Available online at www.sciencedirect.com
ScienceDirect
Bioorganic & Medicinal Chemistry 14 (2006) 8666–8674
Bioorganic & Medicinal Chemistry

Insecticidal lead identification by screening benzopyrano[4,3-*c*]-pyrazol-3(2*H*)-ones library constructed from multiple-parallel synthesis under microwave irradiation

Zhong-Zheng Zhou and Guang-Fu Yang*

Key Laboratory of Pesticide and Chemical Biology, Ministry of Education, College of Chemistry, Central China Normal University, Wuhan 430079, PR China

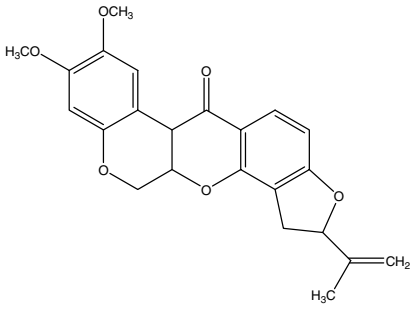
Received 15 June 2006; revised 14 August 2006; accepted 15 August 2006
Available online 1 September 2006

Abstract—A rapid library-generation via liquid-phase multiple-parallel synthesis of 2-(substituted)benzyl-1-benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones, bearing two points of diversity, under microwave irradiation was successfully performed using chromenone-3-carboxylic acids as starting materials. Compared to an identical library generated by conventional parallel synthesis, microwave-assisted parallel synthesis dramatically decreased reaction times from an average of 16 h to 13 min, and the yields of products and intermediates were improved in most cases. A bioassay indicated that the compounds of the library exhibited excellent insecticidal activity against *T. cinnabarinus* at the dosage of 250 mg L^{-1}, and some compounds still exhibited insecticidal activity when the dosage was reduced to 50 mg L^{-1}. This shows that 2-(substituted) benzyl-1-benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones might be used as lead structures for further optimization. To our knowledge, this is the first report about the application of solution-phase multiple-parallel synthesis under microwave irradiation to construct libraries of benzopyrano-[4,3-*c*]pyrazol-3(2*H*)-ones with insecticidal activity. The coupling of microwave technology with liquid-phase parallel synthesis constitutes a novel and particularly attractive avenue for the rapid generation of structurally diverse libraries for lead discovery.

1. Introduction

The demand for structurally diverse compound libraries for screening in lead discovery has driven the development of new technologies for high-throughput parallel synthesis.[1] One of those high-speed techniques is microwave-assisted organic synthesis, which has attracted a substantial amount of attention in the past few years[2] since the first reports in 1986 by Gedye and Giguere.[3] The main benefits of performing reactions under microwave irradiation conditions are the significant rate-enhancements and the higher product yields that can frequently be observed. Not surprisingly, these features have recently also attracted interest from the drug discovery and medicinal chemistry communities,[4] for which reaction speed is of great importance.

The flavonoid is an important heterocyclic scaffold in the field of medicinal and pesticidal chemistry since its derivatives are well known for their diverse biological activities.[5] Some of them have been used as antianaphylactic agents for the treatment of asthma for many years.[5a] For example, rotenone, first isolated from the Derris of tropical Asia, has widespread application as an agricultural insecticide in many countries (Scheme 1).[5b]



Scheme 1. The structure of Rotenone.

Keywords: Microwave-assisted parallel synthesis; Benzopyrano[4,3-*c*]-pyrazol-3(2*H*)-ones; Combinatorial chemistry; Insecticidal activity; Lead structure.
* Corresponding author. Tel.: +86 27 67867706; fax: +86 27 67867141; e-mail: gfyang@mail.ccnu.edu.cn

0968-0896/$ - see front matter © 2006 Elsevier Ltd. All rights reserved.
doi:10.1016/j.bmc.2006.08.020

Our interest was aroused by the fact that various flavonoids exhibited different biological activities. As a part of our research interest in the development of multifunctional libraries of flavonoids, we described herein the multistep microwave-assisted synthesis of flavonoids, 2-(substituted)benzyl-1-benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones, with the aim to evaluate their pesticidal activities. Although a benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one scaffold was first synthesized by Ghosh[6] and attracted interests from medicinal and organic chemists,[7] there are so far no reports about the microwave-assisted synthesis and pesticidal activity of this scaffold.

2. Results and discussion

The benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one scaffold can be synthesized by the direct condensation of chromenone-3-carboxylic acid with arylhydrazine[6] or prepared from intermediates of 3-(2-hydroxyphenyl)-2-pyrazolin-5-ones, which were obtained from the condensation of 4-hydroxycoumarin with arylhydrazines.[7f–1] In view of the demand of introducing various substituents into the 2-position of benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones, the key intermediate 2*H*-benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones should be synthesized at first (Scheme 2). So, we examined the reaction of chromenone-3-carboxylic acid with hydrazine hydrate and the results indicated that 2*H*-benzopyrano[4, 3-*c*]pyrazol-3(2*H*)-ones could be obtained in yields of 58–62% under conventional heating condition. Although the further alkylation of 2*H*-benzopyrano[4,3-*c*]pyrazol-3-ones with (substituted)benzyl chloride under strong basic condition can proceed smoothly with good product yields, 12 h of reaction time was still too long. Then, the microwave irradiation was applied to shorten the reaction time as well as to improve the yields.

2.1. Microwave-assisted syntheses of intermediates (2)

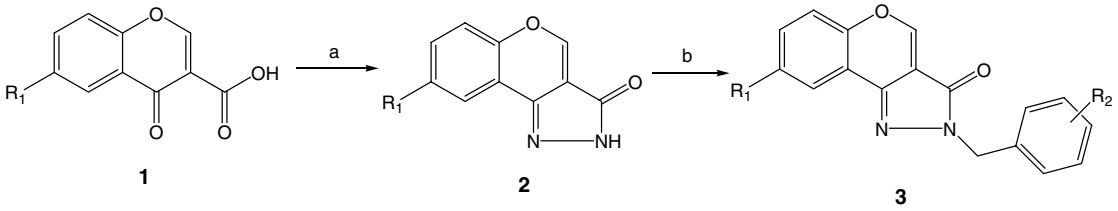
Microwave reactions were performed in sealed heavy-walled Pyrex tubes under controlled conditions in a safe and reproducible procedure. Single mode microwave irradiation was used at a fixed temperature and irradiation power during the reaction time by an automatic power control.

Optimization of the reaction conditions was carried out for the cyclocondensation of chromenone-3-carboxylic acid (**1**) with hydrazine hydrate in acetic acid. Different combinations of temperature and reaction time were studied in order to achieve the maximum chemical yield at the shortest reaction time. Thus, microwave irradia-

Table 2. Bases effect of the synthesis of compounds **3a** under microwave irradiations

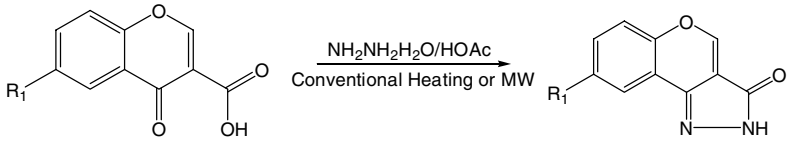
Entry	Temperature (°C)	Time (min)	Base	**2a**/base	Yield[a] (%)
1	100	10	NaOAc	1:1.5	57.2
2	100	10	$NaHCO_3$	1:1.5	61
3	100	10	Na_2CO_3	1:1.5	61
4	100	10	K_2CO_3	1:1.5	79
5	100	10	NaOH	1:1.5	73
6	100	10	KOH	1:1.5	71
7	100	10	$NaOCH_3$	1:1.5	61
8	100	10	NEt_3	1:1.5	4
9	100	10	Pyridine	1:1.5	0
10	100	10	Piperidine	1:1.5	0

[a] Determined by HPLC.



Scheme 2. Synthesis of 2-substituted benzyl-1-benzopyrano [3, 4-*c*] pyrazol-3-ones. Reagents: (a) $NH_2NH_2 \cdot H_2O$, HOAc; (b) substituted benzyl chloride, base.

Table 1. Microwave-assisted synthesis of 2*H*-benzopyrano[4,3-*c*]pyrazol-3-ones



Compound	R^1	Conventional heating		Microwave irradiation	
		Time (h)	Yield (%)[a]	t (min)	Yield[a] (%)
1a	Me	4	58	3	86
1b	Cl	4	63	3	87
1c	H	4	62	3	85

[a] Determined by HPLC.

tion of the mixture containing 6-(substituted)chromenone-3-carboxylic acid (**1**) with hydrazine hydrate at 180 °C for 3 min resulted in complete conversion of the reactants into 2*H*-benzopyrano[4,3-*c*]pyrazol-3-ones (**2**) without the formation of side products or any noticeable decomposition as shown in Table 1. From this we concluded that the yields of 2*H*-benzopyrano[4,3-*c*]pyrazol-3-ones under microwave irradiation were improved greatly compared to that under conventional heating, while the reaction time was reduced from 4 h to 3 min.

Table 3. Optimization of the reaction temperature and time under microwave irradiation

Entry	Temperature (°C)	Reaction time (min)	Yield of products[a] (%)
1	100	10	79
2	120	10	84
3	140	10	88
4	160	10	85
5	180	10	80
6	140	2	75
7	140	4	80
8	140	6	82
9	140	12	84
10	140	14	81

[a] Determined by HPLC.

2.2. Microwave-assisted synthesis of title compounds (3)

We chose the alkylation reaction of 2*H*-benzopyrano[4,3-*c*]pyrazol-3-one (**1c**) with 4-chlorobenzyl chloride as a model reaction to investigate the optimum base. The reactions were carried out at 100 °C for 10 min and the results are summarized in Table 2. Table 2 shows that K_2CO_3 gave the highest yield of product, while other inorganic bases and organic bases gave low yields or no product. Consequently, K_2CO_3 was selected as the base to further optimize the reaction time and temperature and the results are listed in Table 3.

As shown in Table 3, the yields increased as the temperature was increased from 100 to 160 °C. Temperatures above 140 °C caused a reduction in yields (Entries 4 and 5 in Table 3) and formation of side-products, presumably due to the break-up of the thiazolidinone ring

Table 4. Preparation of 2-substituted benzyl-1-benzopyrano[3, 4-*c*]pyrazol-3(2*H*)-ones

Compound	R_1	R_2	Conventional heating		Microwave irradiation	
			Time (h)	Yield[a] (%)	Time (min)	Yield[a] (%)
3a	Me	4-Cl	12	84	10	84
3b	Me	3-Cl	12	83	10	80
3c	Me	2-Cl	12	83	10	95
3d	Me	4-Me	12	88	10	85
3e	Me	3-Me	12	87	10	96
3f	Me	2-Me	12	80	10	86
3g	Me	4-F	12	81	10	89
3h	Me	3-F	12	92	10	87
3i	Me	2-F	12	81	10	93
3j	Me	4-Br	12	86	10	92
3k	Me	2-Br	12	94	10	87
3l	Me	3-MeO	12	84	10	87
3m	Me	H	12	81	10	88
3n	Cl	4-Cl	12	89	10	83
3o	Cl	4-Me	12	90	10	88
3p	Cl	4-F	12	91	10	93
3q	Cl	3-Cl	12	85	10	93
3r	Cl	2-Cl	12	87	10	90
3s	Cl	3-Me	12	89	10	92
3t	Cl	2-Me	12	88	10	83
3u	Cl	3-F	12	85	10	93
3v	Cl	2-F	12	86	10	85
3w	Cl	4-Br	12	90	10	94
3x	Cl	2-Br	12	93	10	85
3y	Cl	3-MeO	12	84	10	95
3z	Cl	H	12	82	10	88
3aa	H	4-Cl	12	85	10	88
3bb	H	3-Cl	12	84	10	96
3cc	H	2-Cl	12	84	10	96
3dd	H	4-Me	12	89	10	97
3ee	H	3-Me	12	88	10	86
3ff	H	2-Me	12	81	10	97
3gg	H	4-F	12	82	10	94
3hh	H	3-F	12	93	10	97
3ii	H	2-F	12	82	10	97
3jj	H	4-Br	12	87	10	87

[a] Determined by HPLC.

at high temperature. Therefore, 140 °C was chosen for all further reaction time optimization for which reactions were carried out varying time from 2 to 14 min in an increment of 2 min (see Table 3). The yields of the compounds varied from 75% to 88% when the reaction time was between 2 and 14 min. The highest yield was obtained when the reaction time was 10 min. So, the optimized conditions for microwave irradiation at 140 °C for 10 min in the presence of K_2CO_3 were applied to the synthesis of all title compounds in the library, and a comparison of the yields from the conventional and microwave-assisted synthesis was performed to demonstrate the advantages of the developed procedure for the parallel synthesis of 2-substituted benzyl-1-benzopyrano[4, 3-*c*]pyrazol-3(2*H*)-one derivatives bearing two sites of diversity (Table 4).

A comparison of the 36 compounds indicated that 24 showed improvement in yield using microwave irradiation. Two of the compounds showed similar yields regardless of the method used for synthesis. Another, 10 of the compounds showed a reduction in yield using microwave irradiation. However, the microwave-assisted synthetic method provided a very rapid means of synthesizing all the compounds. In the conventional syntheses, all the compounds required 12 h of reflux when they were synthesized in parallel, while 10 min was sufficient to produce the same products when microwave irradiation was used, significantly saving time.

Table 5. Insecticidal Activities of some compounds (death rate, %)

Compound	*T. cinnabarinus*		*Nilaparvata legen*	
	250 mg L^{-1}	50 mg L^{-1}	500 mg L^{-1}	100 mg L^{-1}
3a	100	8	44	4
3b	94	6	70	10
3c	97	7	60	0
3d	98	4	32	15
3e	100	13	94	0
3f	8	0	16	0
3g	13	0	10	4
3h	93	11	63	25
3i	87	7	47	10
3j	100	6	61	0
3k	97	2	50	10
3l	100	15	82	0
3m	96	3	40	0
3n	93	2	47	5
3o	4	0	77	15
3p	87	3	63	10
3q	100	4	94	5
3r	96	2	75	0
3s	17	0	50	7
3t	100	0	80	0
3u	100	2	69	0
3v	86	6	53	0
3w	2	0	13	5
3x	100	0	71	10
3y	100	3	75	10
3z	2	0	91	10
3aa	100	11	50	0
3bb	96	4	69	0
3cc	100	7	69	21
3dd	11	0	92	10
3ee	100	47	60	0
3ff	100	5	60	0
3gg	97	15	10	0
3hh	98	23	57	8
3ii	100	3	35	0
3jj	89	2	77	0
2a	100	35	71	4
2b	98	5	53	0
A[a]	—[b]	—	100	—
B[a]	100	100	—	—

[a] A and B refer to Dichlorvos and Pyridabea NC-129, respectively.
[b] Untested.

2.3. Insecticidal activities

The insecticidal activities against *Aphis medicagini*, *Mythima separata*, *Nilaparvata legen* and *T. cinnabarinus* of the library were investigated using some commercial products, Dichlorvos and Pyridabea NC-129, as controls. The results as shown in Table 5 indicated that all compounds in the library had no or very low activities against *A. medicagini* and *M. separata* at the dosage of 250 and 500 mg L^{-1}, respectively. However, some compounds exhibited good insecticidal activities against *T. cinnabarinus* at the dosage of 250 mg L^{-1} and *N. legen* at the dosage of 500 mg L^{-1}. When the concentration was reduced to 100 mg L^{-1}, all of compounds did not exhibit insecticidal activity against *N. legen*. However, some compounds still exhibited insecticidal activity against *T. cinnabarinus* when the concentration was reduced to 50 mg L^{-1}. For example, compounds **2a** and **3**ee exhibit 35% and 47% insecticidal activity against *T. cinnabarinus* at the dosage of 50 mg L^{-1}. From these results we conclude that a systematic study on the structure–activity relationships might further improve the insecticidal activity of the title compound. It should be mentioned that it is very difficult to control *T. cinnabarinus* in China, so the benzopyrano[4,3-*c*]pyrazol-3(2*H*)-one scaffold might be identified as novel insecticidal lead structure.

3. Conclusion

In summary, this paper established the rapid construction of a library of 2-substituted benzyl-1- benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones by combining microwave irradiation with liquid-phase combinatorial chemistry strategy. Bioassay of the library indicated that the benzopyrano[4,3-*c*]-pyrazol-3(2*H*)-one scaffold could be identified as a novel insecticidal lead structure. A comparison with conventional parallel syntheses of the same library revealed that microwave-assisted synthesis resulted in much shorter reaction times. To our knowledge, this is the first report on the application of multistep microwave irradiation in liquid-phase parallel synthesis to facilitate library generation for benzopyrano[4,3-*c*]pyrazol-3(2*H*)-ones. With respect to the time saved during synthesis, the coupling of microwave technology with combinatorial chemistry constitutes a novel and attractive avenue for the rapid generation of structurally diverse libraries for lead discovery. Further optimization and structure–activity relationships of the title compounds are well under way.

4. Experimental

4.1. Materials

Chromenone-3-carboxylic acids were synthesized according to the method described in the literature;[8] the other materials were commercially available and were used directly without further purification unless otherwise stated. The silica gel (200–300 meshes) for flash column chromatography was from Qingdao Marine Chemical in China.

4.2. Analytical methods and instruments

^{1}H NMR spectra were recorded at 400 MHz in $CDCl_3$ solution on a Varian VNMR 400 MHz spectrometer. MS spectra were determined using a Tracems 2000 organic mass spectrometry, and signals were given in *m*/*z*. Melting points were taken on a Buchi B-545 melting point apparatus. Element analysis (EA) was carried out on a Vario ELIII CHNSO elemental analyzer. HPLC were performed on an Agilent 1100 system using a photodiode array detector. A Zorbax XDB-C_8 column (4.6×150 mm) was used for HPLC analysis. All analytes were resolved under isocratic conditions with methanol/water (70:30) as the mobile phase. Conventional heating was carried out on Corning stirrer/hotplates with oil baths. Microwave syntheses were carried out on a Smithe synthesized™.

4.3. General procedure for the conventional synthesis of compounds (2)

A mixture of chromenone-3-carboxylic acid (1.3 g, 6 mmol) and hydrazine hydrate (10.4 mmol, 85%) in 30 mL of acetic acid was refluxed and stirred for 4 h. The progress of the reaction was followed by HPLC. After the reaction was completed, the solvent was removed and 20 mL of ethyl acetate was added. The formed solid was filtered and recrystallized from ethanol to give intermediate **2** as light yellow crystals.

4.4. General procedure for the microwave-assisted synthesis of compounds (2)

A mixture of chromenone-3-carboxylic acid (1 mmol), hydrazine hydrate (1.8 mmol, 85%) and acetic acid (5 mL) was added into a 10-mL glass tube with a magnetic stirring bar and sealed with a plastic cap. The synthesis was carried out at 180 °C for 3 min under microwave irradiation. Completion of the reaction was checked by HPLC and the purification procedure of the products as described above at the end of 3 min. Compound **2a** ($R_1 = CH_3$): mp 231–233 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.47 (s, 3H), 3.95 (s, 1H), 7.22–7.36 (m, 2H), 7.82 (s, 1H), 8.40 (s, 1H); Ms (*m*/*z*) 200 (M^+); Anal. Calcd for $C_{11}H_8N_2O_2$: C, 66.00; H, 4.03; N, 13.99; found: C, 65.85; H, 3.85; N, 13.88; Compound **2b** ($R_1 = Cl$): mp 265–266 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.45 (s, 1H), 7.35 (d, $J = 8.8$ Hz, 1H), 7.45 (dd, $J = 8.8$ Hz, $J = 2.4$ Hz, 1H), 8.02 (d, $J = 2.4$ Hz, 1H), 8.40 (s, 1H); Ms (*m*/*z*) 222 ($(M+1)^+$); Anal. Calcd for $C_{10}H_5ClN_2O_2$: C, 54.44; H, 2.28; N, 12.70; found: C, 54.43; H, 2.27; N, 12.66; Compound **2c** ($R_1 = H$): mp 227–229 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.64 (s, 1H), 7.37–7.55 (m, 3H), 8.00 (d, $J = 7.2$ Hz, 1H), 8.40 (s, 1H); Ms (*m*/*z*) 186 (M^+); Anal. Calcd for $C_{10}H_6N_2O_2$: C, 64.52; H, 3.25; N, 15.05; found: C, 64.41; H, 3.10; N, 15.08.

4.5. General procedure for the conventional synthesis of the title compounds (3)

A mixture of intermediates **2** (2 mmol), NaH (0.09 g, 60%) in anhydrous DMF (10 mL) was stirred for 1 h at room temperature and (substituted) benzyl chloride (2.2 mmol) was added. The resulted solution was stirred for 12–15 h at room temperature until the reaction was completed by TLC. The reaction solution was poured into water and the solid was collected, and recrystallized from acetone or ethanol to give pure title compounds (**3**).

4.6. General procedure for the microwave-assisted synthesis of the title compounds (3)

A mixture of intermediates **2** (1 mmol), substituted benzyl chloride (1.1 mmol) and potassium carbonate (1.5 mmol) in 5 mL of anhydrous DMF was added into a 10-mL glass tube with a magnetic stirring bar and sealed with a plastic cap. The synthesis was carried out at 140 °C for 10 min under microwave irradiation. Completion of the reaction was checked by HPLC, and the purification procedure of the products was done as described above.

4.6.1. Compound 3a. Mp 215–217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.45 (s, 2H), 7.25–7.30 (m, 4H), 7.38 (d, $J = 8.0$ Hz, 2H), 7.86 (s, 1H), 8.12 (s, 1H); Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.20; H, 4.11; N, 9.02.

4.6.2. Compound 3b. Mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.45 (s, 2H), 7.26–7.28, (m, 3H), 7.31 (s, 1H), 7.32–7.35 (m, 2H), 7.87 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.76, 56.49, 108.26, 114.12, 117.18, 122.56, 126.10, 128.13, 128.96, 130.36, 131.26, 132.18, 134.20, 134.96, 136.43, 149.60, 150.93, 157.98; Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.44; H, 3.82; N, 8.85.

4.6.3. Compound 3c. Mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.60 (s, 2H), 7.24–7.37 (m, 5H), 7.45 (d, $J = 8$ Hz, 1H), 7.87 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.78, 54.67, 108.05, 114.24, 117.21, 122.57, 127.54, 130.01, 130.39, 130.57, 131.23, 132.14, 132.41, 133.78, 134.18, 149.54, 150.97, 158.08; Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.19; H, 3.99; N, 8.44.

4.6.4. Compound 3d. Mp 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.43 (s, 3H), 5.43 (s, 2H), 7.21–7.26 (m, 6H), 7.88 (s, 1H), 8.05 (s, 1H);

^{13}C NMR (100 MHz, $CDCl_3$): δ 20.77, 21.13, 57.09, 107.96, 114.33, 117.18, 122.54, 128.38, 129.82, 131.11, 131.16, 131.84, 134.14, 138.89, 149.37, 150.94, 158.14; Ms (*m*/*z*) 304 (M^+); Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 74.81; H, 5.21; N, 9.16.

4.6.5. Compound 3e. Mp 183–185 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 2.43 (s, 3H), 5.43 (s, 2H), 7.12 (s, 1H), 7.20–7.31 (m, 5H), 7.89 (s, 1H), 8.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.69, 21.22, 57.17, 107.89, 114.23, 117.06, 122.46, 125.29, 128.87, 128.93, 129.52, 131.01, 131.91, 134.03, 134.12, 138.89, 149.24, 150.83, 158.05; Ms (*m*/*z*) 304 (M^+); Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 75.11; H, 5.04; N, 9.24.

4.6.6. Compound 3f. Mp 210–212 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.30 (s, 3H), 2.44 (s, 3H), 7.19–7.34 (m, 6H), 7.89 (s, 1H), 7.81 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.87, 20.71, 55.30, 107.74, 114.22, 117.12, 122.44, 126.68, 129.31, 129.67, 130.99, 131.07, 131.65, 131.93, 134.10, 136.91, 149.24, 150.87, 158.08; Ms (*m*/*z*) 304 (M^+); Anal. Calcd for $C_{19}H_{16}N_2O_2$: C, 74.98; H, 5.30; N, 9.20; found: C, 74.86; H, 4.88; N, 9.15.

4.6.7. Compound 3g. Mp 189–191 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.45 (s, 2H), 7.07–7.11 (m, 3H), 7.31–7.34 (m, 3H), 7.86 (s, 1H), 8.11 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.78, 56.50, 108.17, 114.21, 116.03, 116.25, 117.21, 122.53, 130.15, 131.24, 131.90, 134.21, 149.56, 150.95, 158.04, 161.72, 163.92; Ms (*m*/*z*) 308 (M^+); Anal. Calcd for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09; found: C, 69.83; H, 4.54; N, 8.55.

4.6.8. Compound 3h. Mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.47 (s, 2H), 7.01–7.10 (m, 4H), 7.25–7.34 (m, 1H), 7.34 (dd, J = 7.8 Hz, J = 2.2 Hz, 1H), 7.87 (s, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.75, 56.55, 108.25, 114.15, 114.95, 115.70, 117.19, 122.56, 123.58, 130.70, 131.28, 132.21, 134.24, 136.89, 149.60, 150.93, 158.04, 161.80, 163.93; Ms (*m*/*z*) 308 (M^+); Anal. Calcd for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09; found: C, 69.92; H, 4.65; N, 8.75.

4.6.9. Compound 3i. Mp 169–171 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.53 (s, 2H), 7.12–7.20 (m, 3H), 7.24–7.26 (m, 1H), 7.31–7.39 (m, 2H), 7.86 (s, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.75, 50.93, 108.12, 114.22, 115.78, 117.16, 121.61, 122.53, 124.79, 130.65, 131.00, 131.17, 132.16, 134.14, 149.45, 150.93, 158.04, 159.42, 161.89; Ms (*m*/*z*) 308 (M^+); Anal. Calcd for $C_{18}H_{13}FN_2O_2$: C, 70.12; H, 4.25; N, 9.09; found: C, 69.92; H, 4.26; N, 8.68.

4.6.10. Compound 3j. Mp 225–227 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.43 (s, 2H), 7.19 (d, J = 8.0 Hz, 2H), 7.20–7.30 (m, 2H), 7.52 (d, J = 8.4 Hz, 2H), 7.86 (s, 1H), 8.13 (s, 1H); Ms (*m*/*z*) 370 ($(M+1)^+$), 368 ($(M-1)^+$); Anal. Calcd for $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59; found: C, 59.01; H, 3.93; N, 7.12.

4.6.11. Compound 3k. Mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 5.48 (s, 2H), 7.24–7.30 (m, 1H), 7.31–7.34 (m, 2H), 7.39–7.42 (m, 3H), 7.88 (s, 1H), 8.09 (s, 1H); Ms (*m*/*z*) 370 ($(M+1)^+$), 368 ($(M-1)^+$); Anal. Calcd for $C_{18}H_{13}BrN_2O_2$: C, 58.56; H, 3.55; N, 7.59; found: C, 58.87; H, 3.67; N, 7.91.

4.6.12. Compound 3l. Mp 184–186 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.43 (s, 3H), 3.80 (s, 3H), 5.44 (s, 2H), 6.84 (s, 1H), 6.85–6.92 (m, 2H), 7.24–7.26 (m, 1H), 7.28–7.33 (m, 2H), 7.88 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.76, 55.25, 57.19, 108.06, 114.01, 114.09, 114.28, 117.17, 120.39, 122.53, 130.23, 131.14, 132.02, 134.15, 135.71, 149.39, 150.93, 158.09, 160.08; Ms (*m*/*z*) 320 (M^+); Anal. Calcd for $C_{19}H_{16}N_2O_3$: C, 71.24; H, 5.03; N, 8.74; found: C, 70.91; H, 4.97; N, 8.42.

4.6.13. Compound 3m. Mp 178–179 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.42 (s, 3H), 5.48 (s, 2H), 7.26–7.34 (m, 3H), 7.38–7.40 (m, 4H), 7.87 (s, 1H), 8.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 20.76, 57.23, 108.03, 114.28, 117.15, 122.52, 128.24, 128.84, 129.12, 131.12, 134.13, 134.33, 149.38, 150.91, 158.08; Ms (*m*/*z*) 290 (M^+); Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; found: C, 74.00; H, 4.80; N, 9.57.

4.6.14. Compound 3n. Mp 235–237 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (s, 2H), 7.28–7.43 (m, 6H), 8.04 (d, J = 2.4, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.73, 108.23, 115.91, 118.95, 122.43, 129.43, 129.57, 129.95, 130.34, 132.16. 132.69, 135.13, 148.55, 151.27, 157.17; Ms (*m*/*z*) 346 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{10}Cl_2N_2O_2$: C, 59.15; H, 2.92; N, 8.12; found: C, 59.60; H, 3.40; N, 8.46.

4.6.15. Compound 3o. Mp 187–189 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.43 (s, 2H), 7.20–7.30 (m, 5H), 7.38 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 8.05 (s, 1H), 8.08 (s, 1H); Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.41; H, 4.38; N, 8.98.

4.6.16. Compound 3p. Mp 200–202 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.45 (s, 2H), 7.08–7.12 (m, 2H), 7.26–7.35 (m, 3H), 7.41 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H), 8.12 (s, 1H); Ms (*m*/*z*) 330 ($(M+1))^+$; Anal. Calcd for $C_{17}H_{10}ClFN_2O_2$: C, 62.11; H, 3.07; N, 8.52; found: C, 62.44; H, 3.54; N, 8.03.

4.6.17. Compound 3q. Mp 213–215 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2H), 7.20–7.36 (m, 5H), 7.40 (dd, J = 9.0 Hz, J = 2.6 Hz, 1H), 8.05 (d, J = 2.4 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 55.30, 107.04, 115.78, 119.24, 121.43, 126.74, 127.87, 128.15, 128.56, 130.13, 130.63, 133.26, 134.52, 138.27, 147.42, 150.92, 156.28; Ms (*m*/*z*) 346 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{10}Cl_2N_2O_2$: C, 59.15; H, 2.92; N, 8.12; found: C, 58.80; H, 2.75; N, 8.04.

4.6.18. Compound 3r. Mp 188–190 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.61 (s, 2H), 7.29–7.38 (m, 3H), 7.40 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.46 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 2.4 Hz, 1H), 8.19 (s, 1H); Ms (*m*/*z*) 346 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{10}Cl_2N_2O_2$: C, 59.15; H, 2.92; N, 8.12; found: C, 58.85; H, 2.77; N, 8.07.

4.6.19. Compound 3s. Mp 195–197 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 5.44 (s, 2H), 7.13 (s, 1H), 7.19–7.32 (m, 4H), 7.40 (dd, J = 9 Hz, J = 2.6 Hz, 1H), 8.06 (d, J = 2.4 Hz, 1H), 8.10 (s, 1H); Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.09; H, 3.92; N, 8.72.

4.6.20. Compound 3t. Mp 202–204 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3H), 5.49 (s, 2H), 7.23–7.34 (m, 5H), 7.40 (dd, J = 8.8 Hz, J = 2.4 Hz, 1H), 7.94 (s, 1H), 8.07 (d, J = 2.4 Hz, 1H); Ms (*m*/*z*) 326 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_2$: C, 66.57; H, 4.03; N, 8.63; found: C, 66.07; H, 3.93; N, 8.67.

4.6.21. Compound 3u. Mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (s, 2H), 7.02–7.11 (m, 3H), 7.30–7.43 (m, 3H), 8.06 (s, 1H), 8.18 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 55.38, 107.00, 114.72, 115.11, 115.77, 119.20, 121.41, 124.06, 128.55, 130.09, 130.80, 134.49, 138.61, 147.37, 150.89, 156.27, 161.07, 163.12; Ms (*m*/*z*) 330 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{10}ClFN_2O_2$: C, 62.11; H, 3.07; N, 8.52; found: C, 62.58; H, 2.91; N, 8.50.

4.6.22. Compound 3v. Mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (s, 2H), 7.15–7.20 (m, 2H), 7.28–7.41(m, 4H), 8.04 (s, 1H), 8.20 (s, 1H); Ms (*m*/*z*) 330 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{10}ClFN_2O_2$: C, 62.11; H, 3.07; N, 8.52; found: C, 61.75; H, 2.95; N, 8.51.

4.6.23. Compound 3w. Mp 243–245 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (s, 2H), 7.20 (d, J = 8.4 Hz, 2H), 7.30 (d, J = 8.4 Hz, 2H), 7.41 (dd, J = 9.0 Hz, J = 2.8 Hz, 1H), 7.53 (d, J = 8.4 Hz, 1H), 8.04 (d, J = 2.8 Hz, 1H), 8.15 (s, 1H); ^{13}C NMR (100 MHz, DMSO): δ 55.29, 106.96, 115.82, 119.31, 121.42, 128.57, 129.03, 129.87, 130.18, 131.59, 134.42, 135.28, 147.38, 150.94, 156.25; Ms (*m*/*z*) 390 (M^+); Anal. Calcd for $C_{17}H_{10}BrClN_2O_2$: C, 52.40; H, 2.59; N, 7.19; found: C, 52.26; H, 2.89; N, 6.89.

4.6.24. Compound 3x. Mp 180–182 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.60 (s, 2H), 7.27–7.43 (m, 5H), 7.64 (d, J = 8.0 Hz, 1H), 8.05 (s, 1H), 8.19 (s, 1H); Ms (*m*/*z*) 390(M^+); Anal. Calcd for $C_{17}H_{10}BrClN_2O_2$: C, 52.40; H, 2.59; N, 7.19; found: C, 52.05; H, 2.45; N, 7.16.

4.6.25. Compound 3y. Mp 186–187 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 3.81 (s, 3H), 5.45 (s, 2H), 6.85 (s, 1H), 6.90–6.94 (m, 2H), 7.29–7.34 (m, 2H), 7.40 (dd, J = 8.8 Hz, 1H), 8.06 (s, 1H), 8.12 (s, 1H); Ms (*m*/*z*) 342 ($(M+1)^+$); Anal. Calcd for $C_{18}H_{13}ClN_2O_3$: C, 63.44; H, 3.85; N, 8.22; found: C, 63.04; H, 3.95; N, 8.13.

4.6.26. Compound 3z. Mp 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.48 (s, 2H), 7.28–7.41 (m, 7H), 8.05 (d, J = 2.4 Hz, 1H), 8.12 (s, 1H); Ms (*m*/*z*) 312 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.57; N, 9.02; found: C, 65.43; H, 3.58; N, 8.90.

4.6.27. Compound 3aa. Mp 215–217 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2H), 7.26–7.38 (m, 6H), 7.45–7.47 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 8.14 (s, 1H); Ms (*m*/*z*) 312 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.5; N, 9.02; found: C, 65.44; H, 3.29; N, 9.03.

4.6.28. Compound 3bb. Mp 186–188 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2 H), 7.19 (d, J = 6.8 Hz, 1H), 7.21–7.37 (m, 5H), 7.48 (t, J = 7.8 Hz, 1H), 8.09 (d,J = 8.0 Hz, 1H), 8.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.54, 108.25, 114.61, 117.51, 122.71, 124.46, 126.15, 128.19, 129.02, 129.50, 130.39, 132.16, 135.00, 136.37, 149.52, 152.84, 157.79; Ms (*m*/*z*) 312 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.5; N, 9.02; found: C, 65.27; H, 3.31; N, 8.96.

4.6.29. Compound 3cc. Mp 179–181 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.62 (s, 1H), 7.28–7.38 (m, 5H), 7.45 (d, J = 8.0 Hz, 2H), 8.07 (dd, J = 7.8 Hz, J = 1.4 Hz, 1H), 8.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 54.67, 107.97, 114.67, 117.49, 122.69, 124.41, 127.53, 129.99, 130.31, 130.41, 130.56, 132.09, 132.40, 133.78, 149.41, 152.84, 157.86; Ms (*m*/*z*) 312 ($(M+1)^+$); Anal. Calcd for $C_{17}H_{11}ClN_2O_2$: C, 65.71; H, 3.5; N, 9.02; found: C, 65.51; H, 3.26; N, 8.98.

4.6.30. Compound 3dd. Mp 193–195 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.37 (s, 3H), 5.43 (s, 2H), 7.20–7.26 (m, 3H), 7.31 (t, J = 8.0 Hz, 1H), 7.44 (d, J = 8.4 Hz, 2H), 7.48 (t, J = 8.0 Hz, 1H), 8.07 (s, 1H), 8.08 (d, J = 8.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.11, 57.07, 107.87, 114.75, 117.45, 122.62, 124.37, 128.38, 129.78, 130.18, 131.12, 131.83, 138.87, 149.22, 152.80, 157.90; Ms (*m*/*z*) 290 (M^+); Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; found: C, 74.10; H, 4.73; N, 9.71.

4.6.31. Compound 3ee. Mp 198–200 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.36 (s, 3H), 5.44 (s, 2H), 7.1 (s, 1H), 7.19 (d, J = 7.6 Hz, 1H), 7.26–7.34 (m, 3H), 7.38 (d, J = 8.4 Hz, 1H), 7.49 (t, J = 8.4 Hz, 1H), 8.07–8.10 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 21.29, 57.30, 107.95, 114.76, 117.48, 122.66, 124.39, 125.40, 128.99, 129.03, 129.65, 130.22, 131.95, 134.08, 139.02, 149.25, 152.82, 157.93; Ms (*m*/*z*) 290 (M^+); Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; found: C, 74.10; H, 4.69; N, 9.60.

4.6.32. Compound 3ff. Mp 203–205 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 2.31 (s, 3 H), 7.20–7.38 (m, 6H), 7.46 (t, J = 8.4 Hz, 1H), 7.92 (s, 1 H), 8.08 (dd, J = 7.6 Hz, J = 1.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 18.89, 55.30, 107.68, 114.68, 117.41, 122.57,

124.35, 126.68, 129.31, 129.67, 130.18, 130.99, 131.68, 131.96, 136.92, 149.13, 152.75, 157.87; Ms (*m*/*z*) 290 (M^+); Anal. Calcd for $C_{18}H_{14}N_2O_2$: C, 74.47; H, 4.86; N, 9.65; found: C, 74.21; H, 4.76; N, 9.55.

4.6.33. Compound 3gg. Mp 206–208 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.46 (s, 2 H), 7.07–7.12 (m, 2 H), 7.29–7.38 (m, 4 H), 7.45 (t, J = 8.4 Hz, 1H), 8.06 (dd, J = 7.8 Hz, J = 1.4 Hz, 1 H), 8.12 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.48, 108.07, 114.65, 116.00, 117.48, 122.64, 124.43, 130.10, 130.18, 130.32, 131.91, 149.42, 152.81, 157.82, 161.62, 164.10; Ms (*m*/*z*) 294 (M^+); Anal. Calcd for $C_{17}H_{11}FN_2O_2$: C, 69.38; H, 3.77; N, 9.52; found: C, 69.30; H, 3.66; N, 9.52.

4.6.34. Compound 3hh. Mp 178–180 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.49 (s, 2H), 7.02–7.11 (m, 3H), 7.30–7.39 (m, 3H), 7.46 (t, J = 8.4 Hz, 1H), 8.06 (d, J = 8.0 Hz, 1H), 8.17 (s, 1H); Ms (*m*/*z*) 294 (M^+); Anal. Calcd for $C_{17}H_{11}FN_2O_2$: C, 69.38; H, 3.77; N, 9.52; found: C, 69.44; H, 3.63; N, 9.59.

4.6.35. Compound 3ii. Mp 174–176 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.54 (s, 1H), 7.12–7.20 (m, 3H), 7.28–7.48 (m, 4H), 8.05 (d, J = 7.6 Hz, 1H), 8.19 (s, 1H); Ms (*m*/*z*) 294 (M^+); Anal. Calcd for $C_{17}H_{11}FN_2O_2$: C, 69.38; H, 3.77; N, 9.52; found: C, 69.36; H, 3.64; N, 9.57.

4.6.36. Compound 3jj. Mp 216–219 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ 5.44 (s, 1H), 7.19 (d, J = 8.4 Hz, 2H), 7.30 (t, J = 8.0 Hz, 1H), 7.36 (d, J = 8.8 Hz, 1H), 7.46 (t, J = 8.4 Hz, 1H), 7.52 (d, J = 8.4 Hz, 2H), 8.06 (d, J = 7.8 Hz, 1H), 8.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ 56.65, 108.30, 114.69, 117.58, 122.74, 123.10, 124.50, 129.81, 130.32, 132.03, 132.35, 133.46. 149.60, 152.94, 157.79; Ms (*m*/*z*) 356 ($(M+1)^+$), 354 ($(M-1)^+$); Anal. Calcd for $C_{17}H_{11}BrN_2O_2$: C, 57.49; H, 3.12; N, 7.89; found: C, 57.26; H, 3.01; N, 7.94.

4.7. Biological assay

This study was carried out with the following insect species: *T. cinnabarinus*, *N. lugen*, *M. separata* and *A. medicagini*. These insects were reared in a room maintained at 25 (±1) °C, 60 (±5)% relative humidity, and 14 h light photoperiod. Stock solutions of each test compound were prepared in acetone at a concentration of 1.0 g L^{-1} and then diluted to the required test concentrations with water containing Triton X-100 (0.1 mL L^{-1}). Groups of 10 insects of each species were transferred to glass Petri dishes and sprayed with test solutions using a Potter sprayer. After air-drying, they were kept in a room for normal cultivation. The mortality was determined in 72 h by the number and size of live larvae in the treated bottles relative to that in the untreated controls. In the case of *N. lugen*, rice seedlings (second semester) were dipped in the test solution for 5 s, air-dried and then placed in a large test tube. Each test rube contained 20 seedlings. Twenty insects (fifth instar) were introduced into the tube, and the mouth of the tube was covered with white cheesecloth. The tube was kept at room temperature, and the number of live and dead insects counted after 72 h. In a control experiment, carried out under the same conditions, 1 mL of acetone was applied on each insect. All experiments and the respective controls were carried out in three replicates and the data were subjected to probit analysis.

Acknowledgments

We thank Dr. Jie Chen for the tests of insecticidal activity. We also should thank the financial support from the National Key Project for Basic Research (Nos. 2003CB114400, 2002CCA00500), National NSFC (Nos. 20572030, 20432010 and 20528201), Key project of Ministry of Education (Nos. 103116 and 104205), Program for New Century Excellent Talents in University of China and Program for Excellent Research Group of Hubei Province (No. 2004ABC002).

References and notes

1. (a) Czarnik, A. W.; DeWitt, S. H. *A Practical Guide to Combinatorial Chemistry*; American Chemical Society: Washington, DC, 1997; (b) Fenniri, H. *Combinatorial Chemistry*; Oxford University Press: New York, 2000; (c) Seneci, P. *Solid-Phase Synthesis and Combinatorial Technologies*; John Wileys & Sons: New York, 2000.
2. (a) Nielsen, J.; Hoel, A. M. L. *Tetrahedron Lett.* **1999**, *40*, 3941–3944; (b) Chandrasekhar, S.; Padmaja, M. B.; Raza, A. *Synlett* **1999**, *10*, 1597–1599; (c) Stadler, A.; Kappe, C. O. *J. Comb. Chem.* **2001**, *3*, 624–630; (d) Brain, C. T.; Brunton, S. A. *Synlett* **2001**, *3*, 382–384; (e) Bendale, P. M.; Sun, C. M. *J. Comb. Chem.* **2002**, *4*, 359–361; (f) Wu, C. Y.; Sun, C. M. *Synlett* **2002**, *17*, 1709–1711; (g) Dallinger, D.; Gorobets, N. Y.; Kappe, C. O. *Org. Lett.* **2003**, *5*, 1205–1208; (h) Chang, W. J.; Yeh, W. B.; Sun, C. M. *Synlett* **2003**, *18*, 1688–1692; (i) Lin, M. J.; Sun, C. M. *Synlett* **2004**, *18*, 663–666; (j) Lee, M. J.; Sun, C. M. *Tetrahedron Lett.* **2004**, *45*, 437–440; (k) Tung, C. L.; Sun, C. M. *Tetrahedron Lett.* **2004**, *45*, 1159–1162; (l) Nuchter, M.; Ondruschka, B.; Bonrath, W.; Gum, A. *Green Chem.* **2004**, *6*, 128–141.
3. (a) Gedye, R.; Smith, F.; Westway, K.; Ali, H.; Baldisera, L.; Laberge, L.; Rousell, J. *Tetrahedron Lett.* **1986**, *27*, 279–282; (b) Giguerre, R. J.; Bray, T. L.; Duncan, S. M. *Tetrahedron Lett.* **1986**, *27*, 4945–4948.
4. (a) Larhed, M.; Hallberg, A. *Drug Discovery Today* **2001**, *6*, 406–416; (b) Kappe, C. O. *Curr. Opin. Chem. Biol.* **2002**, *6*, 314–320; (c) Santagada, V.; Frecentese, F.; Perissutti, E.; Favretto, L.; Caliendo, G. *QSAR Comb. Sci.* **2004**, *23*, 919–944; (d) Santagada, V.; Perissutti, E.; Caliendo, G. *Curr. Med. Chem.* **2002**, *9*, 1251–1283; (e) Katritzky, A. R.; Singh, S. K. *Curr. Top. Med. Chem.* **2004**, *4*, 773–792.
5. (a) Nohara, A.; Kuriki, H.; Saijo, T.; Ukawa, K.; Murata, T.; Kanno, M.; Sanno, Y. *J. Med. Chem.* **1975**, *18*, 34; (b) Yenesew, A.; Derese, S.; Midiwo, J. O.; Heydenreich, M.; Peter, M. G. *Pest. Manage. Sci.* **2003**, *59*, 1159–1161; (c) Cabizza, M.; Angioni, A.; Melis, M.; Cabras, M.; Tuberoso, C. V.; Cabras, P. *J. Agric. Food Chem.* **2004**, *52*, 288–293; (d) Nussbaumer, P.; Lehr, P.; Billich, A. *J. Med. Chem.* **2002**, *45*, 4310; (e) Joo, Y. H.; Kim, J. K.; Kang, S.-H.; Noh, M.-S.; Ha, J.-Y.; Choi, J. K.; Lim, K. M.; Lee, C. H.; Chung, S. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 413; (f) Pal, M.; Subramanian, V.; Parasuraman, K.; Yeleswarapu, K. R. *Tetrahedron* **2003**, *59*, 9563; (g) Maliar, T.; Jedinak, A.; Kadrabova, J.; Sturdik, E. *Eur. J. Med. Chem.* **2004**, *39*, 241–248.

6. Ghosh, C. K.; Mukhopadhyay, K. K. *Synthesis* **1978**, *10*, 779–781.
7. (a) Ghosh, C. K.; Khan, S. *Indian J. Chem., Sect B* **1979**, *18B*, 128–130; (b) Chantegrel, B.; Gelin, S. *Synthesis* **1985**, *5*, 548–550; (c) Ghosh, C. K.; Pal, C. *Indian J. Chem., Sect B* **1985**, *B*, 1288–1290; (d) Colotta, V.; Cecchi, L.; MeLani, F.; Palazzino, G.; Filacchioni, G. *Tetrahedron Lett.* **1987**, *28*, 5165–5168; (e) Colotta, V.; Cecchi, L.; Melani, F.; Palazzino, G.; Filacchioni, G.; Martini, C.; Giannaccini, G.; Lucacchini, A. *J. Pharm. Sci.* **1989**, *78*, 239–242; (f) Bowen, J. G.; Hockley, M. H.; Housley, J. R.; Hunneyball, I. M.; Titman, R. B.; Webber, D. G. *EP* 354693, 1990-02-14.; (g) Titman, R. B.; Hockley, M. H. *WO* 9112255, 1991-08-22.; (h) Titman, R. B.; Hockley, M. H.; Gill, O. S. *WO* 9111448, 1991-08-08.; (i) Bowen, J. G.; Hockley, M. H.; Housley, J. R. *CN* 1053921, 1991-08-21.; (j) Titman, R. B.; Hockley, M. H. *WO* 9303036, 1993-02-18; (k) Froggett, J. A.; Hockley, M. H.; Titman, R. B. *J. Chem. Res. Synop.* **1997**, *1*, 30–31; (l) Bjoerk, P. A.; Fex, T.; Pettersson, L. O. G.; Sorensen, P.; Da Graca, T. D. *WO* 2003004495, 2003-01-16.
8. (a) Cremins, P. J.; Saengchantara, S. T.; Wallace, T. W. *Tetrahedron* **1987**, *43*, 3075–3082; (b) Machida, Y.; Nomoto, S.; Negi, S.; Ikuta, H.; Saito, I. *Synth. Commun.* **1980**, *10*, 889–895.