005, 940, 825, 744; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.43 (s, 1H, NH), 7.46 (t, *J*=8.2 Hz, 1H, PhH), 7.27 (d, *J*=8.2 Hz, 2H, PhH), 7.23 (d, *J*=8.5 Hz, 2H, PhH), 7.06 (d, *J*=8.6 Hz, 2H, PhH), 4.18 (q, *J*=7.0 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.15 (t, *J*=7.0 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.13, 149.22, 145.08, 136.13, 129.31, 129.03, 127.48, 123.03, 121.15, 114.63, 65.33, 17.61, 14.31; EI-MS, *m*/*z* (%): 420 (M^+, 100), 331 (16), 258 (55), 140 (27), 127 (32), 107 (25), 77 (11); Anal. Calcd. for $C_{20}H_{21}N_2O_6Cl$ (420.85): C, 57.08; H, 5.03; N, 6.66. Found: C, 57.15; H, 5.07; N, 6.60.

Data for compound **5F$_3$**: White powder; yield, 78.6%; mp, 95.1–96.7°C; IR (KBr, cm^{-1}) *v*: 3331, 2974, 2934, 2878, 1763, 1736, 1598, 1505, 1489, 1460, 1394, 1255, 1219, 939, 826, 743; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.45 (s, 1H, NH), 7.47 (t, *J*=8.2 Hz, 1H, PhH), 7.27 (d, *J*=8.2 Hz, 2H, PhH), 7.23 (d, *J*=8.9 Hz, 2H, PhH), 7.05 (d, *J*=8.9 Hz, 2H, PhH), 4.09 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.48–1.59 (m, 4H, 2×CH_2), 0.80 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.24, 149.23, 145.08, 135.90, 129.29, 128.99, 127.54, 123.01, 121.19, 114.63, 70.66, 21.81, 17.56, 10.32; EI-MS, *m*/*z* (%): 448 (M^+, 100), 345 (15), 258 (61), 140 (27), 127 (29), 107 (18), 77 (8); Anal. Calcd. for $C_{22}H_{25}N_2O_6Cl$ (448.90): C, 58.86; H, 5.61; N, 6.24. Found: C, 58.86; H, 5.65; N, 6.19.

Data for compound **5G$_1$**: White powder; yield, 41.7%; mp, 84.1–85.8°C; IR (KBr, cm^{-1}) *v*: 3360, 2963, 2856, 1766, 1591, 1499, 1439, 1243, 1211, 956, 931, 835, 737; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 8.46 (s, 1H, NH), 7.46–7.57 (m, 2H, PhH), 7.24–7.40 (m, 4H, PhH), 3.77 (s, 6H, 2×OCH_3), 2.19 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.74, 149.13, 141.13, 140.93, 129.82, 129.10, 128.41, 126.93, 123.98, 121.33, 118.68, 115.97, 56.19, 17.26; EI-MS, *m*/*z* (%): 428 (M^++1, 68), 426 (M^+–1, 100), 351 (41), 293 (21), 174 (24), 161 (73), 149 (22), 107 (29), 77 (23), 59 (63); Anal. Calcd. for $C_{18}H_{16}N_2O_6Cl_2$ (427.23): C, 50.60; H, 3.77; N, 6.56. Found: C, 50.72; H, 3.78; N, 6.50.

Data for compound **5G$_2$**: White powder; yield, 57.1%; mp, 85.7–86.9°C; IR (KBr, cm^{-1}) *v*: 3371, 2985, 2911, 1751, 1592, 1506, 1476, 1453, 1365, 1245, 1217, 1010, 818, 743; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 8.46 (s, 1H, NH), 7.46–7.59 (m, 2H, PhH), 7.25–7.39 (m, 4H, PhH), 4.19 (q, *J*=7.0 Hz, 4H, 2×OCH_2), 2.18 (s, 3H, CH_3), 1.15 (t, *J*=7.0 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.10, 149.14, 141.12, 140.92, 129.80, 129.04, 128.34, 126.99, 123.97, 121.24, 118.68, 116.19, 65.40, 17.18, 14.29; EI-MS, *m*/*z* (%): 456 (M^++1, 70), 454 (M^+–1, 100), 365 (20), 292 (33), 174 (25), 161 (34), 150 (22), 107 (38), 77 (12); Anal. Calcd. for $C_{20}H_{20}N_2O_6Cl_2$ (455.29): C, 52.76; H, 4.43; N, 6.15. Found: C, 52.86; H, 4.43; N, 6.09.

Data for compound **5G$_3$**: White powder; yield, 78.6%; mp, 95.1–96.7°C; IR (KBr, cm^{-1}) *v*: 3358, 2973, 2936, 2878, 1756, 1592, 1496, 1459, 1391, 1212, 1034, 933, 874, 743; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 8.44 (s, 1H, NH), 7.48–7.52 (m, 2H, PhH), 7.23–7.38 (m, 4H, PhH), 4.09 (t, *J*=6.6 Hz, 4H, 2×OCH_2), 2.17 (s, 3H, CH_3), 1.49–1.58 (m, 4H, 2×CH_2), 0.80 (t, *J*=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 152.23, 149.14, 140.93, 140.88, 129.81, 129.00, 128.35, 127.06, 123.96, 121.31, 118.71, 116.27, 70.73, 21.80, 17.16, 10.30; EI-MS, *m*/*z* (%): 484 (M^++1, 72), 482 (M^+–1, 100), 379 (15), 293 (34), 174 (30), 161 (44), 150 (31), 107 (16), 77 (11); Anal. Calcd. for $C_{22}H_{24}N_2O_6Cl_2$ (483.34): C, 54.67; H, 5.01; N, 5.80. Found: C, 54.78; H, 5.05; N, 5.78.

Data for compound **5H$_1$**: White powder; yield, 52.4%; mp, 109.1–111.2°C; IR (KBr, cm^{-1}) *v*: 3345, 2958, 2851, 1755, 1589, 1518, 1486, 1439, 1367, 1277, 1216, 1153, 964, 824, 742; ^{1}H NMR (400 MHz, DMSO-d_6) *δ*: 9.45 (s, 1H, NH), 7.48 (t, *J*=8.2 Hz, 1H, PhH), 7.36 (d, *J*=8.7 Hz, 2H, PhH), 7.29 (d, *J*=8.2 Hz, 2H, PhH), 7.00 (d, *J*=8.7 Hz, 2H, PhH), 3.76 (s, 6H, 2×OCH_3), 2.07 (s, 3H, CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) *δ*: 153.76, 149.19, 145.42, 136.14, 131.93, 129.34, 127.36, 121.25, 115.07, 110.72, 56.14, 17.68; EI-MS, *m*/*z* (%): 438 (M^++1, 100), 436 (M^+–1, 100), 363 (37), 304 (25), 171 (72), 149 (19), 107 (31), 91 (50), 77 (23), 59 (57); Anal. Calcd. for $C_{18}H_{17}N_2O_6Br$ (437.25): C, 49.45; H, 3.92; N, 6.41. Found: C, 49.58; H, 3.94; N, 6.37.

Data for compound **5H$_2$**: Yellow powder; yield, 61.7%; mp, 106.4–108.2°C; IR (KBr, cm^{-1}) *v*: 3345, 2958, 2851, 1755, 1591, 1486, 1439, 1367, 1251, 1218, 1153, 963, 823, 742; ^{1}H NMR

(400 MHz, DMSO-d_6) δ: 9.45 (s, 1H, NH), 7.47 (t, J=8.2 Hz, 1H, PhH), 7.35 (d, J=8.8 Hz, 2H, PhH), 7.27 (d, J=8.2 Hz, 2H, PhH), 7.01 (d, J=8.8 Hz, 2H, PhH), 4.18 (q, J=7.1 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.15 (t, J=7.1 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.11, 149.21, 145.46, 136.25, 131.86, 129.32, 127.46, 121.14, 115.14, 110.69, 65.33, 17.61, 14.31; EI-MS, m/z (%): 466 (M^++1, 98), 464 (M^+–1, 100), 377 (12), 304 (42), 171 (24), 150 (11), 107 (32), 91 (19), 77 (13); Anal. Calcd. for $C_{20}H_{21}N_2O_6Br$ (465.30): C, 51.63; H, 4.55; N, 6.02. Found: C, 51.67; H, 4.58; N, 5.96.

Data for compound **5H$_3$**: Yellow powder; yield, 58.3%; mp, 126.3–127.0°C; IR (KBr, cm^{-1}) v: 3330, 2972, 2939, 2895, 2878, 1762, 1735, 1593, 1487, 1459, 1395, 1255, 1217, 939, 825, 743; ^{1}H NMR (400 MHz, DMSO-d_6) δ: 9.45 (s, 1H, NH), 7.47 (t, J=8.2 Hz, 1H, PhH), 7.34 (d, J=8.8 Hz, 2H, PhH), 7.27 (d, J=8.2 Hz, 2H, PhH), 7.01 (d, J=8.8 Hz, 2H, PhH), 4.09 (t, J=6.6 Hz, 4H, 2×OCH_2), 2.07 (s, 3H, CH_3), 1.47–1.59 (m, 4H, 2×CH_2), 0.80 (t, J=7.4 Hz, 6H, 2×CH_3); ^{13}C NMR (101 MHz, DMSO-d_6) δ: 153.25, 149.20, 145.44, 135.98, 131.84, 129.32, 127.53, 121.22, 115.13, 110.66, 70.66, 21.81, 17.60, 10.33; EI-MS, m/z (%): 494 (M^++1, 100), 492 (M^+–1, 98), 391 (12), 304 (48), 171 (28), 150 (15), 107 (22), 91 (16), 77 (9); Anal. Calcd. for $C_{22}H_{25}N_2O_6Br$ (493.35): C, 53.56; H, 5.11; N, 5.68. Found: C, 53.68; H, 5.11; N, 5.64.

3. Crystallographic study

The crystal of compound **5D$_6$** was recrystallized from a mixture of dichlormethane and *n*-hexane to obtain a suitable single crystal. The X-ray single crystal diffraction data were collected on a Bruker Smart APEX II CCD diffractometer at 296(2) K using Mo$K\alpha$ radiation (λ=0.71073 Å) using the ω and 2θ scan modes. The SAINT program was used to integrate the diffraction profiles. The structure was solved directly and refined by full-matrix least-squares method *via* SHELXTL.[30] All non-hydrogen atoms of compound **5D$_6$** were refined with anisotropic thermal parameters; all hydrogen atoms were placed in geometrically idealized positions and constrained to ride on their parent atoms.

4. In vitro *antifungal bioassay*

Antifungal activities were screened as described by previous researchers[31,32] and evaluated against three pathogenic fungi—*B. cinerea*, *R. solani* and *C. capsici*—*in vitro* with a mycelial growth test on potato sucrose agar (PSA) medium. The compounds were dissolved in DMSO and mixed with sterile molten PSA to obtain a final concentration of 10 mg/L. Portions of PSA with different compounds were poured into 90 mm Petri dishes (20 mL·dish^{-1}), on which 5-mm mycelial disks of the three fungi were placed at the center. The disks were obtained from a pure PSA culture plate by punching at the edge of the actively growing mycelia colony. Each treatment condition was produced in three replicates. The commercial fungicide drazoxolon served as a positive control.

After a certain incubation period (1.5 d for *R. solani*, 2.5 d for *B. cinerea*, and 4 d for *C. capsici*, according to their respective mycelia growth rates) at 25±1°C in a dark environment, the diameters of mycelial growth were measured, and the data were statistically analyzed. Inhibitory percentages of the title compounds *in vitro* on these fungi were calculated as $I(\%)=[(C-T)/(C-0.5)]\times100$, where C represents the diameter of fungal growth on untreated PSA, T represents the diameter of fungi on treated PSA, and I represents the inhibition rate.

Furthermore, the fungicidal activities of these compounds against *R. solani*, *B. cinerea*, and *C. capsici* were further assessed *via* the same method. Per the preliminary test record, these compounds were dissolved in DMSO and diluted with medium to obtain different final concentration grades. The diameters of the mycelial growth were measured, and the inhibition percentages relative to the control were calculated; EC_{50} values were calculated *via* linear-regression analysis.

Results and Discussion

1. Synthesis

The synthesis procedure for the title compounds is illustrated in Fig.1. Different substituted phenylhydrazines were treated to form the -NHN=C- substructure and to investigate the manner in which respective substituents on the phenyl ring influence their activities. Different chloroformic esters were also tested for their ability to strengthen the liposolubility and increase the

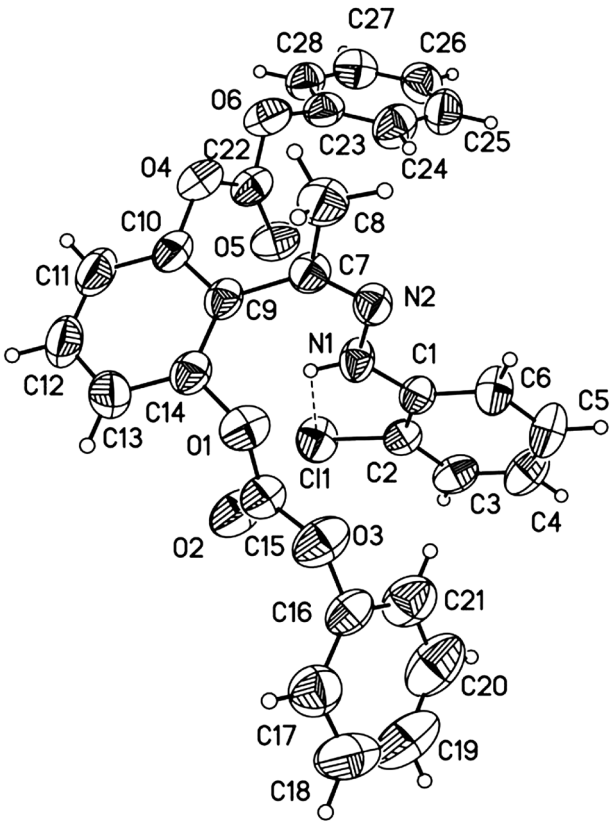

Fig. 2. ORTEP plot of compound **5D$_6$** at 50% probability level of ellipsoids. The dashed line shows hydrogen bonds.

compound types. ^{1}H NMR, ^{13}C NMR, EI-MS spectra and elemental analysis data of the remaining compounds (**5A$_4$**–**5A$_6$**, **5B$_4$**–**5B$_6$**, **5C$_4$**–**5C$_6$**, **5D$_4$**–**5D$_6$**, **5E$_4$**–**5E$_6$**, **5F$_4$**–**5F$_6$**, **5G$_4$**–**5G$_6$**, and **5H$_4$**–**5H$_6$**) are given in the Supporting Information section in accordance with their assigned structures.

2. Compound 5D$_6$ crystal structure

The crystal data of compound **5D$_6$** are presented in Supplemental Table 1. Fig.2 gives a perspective view of **5D$_6$** with the atomic labeling system. The crystal is representative of a monoclinic system, the $P2_1/c$ space group with a=13.2316(15) Å, b=10.7573(12) Å, c=18.392(2) Å, α=90°, β=91.171(2)°, γ=90°, Z=4, D_c=1.312 g/cm^3, V=2617.2(5) Å^3, R_1=0.0443, and wR_2=0.1277. The maximum and minimum residual electron density peaks are 0.325 eÅ^{-3} and −0.475 eÅ^{-3}, respectively. The bond bears an ***E*** conformation.

3. Antifungal activities in vitro

The preliminary bioassay results of the title compounds against three phytopathogenic fungi are shown in Table 2. All of the compounds were active against *R. solani*, with only three (**5B$_6$**, **5D$_6$**, and **5E$_5$**) lower than 10% and the others mostly higher than 40%; 20 of them exceeded 50%. The inhibitory effects of the compounds on *B. cinerea* and *C. capsici* were similar; at the tested dose, 14 compounds inhibited *B. cinerea* at rates greater than 50%, while those remaining were active but lower than 50%. The same numbers apply to the results of *C. capsici*—that is to say, most of our compounds showed moderate inhibition against both *B. cinerea* and *C. capsici* but more actively inhibited *R. solani* mycelial growth *in vitro*. Accordingly, *R. solani* was selected as the target fungus for further assessment.

The inhibition rates against *R. solani* indicate that the fungicidal activities of the title compounds we obtained from small chloroformic esters were higher than those obtained from bulky ones. For example, the antifungal activities of compounds **5A$_1$**, **5A$_2$**, and **5A$_3$** were higher than those of **5A$_4$**, **5A$_5$**, and **5A$_6$**. Similarly, the antifungal activities of compounds **5B$_1$**, **5B$_2$**, and **5B$_3$** were higher than those of **5B$_4$**, **5B$_5$**, and **5B$_6$**. For this reason, we selected compounds with small carbonate groups (subscripts 1, 2, and 3) for further study of their antifungal activities. As for other pathogens, we chose compounds with preliminary inhibition rates higher than 50% to verify their broad-spectrum activities.

EC_{50} values were calculated using linear regression with drazoxolon as the positive control (Table 3). Except for **5D$_3$**, **5G$_2$**, and **5G$_3$**, all other compounds showed substantial inhibitory activities against *R. solani*. Among them, the EC_{50} values of 21 compounds were less than 10 mg/L, and four of them (**5F$_1$**, **5F$_2$**,

Table 2. Fungicidal activity of title compounds at concentration of 10 mg/L

Comp	Inhibitory effect of compounds (%)			Comp	Inhibitory effect of compounds (%)		
	B. cinerea	*R. solani*	*C. capsici*		*B. cinerea*	*R. solani*	*C. capsici*
5A$_1$	35.0±2.0	65.1±3.9	69.7±1.1	**5E$_1$**	60.7±2.3	72.5±0.9	50.9±1.7
5A$_2$	29.3±1.5	65.1±1.2	49.7±2.1	**5E$_2$**	40.5±0.9	63.8±1.3	45.1±0.9
5A$_3$	19.1±1.2	63.9±1.6	44.2±1.7	**5E$_3$**	21.4±1.1	49.8±2.5	31.5±1.9
5A$_4$	8.6±0.9	45.4±2.0	38.0±1.4	**5E$_4$**	10.1±2.7	42.3±1.7	15.5±2.4
5A$_5$	12.9±1.8	30.8±1.3	28.7±0.7	**5E$_5$**	3.0±2.1	1.5±0.9	5.2±1.7
5A$_6$	11.0±1.2	22.1±2.3	40.9±2.1	**5E$_6$**	5.7±1.3	25.9±2.1	6.7±0.7
5B$_1$	61.7±2.1	80.5±3.0	86.3±1.6	**5F$_1$**	75.6±1.5	74.6±0.8	73.2±2.0
5B$_2$	53.3±1.7	81.5±1.0	79.4±1.1	**5F$_2$**	76.5±2.6	72.0±0.8	49.8±1.5
5B$_3$	44.5±1.1	68.0±1.2	69.2±1.6	**5F$_3$**	53.3±2.9	53.9±1.1	48.9±0.7
5B$_4$	20.0±1.3	49.7±1.6	49.1±1.7	**5F$_4$**	39.0±3.0	46.6±1.1	35.0±2.3
5B$_5$	14.5±2.6	17.3±1.5	28.2±1.1	**5F$_5$**	26.5±1.3	36.7±1.2	41.1±1.7
5B$_6$	6.9±1.1	6.2±1.4	41.7±1.2	**5F$_6$**	72.9±1.3	47.1±1.2	60.1±3.3
5C$_1$	69.1±0.9	74.2±1.1	62.9±2.9	**5G$_1$**	57.9±1.5	69.7±1.6	72.9±0.8
5C$_2$	59.5±3.5	74.2±0.6	56.3±1.8	**5G$_2$**	38.3±2.1	34.6±0.9	61.6±1.7
5C$_3$	38.1±1.5	71.5±0.8	26.3±1.9	**5G$_3$**	20.5±1.7	25.4±0.9	39.4±2.0
5C$_4$	13.7±3.1	48.3±0.8	9.9±2.6	**5G$_4$**	13.8±1.5	24.4±2.3	32.6±1.5
5C$_5$	22.0±3.1	48.1±1.7	40.6±1.7	**5G$_5$**	10.0±1.3	20.8±1.3	7.4±1.7
5C$_6$	70.5±1.0	43.7±1.1	47.3±1.2	**5G$_6$**	7.9±1.5	26.4±2.7	23.8±1.1
5D$_1$	42.9±0.9	79.5±0.8	82.4±0.7	**5H$_1$**	75.9±1.9	72.5±0.9	61.3±1.5
5D$_2$	26.2±1.5	67.4±1.2	69.0±1.1	**5H$_2$**	72.3±1.0	69.1±1.5	46.7±1.1
5D$_3$	11.9±2.2	39.7±2.3	45.1±1.5	**5H$_3$**	53.1±0.9	53.4±1.1	31.7±2.9
5D$_4$	9.3±1.5	24.6±1.4	26.9±1.7	**5H$_4$**	30.1±1.3	42.3±2.7	40.8±1.8
5D$_5$	5.0±2.0	22.3±2.3	19.2±1.1	**5H$_5$**	15.5±2.1	36.5±1.7	14.8±2.9
5D$_6$	3.6±2.4	8.2±1.6	14.6±2.1	**5H$_6$**	36.3±0.9	38.7±1.2	29.8±1.9

Table 3. EC_{50} values of some selected compounds against *R. solani*, *B. cinerea*, and *C. capsici in vitro*

Comp	EC_{50}±SE (mg/L)			Comp	EC_{50}±SE (mg/L)		
	B. cinerea	*R. solani*	*C. capsici*		*B. cinerea*	*R. solani*	*C. capsici*
5A$_1$	>10	6.89±0.14	6.94±0.15	**5E$_1$**	5.22±0.10	4.52±0.17	5.56±0.08
5A$_2$	>10	7.73±0.22	>10	**5E$_2$**	>10	8.01±0.15	>10
5A$_3$	>10	9.36±0.11	>10	**5E$_3$**	>10	9.18±0.14	>10
5B$_1$	6.11±0.05	3.13±0.13	3.59±0.14	**5F$_1$**	1.68±0.05	2.69±0.11	3.19±0.19
5B$_2$	7.69±0.14	4.00±0.14	5.24±0.27	**5F$_2$**	2.59±0.07	2.37±0.11	>10
5B$_3$	>10	5.37±0.17	7.03±0.23	**5F$_3$**	3.81±0.09	5.12±0.09	>10
5C$_1$	2.72±0.05	3.14±0.10	3.82±0.10	**5G$_1$**	5.08±0.08	3.96±0.10	6.40±0.08
5C$_2$	4.83±0.13	3.48±0.10	6.37±0.16	**5G$_2$**	>10	>10	9.96±0.10
5C$_3$	>10	5.15±0.05	>10	**5G$_3$**	>10	>10	>10
5D$_1$	>10	5.58±0.12	6.17±0.20	**5H$_1$**	1.87±0.05	1.91±0.08	4.25±0.17
5D$_2$	>10	5.88±0.16	6.14±0.10	**5H$_2$**	3.28±0.08	2.22±0.09	>10
5D$_3$	>10	>10	>10	**5H$_3$**	5.85±0.04	5.65±0.10	>10
Dra[a)]	0.45±0.11	1.94±0.12	19.46±0.21				

[a)] Dra: Drazoxolon

5H$_1$, and **5H$_2$**) were close to 2 mg/L. Compound **5H$_1$** showed the highest inhibitory activity, with an EC_{50} value of 1.91 mg/L, which is equal to the control drazoxolon. Compounds **5F$_1$** and **5H$_1$** exhibited EC_{50} values under 2 mg/L against *B. cinerea*. All compounds presented higher EC_{50} values than that of drazoxolon. Compounds **5B$_1$**, **5C$_1$**, **5F$_1$**, and **5H$_1$** showed EC_{50} values under 5 mg/L against *C. capsici*; all tested compounds presented lower EC_{50} values than that of drazoxolon.

The structure–activity relationships (SARs) against *R. solani* formed three general rules. First, small carbonate groups improve the antifungal activity of a title compound; when the compounds possessed the same substituent at the phenylhydrazone phenyl ring, the antifungal activity decreased as the carbonate group volume increased. Taking 4-bromine substituents (**5H$_1$**−**5H$_3$**) into account, the compounds fell into order by activity as **5H$_1$**(1.91)>**5H$_2$**(2.22)>**5H$_3$**(5.65). This rule was also observed in **5A$_1$**−**5A$_3$**, **5B$_1$**−**5B$_3$**, **5C$_1$**−**5C$_3$**, **5D$_1$**−**5D$_3$**, and **5E$_1$**−**5E$_3$**. Second, electron-withdrawing groups at the phenyl ring are preferable to their non-substituted counterparts; all mono-substituted halogen atoms were more potent than their non-substituted counterparts (except **5D$_3$**), although the 2,4-dichloro substituent (**5G**) was able to weaken their activity. Third, halogen at the *para* position was more beneficial than at the *ortho* or *meta* position. By taking the chlorine substituent (**5D$_1$**−**5D$_3$**, **5E$_1$**−**5E$_3$**, and **5F$_1$**−**5F$_3$**) into account, the compounds fall into order as **5F$_1$**(*p*-Cl, 2.69)>**5E$_1$**(*m*-Cl, 4.52)>**5D$_1$**(*o*-Cl, 5.58). This rule was also observed in **5F$_2$**>**5D$_2$** and **5E$_2$**, **5F$_3$**>**5E$_3$** and **5D$_3$**.

Conclusion

Forty-eight novel phenylhydrazone derivatives containing carbonic acid ester groups (**5A$_1$**−**5H$_6$**) were successfully synthesized in this study. The structures of these compounds were well supported by spectroscopic data, elemental analysis, and single-crystal XRD analysis. Antifungal evaluations indicated that some of the compounds were highly active against phytopathogenic fungi and, thus, have potential value as broad-spectrum fungicide components. The structure–activity relationships were found to conform to three main rules. Further assessment of the biological efficacy, crop safety, and toxicity of these compounds is underway.

Acknowledgements

This work was supported by the Fund for Independent Innovation of Agricultural Sciences in Jiangsu Province of China (No. CX(15)1001), and the Fundamental Research Funds for the Central Universities of China (No. KYTZ201604).

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