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ARTICLE

Design, synthesis, crystal structure and fungicidal activity of (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one analogues†

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A practical method of four step synthesis towards novel (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin -4(1H)-one antifungals was presented, where a commercial available intermediate of the pesticide and the pharmacology, (E)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino) acetate (**1**), was used as starting material. These compounds were confirmed by ^{1}H NMR, ^{13}C NMR, high-resolution mass spectroscopy and X-ray crystal structure. Via *in vitro* fungicidal evaluation, the moderate to high activities of several compounds against eight phytopathogenic fungi were demonstrated. Especially, the fungicidal activity of compound **5-03** and **5-09** were comparable to the control azoxystrobin and trifloxystrobin in precise virulence measurements to four fungi. These results suggested that dihydrobenzo[e][1,2]oxazepin-4(1H)-one analogues could be considered as potential fungicidal candidates for crop protection.

Introduction

Among the Oxazepine compounds, benzoxazepinones and their derivatives have a central place in the pharmaceutical chemistry.[1] For example, GSK'481(I) is a highly potent and monoselective receptor interacting protein 1 kinase;[2] Neochromine S5(II) can inhibit proliferation and increase apoptosis of activated T cells;[3] GDC-0032(III) is a β-sparing phosphoinositide 3-kinase inhibitor and has been evaluated as potential treatment for human malignancies;[4] Tetrahydro-pyrazolo-oxazepin-one (IV) derivatives as potential telomerase inhibitors exhibit high anticancer activity.[5] (Figure 1) As such, all the representative compounds containing benzoxazepinone moiety reportedly show outstanding biological activity.

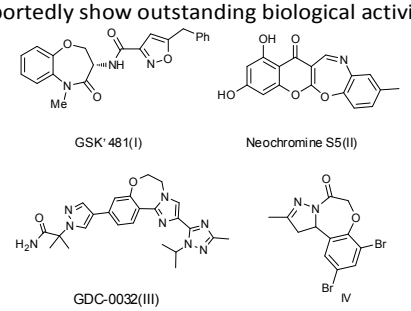
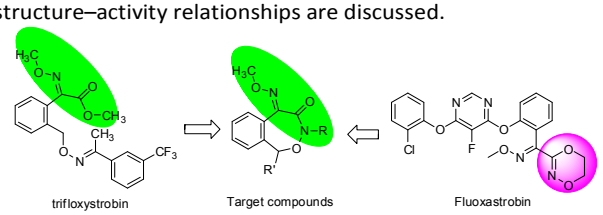


Figure 1 Biologically active compounds containing benzoxazepinone moiety

Consequently, the widely practical interest of this important heterocyclic ring system motivates continuous efforts of the exploitation of both efficient compounds and synthetic methods, but almost reported benzoxazepinones are 1,4-benzoxazepinone. [6-12] By comprehensive literature search and analysis, we find that the 1,2-benzoxazepinone skeleton is a new fragment. The method to synthesize a variety of 1,2-benzoxazepinone, where N-O bond are adjacent to carbonyl group, is lacking.

On the basis of the development of fungicides targeting at cytochrome bc1 complex and prompted by the excellent biological activity of trifloxystrobin and fluoxastrobin, we attempted to investigate and optimize the structure of strobilurins, target compounds were designed and synthesized. These compounds were evaluated against eight phytopathogenic fungi. In this work, we present a mild and convenient synthesis as well as systemically bioactive investigations of this new variety of (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one(**5**), which have nearby hetero-atoms (N and O) at the seven members ring. Meanwhile, the corresponding chemical problems and their structure–activity relationships are discussed.



Scheme 1 Strategies for the target compound designing

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Electronic Supplementary Information (ESI) available: [^{1}H, ^{13}C spectra of title compounds and single crystal X-Ray data for compound **5-09**]. See DOI: 10.1039/x0xx00000x

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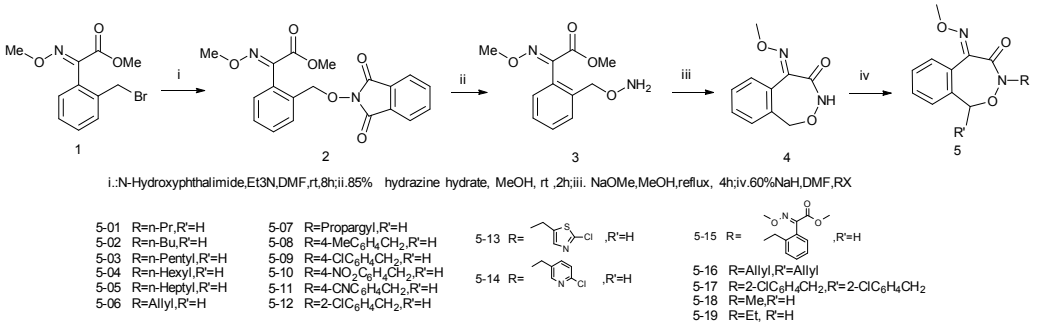
Results and discussion

Chemistry



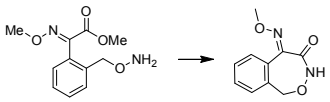
Scheme 2 Preparation of title compounds

The specific synthetic route to compound **4** and **5** from the commercial available starting material was depicted in scheme 2. Precursor **3** was prepared as literature reported.[15] Starting material **1** was reacted with N-Hydroxyphthalimide to give intermediate **2**, the later was hydrazinolated to produce the key precursor **3**. Initial studies found that substrate **3** reacted without any additive giving compound **4** only yield 7% at room temperature (RT) for 4 hours. We began our investigations by choosing **3** as the exclusive substrate for optimizing the reaction conditions. Firstly, the reactive temperature was investigated (Table 1, entries 2, 3). It was found that, the yield of reflux temperature (15%) is a little higher than it of RT (9%) after as long as 24 hours of reaction, where majority of substrate remained unconverted at these conditions. Then, some organic and inorganic bases were screened, and NaOMe furnished good yield, at reflux for 4 hours, whereas other bases, such as Et_3N, NaOH and K_2CO_3, gave either low product yields or more byproduct.

The present optimized synthesis of benzoxazepinone **4** involved stirring of **3** with NaOMe in methanol at reflux for 4 hours. The method was amenable to gram scale synthesis under optimized conditions. NaOMe stimulated the cleavage of a molecule of methanol in the intramolecular cyclization procedure. Compound 4 was obtained with good yields. Then compound 4 was reacted with various halides in DMF in the presence of NaH to afford corresponding compounds 5. Most of compounds **5** were obtained in moderate to good yields. However, the synthetic yields of compound **5-06** and **5-12** were only 34% and 24%, the reason was that compound **5-06** and **5-12** could be further alkylated to give double substituted compound **5-16** and **5-17**, respectively. (Scheme 5) In addition, the structure of **5** was further identified by X-ray diffraction studies (Figure 2).

Crystal Structure Analysis. To provide more evidence for the proposed molecular structure and establish the conformation of the target compounds, the compound **5-09** was recrystallized by a slow evaporation from a dichloromethane/n-hexane (v/v = 1:5) solution. Single-crystal X-ray diffraction analysis showed that the crystal structure of compound **5-09** belongs to the orthorhombic system, space group $P2_12_12_1$. The details of the crystallographic data and structure refinement parameters are summarized in Table (S1-S7). The molecular structure of compound **5-09** is shown in Figure 2. The seven ring appears to be twisted and the double bonds C(1)=O(2) and C(2)=N(2) in compound **5-09** is pushed in opposite directions. The bond lengths of compound **5-09** are within the normal range.

Table 1 Optimization of the reaction condition for the cyclization of 2 to afford 5



Entry	Base	Temperture	Time (h)	Yield (%)[a]
1	-	RT	4	7
2	-	RT	24	9
3	-	reflux	24	15
4	NaOMe	RT	8	57
5	NaOMe	reflux	4	81
6	Et_3N	reflux	4	45
7	NaOH	reflux	4	67
8	Na_2CO_3	reflux	4	56

[a]:isolated yield.

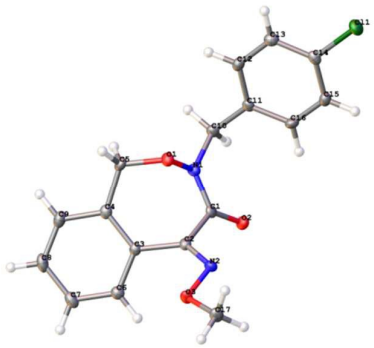


Figure 2 X-ray crystal structure of **5-09**(CCDC-1518111).

Structure-Activity Relationship (SAR)

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(E)-methyl 2-(2-(bromomethyl)phenyl)-2-(methoxyimino) acetate (**1**), a bromoalkane with the bromobenzyl group and the 2-(methoxyimino)acetate group, as the starting material, which has been mass-produced, is an essential intermediate of agricultural fungicides originating in natural product strobilurin A, becoming an attractive area of research in pharmaceutical and agricultural chemistry.[16] Furthermore, it is not only been widely used as key intermediates in fungicides synthesis but also serve as scaffolds to access other pesticides. [17] Fungicides with this intermediates have proved broad spectrum, high efficiency and low toxicity as through field experiments and all kind of toxicity tests.[18] Compounds **4** and **5** not only keep the important scaffold of methoxyacrylates, including benzene ring, methoxyimino and carbonyl, but also combine two heteroatoms (N,O) into one molecule which plays important role in biological activity.[19,20] Accordingly, fungicidal activity of these compounds was tested against eight phyto-pathogenic fungi.

The antifungal activities of title compounds (compound **5-01** to **5-19**) were measured *in vitro* and the corresponding results were summarized in Table 2. Byproducts **5-16** and **5-17** were tested under the same conditions as well. In general, most of the compounds displayed considerable to excellent fungicidal activities against eight phytopathogens except compound **5-07 5-15, 5-18**and **5-19**. Most of these compounds were highly active against *phytophthora infestans, pythium aphanidermatum, setosphaeria turcica and pyricularia grisea* in vitro at 50 μg/mL. Compound **5-16** and **5-17** exhibited certain fungicidal activities. No obvious difference of fungicidal activity between aliphatic and aromatic series was observed. For aliphatic series (compound **5-01** to **5-07, 5-18** and **5-19**), however, the fungicidal activity is determined by the length of aliphatic chain, where title compounds with shorter aliphatic chain exhibited relatively lower bioactivity than that with longer chain, i.e. compound: **5-18** < **5-19** < **5-01** < **5-02** < **5-03** ≈ **5-04** ≈ **5-05** (Figure 3). For the substituent benzene of aromatic series (compound **5-08** to **5-12**), a *para*-substituent (*para*-alkyl of compound **5-08**, *para*-Cl of compound **5-09**, *para*-nitro of compound **5-10** and *para*-cyano of compound **5-11**), no matter it is electron-withdrawing (-Cl, -nitro and –cyano) or -donating (-alkyl), was the most important factor to enhance the bioactivity comparing with *ortho*-substituent (*ortho*-alkyl of compound **5-12**). In contrast, for the hetero-aromatic series (compound **5-13** and **5-14**), the inhibitory rate was relatively lower than that of substituent benzene series. In all, several compounds displayed higher activity than the commercial fungicides (azoxystrobin and trifloxystrobin), including compounds **5-03**, **5-08**, **5-09** against *phytophthora infestans* and compounds **5-03** to **5-05**, **5-08** to **5-11** against *Setosphaeria turcica*. The inhibitory rates of compounds **5-03** to **5-05**, **5-08** to **5-11** were comparable to azoxystrobin and trifloxystrobin against *pyricularia grisea* and *colletotrichum orbiculare.*

Table 2 In vitro fungicidal activity of target copmounds against Phytopathogensa

Compd.	mycelium growth inhibitory rate (%) at 50 μg/mL							
	SS	BC	PI	PA	RS	ST	PG	CO
4	22.8	5.0	11.7	2.9	8.6	36.7	14.0	15.3
5-01	NA	20.3	24.2	9.6	10.0	26.8	21.9	19.1
5-02	13.3	27.5	35.5	22.3	20.0	45.4	35.9	22.1
5-03	60.0	40.6	56.5	46.2	35.0	69.2	51.6	36.8
5-04	57.3	40.6	48.4	40.1	33.3	65.7	50.0	38.2
5-05	58.7	40.6	37.1	35.5	25.0	70.0	53.1	36.8
5-06	15.6	12.8	23.3	11.0	10.9	15.3	16.1	14.7
5-07	NA	NA	NA	11.0	NA	25.4	3.2	5.1
5-08	65.3	36.2	58.1	40.1	28.0	56.9	46.9	32.4
5-09	72.0	40.6	56.5	54.7	28.3	67.7	62.5	32.4
5-10	22.7	31.9	46.8	41.2	25.0	65.7	51.6	25.0
5-11	41.3	36.4	52.5	42.3	35.0	62.3	50.7	29.4
5-12	15.4	5.2	18.2	4.7	11.7	14.4	13.4	5.7
5-13	41.7	29.7	30.1	34.3	24.6	49.2	35.5	15.3
5-14	17.3	34.8	35.5	23.8	16.7	42.2	29.7	17.6
5-15	NA	7.3	9.2	7.6	4.6	15.8	14.5	10.2
5-16	5.6	4.4	5.7	4.9	5.7	24.2	19.4	5.7
5-17	14.3	15.1	25.5	25.6	7.4	27.1	22.0	17.0
5-18	13.6	13.0	8.9	9.3	1.7	19.8	5.4	5.1
5-19	6.1	9.6	25.2	5.2	15.4	30.5	4.8	6.8
Azoxystrobin	98.7	72.5	56.5	57.3	43.3	49.5	53.1	36.8
Trifloxystrobin	99.6	49.3	53.2	62.5	41.7	54.9	50.0	23.5

SS =*Sclerotinia sclerotiorum (Lib.) de Bary;* BC =*Botrytis cinerea;* PI =*Phytophthora infestans* (Mont.) De Bary; P A = *Pythium aphanidermatum;* R S = *Rhizoctonia solani*; ST = *Setosphaeria turcica*; PG = *Pyricularia grisea* ;CO = *Colletotrichum. orbiculare* (Berk. & Ment.)

[a]NA : No activity.

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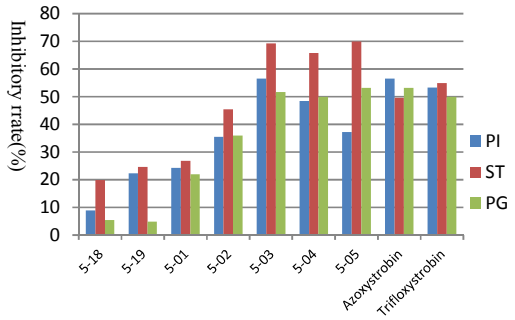

Figure 3 Inhibitory rates of partial compounds against PI, ST and PG

In order to study the activities of the superior target compounds further, five compounds were chose for precise virulence measurements to the four fungi, and their EC_{50} values were summarized in Table 3. These compounds were highly effective against *setosphaeria turcica* and compound **5-03**, **5-05** and **5-09** exhibited lower EC_{50} values antifungal activity than the control azoxystrobin and trifloxystrobin. Compound **5-03** was effective to *phytophthora infestans*, *pyricularia grisea* and *setosphaeria turcica* with the EC_{50} values of 17.8, 26.1 and 9.6, respectively. Compounds **5-09** displayed excellent activities against *sclerotinia sclerotiorum*, *phytophthora infestans*, *pyricularia grisea* and *setosphaeria turcica* with the EC_{50} values of 21.7, 15.0, 16.7 and 7.8, respectively.

As a conclusion, several compounds displayed comparable activity to the commercial fungicides (azoxystrobin and trifloxystrobin) against some fungi. In particularly, the compound **5-03** and **5-09** showed better bioactivities than the other compounds against most phytopathogens, suggesting they might deserve to be developed as potential agricultural fungicides.

Table 3. EC_{50} values of target compounds against four fungi

Compd.	EC_{50} (μg/ml)			
	SS	PI	PG	ST
5-03	38.9	17.8	26.1	9.6
5-04	47.2	35.9	35.4	16.1
5-05	43.0	>100	25.3	6.5
5-09	21.7	15.0	16.7	7.8
5-11	75.0	40.0	55.5	23.5
Azoxystrobin	1.8	12.2	21.0	15.1
Trifloxystrobin	1.6	18.0	18.4	16.9

Quantitative Structure-Activity Relationship (QSAR) Analyses. During biological screening, models of the new compounds were constructed using topomer CoMFA with Sybyl 7.3 to find the relationship between structure and activity in theory. Cross-validation q^2 value of 0.594 and a non-cross-validation r^2 value of 0.899 with an optimized component of 3 were obtained, which suggested that the model has good predictive ability (q^2 > 0.5). In the sterically favoured and disfavoured region are shown in green and yellow. For the electrostatic field, the positively charged favoured regions are shown in blue, and the negatively charge favoured regions are shown in red.

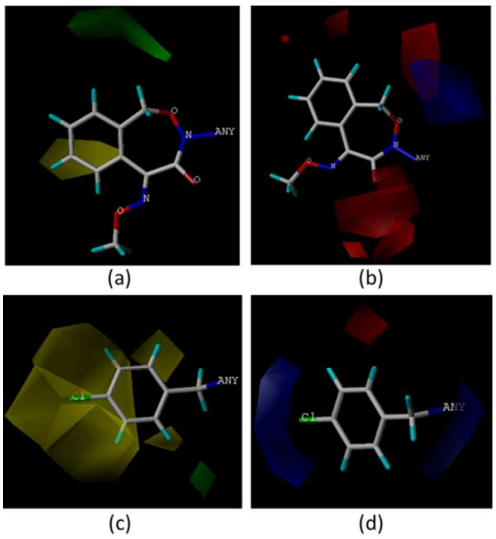

Figure 4 Topomer CoMFA contour maps of compound **5-09**. (a) steric field around benzoxazepinone moiety (b) electrostatic field around benzoxazepinone moiety (c) steric field around R group(4-$ClC_6H_4CH_2$) (d) electrostatic field around R group(4-$ClC_6H_4CH_2$)

In contour maps of aliphatic series, the length of R group of compounds 5-03 to 5-05 was comparable to aromatic substituent and compounds 5-03 to 5-05 also exhibited excellent fungicidal activity. For the substituent benzene of aromatic series, compounds with a para-substituent showed better fungicidal activity than with *ortho*-substituent compounds. Compound **5-09,** which has the highest activity, was selected as a representative molecule, making it is easier to explain the contour map. The benzene ring of benzoxazepinone moiety with small substituent exhibits stronger bioactivities in the map of the steric field (Figure 4a). In the electrostatic field, the carbonyl group benzoxazepinone moiety hovered red blocks (Figure 4b), indicating the electronegative was beneficial for the antifungal activity. In Figure 4c, reducing the steric hindrance of benzyl was beneficial to the activity and a large substituent such as a tert-butyl group, a cyclohexyl group in the para position of benzene ring was unfavorable. Para-position of benzene ring hovered blue blocks in the electrostatic field (Figure 4d), indicating the introducing of electropositive group was beneficial for the antifungal activity. The above discussions about SARs are conducive to further structure optimization of this series of compounds.

Experimental

Intruments and Materials

^{1}H NMR and ^{13}C NMR spectra were obtained at 300 MHz using a Bruker Avance DPX300 spectrometer in $CDCl_3$ or DMSO-d_6 solution with tetramethylsilane as the internal standard. Chemical shift values (δ) are given in parts per million. High resolution mass spectrometry data were obtained with an Accurate-Mass-Q-TOF MS 6520 system equipped with an electrospray ionization (ESI) source. The single crystal

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structure analysis was performed using X-ray diffraction on Thermo Fisher ESCALAB 250 diffractometer. The melting points were determined on a Cole-Parmer microscope melting point apparatus and are uncorrected. Intermediate **3** synthesized as literature report.[21] All the title compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.

Synthetic procedures

Optimized Synthetic Procedure for Compound 4

Compound **3** (50 mmol) and methanol (50 mL) was stirred in an ice bath. Sodium methoxide (2.67 g,50 mmol),was added slowly then the reaction mixture was heated to reflux for 4 h. and After cooling, the solid was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel using petroleum ether/ethyl acetate (EtOAc:PE = 3: 1) as eluent to give Compound **4** 81%.

Data for (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**4**): yield 81 %; white solid; mp 146 ℃; ^{1}H NMR (300 MHz, DMSO) δ 11.63 (s, 1H), 7.60 (d, *J* = 7.8 Hz, 1H), 7.42 (dt, *J* = 7.6, 3.8 Hz, 1H), 7.32 (t, *J* = 7.1 Hz, 1H), 7.22 (d, *J* = 7.7 Hz, 1H), 5.19 (s, 2H), 3.90 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ 168.42, 136.45, 130.44, 130.11, 126.53, 125.92, 124.63, 76.08, 62.52. HRMS (ESI) *m/z* calcd for $C_{10}H_{10}N_2O_3$ $(M+H)^+$ 207.0764, found 207.0765.

General procedure for the preparation of title compounds 5

Intermediate **4**(3 mmol) was dissolved in DMF (10 mL), and a catalytic amount of KI was added to the mixture, followed by the addition of 60% NaH(0.18 g, 4.5 mmol) at 10 °C. The reaction was allowed to stir for 1 h at this temperature. A solution of halides (3.3 mmol) in 2 mL of DMF was then added dropwise to the mixture, and the progress of the reaction was monitored by thin-layer chromatography. Upon completion, 30ml H_2O was added to the mixture, then extracted by ethyl acetate (3×60mL) and concentrated the organic layer to an oil. The pure compounds **5** was obtained by column chromatography (EtOAc:PE = 4:1) purification.

Data for (E)-5-(methoxyimino)-3-propyl-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-01)**. White crystal; yield, 52%; mp: 83-85°C. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.80 (d, *J* = 7.6 Hz, 1H), 7.46 – 7.31 (m, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.23 (s, 2H), 4.08 (s, 3H), 3.84 – 3.53 (m, 2H), 1.80 (tt, *J* = 14.3, 7.1 Hz, 2H), 1.01 (t, *J* = 7.4 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.27, 152.38, 135.28, 130.84, 129.60, 126.24, 124.86, 124.60, 74.26, 62.62, 47.50, 19.90, 10.93. HRMS (ESI) *m/z* calcd for $C_{13}H_{16}N_2O_3$ $(M+H)^+$ 249.1234, found 249.1234.

Data for (E)-3-butyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-02**): yield 57 %; white solid; mp 54-55 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88 – 7.71 (m, 1H), 7.40 (ddd, *J* = 20.1, 9.9, 3.9 Hz, 2H), 7.13 (d, *J* = 7.7 Hz, 1H), 5.24 (s, 2H), 4.09 (s, 3H), 3.81 – 3.62 (m, 2H), 1.77 (dt, *J* = 15.0, 7.6 Hz, 2H), 1.44 (dq, *J* = 14.7, 7.3 Hz, 2H), 1.00 (t, *J* = 7.3 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.23, 152.38, 135.28, 130.86, 129.59, 126.24, 124.88, 124.59, 74.28, 62.62, 45.69, 28.59, 19.68, 13.40. HRMS (ESI) *m/z* calcd for $C_{14}H_{18}N_2O_3$ $(M+H)^+$ 263.1390, found 263.1391.

Data for (E)-5-(methoxyimino)-3-pentyl-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-03**): yield 69 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.77 – 7.66 (m, 1H), 7.41 – 7.18 (m, 2H), 7.06 (d, *J* = 7.5 Hz, 1H), 5.16 (s, 2H), 4.00 (s, 3H), 3.70 – 3.54 (m, 2H), 1.84 – 1.60 (m, 2H), 1.45 – 1.19 (m, 4H), 0.88 (t, *J* = 6.8 Hz, 3H).^{13}C NMR (75 MHz,$CDCl_3$) δ 167.05, 152.39, 135.29, 130.71, 129.55, 126.13, 124.76, 124.63, 74.16, 62.48, 45.76, 28.47, 26.12, 21.91, 13.54. HRMS (ESI) *m/z* calcd for $C_{15}H_{20}N_2O_3$ $(M+H)^+$ 277.1547, found 277.1547.

Data for (E)-3-hexyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-04**): yield 75 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.71 (d, *J* = 7.6 Hz, 1H), 7.40 – 7.16 (m, 2H), 7.04 (d, *J* = 7.6 Hz, 1H), 5.14 (s, 2H), 3.98 (s, 3H), 3.71 – 3.48 (m, 2H), 1.68 (dd, *J* = 14.2, 7.1 Hz, 2H), 1.39 – 1.20 (m, 6H), 0.86 (t, *J* = 6.6 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.06, 152.38, 135.29, 130.71, 129.54, 126.12, 124.77, 124.62, 74.17, 62.46, 45.79, 31.02, 26.39, 26.00, 22.07, 13.59.HRMS (ESI) *m/z* calcd for $C_{16}H_{23}N_2O_3$ $(M+H)^+$ 291.1703, found 291.1702.

Data for (E)-3-heptyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-05**): yield 73 %; colorless oil; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.82 – 7.60 (m, 1H), 7.41 – 7.15 (m, 2H), 7.03 (d, *J* = 7.6 Hz, 1H), 5.13 (s, 2H), 3.98 (s, 3H), 3.74 – 3.51 (m, 2H), 1.79 – 1.60 (m, 2H), 1.41 – 1.18 (m, 8H), 0.85 (t, *J* = 6.7 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.03, 152.38, 135.29, 130.69, 129.51, 126.10, 124.77, 124.61, 74.16, 62.43, 45.76, 31.23, 28.49, 26.43, 26.28, 22.13, 13.64. HRMS (ESI) *m/z* calcd for $C_{17}H_{25}N_2O_3$ $(M+H)^+$ 305.1860, found 305.1864.

Data for (E)-3-allyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-06**): yield 34 %; white solid; mp 62-63 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, *J* = 7.6 Hz, 1H), 7.38 (dq, *J* = 14.2, 6.4 Hz, 2H), 7.13 (d, *J* = 7.5 Hz, 1H), 5.96 (ddt, *J* = 16.5, 10.1, 6.3 Hz, 1H), 5.38 (ddd, *J* = 13.6, 11.1, 1.1 Hz, 2H), 5.24 (s, 2H), 4.34 (d, *J* = 6.2 Hz, 2H), 4.09 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.35, 152.22, 135.36, 130.80, 130.63, 129.66, 126.22, 124.75, 124.69, 119.43, 74.79, 62.65, 48.80. HRMS (ESI) *m/z* calcd for $C_{13}H_{14}N_2O_3$ $(M+H)^+$ 247.1077, found 247.1078.

Data for (E)-5-(methoxyimino)-3-(prop-2-yn-1-yl)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-07**): yield 52.5 %; yellowish solid; mp 82-83 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.67 – 8.55 (m, 1H), 7.96 (s, 1H), 7.55 – 7.34 (m, 2H), 7.22 (d, *J* = 6.8 Hz, 1H), 5.26 (d, *J* = 15.0 Hz, 1H), 5.06 (d, *J* = 15.0 Hz, 1H), 4.77 (dd, *J* = 61.2, 2.6 Hz, 2H), 4.08 (d, *J* = 12.2 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 159.64, 157.22, 143.08, 135.42, 131.15, 129.91, 126.97, 124.23, 123.79, 123.01, 89.08, 65.23, 62.98. HRMS (ESI) *m/z* calcd for $C_{13}H_{12}N_2O_3$ $(M+H)^+$ 245.0921, found 245.0921.

Data for (E)-5-(methoxyimino)-3-(4-methylbenzyl)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one

(**5-08**): yield 50.9 %; white solid; mp 72-74 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 – 7.70 (m, 1H), 7.42 – 7.31 (m, 4H), 7.21 (d, *J* = 7.9 Hz, 2H), 7.01 (d, *J* = 7.1 Hz, 1H), 4.98 (s, 2H), 4.84 (s, 2H), 4.09 (s, 3H), 2.40 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.47, 152.28, 137.54, 135.42, 131.63, 130.89, 129.56, 129.07, 128.65, 126.20, 124.82, 124.57, 74.80, 62.70, 49.64, 20.84. HRMS (ESI) *m/z* calcd for $C_{18}H_{18}N_2O_3$ $(M+H)^+$ 311.1390, found 311.1390.

Data for (E)-3-(4-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-09**): yield 75 %; white solid; mp 93-94 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.84 –

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7.64 (m, 1H), 7.37 – 7.25 (m, 6H), 6.98 (d, *J* = 6.4 Hz, 1H), 4.95 (s, 2H), 4.77 (s, 2H), 4.03 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.66, 152.02, 135.14, 133.78, 133.24, 130.92, 130.03, 129.68, 128.60, 126.31, 124.72, 124.60, 74.83, 62.76, 49.27. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}ClN_2O_3$ $(M+H)^+$ 331.0844, found 331.0847.

Data for (E)-5-(methoxyimino)-3-(4-nitrobenzyl)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-10**): yield 56 %; yellowish solid; mp 92-93 ℃; ^{1}H NMR (300 MHz, DMSO) δ 8.39 – 8.20 (m, 2H), 7.66 (dd, *J* = 12.7, 4.9 Hz, 3H), 7.49 (td, *J* = 7.6, 1.4 Hz, 1H), 7.38 (t, *J* = 6.9 Hz, 1H), 7.27 (d, *J* = 7.8 Hz, 1H), 5.33 (s, 2H), 5.06 (s, 2H), 3.95 (s, 3H).^{13}C NMR (75 MHz, DMSO) δ 166.11, 152.38, 147.24, 143.36, 135.97, 130.49, 130.28, 129.47, 126.65, 125.86, 124.37, 123.92, 74.00, 62.68, 48.10. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}N_3O_5$ $(M+H)^+$ 342.1086, found 342.1084.

Data for (E)-4-((5-(methoxyimino)-4-oxo-4,5-dihydrobenzo[e][1,2]oxazepin-3(1H)-yl)methyl)benzonitrile (**5-11)**. Yellowish oil; yield, 26%. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 – 7.75 (m, 1H), 7.70 (d, *J* = 8.4 Hz, 2H), 7.54 (d, *J* = 8.4 Hz, 2H), 7.46 – 7.33 (m, 2H), 7.07 (d, *J* = 6.6 Hz, 1H), 5.08 (s, 2H), 4.92 (s, 2H), 4.09 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.80, 151.71, 140.07, 134.84, 132.22, 130.96, 129.80, 129.05, 126.46, 124.63, 124.60, 118.14, 111.79, 74.73, 62.84, 49.48. HRMS (ESI) m/z calcd for $C_{18}H_{16}N_3O_3$ (M+H)+ 322.1186, found 322.1185.

Data for (E)-3-(2-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-12**): yield 24 %; white solid; mp 69-70℃. ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.90 (d, *J* = 8.0 Hz, 1H), 7.60 – 7.50 (m, 1H), 7.41 (dd, *J* = 8.1, 5.6 Hz, 2H), 7.32 (t, *J* = 6.4 Hz, 2H), 7.29 (s, 1H), 7.15 (d, *J* = 7.6 Hz, 1H), 5.38 (s, 2H), 5.23 (s, 2H), 4.09 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 171.17, 147.18, 137.83, 133.12, 132.63, 130.31, 129.92, 129.34, 129.23, 129.15, 126.49, 125.88, 125.07, 71.84, 67.44, 62.82. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}ClN_2O_3$ $(M+H)^+$ 331.0844, found 331.0843.

Data for (E)-3-((2-chlorothiazol-5-yl)methyl)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-13**): yield 66 %; yellowish solid; mp 109-111 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.75 (d, *J* = 7.7 Hz, 1H), 7.58 (s, 1H), 7.36 (dt, *J* = 20.5, 6.7 Hz, 2H), 7.09 (d, *J* = 7.5 Hz, 1H), 5.19 (s, 2H), 4.92 (s, 2H), 4.05 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 168.12, 152.45, 151.55, 141.23, 134.91, 133.22, 130.89, 129.82, 126.37, 124.73, 124.50, 75.08, 62.83, 42.28. HRMS (ESI) *m/z* calcd for $C_{14}H_{12}ClN_3O_3S$ $(M+H)^+$ 338.0361, found 338.0367.

Data for (E)-3-((6-chloropyridin-3-yl)methyl)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-14**): yield 68 %; yellowish solid; mp 109-111 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.45 (d, *J* = 2.4 Hz, 1H), 7.84 – 7.71 (m, 2H), 7.46 – 7.31 (m, 3H), 7.07 (d, *J* = 7.3 Hz, 1H), 5.09 (s, 2H), 4.84 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.01, 151.67, 151.10, 149.71, 139.17, 134.82, 130.93, 129.79, 129.41, 126.43, 124.66, 124.56, 124.14, 74.84, 62.84, 46.73.HRMS (ESI) *m/z* calcd for $C_{16}H_{15}ClN_3O_3$ $(M+H)^+$ 332.0796, found 332.0792.

Data for (E)-methyl 2-(methoxyimino)-2-(2-(((E)-5-(methoxyimino)-4-oxo-4,5-dihydrobenzo[e][1,2]oxazepin-3(1H)-yl)methyl)phenyl)acetate (**5-15**): yield 63 %; white solid; mp 147 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 – 7.66 (m, 1H), 7.55 – 7.37 (m, 3H), 7.35 – 7.25 (m, 2H), 7.19 (dd, *J* = 5.4, 3.6 Hz, 1H), 6.94 (d, *J* = 7.7 Hz, 1H), 4.77 (s, 2H), 4.68 (s, 2H), 4.04 (s, 3H), 3.95 (s, 3H), 3.64 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.76, 162.98, 152.13, 148.36, 135.70, 133.15, 130.79, 130.49, 129.82, 129.47, 129.36, 128.45, 127.79, 126.03, 124.77, 124.62, 75.01, 63.46, 62.71, 52.48, 48.45. HRMS (ESI) *m/z* calcd for $C_{21}H_21N_3O_6$ $(M+H)^+$ 412.1503, found 412.1503.

Data for (E)-1,3-diallyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-16**): yield 42%; white solid; mp 52 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.61 (dd, *J* = 6.3, 2.8 Hz, 1H), 7.35 (ddd, *J* = 3.9, 3.2, 1.1 Hz, 2H), 7.22 – 7.06 (m, 1H), 6.13 (ddd, *J* = 17.2, 10.2, 7.0 Hz, 1H), 5.96 – 5.66 (m, 1H), 5.54 – 5.36 (m, 2H), 5.36 – 5.17 (m, 2H), 5.11 (d, *J* = 7.0 Hz, 1H), 5.00 (d, *J* = 14.9 Hz, 1H), 4.82 (d, *J* = 14.9 Hz, 1H), 4.61 (dd, *J* = 15.1, 4.7 Hz, 1H), 3.96 (d, *J* = 1.0 Hz, 3H), 3.44 (dd, *J* = 15.1, 8.2 Hz, 1H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 162.86, 154.10, 136.19, 133.16, 131.77, 130.73, 129.02, 127.25, 125.41, 119.11, 119.06, 90.77, 69.03, 62.06, 46.37. HRMS (ESI) *m/z* calcd for $C_{16}H_{18}N_2O_3$ $(M+H)^+$ 287.1390, found 287.1391.

Data for (E)-1,3-bis(2-chlorobenzyl)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-17**): yield 54 %; white solid; mp 96-97 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.74 (m, 1H), 7.68 (dd, *J* = 5.8, 3.3 Hz, 1H), 7.42 – 7.23 (m, 7H), 7.22 – 7.09 (m, 3H), 6.24 (s, 1H), 5.19 – 5.01 (m, 2H), 4.80 (d, *J* = 14.9 Hz, 1H), 4.31 (d, *J* = 15.5 Hz, 1H), 3.91 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ164.96, 154.11, 135.48, 133.75, 133.23, 133.19, 133.14, 130.61, 130.19, 129.89, 129.34, 129.28, 129.02, 128.63, 128.30, 127.62, 127.49, 126.71, 126.55, 125.89, 89.11, 72.15, 62.17, 44.21. . HRMS (ESI) *m/z* calcd for $C_{24}H_{20}Cl_2N_2O_3$ $(M+H)^+$ 455.0924, found 455.0930.

Data for (E)-5-(methoxyimino)-3-methyl-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-18**): yield 83 %; white solid; mp 106-107 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 – 7.70 (m, 1H), 7.39 (ddd, J = 15.3, 10.5, 4.3 Hz, 2H), 7.13 (d, J = 7.6 Hz, 1H), 5.24 (s, 2H), 4.08 (s, 3H), 3.32 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 167.36, 152.08, 135.24, 130.88, 129.63, 126.27, 124.82, 124.65, 73.65, 62.69, 32.44. HRMS (ESI) m/z calcd for $C_{11}H_{12}N_2O_3$ $(M+H)^+$ 221.0921, found 221.0919.

Data for (E)-3-ethyl-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one (**5-19**): yield 63 %; white solid; mp 61-62 ℃; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79 (d, J = 6.8 Hz, 1H), 7.45 – 7.31 (m, 2H), 7.13 (d, J = 7.7 Hz, 1H), 5.25 (s, 2H), 4.08 (s, 3H), 3.77 (q, J = 7.1 Hz, 2H), 1.36 (t, J = 7.1 Hz, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 167.38, 152.40, 135.34, 130.89, 129.59, 126.23, 124.94, 124.58, 74.57, 62.65, 40.94, 11.68. HRMS (ESI) m/z calcd for $C_{12}H_{14}N_2O_3$ $(M+H)^+$ 235.1070, found 235.1070.

X-ray Diffraction. Compound **5-09** was recrystallized by a slow evaporation from a dichloromethane/n-hexane (v/v = 1:5) solution to afford a single crystal suitable for X-ray crystallography and mounted in inert oil and transferred to the cold gas stream of the diffractometer. Cell dimensions and intensities were measured using a Thermo Fisher ESCALAB 250 diffractometer with graphite monochromated Mo Kα radiation. Compound **5-09**: orthorhombic, *a* =8.7758(3) Å, *b* = 10.3761(4) Å, *c* =16.7996(6) Å, *U* =1529.75(10) Å^3, *T* =104.8, space group $P2_12_12_1$ (no. 19), *Z* = 4, μ(Mo Kα) =0.267. A total of

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6446 reflections were measured, of which 3009 were unique (R_{int} = 0.0255) in the range of 6.54 <2Θ< 52°(-10 ≤ h ≤ 10, -12 ≤ k ≤ 10, -20 ≤ l ≤ 20), and 3009 observed reflections with I > 2σ (I) were used in the refinement on F2. The structure was solved by direct method with the SHELXTL-97 program. All of the non-H atoms were refined anisotropically by fullmatrix least-squares to give the final $wR(F_2)$= 0.0675. The atomic coordinates for **5-09** have been deposited at the Cambridge Crystallographic Data Centre. CCDC-1518111 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via CCDC CIF Depository Request Form for data published from 1994.Crystallographic data in CIF format are in the Supporting Information.

Biological Assays

Fungicidal Activity. The test fungi, *Sclerotinia sclerotiorum (Lib.) de Bary, Botrytis cinerea, Phytophthora infestans* (Mont.) De Bary, *Pythium aphanidermatum, Rhizoctonia solani*, *Setosphaeria turcica*, *Pyricularia grisea* and *Colletotrichum. orbiculare* (Berk. & Ment.) were provided by the Laboratory of Institute of Plant Protection, Chinese Academy of Agricultural Sciences. After retrieval from the storage tube, the strains were incubated in PDA at 25 °C for several days to get new mycelia for the antifungal assay.[22] Azoxystrobin and trifloxystrobin, gifts from Jiangsu Frey Chemicals Co. were used as control. The synthesized compounds and controls were dissolved in DMSO to prepare the 20 mg·mL-1 stock solution before mixing with molten agar. The media containing compounds at a concentration of 50 μg·mL-1 for initial screening were then poured into sterilized Petri dishes for the initial screening. Their relative inhibition ratio (%) was calculated as following equation:

(colony diameter of control − colony diameter of treatment) / (colony diameter of control − mycelial disks diameter) × 100%.

This experiment was conducted twice with three replicates. The fungicidal activity is listed in table 2.

The 20 $mg \cdot mL^{-1}$ stock solution was diluted diluted with PDA to obtain a series of concentrations, repeat the experiments above, and calculated the inhibition rate separately. The EC50 was calculated by spss statistics v17.0 and listed in table 3.

QSAR Analyses. Topomer CoMFA (in the SYBYL X 7.3 program) was performed to analysis the relationship between structure and activity. Topomer CoMFA is an alignment-independent 3D-QSAR method that combines the topomer search method[23] with the conventional CoMFA method. Besides the core of the molecule, we split the functional of compound into two R-groups that refer to the R_1 (benzoxazepinone moiety) and R_2(R substituent) groups. In total, 20 compounds obtained from synthesis were used to create a data set in which the inhibition rate of all compounds was determined (Table 1) against *setosphaeria turcica*. Three-dimensional of the target compounds structures were built by the Chem3D software version 12.0.

Conclusions

In summary, we provid a novel and scalable method to prepare (E)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1H)-one through a commercial available intermediate as raw material. Compound **3** underwent an efficient intramolecular cyclization and provided good isolated yields of **4** under optimized reacting condition. Interestingly, some of these compounds displayed excellent agricultural fungicidal activities, even comparing with recently commercial products. Overall, we report a practical way to access these benzoxazepinones for their novel structure and fungicidal activities that could be of great utility for pharmacist as new scaffolds for SAR studies of their nitrogen and oxygen containing heterocycles and clearly point out the direction of the optimization of better fungicide candidate. Thus, it is significantly important for new pestcide design and development.

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Notes and references

The authors declare no competing financial interest.

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