Med Chem Res (2013) 22:3621–3628
DOI 10.1007/s00044-012-0380-8

MEDICINAL CHEMISTRY RESEARCH

ORIGINAL RESEARCH

Novel salicylamide derivatives incorporating neonicotinoid pharmacophore: design, synthesis, characterization, and biological evaluation

Shaoyong Ke · Zhigang Zhang · Tong Long · Ying Liang · Ziwen Yang

Received: 19 September 2012 / Accepted: 16 November 2012 / Published online: 28 November 2012

Abstract A series of novel salicylamide derivatives containing neonicotinoid pharmacophore were designed and synthesized via multi-step reactions. These compounds were characterized by satisfied spectrum analyses mainly including ^{1}H NMR and ESI-MS. The preliminary bioassays indicated that some of target compounds exhibited excellent insecticidal activities against *Heliothis armigera* and *Plutella xylostella* at the dosage of 31.25 μg/mL.

Keywords Salicylamide derivatives · Neonicotinoid pharmacophore · Synthesis · Biological activity

Introduction

The application of agrochemicals to protect crops and vegetables is still an important part of current integrated pest management (IPM) (Qian *et al.*, 2010). However, a search for ecofriendly safer alternatives for pest control is urgently needed with the increase of worldwide emergence of drug-resistant.

Salicylic acid (SA) is a well-known natural phenolic compound that distributes in many plants and is now considered as a hormone-like substance, which plays an important role in the regulation of plant growth and development (Klessig and Malamy, 1994; Tuna *et al.*, 2007). During the last 20 years, this compound has drawn the attention of researchers because of its ability to induce systemic acquired resistance (SAR) in plants (Humphreys and Chapple, 2002; Raskin, 1992; Vlot *et al.*, 2009). Recently, more and more compounds (Fig. 1) derived from SA present extensive bio-activities including antibacterial, antifungal, herbicidal, antimycobacterial, and anti-inflammatory, among others (Férriz *et al.*, 2010; Brown *et al.*, 2008; Parmar *et al.*, 2010; Tang *et al.*, 2010; Guo *et al.*, 2007; Huang *et al.*, 2007; Zuhair *et al.*, 2009; Cheng *et al.*, 2009; Zhang *et al.*, 2006).

Meanwhile, neonicotinoids insecticides, a new generation of synthetic insecticides, have attracted considerable attention for decades (Jeschke and Nauen, 2008; Nauen and Denholm, 2005; Matsuda *et al.*, 2001). The special chloropyridine and chlorothiazole heterocycles in these compounds have been demonstrated to be as key pharmacophores. Very recently, many examples (Wang *et al.*, 2004; Dai *et al.*, 2008; Shang *et al.*, 2010) have been reported to confirm that the introduction of these pharmacophores can result in high activity and broader activity spectra. On the other hand, the extensive bio-activities of carboxamides scaffold have been known for a long time (Gucma and Gołębiewski, 2010; Ohno *et al.*, 2010; Ohno *et al.*, 2004; Shiga *et al.*, 2003), and many commercial agrochemicals (such as Flonicamid, Penthiopyrad, Tolfenpyrad, Tiadinil, and Mandipropamid) contain this unit, and so which have played significantly important role in agrochemical industry.

Thus, based on the aforementioned results, we hypothesized that masking the phenolic hydroxyl in SA by neonicotinoid pharmacophore may protect the molecule against extensive first-pass metabolism, broaden its activity profile and improve its physico-chemical and pharmacokinetic properties. As part of our agrochemistry program aimed at the search for novel natural product-oriented

Shaoyong Ke and Zhigang Zhang contributed equally to this study.

S. Ke (✉) · Z. Zhang · T. Long · Y. Liang · Z. Yang
National Biopesticide Engineering Research Center, Hubei Academy of Agricultural Sciences, Wuhan 430064, People's Republic of China
e-mail: keshaoyong@163.com

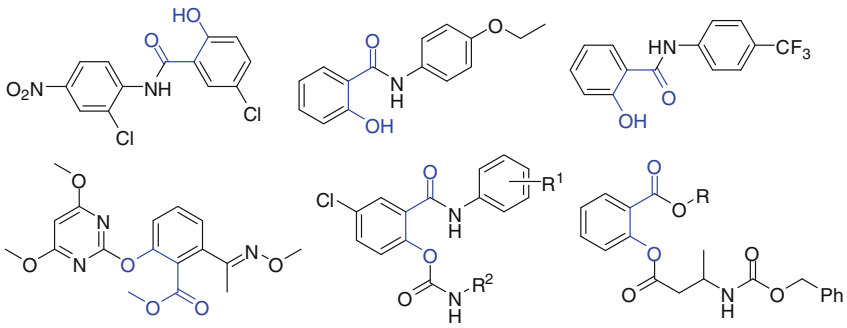

Fig. 1 Representative examples of bioactive compounds derived from SA

bioactive molecules, we wish to describe herein the molecule design, convenient synthesis, and bio-evaluation of novel series of salicylamide derivatives containing neonicotinoid pharmacophore (Fig. 2) as potential plant protective agents.

Materials and methods

Instrumentation and chemicals

All chemicals or reagents used for synthesis were commercially available and were of AR grade. Anhydrous solvents were dried according to standard methods (Armarego and Chai, 2003) before used. Melting points (m.p.) were determined with a digital model X-5 apparatus and are uncorrected. ^{1}H NMR spectra were recorded on a Brucker spectrometer at 600 MHz with $CDCl_3$ as the solvent and TMS as the internal standard. Chemical shifts are reported in δ (parts per million) values, and coupling constants ^nJ are reported in Hertz. Mass spectra were performed on a MicroMass Quattro *micro*^{TM} API instrument. All reactions were detected by thin-layer chromatography (TLC) on precoated plates, and the spots were visualized with ultraviolet light.

General synthetic procedure for intermediates **3** and **4**

The key intermediates methyl 2-((6-chloropyridin-3-yl) methoxy)benzoate **3** and 2-((6-chloropyridin-3-yl)methoxy) benzoic acid **4** was routinely prepared according to document method (Li *et al.*, 2012). The compound **3** was obtained as colorless crystal, yield 92 %, m.p. 70–73 °C, ESI-MS: 278.6 ($C_{14}H_{13}ClNO_3^+$, $[M+H]^+$). The compound **4** was obtained as a white powder, yield 91 %, m.p. 150–151 °C, ESI-MS: 264.5 ($C_{13}H_{11}ClNO_3^+$, $[M+H]^+$).

General synthetic procedure for 2-((6-chloropyridin-3-yl) methoxy)benzoyl chloride **5**

2-((6-Chloropyridin-3-yl)methoxy)benzoic acid **4** (50 mmol), 10 mL of toluene and thionyl chloride (15 mL) were placed in a dried round-bottomed flask containing a magnetic stirrer bar and stirred at about 60 °C for 2 h. Then the superfluous thionyl chloride was removed by distillation in *vacuo* at room temperature, and the residue was dissolved in dry CH_2Cl_2 and the solvent removed as before; this procedure was repeated twice to give 2-((6-chloropyridin-3-yl) methoxy)benzoyl chloride **5**, which was used for the next reaction without further purification.

General synthetic procedure for the target compounds **6a–s**

The typical process of synthesis of novel salicylamide derivatives containing 2-chloro-5-pyridyl moiety **6a–s** is shown as following: the freshly formed acylchloride **5** (2.2 mmol) dissolved in dry dichloromethane was added dropwise to a solution of the substituted aniline (2 mmol), Et_3N (2.5 mmol), and catalytic amount of DMAP in dry dichloromethane under ice-bath. The resultant solution was stirred at room temperature for 2–5 h, which was detected by TLC. Then the mixture was washed to neutral with water and dried via anhydrous Na_2SO_4. After filtered and concentrated, the organic residue is purified by silica gel

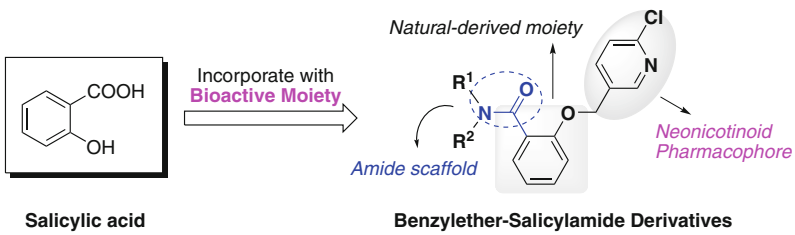

Fig. 2 Design strategy of salicylamide derivatives based on pharmacophore hybrid

column chromatography (ethyl acetate/petroleum ether) or recrystallization to give solid or crystal. Their physicochemical properties and the spectra data are as follows:

2-((6-Chloropyridin-3-yl)methoxy)-N-(4-methoxyphenyl)benzamide ***6a***

This compound was obtained as grayest solid following the above method, yield 91 %, m.p. 135.6–137.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.41 (s, 1H, NH), 8.57 (s, 1H, Py–H), 8.29 (d, $J = 7.8$ Hz, 1H, Py–H), 7.82 (d, $J = 7.8$ Hz, 1H, Py–H), 7.52–7.19 (m, 6H, Ph–H), 7.09 (d, $J = 8.4$ Hz, 1H, Ph–H), 6.83 (d, $J = 9$ Hz, 1H, Ph–H), 5.25 (s, 2H, OCH_2), 3.79 (s, 2H, OCH_3); ESI-MS: calcd for $C_{20}H_{17}ClN_2O_3$ ($[M]^+$), 369.1; found 369.7.

2-((6-Chloropyridin-3-yl)methoxy)-N-phenylbenzamide ***6b***

This compound was obtained as yellowish solid following the above method, yield 86 %, m.p. 162.3–163.8 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H, NH), 8.57 (s, 1H, Py–H), 8.30 (d, $J = 7.8$ Hz, 1H, Py–H), 7.83 (d, $J = 7.8$ Hz, 1H, Py–H), 7.53–7.08 (m, 9H, Ph–H), 5.26 (s, 2H, OCH_2); ESI-MS: calcd for $C_{19}H_{15}ClN_2O_2$ ($[M]^+$), 339.1; found 339.6.

2-((6-Chloropyridin-3-yl)methoxy)-N-cyclohexylbenzamide ***6c***

This compound was obtained as white powder following the above method, yield 88 %, m.p. 133.8–136.2 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H, NH), 8.19 (q, $J = 7.8$ Hz, 1H, Py–H), 7.79 (q, $J = 7.8$ Hz, 1H, Py–H), 7.46–7.42 (m, 3H, Ph–H and Py–H), 7.14 (t, $J = 7.8$ Hz, 1H, Ph–H), 7.03 (d, $J = 8.4$ Hz, 1H, Ph–H), 5.16 (s, 2H, OCH_2), 3.96 (t, $J = 3.9$ Hz, 1H, N–CH), 1.83 (d, $J = 9$ Hz, 2H, Cy–H), 1.51–1.32 (m, 5H, Cy–H), 1.13–1.00 (m, 3H, Cy–H); ESI-MS: calcd for $C_{19}H_{21}ClN_2O_2$ ($[M]^+$), 345.1; found 345.7.

N-(4-Bromophenyl)-2-((6-chloropyridin-3-yl)methoxy)benzamide ***6d***

This compound was obtained as light yellow solid following the above method, yield 82 %, m.p. 114.7–116.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.56 (s, 1H, NH), 8.58 (s, 1H, Py–H), 8.28 (d, $J = 7.2$ Hz, 1H, Py–H), 7.81 (q, $J = 7.2$ Hz, 1H, Py–H), 7.53 (t, $J = 7.8$ Hz, 1H, Ph–H), 7.44 (d, $J = 8.4$ Hz, 1H, Ph–H), 7.39 (d, $J = 9$ Hz, 2H, Ph–H), 7.23–7.20 (m, 3H, Ph–H), 7.10 (d, $J = 8.4$ Hz, 1H, Ph–H), 5.26 (s, 2H, OCH_2); ESI-MS: calcd for $C_{19}H_{14}BrClN_2O_2$ ($[M]^+$), 417.0; found 417.6.

2-((6-Chloropyridin-3-yl)methoxy)-N-(4-isopropylphenyl)benzamide ***6e***

This compound was obtained as brown solid following the above method, yield 74 %, m.p. 124.5–126.7 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.47 (s, 1H, NH), 8.57 (s, 1H, Py–H), 8.30 (d, $J = 7.8$ Hz, 1H, Py–H), 7.83 (d, $J = 8.4$ Hz, 1H, Py–H), 7.52–7.09 (m, 8H, Ph–H), 5.25 (s, 2H, OCH_2), 2.87 (t, $J = 6.6$ Hz, 1H, CH), 1.23 (q, $J = 6.2$ Hz, 6H, CH_3); ESI-MS: calcd for $C_{22}H_{21}ClN_2O_2$ ($[M]^+$), 381.0; found 381.8.

2-((6-Chloropyridin-3-yl)methoxy)-N-(4-(trifluoromethyl)phenyl)benzamide ***6f***

This compound was obtained as yellowish solid following the above method, yield 85 %, m.p. 108.6–111.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.72 (s, 1H, NH), 8.60 (d, $^4J = 1.8$ Hz, 1H, Py–H), 8.30 (d, $J = 6.6$ Hz, 1H, Py–H), 7.83 (q, $J = 8.4$ Hz, 1H, Py–H), 7.57–7.42 (m, 6H, Ph–H), 7.23 (t, $J = 7.2$ Hz, 1H, Ph–H), 7.12 (d, $J = 7.8$ Hz, 1H, Ph–H), 5.28 (s, 2H, OCH_2); ESI-MS: calcd for $C_{20}H_{14}ClF_3N_2O_2$ ($[M]^+$), 407.1; found 407.8.

N-(3,5-Bis(trifluoromethyl)phenyl)-2-((6-chloropyridin-3-yl)methoxy)benzamide ***6g***

This compound was obtained as light yellow crystal following the above method, yield 90 %, m.p. 169.1–170.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.98 (s, 1H, NH), 8.60 (d, $^4J = 1.8$ Hz, 1H, Py–H), 8.31 (d, $J = 7.8$ Hz, 1H, Py–H), 7.88 (q, $J = 7.8$ Hz, 1H, Py–H), 7.78 (s, 2H, Ph–H), 7.60–7.48 (m, 3H, Ph–H), 7.25–7.14 (m, 2H, Ph–H), 5.28 (s, 2H, OCH_2); ESI-MS: calcd for $C_{21}H_{13}ClF_6N_2O_2$ ($[M]^+$), 475.1; found 475.9.

2-((6-Chloropyridin-3-yl)methoxy)-N-(pyridin-2-yl)benzamide ***6h***

This compound was obtained as light-brown solid following the above method, yield 76 %, m.p. 153.2–154.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.51 (s, 1H, NH), 8.36 (s, 1H, Py–H), 7.93 (d, $J = 7.2$ Hz, 1H, Py–H), 7.79 (d, $J = 8.4$ Hz, 1H, Py–H), 7.59–7.57 (m, 2H, Py–H), 7.18–7.01 (m, 6H, Ph–H and Py–H), 5.08 (s, 2H, OCH_2); ESI-MS: calcd for $C_{18}H_{14}ClN_3O_2$ ($[M]^+$), 340.1; found 339.7.

2-((6-Chloropyridin-3-yl)methoxy)-N-o-tolylbenzamide ***6i***

This compound was obtained as yellow crystal following the above method, yield 85 %, m.p. 152.6–153.8 °C; ^{1}H

NMR (600 MHz, $CDCl_3$) δ 9.26 (s, 1H, NH), 8.52 (s, 1H, Py–H), 8.33 (d, $J = 7.8$ Hz, 1H, Py–H), 8.11 (d, $J = 7.8$ Hz, 1H, Py–H), 7.76 (q, $J = 8.4$ Hz, 1H, Ph–H), 7.50 (t, $J = 7.2$ Hz, 1H, Ph–H), 7.38 (d, $J = 8.4$ Hz, 1H, Ph–H), 7.25–7.04 (m, 5H, Ph–H), 5.30 (s, 2H, OCH_2), 1.92 (s, 3H, CH_3); ESI-MS: calcd for $C_{20}H_{17}ClN_2O_2$ ($[M]^+$), 353.1; found 353.7.

N-(4-Chloro-2-methylphenyl)-2-((6-chloropyridin-3-yl) methoxy)benzamide ***6j***

This compound was obtained as white solid following the above method, yield 92 %, m.p. 106.8–109.4 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.26 (s, 1H, NH), 8.52 (s, 1H, Py–H), 8.32 (d, $J = 7.2$ Hz, 1H, Py–H), 8.09 (d, $J = 8.4$ Hz, 1H, Py–H), 7.75 (d, $J = 7.8$ Hz, 1H, Ph–H), 7.52 (t, $J = 7.2$ Hz, 1H, Ph–H), 7.39 (d, $J = 8.4$ Hz, 1H, Ph–H), 7.22–7.02 (m, 4H, Ph–H), 5.29 (s, 2H, OCH_2), 1.85 (s, 3H, CH_3); ESI-MS: calcd for $C_{20}H_{16}Cl_2N_2O_2$ ($[M]^+$), 387.1; found 387.4.

2-((6-Chloropyridin-3-yl)methoxy)-N-(4-fluorophenyl)benzamide ***6k***

This compound was obtained as white solid following the above method, yield 82 %, m.p. 140.3–143.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.52 (s, 1H, NH), 8.58 (d, $^4J = 1.8$ Hz, 1H, Py–H), 8.29 (q, $^4J = 1.2$ Hz, $J = 6.6$ Hz, 1H, Py–H), 7.82 (q, $^4J = 2.1$ Hz, $J = 6.0$ Hz, 1H, Py–H), 7.54–7.29 (m, 4H, Ph–H), 7.20 (t, $J = 7.8$ Hz, 1H, Ph–H), 7.10 (d, $J = 8.4$ Hz, 1H, Ph–H), 6.98 (t, $J = 8.4$ Hz, 2H, Ph–H), 5.26 (s, 2H, OCH_2); ESI-MS: calcd for $C_{19}H_{14}ClFN_2O_2$ ($[M]^+$), 357.1; found 357.4.

2-((6-Chloropyridin-3-yl)methoxy)-N-f(4-iodophenyl)benzamide ***6l***

This compound was obtained as colorless crystal following the above method, yield 78 %, m.p. 146.5–148.3 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.56 (s, 1H, NH), 8.58 (d, $^4J = 2.4$ Hz, 1H, Py–H), 8.28 (d, $J = 7.8$ Hz, 1H, Py–H), 7.82 (d, $J = 6.0$ Hz, 1H, Py–H), 7.58–7.53 (m, 3H, Ph–H), 7.44 (d, $J = 8.4$ Hz, 1H, Ph–H), 7.21 (t, $J = 7.5$ Hz, 1H, Ph–H), 7.11 (d, $J = 8.4$ Hz, 3H, Ph–H), 5.26 (s, 2H, OCH_2); ESI-MS: calcd for $C_{19}H_{14}ClIN_2O_2$ ($[M]^+$), 465.0; found 465.4.

2-((6-Chloropyridin-3-yl)methoxy)-N-(3,5-dichloro-4-(1,1,2,2-tetrafluoroethoxy)phenyl)benzamide ***6m***

This compound was obtained as white powder following the above method, yield 76 %, m.p. 183.5–185.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 9.75 (s, 1H, NH), 8.61 (s, 1H, Py–H), 8.27 (d, $J = 7.2$ Hz, 1H, Py–H), 7.87 (d, $J = 7.8$ Hz, 1H, Py–H), 7.58–7.51 (m, 2H, Ph–H), 7.31 (s, 2H, Ph–H), 7.22 (t, $J = 7.2$ Hz, 1H, Ph–H), 7.12 (d, $J = 8.4$ Hz, 1H, Ph–H), 6.04 (t, $J = 52.50$ Hz, 1H, CHF_2), 5.26 (s, 2H, OCH_2); ESI-MS: calcd for $C_{21}H_{13}Cl_3F_4N_2O_3$ ($[M\text{-}OCF_2CHF_2]^+$), 405.0; found 405.4.

2-((6-Chloropyridin-3-yl)methoxy)-N-isopropylbenzamide ***6n***

This compound was obtained as white powder following the above method, yield 83 %, m.p. 93.5–95.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.53 (s, 1H, NH), 8.19 (q, $^4J = 1.8$ Hz, $J = 7.6$ Hz, 1H, Py–H), 7.79 (q, $^4J = 2.4$ Hz, $J = 8.4$ Hz, 1H, Py–H), 7.47–7.40 (m, 3H, Ph–H and Py–H), 7.14 (t, $J = 7.8$ Hz, 1H, Ph–H), 7.03 (d, $J = 8.4$ Hz, 1H, Ph–H), 5.17 (s, 2H, OCH_2), 4.21 (q, $J = 6.6$ Hz, 1H, N–CH), 1.07 (d, $J = 6.6$ Hz, 6H, $CH(CH_3)_2$); ESI-MS: calcd for $C_{16}H_{17}ClN_2O_2$ ($[M]^+$), 305.1; found 305.4.

2-((6-Chloropyridin-3-yl)methoxy)-N,N-diisopropylbenzamide ***6o***

This compound was obtained as white powder following the above method, yield 86 %, m.p. 138.0–139.5 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.43 (s, 1H, Py–H), 7.81 (d, $J = 7.8$ Hz, 1H, Py–H), 7.35–7.30 (m, 2H, Py–H and Ph–H), 7.19 (d, $J = 7.2$ Hz, 1H, Ph–H), 7.03 (t, $J = 7.2$ Hz, 1H, Ph–H), 6.95 (d, $J = 8.4$ Hz, 1H, Ph–H), 5.08 (s, 2H, OCH_2), 3.69 (q, $J = 7.2$ Hz, 1H, N–CH), 3.46 (q, $J = 7.2$ Hz, 1H, N–CH), 1.55 (d, $J = 6.6$ Hz, 3H, CH_3), 1.48 (d, $J = 6.0$ Hz, 3H, CH_3), 1.03 (q, $J = 7.2$ Hz, 6H, $CH(CH_3)_2$); ESI-MS: calcd for $C_{19}H_{23}ClN_2O_2$ ($[M]^+$), 347.1; found 347.5.

2-((6-Chloropyridin-3-yl)methoxy)-N,N-diethylbenzamide ***6p***

This compound was obtained as white solid following the above method, yield 80 %, m.p. 100.5–101.0 °C; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.42 (d, $^4J = 1.8$ Hz, 1H, Py–H), 7.76 (q, $^4J = 1.8$ Hz, $J = 7.0$ Hz, 1H, Py–H), 7.35–7.24 (m, 3H, Py–H and Ph–H), 7.05 (t, $J = 7.2$ Hz, 1H, Ph–H), 6.96 (d, $J = 7.8$ Hz, 1H, Ph–H), 5.09 (s, 2H, OCH_2), 3.74 (bs, 1H, N–CH_2), 3.35 (bs, 1H, N–CH_2), 3.16–3.10 (m, 2H, CH_2), 1.18 (t, $J = 7.2$ Hz, 3H, CH_3), 1.01 (t, $J = 7.2$ Hz, 3H, CH_3); ESI-MS: calcd for $C_{17}H_{19}ClN_2O_2$ ($[M]^+$), 319.1; found 319.4.

2-((6-Chloropyridin-3-yl)methoxy)-N-(cyanomethyl)-N-phenylbenzamide ***6q***

This compound was obtained as white solid following the above method, yield 73 %, m.p. 134–136 °C; 1H NMR

(600 MHz, $CDCl_3$) δ 8.35 (s, 1H, Py–H), 7.80 (d, $J = 8.4$ Hz, 1H, Py–H), 7.41 (d, $J = 7.8$ Hz, 1H, Py–H), 7.25–6.90 (m, 8H, Ph–H), 6.70 (d, $J = 7.8$ Hz, 1H, Ph–H), 4.92 (s, 2H, OCH_2), 4.74 (s, 2H, CNCH2); ESI-MS: calcd for $C_{21}H_{16}ClN_3O_2$ ($[M]^+$), 378.1; found 378.5.

(2-((6-Chloropyridin-3-yl)methoxy)phenyl)(piperidin-1-yl) methanone ***6r***

This compound was obtained as colorless crystal following the above method, yield 83 %, m.p. 116.8–118.2 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H, Py–H), 7.76 (q, $^4J = 1.8$ Hz, $J = 7.4$ Hz, 1H, Py–H), 7.39–7.25 (m, 3H, Ph–H and Py–H), 7.05 (t, $J = 7.6$ Hz, 1H, Ph–H), 6.94 (d, $J = 8.4$ Hz, 1H, Ph–H), 5.12 (s, 2H, OCH_2), 3.76–3.08 (m, 4H, CH_2), 1.61–1.39 (m, 6H, CH_2); ESI-MS: calcd for $C_{18}H_{19}ClN_2O_2$ ($[M]^+$), 331.1; found 331.5.

(2-((6-Chloropyridin-3-yl)methoxy)phenyl)(morpholino)methanone ***6s***

This compound was obtained as yellowish crystal following the above method, yield 80 %, m.p. 124.3–125.6 °C; ^1H NMR (600 MHz, $CDCl_3$) δ 8.42 (s, 1H, Py–H), 7.74 (q, $^4J = 1.8$ Hz, $J = 8.2$ Hz, 1H, Py–H), 7.38–7.28 (m, 3H, Ph–H and Py–H), 7.07 (t, $J = 7.2$ Hz, 1H, Ph–H), 6.96 (d, $J = 7.8$ Hz, 1H, Ph–H), 5.12 (s, 2H, OCH_2), 3.81–3.67 (m, 4H, CH_2), 3.52 (s, 2H, CH_2), 3.26 (s, 2H, CH_2); ESI-MS: calcd for $C_{17}H_{17}ClN_2O_3$ ($[M]^+$), 333.1; found 333.4.

Biological assay

Heliothis armigera and *Plutella xylostella* from our laboratory cultivate were used as general tested species. The standard assay (Xu *et al.*, 2003; Huang *et al.*, 2010) was performed by placing artificial diets (300 μL) in a 24-well or 96-well microtiter plates, which were covered with the solution of different tested concentration compounds in ethanol (20 μL). Ethanol alone was used as a control. When the ethanol was completely evaporated leaving the effective compounds as a coat on the surface of the artificial diets, the tested species were introduced and the culture plates was closed with a plastic cover. Mortality in these assays was recorded at 96 h, and each treatment was replicated three times.

Results and discussion

Synthesis of salicylamide derivatives

In this study, a series of novel salicylamide derivatives were constructed by reacting functionalized SA with various amines or its derivatives. The general method for the preparation of salicylamide derivatives containing chloropyridine moiety **6a–s** are outlined in Scheme 1.

The key intermediate 2-((6-chloropyridin-3-yl)methoxy) benzoic acid **4** was routinely prepared from SA via three steps including esterification, alkylation, and hydrolysis reactions. Then the compound **4** was treated with thionyl chloride to provide the corresponding acid chloride **5**, which is further used to couple with various aromatic or heteroaromatic amines typically in the presence of triethylamine to give salicylamide derivatives **6a–s**. Yields were usually good except in cases of weakly nucleophilic aromatic amines with electron-withdrawing group, and some side reactions took place because of degradation of acid chlorides. All the target salicylamide derivatives **6a–s** gave satisfactory chemical analyses, and the chemical structures of the synthesized compounds were summarized in Table 1.

Spectroscopy

Structures of target compounds **6a–s** were confirmed by their ^1H NMR and ESI-MS spectra, and the ^1H NMR and ESI-MS spectra analyses were consistent with the assigned structures. Their ^1H NMR spectra showed distinctive signals of methylene between oxygen and chloropyridine ring, which presented a singlet at about 4.92–5.29 ppm. The signals at 6.04–8.61 ppm in the ^1H NMR spectra of compounds **6a–s** were assigned to the aromatic proton in aryl(het)-cycles moieties. For some compounds, the signals that appeared in their ^1H NMR spectra in the range

Scheme 1 General synthetic route for novel salicylamide derivatives **6a–s**

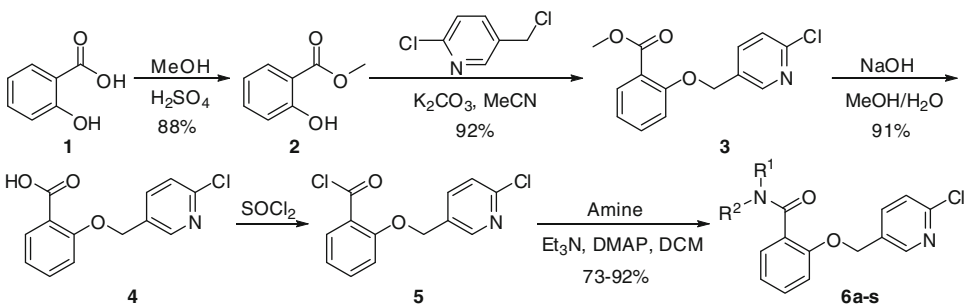

Table 1 The chemical structure of salicylamide derivatives **6a–s**

Entry	Compounds	Substituents		Appearance	Mp (°C)	Yield (%)[a]
		R^1	R^2			
1	**6a**	4-MeO-Ph	H	Grayst solid	135.6–137.2	91
2	**6b**	Ph	H	Yellowish solid	162.3–163.8	86
3	**6c**	Cy	H	White powder	133.8–136.2	88
4	**6d**	4-Br-Ph	H	Yellow solid	114.7–116.4	82
5	**6e**	4-^{i}Pr-Ph	H	Brown solid	124.5–126.7	74
6	**6f**	4-CF_3-Ph	H	Yellowish solid	108.6–111.3	85
7	**6g**	3,5-$(CF_3)_2$-Ph	H	Yellow crystal	169.1–170.3	90
8	**6h**	2-Py	H	Light-brown solid	153.2–154.5	76
9	**6i**	2-Me-Ph	H	Yellow crystal	152.6–153.8	85
10	**6j**	2-Me-4-Cl-Ph	H	White solid	106.8–108.4	92
11	**6k**	4-F-Ph	H	White solid	140.3–143.5	82
12	**6l**	4-I-Ph	H	Colorless crystal	146.5–148.3	78
13	**6m**	3,5-Cl_2-4-CHF_2CF_2O-Ph	H	White powder	183.5–185.0	76
14	**6n**	^{i}Pr	H	White powder	93.5–95.0	83
15	**6o**	^{i}Pr	^{i}Pr	White powder	138.0–139.5	86
16	**6p**	Et	Et	White solid	100.5–101.0	80
17	**6q**	Ph	$CNCH_2$	White solid	134.0–136.0	73
18	**6r**	$-(CH_2)_5-$		Colorless crystal	116.8–118.2	83
19	**6s**	$-(CH_2)_2O(CH_2)_2-$		Yellowish crystal	124.3–125.6	80

[a] Isolated yields

8.51–9.98 ppm were attributed to the N–H protons of the amide.

Structure–activity relationship

The bioactivity of synthesized salicylamide derivatives **6a–s** against selective agricultural pests mainly including *H. armigera* and *P. xylostella* were evaluated according to the standard method (Xu *et al.*, 2003; Huang *et al.*, 2010), and the bioassay results are listed in Table 2.

As we can see from Table 2, the preliminary assay showed that most of target molecules (such as compounds **6a**, **6b**, **6e**, **6k**, **6l**, **6m**, and **6n**) displayed obviously good and selective insecticidal activity against *P. xylostella*, but presented low activities against *H. armigera*. For *H. armigera*, compounds **6d**, **6e**, and **6f** exhibited good insecticidal activities, and up to the seventh, fifth, and seventh levels at the concentration of 31.25 μg/mL, respectively. For *P. xylostella*, compounds **6a**, **6d**, and **6f** presented better activities at the same level of concentrations, especially compound **6f** is still has good insecticidal activity (ninth level) at lower concentration. On the other hand, compounds **6l**, **6m**, **6n**, and **6o** have better activities against *P. xylostella* than that of *H. armigera*. By comprehensive consideration all activities against *P. xylostella* and *H. armigera*, compounds **6d**, **6e**, and **6f** showed better activities, which are worth to further research on systemic assay for development novel pests control agents.

In addition, from the structural profiles, some electron-withdrawing groups and electron-donating substituents were introduced into the molecules for exploring the influence of structural changes on activities. As the results described in Table 1, the different substituent at the periphery of the molecules **6a–s** can lead to the obviously different insecticidal activities. Generally, the amines with lager substituents at the contraposition of phenyl ring showed comparatively good insecticidal activities, which can be further demonstrated from the activities of compounds **6d**, **6e**, and **6f**. However, compound **6a** bearing a 4-methoxyphenyl groups also presented good activity against *P. xylostella*. The highest activity was found for compounds with electron-withdrawing groups, and was particularly outstanding in case of *p*-CF_3 substituted amine **6f**. On the other hand, the substitution pattern was also crucial. Most of amines with a group at position 4 were active, whereas 2-substituted products (**6h** and **6i**) were devoid of activity. Especially, the compound containing two CF_3 groups on the phenyl ring **6g** (Entry 7), which exhibited diametrically opposite results on the best one **6f** (Entry 6).

All the structure evolution here was to replace the substituents on amines (Fig. 3). According to the results

Table 2 Insecticidal activities of target compounds **6a–s** against agricultural pests

Entry	Compounds	Insecticidal activity[a] (μg/mL)											
		Heliothis armigera						*Plutella xylostella*					
		1,000	500	250	125	62.5	31.25	1,000	500	250	125	62.5	31.25
1	**6a**	0	0	0	0	0	0	10	10	10	10	9	5
2	**6b**	0	0	0	0	0	0	9	9	5	5	0	0
3	**6c**	0	0	0	0	0	0	5	0	0	0	0	0
4	**6d**	10	10	9	9	7	7	10	10	10	10	10	5
5	**6e**	10	9	7	7	5	5	10	10	10	5	5	0
6	**6f**	10	10	10	10	10	7	10	10	10	10	10	9
7	**6g**	0	0	0	0	0	0	0	0	0	0	0	0
8	**6h**	0	0	0	0	0	0	10	5	5	0	0	0
9	**6i**	0	0	0	0	0	0	0	0	0	0	0	0
10	**6j**	10	5	5	0	0	0	10	5	5	5	0	0
11	**6k**	5	5	5	5	0	0	10	9	5	5	0	0
12	**6l**	0	0	0	0	0	0	10	10	10	5	0	0
13	**6m**	10	5	5	0	0	0	10	10	10	10	5	5
14	**6n**	5	5	0	0	0	0	10	10	10	5	0	0
15	**6o**	10	10	5	5	0	0	10	10	10	5	0	0
16	**6p**	5	0	0	0	0	0	5	0	0	0	0	0
17	**6q**	10	9	5	5	0	0	0	0	0	0	0	0
18	**6r**	5	0	0	0	0	0	5	5	0	0	0	0
19	**6s**	10	5	0	0	0	0	5	0	0	0	0	0

[a] Scale: 0 (0–10 % mortality); 1 (11–20 % mortality); 3 (21–40 % mortality); 5 (41–60 % mortality); 7 (61–80 % mortality); 9 (81–99 % mortality); 10 (100 % mortality)

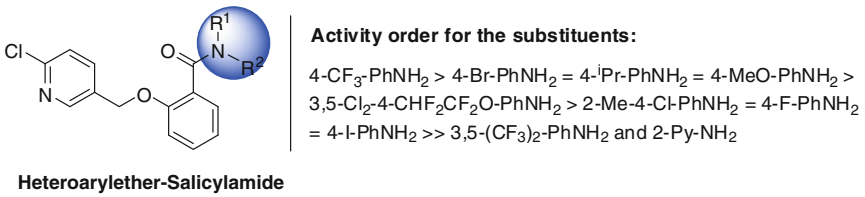

Fig. 3 General structure–activity profile for the salicylamide derivatives

presented in Table 2, we can obtain the preliminary structure–activity profile for these salicylamide derivatives.

Conclusion

In summary, we have described the molecular design, synthesis, and biological evaluation of a series of novel salicylamide derivatives containing neonicotinoid pharmacophore. Nineteen novel salicylamide derivatives have been conveniently synthesized, and characterized by ^{1}H NMR, ESI-MS spectra analyses. The preliminary bioassay indicated that some of target compounds exhibited obvious insecticidal activity. To our best knowledge, this is the first report on the syntheses and insecticidal activity of neonicotinoid pharmacophore-functional salicylamide derivatives, which are promising lead compounds for further developing novel agrochemicals. Further structural optimization and activity profiles about the designed novel amide derivatives are well ongoing in our laboratory.

Acknowledgments We gratefully acknowledge the support of this work by the Projects in the Youth Science Foundation of Hubei Academy of Agricultural Sciences (2011NKYJJ19) and the National Natural Science Foundation of China (31000867). The authors also gratefully acknowledge the partial support from Hubei Biopesticide Engineering Research Centre.

References

Armarego WLF, Chai CLL (2003) Purification of laboratory chemicals, 5th edn. Elsevier, Amsterdam

Brown ME, Fitzner JN, Stevens T, Chin W, Wright CD, Boyce JP (2008) Salicylanilides: selective inhibitors of interleukin-12p40

production. Bioorg Med Chem 16:8760–8764. doi:10.1016/j.bmc.2008.07.024
Cheng K, Zheng Q, Qian Y, Shi L, Zhao J, Zhu H (2009) Synthesis, antibacterial activities and molecular docking studies of peptide and Schiff bases as targeted antibiotics. Bioorg Med Chem 17:7861–7871. doi:10.1016/j.bmc.2009.10.037
Dai H, Li Y, Du D, Qin X, Zhang X, Yu H, Fang J (2008) Synthesis and biological activities of novel pyrazole oxime derivatives containing a 2-chloro-5-thiazolyl moiety. J Agric Food Chem 56:10805–10810. doi:10.1021/jf802429x
Férriz JM, Vávrová K, Kunc F, Imramovský A, Stolaříková J, Vavříková E, Vinšová J (2010) Salicylanilide carbamates: antitubercular agents active against multidrug-resistant *Mycobacterium tuberculosis* strains. Bioorg Med Chem 18:1054–1061. doi:10.1016/j.bmc.2009.12.055
Gucma M, Gołębiewski WM (2010) Synthesis and biological activity of 3-substituted isoxazolecarboxamides. Monatsh Chem 141:461–469. doi:10.1007/s00706-010-0265-9
Guo L, Wang Q, Jiang Q, Jiang Q, Jiang Y (2007) Anion-triggered substituent-dependent conformational switching of salicylanilides. New hints for understanding the inhibitory mechanism of salicylanilides. J Org Chem 72:9947–9953. doi:10.1021/jo701823d
Huang C, Hsieh Y, Huang W, Lee A (2007) Synthesis of *N*-(chlorophenyl)-2-hydroxynicotinanilides as potential anti-inflammatory agents. Taiwan Pharm J 59:39–46
Huang S, Zhang Z, Li Y, Li Y, Xu H (2010) Anti-insect activity of the methanol extracts of fern and gymnosperm. Agric Sci China 9:249–256. doi:10.1016/S1671-2927(09)60090-0
Humphreys JM, Chapple C (2002) Rewriting the lignin roadmap. Curr Opin Plant Biol 5:224–229. doi:10.1016/S1369-5266(02)00257-1
Jeschke P, Nauen R (2008) Neonicotinoids—from zero to hero in insecticide chemistry. Pest Manag Sci 64:1084–1098. doi:10.1002/ps.1631
Klessig DF, Malamy J (1994) The salicylic acid signal in plants. Plant Mol Biol 26:1439–1458. doi:10.1007/BF00016484
Li S, Cao X, Chen C, Ke S (2012) Novel salicylic acid-oriented thiourea-type receptors as colorimetric chemosensor: synthesis, characterizations and selective naked-eye recognition properties. Spectrochim Acta A 96:18–23. doi:10.1016/j.saa.2012.04.102
Matsuda K, Buckingham SD, Kleier D, Rauh JJ, Grauso M, Sattelle DB (2001) Neonicotinoids: insecticides acting on insect nicotinic acetylcholine receptors. Trends Pharm Sci 22:573–580. doi:10.1016/S0165-6147(00)01820-4
Nauen R, Denholm I (2005) Resistance of insect pests to neonicotinoid insecticides: current status and future prospects. Arch Insect Biochem Physiol 58:200–215. doi:10.1002/arch.20043
Ohno R, Watanabe A, Matsukawa T, Ueda T, Sakurai H, Hori M, Hirai K (2004) Synthesis and herbicidal activity of new pyrazole-4-carboxamide derivatives. J Pestic Sci 29:15–26
Ohno R, Nagaoka M, Hirai K, Uchida A, Kochi S, Yamada O, Tokumura J (2010) Synthesis and insecticidal activity of novel 1-alkyl-3-sulfonyloxypyrazole-4-carboxamide derivatives. J Pestic Sci 35:15–22. doi:10.1584/jpestics.G09-50
Parmar KA, Suthar BG, Parajapati S (2010) Synthesis and antibacterial evaluation of some novel 2-arylamino-4-phenyl-thiazolyl derivatives. Bull Korean Chem Soc 31:793–797. doi:10.5012/bkcs.2010.31.04.793
Qian X, Lee PW, Cao S (2010) China: forward to the green pesticides via a basic research program. J Agric Food Chem 58:2613–2623. doi:10.1021/jf904098w
Raskin I (1992) Role of salicylic acid in plants. Annu Rev Plant Physiol Plant Mol Biol 43:439–463. doi:10.1146/annurev.pp.43.060192.002255
Shang J, Sun R, Li Y, Huang R, Bi F, Wang Q (2010) Synthesis and insecticidal evaluation of *N*-*tert*-butyl-*N*′-thio[1-(6-chloro-3-pyridylmethyl)-2-nitroiminoimidazolidine]-*N*,*N*′-diacylhydrazines. J Agric Food Chem 58:1834–1837. doi:10.1021/jf903642s
Shiga Y, Okada I, Ikeda Y, Takizawa E, Fukuchi T (2003) Insecticidal activity of *N*-acyl-*N*-(4-aryloxybenzyl)pyrazole-5-carboxamides. J Pestic Sci 28:313–314
Tang W, Yu Z, Shi D (2010) Synthesis, crystal structure, and herbicidal activity of pyrimidinyl benzylamine analogues containing a phosphonyl group. Heteroatom Chem 21:148–155. doi:10.1002/hc
Tuna AL, Kaya C, Dikilitas M, Yokas İ, Burun B, Altunlu H (2007) Comparative effects of various salicylic acid derivatives on key growth parameters and some enzyme activities in salinity stressed maize (*Zea Mays* L.) plants. Pak J Bot 39:787–798
Vlot AC, Dempsey DA, Klessig DF (2009) Salicylic acid, a multifaceted hormone to combat disease. Annu Rev Phytopathol 47:177–206. doi:10.1146/annurev.phyto.050908.135202
Wang Q, Li H, Li Y, Huang R (2004) Synthesis and herbicidal activity of 2-cyano-3-(2-chlorthiazol-5-yl)methylaminoacrylates. J Agric Food Chem 52:1918–1922. doi:10.1021/jf035312a
Xu H, Zhang N, Casida JE (2003) Insectivides in Chinese medicinal plants: survey leading to Jacaranone, a neurotoxicant and glutathione-reactive quinol. J Agric Food Chem 51:2544–2547. doi:10.1021/jf021164x
Zhang H, Li Z, Ni C, Shen Z, Fan Z, Liu X (2006) Synthesis and bioactivity of salicylic acid 3-*N*′-benzyloxycarbony-β-aminobutyric ester. Chem J Chin Univ 27:468–471
Zuhair M, Sameera F, Sadik A, Muhanned S, Elham A (2009) Synthesis and anti-inflammatory activities of novel salicylic acid and diflunisal amide derivatives. Jordan J Pharm Sci 2:99–109