Molecular Diversity (2021) 25:159–169
https://doi.org/10.1007/s11030-020-10035-z

ORIGINAL ARTICLE

Design, synthesis and antifungal activity of (*E*)-3-acyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one analogues

Dongyan Yang[1] · Haixia Wang[1] · Zhijin Fan[1] · Zhengming Li[1] · Shuang Zhou[1] · Zesheng Hao[1] · You Lv[1] · Tatiana A. Kalinina[2] · Tatiana V. Glukhareva[2]

Received: 29 September 2019 / Accepted: 8 January 2020 / Published online: 21 January 2020

Abstract

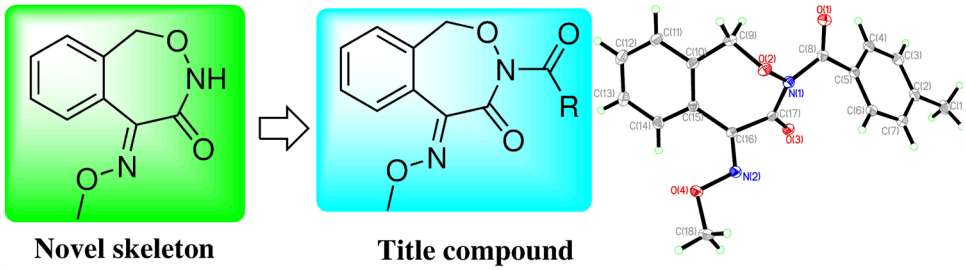
Nitrogen- or oxygen-containing organic compounds which have significant antifungal activity, twenty one novel nitrogen or oxygen-containing (*E*)-3-acyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one analogues were designed and synthesized, and their structures were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS. Preliminary bioassay showed that most of them exhibited certain-to-good antifungal activity. Compounds **5k-2**, **5n**, **5p** and **5r** exhibited over 80% inhibitory rate against *Sclerotinia sclerotiorum* at 50 μg/mL, and **5r** exhibited good antifungal activity against *S. sclerotiorum* with EC_{50} of 7.21 μg/mL. Compounds **5a** and **5r** also showed over 90% inhibition against *Botrytis cinerea*. In particular, **5r** showed significant higher activity with the lowest EC_{50} of 7.92 μg/mL than the positive control trifloxystrobin (21.96 μg/mL) and azoxystrobin (9.43 μg/mL).

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s11030-020-10035-z) contains supplementary material, which is available to authorized users.

Extended author information available on the last page of the article

Graphic abstract

Providing a practical method for the synthesis of new scaffolds 1,2-Benzoxazepinone and systematically investigate their antifungal activity.



Compd \ Fungi	EC_{50}/ μg/mL	
	Botrytis cinerea	*Sclerotinia sclerotiorum*
5r	7.92	7.21
Trifloxystrobin	21.96	0.89
Azoxystrobin	9.43	2.52

Keywords Heterocyclic · Benzoxazepinone · Synthesis · Antifungal activity

Introduction

Natural product-based lead derivation is one of the most important methods for novel pesticide development [1]; however, heterocyclic compounds are important source of pharmaceuticals, agrochemicals and materials [1–3]. The introduction of heteroatoms into drug leads often to improve their biological activity and permeability [4]. In addition, nitrogen- or oxygen-containing heterocyclic compounds are widely used as pesticide for plant protection [5–8]. Medium-size heterocycles attract the attention of chemists, especially seven-member heterocycles. Compounds containing a seven-member heterocycle skeleton have aroused great interest from chemists and have been reported to have various kinds of activities including antitumor, anticancer, anti-histamine and mammalian target of rapamycin inhibitory effect [9–13]. Benzoxazepinones are bicyclic compounds consisting benzene and an oxazepane ring, and were described to possess a wide range of biological activities [14, 15].

In view of the outstanding biological activity of benzoxazinone, the search for the methods for synthesizing such compounds has become a topic of great interest to chemists. The groups of Pifferi presented a one-step transformation of o-bromomethylphenethyl bromide and the potassium salt of *N*-hydroxyurethan into 1,2-benzoxazepinone (Fig. 1 eq. 1) [16]. Bailey and Bremner reported a Meisenheimer rearrangement method to prepare benzoxazepines from dibenzazepine *N*-oxide derivative (Fig. 1 eq. 2) [17, 18]. Seomoon and co-workers reported palladium-catalyzed cross-coupling reactions of allyl to form benzoxazepines (Fig. 1 eq. 3) [19]. However, methods for the synthesis of 1,2-benzoxazepinone skeleton from commercial available materials and their applications in agriculture are still limited.

In recent decades, more and more fungicides targeting at respiratory chain complex III have been developed, for example trifloxystrobin, azoxystrobin and kresoxim-methyl [20]. Based on the pesticide design principle, we reported the synthesis of a novel compound by combining active substructures of plant elicitor with strobilurins, the compound exhibited excellent fungicidal activities [21]. During the preparation of compound I, compound II was obtained as a main by-product. For the interest in bicyclic compounds, especially nitrogen- and oxygen-containing heterocycles and in order to investigate the structure–activity relationship in agriculture and as a continuation of our previous work [22], we modified this skeleton of benzoxazepinone as a lead compound to obtain a series of title compounds (Fig. 2). Here, we present a mild and easy method to construct

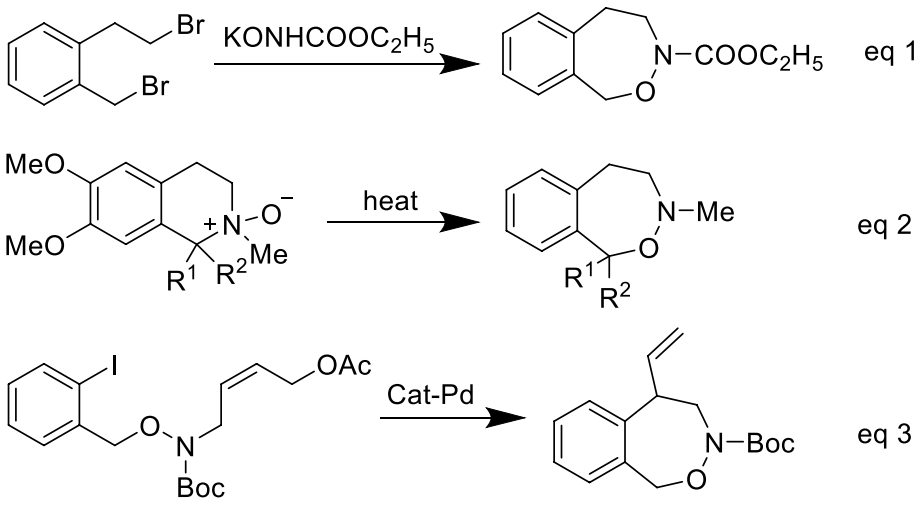


Fig. 1 1,2-benzoxazepinone skeleton synthesis

(*E*)-3-acyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2] oxazepin-4(3*H*)-one analogues through four steps with the commercially available reagent as a starting material, and antifungal activity against nine common plant pathogens of all target compounds was evaluated, and several derivatives exhibited excellent antifungal activity and were chosen for EC_{50} assessment.

Results and discussion

Chemistry

The synthetic route to target compounds **5a–5u** from the commercially available starting materials is given in Scheme 1. The starting material **1** was an important intermediate of agricultural fungicide strobilurin, which was widely used for efficient fungicide production and was mass produced. The starting material **1** was reacted with N-hydroxyphthalimide to yield the intermediate **2**; hydrazinolysis of the intermediate **2** in the solution of hydrazine hydrate in methanol obtained the key intermediate **3**. The precursor **4** (*E*)-5-(methoxyimino)-1,5-dihydrobenzo[e] [1,2]oxazepin-4(3*H*)-one was obtained by intramolecular cyclization of the intermediate **3** at sodium methoxide–methanol solution under reflux condition. Target compounds **5a–5u** were synthesized by an amidation reaction from the precursor **4** with different acyl chloride in the presence of triethylamine and had favorable yields. In the last step reaction progress (Scheme 2), we found that **4** reacted with p-toluoyl chloride, giving not only compound **5k** but also by-product **5k-2**. The reason was that **4** underwent prototropic tautomerism resulting enol species, and then underwent acylation in amidation reaction. In the literature, only a fewer examples reported tautomerism when acyl chloride reacted with acylamide [23]. In addition, the structures of **5k** and **5k-2** were further identified by X-ray diffraction studies.

Crystal structure analysis

In order to confirm the structure of the target compounds and by-products, the crystal of compound **5k** and **5k-2** were cultured from the corresponding solvent mixture of CH_2Cl_2 and n-hexane (v/v = 1:5), and the structures are shown in Figs. 3 and 4. Single-crystal X-ray diffraction analysis showed that the crystal structure of compound **5k** belonged to the orthorhombic crystal system, space group Pca2(1), and compound **5k-2** belonged to the triclinic crystal system, space group P-1. As shown in Figs. 3 and 4, The seven-membered ring of compound **5k** and **5k-2** were twisted and the two amide bonds of compound **5k** were opposite which was contrast to **5k-2**. The details of the crystallographic data and structure refinement parameters were summarized and listed in the supporting information.

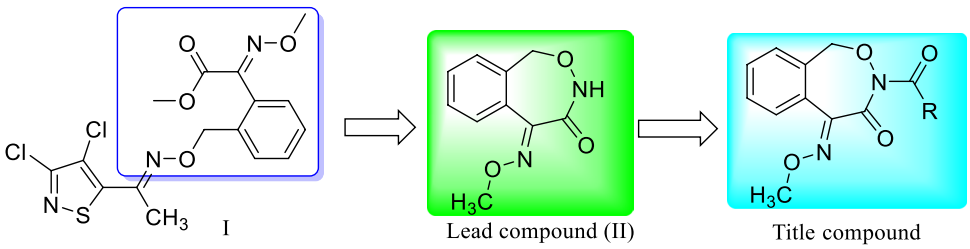
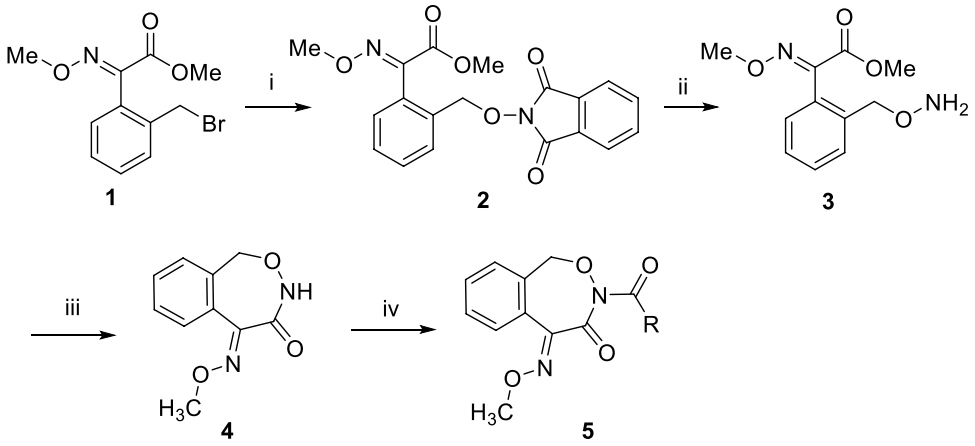
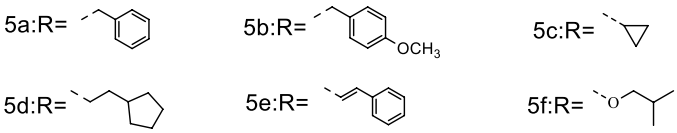


Fig. 2 Designation approach for novel benzoxazepinone molecules

Scheme 1 General synthesis procedure for compounds **5a–5u**

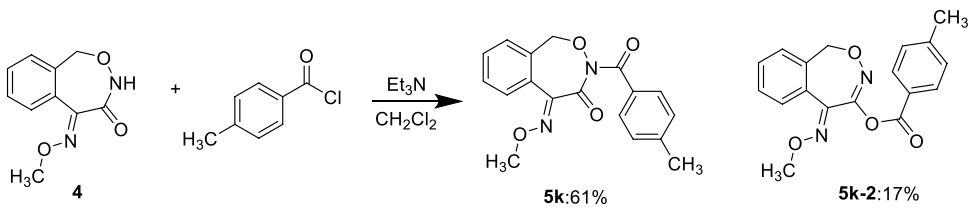


i.:N-Hydroxyphthalimide,Et_3N,DMF,rt,8h; ii.85% hydrazine hydrate, MeOH, rt ,2h; iii. NaOMe,MeOH,reflux, 4h; iv. Et_3N,CH_2Cl_2,RCOCl



5g:R=Me, 5h:R=Et, 5i:R=Ph, 5j:R=4-OCH_3-Ph, 5k:R=4-CH_3-Ph, 5l:R=3-Cl-4-F-Ph, 5m:R=4-CF_3-Ph, 5n:R=4-tBu-Ph, 5o:R=2-F-Ph, 5p:R=3-F-Ph, 5q:R=4-F-Ph, 5r:R=4-N,N$(CH_3)_2$-Ph, 5s:R=4-Cl-Ph, 5t:R=vinyl, 5u:R=n-pentyl.

Scheme 2 Side reactions in the amidation progress



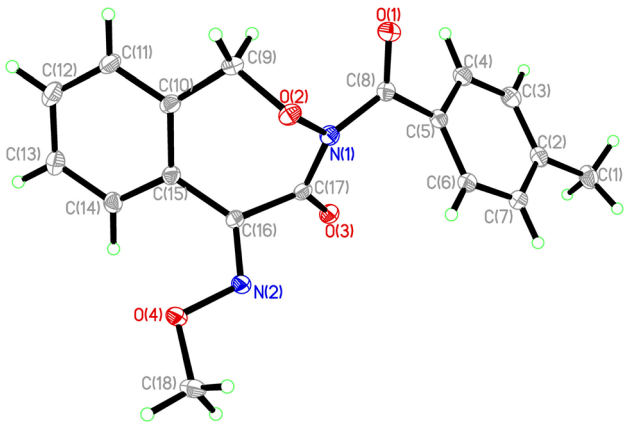


Fig. 3 X-ray crystal structure of **5k** (CCDC-1953743)

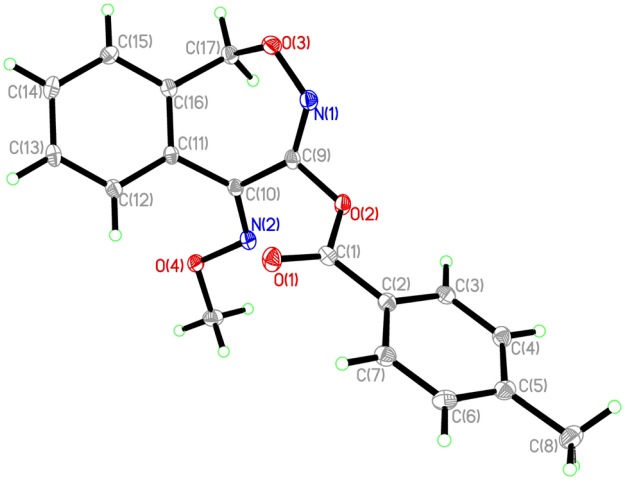


Fig. 4 X-ray crystal structure of **5k-2** (CCDC-1953744)

Antifungal activity

Initially antifungal activities of **5a–5u** against nine common phytopathogens at 50 μg/mL and by-product **5k-2** were evaluated under the same conditions. The results are given in Table 1. As can be seen, most of target compounds exhibited certain-to-high antifungal activities at 50 μg/mL. Several compounds exhibited excellent antifungal activity against *B. cinerea* and *S. sclerotiorum* at 50 μg/mL in vitro. Compounds **5a**, **5j**, **5o** and **5r** showed higher than 70% inhibition against *B. cinerea.* In particular, **5a** and **5r** exhibited outstanding activity (> 90%), which was comparable to the positive controls trifloxystrobin and azoxystrobin. Compounds **5n**, **5p** and **5r** and by-product **5k-2** showed higher than 80% inhibition rate against *S. sclerotiorum.* In general, compounds with aryl group substitution (**5i–5s**) showed better antifungal activity than alkyl substitute compounds (**5c–5h**, **5t**, **5u**). As compared with commercial strobilurin fungicides, target compounds were not as broad spectrum as trifloxystrobin and azoxystrobin.

On the basis of the results of initial antifungal activities at 50 μg/mL, the compounds with good inhibition were selected for further potency determination. As shown in Table 2, **5p** and **5r** exhibited good antifungal activity against *S. sclerotiorum* with an EC_{50} value of 8.72 μg/mL, 7.21 μg/mL, respectively, at the same level as that of the positive control azoxystrobin with an EC_{50} value of 2.52 μg/mL. Compound **5j** with 4-OCH_3-ph substitution and **5r** with 4-*N*,*N*-$(CH_3)_2$Ph substitution were not only effective against *S. sclerotiorum* but also *B. cinerea*. Compound **5r** exhibited strong inhibition of the growth of *B. cinerea*, with an EC_{50} value of 7.92 μg/mL, it was much better than those of positive control trifloxystrobin and azoxystrobin with a corresponding EC_{50} value of 21.96 μg/mL and 9.43 μg/mL, respectively. Compound **5r** with 4-*N*,*N*-$(CH_3)_2$-ph substitution was the most effective agent against these fungi and could be as an antifungal lead for further optimization.

Table 1 *In vitro* antifungal activity of target compounds against phytopathogens

Compd.	Mycelium growth inhibitory rate (%) at 50 μg/mL								
	AS	BC	CA	GZ	PI	PP	PS	RC	SS
5a	17 ± 0	98 ± 0	3 ± 3	50 ± 2	4 ± 0	4 ± 2	10 ± 0	11 ± 0	46 ± 0
5b	15 ± 0	6 ± 0	3 ± 0	14 ± 0	6 ± 0	14 ± 0	20 ± 2	NA	62 ± 0
5c	13 ± 0	17 ± 4	3 ± 3	11 ± 2	9 ± 2	13 ± 0	12 ± 0	NA	46 ± 0
5d	17 ± 4	66 ± 0	6 ± 0	55 ± 0	15 ± 0	11 ± 3	18 ± 0	2 ± 2	54 ± 4
5e	15 ± 0	13 ± 0	6 ± 0	39 ± 0	4 ± 0	21 ± 2	14 ± 0	9 ± 2	62 ± 7
5f	15 ± 0	21 ± 4	NA	9 ± 0	6 ± 0	2 ± 2	10 ± 0	9 ± 2	4 ± 0
5g	9 ± 4	13 ± 0	3 ± 0	7 ± 0	6 ± 0	9 ± 4	8 ± 0	5 ± 3	58 ± 4
5h	13 ± 4	64 ± 2	3 ± 3	55 ± 4	6 ± 2	2 ± 0	14 ± 2	8 ± 2	12 ± 4
5i	15 ± 4	6 ± 4	6 ± 0	14 ± 0	6 ± 0	13 ± 3	16 ± 0	8 ± 2	10 ± 9
5j	28 ± 0	79 ± 2	20 ± 3	48 ± 5	13 ± 0	41 ± 3	29 ± 2	58 ± 2	73 ± 0
5k	13 ± 4	34 ± 0	3 ± 0	23 ± 0	9 ± 2	14 ± 0	14 ± 0	3 ± 0	69 ± 0
5k-2	26 ± 4	36 ± 0	20 ± 0	36 ± 0	19 ± 4	NA	24 ± 4	11 ± 2	88 ± 0
5l	13 ± 0	40 ± 0	17 ± 3	25 ± 4	11 ± 2	14 ± 2	33 ± 0	9 ± 0	65 ± 4
5m	20 ± 0	32 ± 0	11 ± 0	30 ± 0	13 ± 2	20 ± 2	20 ± 2	25 ± 0	54 ± 4
5n	20 ± 0	63 ± 2	23 ± 0	52 ± 0	34 ± 0	32 ± 0	39 ± 2	23 ± 0	100
5o	17 ± 0	77 ± 2	6 ± 0	41 ± 0	11 ± 0	16 ± 2	10 ± 0	2 ± 0	50 ± 0
5p	20 ± 0	38 ± 0	11 ± 0	32 ± 0	9 ± 0	18 ± 0	20 ± 0	11 ± 0	81 ± 0
5q	17 ± 0	9 ± 0	9 ± 3	30 ± 0	13 ± 0	21 ± 0	8 ± 4	8 ± 3	58 ± 4
5r	24 ± 2	94 ± 0	17 ± 0	52 ± 0	30 ± 4	45 ± 0	24 ± 2	40 ± 2	88 ± 0
5s	15 ± 2	19 ± 0	11 ± 0	23 ± 0	21 ± 0	5 ± 3	22 ± 4	12 ± 0	77 ± 0
5t	15 ± 0	11 ± 0	6 ± 0	11 ± 4	2 ± 0	27 ± 2	12 ± 0	6 ± 0	31 ± 0
5u	15 ± 2	26 ± 4	3 ± 0	2 ± 0	4 ± 0	9 ± 2	8 ± 2	12 ± 2	50 ± 0
Trifloxystrobin	54 ± 0	98 ± 0	74 ± 0	82 ± 8	81 ± 0	79 ± 6	88 ± 0	89 ± 0	94 ± 2
Azoxystrobin	48 ± 4	96 ± 0	69 ± 0	79 ± 1	76 ± 1	82 ± 1	73 ± 1	63 ± 0	100

AS, *Alternaria solani*; BC, *Botrytis cinerea*; CA, *Cercospora arachidicola*; GZ, *Gibberella zeae*; PI, *Phytophthora infestans* (Mont) de Bary; PP, *Physalospora piricola*; PS, *Pellicularia sasakii*; RC, *Rhizoctonia cerealis*; SS, *Sclerotinia sclerotiorum*

NA no activity

Table 2 In vitro antifungal EC_{50} (μg/mL) of the selected compounds

Fungi	Compd.	EC_{50}	Regression equation	R^2
SS	**5j**	11.57	$y = 3.6417 + 1.3227\,x$	0.9807
	5k-2	26.33	$y = 3.1687 + 1.2943\,x$	0.9895
	5n	15.71	$y = 1.6604 + 2.8359\,x$	0.9825
	5p	8.72	$y = 4.0407 + 1.0211\,x$	0.9175
	5r	7.21	$y = 4.1390 + 1.0330\,x$	0.9823
	5s	20.14	$y = 2.8727 + 1.6550\,x$	0.9686
	Trifloxystrobin	0.89	$y = 5.0464 + 0.8075\,x$	0.9839
	Azoxystrobin	2.52	$y = 4.4666 + 1.4417\,x$	0.9418
BC	**5a**	13.20	$y = 2.4937 + 2.2901\,x$	0.9267
	5j	22.69	$y = 2.8942 + 1.5604\,x$	0.9718
	5o	17.30	$y = 3.8021 + 0.9955\,x$	0.9879
	5r	7.92	$y = 2.9953 + 2.3250\,x$	0.9894
	Trifloxystrobin	21.96	$y = 2.7578 + 1.7124\,x$	0.9144
	Azoxystrobin	9.43	$y = 3.4896 + 1.6002\,x$	0.9521

Conclusions

In summary, the (*E*)-3-acyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one analogues were prepared and systematically evaluated for their antifungal activities. Most of these seven-member heterocyclic contained compounds showed certain-to-high antifungal activity. In particular, **5r** showed excellent activity against *B. cinerea* and *S. sclerotiorum* with the EC_{50} value 7.92 μg/mL, 7.21 μg/mL, respectively. Combining the active substructure in hand, this work is significantly important for the investigation of the structure–activity relationship of the novel nitrogen- and oxygen-containing heterocyclic benzoxazepine derivatives.

Experimental

Instrumentation and materials

The melting points of all compounds were determined using an X-4 microscope (Gongyi Technical Instrument Co., Chengzhou, China), and the thermometer was not corrected. ^{1}HNMR and ^{13}C NMR spectra were obtained at 400 MHz using a Bruker Avance AV400 spectrometer in $CDCl_3$ with tetramethylsilane as the internal standard. Chemical shift values (δ) were given in parts per million. High-resolution mass spectrometry data were obtained with an Agilent 6520 Q-TOF LC/MS system equipped with electrospray ionization (ESI) source. The single-crystal structure analysis was performed using X-ray diffraction with a Rigaku 007 Saturn 70 diffractometer. The yields of target compounds were not optimized. For all reactions, solvents and chemical reagents were of analytical or synthetic grade and used without further purification. The key intermediates **3** and **4** were prepared in our laboratory before [22, 24]. All the target compounds were confirmed by ^{1}H NMR, ^{13}C NMR and HRMS.

General procedures for the preparation of target compounds 5a–5u

Compounds **5a–5u** were synthesized by the reaction of intermediate **4** with corresponding acyl chloride. The mixture of intermediate **4** (0.40 mmol) and triethylamine (Et_3N) (1.2 mmol) was stirred in dry CH_2Cl_2 (10 mL) in an ice water bath for 10 min. Then, corresponding acyl chloride (0.44 mmol) was dissolved in 10 mL of CH_2Cl_2 and added to the mixture solution. The reaction mixture was then stirred at room temperature for 2–4 h and monitored with thin layer chromatography (TLC). Subsequently, 20 mL of water was added to the mixture, and the reaction was extracted with CH_2Cl_2 (3 × 20 mL). The combined organic layers were washed with saturated sodium bicarbonate (20 mL) and brine (20 mL) and dried over anhydrous sodium sulfate, and then concentrated in vacuum. The residue was purified by column chromatography on silica gel to give compounds **5a–5u**.

Data for (*E*)-5-(methoxyimino)-3-(2-phenylacetyl)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5a**): Yield 71%; white solid; mp 115–116 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.8, 1.4 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.24 (m, 6H), 7.16–7.07 (m, 1H), 5.34 (s, 2H), 4.20 (s, 2H), 4.10 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 7.75 (dd, J = 7.8, 1.4 Hz, 1H), 7.44 (td, J = 7.5, 1.4 Hz, 1H), 7.41–7.24 (m, 6H), 7.16–7.07 (m, 1H), 5.34 (s, 2H), 4.20 (s, 2H), 4.10 (s, 3H). HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_4$ $(M+H)^+$ 325.1183, found 325.1185.

Data for (*E*)-5-(methoxyimino)-3-(2-(4-methoxyphenyl)acetyl)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5b**): Yield 82%; white solid; mp 120–121 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.9, 1.4 Hz, 1H), 7.39 (dtd, J = 26.4, 7.5, 1.4 Hz, 2H), 7.22–7.13 (m, 2H), 7.10 (d, J = 7.7 Hz, 1H), 6.91–6.72 (m, 2H), 5.31 (s, 2H), 4.12 (s, 2H), 4.08 (s, 3H), 3.78 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 168.35, 164.45, 158.85, 151.68, 134.89, 131.19, 130.73, 130.53, 127.13, 125.25, 124.48, 123.67, 114.00, 75.94, 63.42, 55.24, 42.67. HRMS (ESI) *m/z* calcd for $C_{19}H_{19}N_2O_5$ $(M+H)^+$ 355.1288, found 355.1288.

Data for (*E*)-3-(cyclopropanecarbonyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5c**): Yield 73%; white solid; mp 126–127 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.7 Hz, 1H), 7.54–7.31 (m, 2H), 7.13 (d, J = 7.7 Hz, 1H), 5.33 (s, 2H), 4.08 (s, 3H), 2.89–2.73 (m, 1H), 1.23 (t, J = 4.0 Hz, 2H), 1.05 (dq, J = 7.8, 3.9 Hz, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 171.43, 164.71, 151.93, 135.03, 131.21, 130.48, 127.10, 125.23, 123.90, 76.06, 63.37, 14.74, 11.27. HRMS

(ESI) *m/z* calcd for $C_{14}H_{15}N_2O_4$ $(M+H)^+$ 275.1026, found 275.1028.

Data for (*E*)-3-(3-cyclopentylpropanoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5d**): Yield 83%; white solid; mp 121–122 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, J = 7.8 Hz, 1H), 7.39 (dt, J = 28.3, 7.5 Hz, 2H), 7.12 (d, J = 7.7 Hz, 1H), 5.33 (s, 2H), 4.07 (s, 3H), 2.83 (t, J = 7.7 Hz, 2H), 1.74 (ddq, J = 31.2, 14.5, 7.1 Hz, 5H), 1.60 (td, J = 7.6, 3.2 Hz, 2H), 1.55–1.42 (m, 2H), 1.19–0.99 (m, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.26, 164.36, 151.82, 134.99, 131.20, 130.52, 127.13, 125.25, 123.75, 76.00, 63.39, 39.53, 36.83, 32.41, 30.21, 25.11. HRMS (ESI) *m/z* calcd for $C_{18}H_{23}N_2O_4$ $(M+H)^+$ 331.1652, found 331.1659.

Data for (*E*)-3-cinnamoyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5e**): Yield 81%; white solid; mp 127–128 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.95 (d, J = 15.7 Hz, 1H), 7.77 (dd, J = 7.8, 1.4 Hz, 1H), 7.64–7.56 (m, 2H), 7.51 (d, J = 15.7 Hz, 1H), 7.47–7.34 (m, 5H), 7.15 (d, J = 7.7 Hz, 1H), 5.43 (s, 2H), 4.11 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.62, 162.80, 151.84, 147.58, 134.95, 134.27, 131.20, 131.00, 128.96, 128.68, 127.15, 125.26, 123.86, 117.94, 99.99, 76.22, 63.41. HRMS (ESI) *m/z* calcd for $C_{19}H_{17}N_2O_4$ $(M+H)^+$ 337.1183, found 337.1188.

Data for isobutyl (*E*)-5-(methoxyimino)-4-oxo-4,5-dihydrobenzo[e][1,2]oxazepine-3(1*H*)-carboxylate (**5f**): Yield 91%; white solid; mp 132–133 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (d, J = 7.9 Hz, 1H), 7.42 (td, J = 7.6, 1.4 Hz, 1H), 7.35 (td, J = 7.7, 1.3 Hz, 1H), 7.13 (d, J = 7.7 Hz, 1H), 5.35 (s, 2H), 4.13 (d, J = 6.5 Hz, 2H), 4.06 (s, 3H), 2.06 (dp, J = 13.3, 6.7 Hz, 1H), 1.00 (d, J = 6.8 Hz, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 162.79, 151.80, 150.04, 134.54, 131.23, 130.43, 127.12, 125.18, 124.09, 76.23, 73.98, 63.33, 27.78, 18.88. HRMS (ESI) *m/z* calcd for $C_{15}H_{19}N_2O_5$ $(M+H)^+$ 307.1288, found 307.1295.

Data for (*E*)-3-acetyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5g**): Yield 75%; white solid; mp134–135 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (dd, J = 8.0, 1.4 Hz, 1H), 7.43 (td, J = 7.6, 1.4 Hz, 1H), 7.36 (td, J = 7.6, 1.3 Hz, 1H), 7.18–7.07 (m, 1H), 5.34 (s, 2H), 4.08 (s, 3H), 2.52 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.71, 164.46, 151.64, 134.89, 131.21, 130.55, 127.16, 125.25, 123.70, 76.05, 63.41, 25.39. HRMS (ESI) *m/z* calcd for $C_{12}H_{13}N_2O_4$ $(M+H)^+$ 249.0870, found 249.0873.

Data for (*E*)-5-(methoxyimino)-3-propionyl-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5h**): Yield 83%; white solid; mp 105–106 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dd, J = 7.9, 1.3 Hz, 1H), 7.47–7.29 (m, 2H), 7.12 (d, J = 7.7 Hz, 1H), 5.34 (s, 2H), 4.07 (s, 3H), 2.84 (q, J = 7.3 Hz, 2H), 1.19 (t, J = 7.3 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.82, 164.41, 151.79, 134.99, 131.19, 130.51, 127.11, 125.24, 123.75, 75.99, 63.36, 31.13, 8.13. HRMS (ESI) *m/z* calcd for $C_{13}H_{15}N_2O_4$ $(M+H)^+$ 263.1026, found 263.1030.

Data for (*E*)-3-benzoyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5i**): Yield 30%; white solid; mp 164–165 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80–7.71 (m, 1H), 7.61 (d, J = 7.4 Hz, 2H), 7.58–7.51 (m, 1H), 7.46 (tt, J = 7.6, 1.3 Hz, 1H), 7.43–7.35 (m, 3H), 7.17 (d, J = 7.7 Hz, 1H), 5.37 (s, 2H), 4.08 (d, J = 1.1 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.75, 164.66, 151.49, 134.76, 132.97, 132.81, 131.42, 130.57, 128.92, 128.27, 127.19, 125.33, 124.22, 76.77, 63.48. HRMS (ESI) *m/z* calcd for $C_{17}H_{15}N_2O_4$ $(M+H)^+$ 311.1026, found 311.1031.

Data for (*E*)-3-(4-methoxybenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5j**): Yield 67%; white solid; mp 129–130 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, J = 7.8 Hz, 1H), 7.68–7.57 (m, 2H), 7.51–7.31 (m, 2H), 7.15 (d, J = 7.7 Hz, 1H), 6.91–6.74 (m, 2H), 5.35 (s, 2H), 4.07 (d, J = 1.5 Hz, 3H), 3.84 (d, J = 2.4 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.04, 165.02, 163.70, 151.69, 134.88, 131.77, 131.39, 130.51, 127.12, 125.29, 124.66, 124.35, 113.63, 76.75, 63.43, 55.50. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_5$ $(M+H)^+$ 341.1132, found 341.1132.

Data for (*E*)-5-(methoxyimino)-3-(4-methylbenzoyl)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5k**): Yield 61%; white solid; mp 165–166 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (dd, J = 7.8, 1.4 Hz, 1H), 7.60–7.54 (m, 2H), 7.45 (dtd, J = 26.6, 7.5, 1.4 Hz, 2H), 7.26–7.13 (m, 3H), 5.39 (s, 2H), 4.11 (s, 3H), 2.43 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.67, 164.77, 151.61, 144.03, 134.83, 131.40, 130.53, 129.85, 129.23, 128.99, 127.15, 125.31, 124.28, 76.76, 63.45, 21.76. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_4$ $(M+H)^+$ 325.1183, found 325.1187.

Data for (*E*)-5-(methoxyimino)-3-(4-methylbenzoyl)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5k-2**): Yield 17%; white solid; mp 156–157 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.08–7.98 (m, 2H), 7.89–7.82 (m, 1H), 7.46–7.35 (m, 2H), 7.29 (d, J = 8.0 Hz, 2H), 7.23 (dd, J = 7.2, 1.7 Hz, 1H), 5.27 (s, 2H), 3.95 (s, 3H), 2.44 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.79, 159.80, 146.62, 145.34, 135.52, 130.67, 130.58, 130.51, 129.42, 127.72, 127.47, 126.60, 125.16, 73.98, 63.61, 21.86. HRMS (ESI) *m/z* calcd for $C_{18}H_{17}N_2O_4$ $(M+H)^+$ 325.1183, found 325.1188.

Data for (*E*)-3-(3-chloro-4-fluorobenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5l**): Yield 65%; white solid; mp 170–171 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84–7.66 (m, 2H), 7.56–7.35 (m, 3H), 7.24–7.05 (m, 2H), 5.38 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.72, 164.59, 162.11, 159.56, 151.15, 134.49, 131.81, 131.48, 130.68, 129.89, 129.85, 129.51, 129.42, 127.33, 125.30, 123.99, 116.72, 116.50,

76.93, 63.57. HRMS (ESI) *m/z* calcd for $C_{17}H_{13}ClFN_2O_4$ $(M+H)^+$ 363.0542, found 363.0540.

Data for (*E*)-5-(methoxyimino)-3-(4-(trifluoromethyl) benzoyl)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5m**): Yield 36%; white solid; mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, $J=7.8$, 1.4 Hz, 1H), 7.72–7.63 (m, 4H), 7.48 (td, $J=7.6$, 1.5 Hz, 1H), 7.40 (t, $J=7.1$ Hz, 1H), 7.18 (d, $J=7.7$ Hz, 1H), 5.40 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.61, 164.53, 151.06, 136.26, 134.49, 134.28, 133.94, 131.46, 130.69, 129.01, 127.33, 125.38, 125.33, 125.31, 125.27, 123.98, 122.07, 76.89, 63.58. HRMS (ESI) *m/z* calcd for $C_{18}H_{14}F_3N_2O_4$ $(M+H)^+$ 379.0900, found 379.0902.

Data for (*E*)-3-(4-(*tert*-butyl)benzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5n**): Yield 40%; white solid; mp 174–175 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J=7.9$ Hz, 1H), 7.57 (d, $J=8.2$ Hz, 2H), 7.50–7.33 (m, 4H), 7.15 (d, $J=7.7$ Hz, 1H), 5.35 (s, 2H), 4.07 (d, $J=0.9$ Hz, 3H), 1.31 (s, 9H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.63, 164.80, 156.91, 151.56, 134.82, 131.41, 130.52, 129.73, 129.10, 127.15, 125.30, 124.32, 76.77, 63.47, 35.16, 31.05. HRMS (ESI) *m/z* calcd for $C_{21}H_{23}N_2O_4$ $(M+H)^+$ 367.1652, found 367.1656.

Data for (*E*)-3-(2-fluorobenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5o**): Yield 70%; white solid; mp 189–190 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, $J=7.9$ Hz, 1H), 7.47 (ddt, $J=45.6$, 30.7, 7.3 Hz, 4H), 7.31–7.10 (m, 2H), 6.99 (t, $J=9.3$ Hz, 1H), 5.43 (s, 2H), 4.06 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 163.85, 161.83, 159.30 (d, $J=252.2$ Hz), 151.21, 134.66, 133.83 (d, $J=8.7$ Hz), 131.30, 130.52, 129.97 (d, $J=2.2$ Hz), 127.15, 125.30, 124.46 (d, $J=3.4$ Hz), 123.94, 122.39 (d, $J=14.1$ Hz), 115.78 (d, $J=21.5$ Hz), 76.61, 63.53. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}FN_2O_4$ $(M+H)^+$ 329.0932, found 329.0937.

Data for (*E*)-3-(3-fluorobenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5p**): Yield 62%; white solid; mp 143–144 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (d, $J=7.8$ Hz, 1H), 7.51–7.33 (m, 4H), 7.31 (dd, $J=8.9$, 2.5 Hz, 1H), 7.24 (q, $J=3.3$ Hz, 1H), 7.17 (d, $J=7.7$ Hz, 1H), 5.37 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.56, 164.61, 162.16 (d, $J=248.1$ Hz), 151.23, 134.78 (d, $J=7.7$ Hz), 134.56, 131.46, 130.65, 130.04 (d, $J=7.9$ Hz), 127.29, 125.32, 124.57 (d, $J=3.1$ Hz), 124.07, 119.95 (d, $J=21.2$ Hz), 115.88 (d, $J=23.6$ Hz), 76.86, 63.55. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}FN_2O_4$ $(M+H)^+$ 329.0932, found 329.0940.

Data for (*E*)-3-(4-fluorobenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5q**): Yield 52%; white solid; mp 153–154 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J=7.0$ Hz, 1H), 7.70–7.61 (m, 2H), 7.47 (td, $J=7.6$, 1.5 Hz, 1H), 7.40 (t, $J=7.3$ Hz, 1H), 7.17 (d, $J=8.2$ Hz, 1H), 7.12–7.04 (m, 2H), 5.38 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 166.82, 165.63, 164.80, 164.29, 151.37, 134.67, 132.84 (d, $J=9.9$ Hz), 131.75 (d, $J=9.8$ Hz),130.60, 128.89 (d, $J=4.3$ Hz), 127.24, 125.30, 124.16, 115.58 (d, $J=22.8$ Hz), 76.84, 63.51. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}FN_2O_4$ $(M+H)^+$ 329.0932, found 329.0935.

Data for (*E*)-3-(4-(dimethylamino)benzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5r**): Yield 43%; yellow solid; mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (dd, $J=7.9$, 1.4 Hz, 1H), 7.70–7.59 (m, 2H), 7.42 (dtd, $J=25.1$, 7.5, 1.4 Hz, 2H), 7.15 (dd, $J=7.9$, 1.3 Hz, 1H), 6.64–6.54 (m, 2H), 5.36 (s, 2H), 4.09 (s, 3H), 3.06 (s, 6H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.98, 165.33, 153.82, 152.08, 135.18, 132.19, 131.36, 130.36, 126.97, 125.25, 124.62, 118.34, 110.42, 76.67, 63.34, 40.01. HRMS (ESI) *m/z* calcd for $C_{19}H_{20}N_3O_4$ $(M+H)^+$ 354.1448, found 354.1454.

Data for (*E*)-3-(4-chlorobenzoyl)-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5s**): Yield 42%; white solid; mp 183–184 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.76 (d, $J=7.7$ Hz, 1H), 7.60–7.53 (m, 2H), 7.47 (td, $J=7.6$, 1.5 Hz, 1H), 7.43–7.35 (m, 3H), 7.17 (d, $J=7.7$ Hz, 1H), 5.38 (s, 2H), 4.08 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 165.78, 164.69, 151.29, 139.42, 134.62, 131.44, 131.14, 130.62, 130.41, 128.65, 127.27, 125.30, 124.11, 76.86, 63.53. HRMS (ESI) *m/z* calcd for $C_{17}H_{14}ClN_2O_4$ $(M+H)^+$ 345.0637, found 345.0636.

Data for (*E*)-3-acryloyl-5-(methoxyimino)-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5t**): Yield 64%; white solid; mp 119–120 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (dt, $J=7.9$, 1.4 Hz, 1H), 7.49–7.29 (m, 2H), 7.19–7.00 (m, 2H), 6.63 (dq, $J=17.0$, 1.7 Hz, 1H), 5.94 (dq, $J=10.5$, 1.7 Hz, 1H), 5.37 (s, 2H), 4.07 (s, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 164.47, 162.34, 151.64, 134.84, 133.02, 131.23, 130.58, 128.41, 127.18, 125.27, 123.73, 76.15, 63.46. HRMS (ESI) *m/z* calcd for $C_{13}H_{13}N_2O_4$ $(M+H)^+$ 261.0870, found 261.0871.

Data for (*E*)-5-(methoxyimino)-3-pentanoyl-1,5-dihydrobenzo[e][1,2]oxazepin-4(3*H*)-one (**5u**): Yield 85%; white solid; mp 78–79 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.75 (dd, $J=7.9$, 1.3 Hz, 1H), 7.44 (td, $J=7.6$, 1.5 Hz, 1H), 7.37 (td, $J=7.6$, 1.3 Hz, 1H), 7.14 (dd, $J=7.9$, 1.3 Hz, 1H), 5.35 (s, 2H), 4.09 (s, 3H), 2.84 (t, $J=7.5$ Hz, 2H), 1.68 (p, $J=7.3$ Hz, 2H), 1.39 (h, $J=7.4$ Hz, 2H), 0.93 (t, $J=7.4$ Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 170.11, 164.37, 151.81, 134.98, 131.20, 130.51, 127.12, 125.24, 123.75, 76.01, 63.37, 37.17, 26.08, 22.16, 13.77. HRMS (ESI) *m/z* calcd for $C_{15}H_{19}N_2O_4$ $(M+H)^+$ 291.1339, found 291.1338.

X-ray diffraction

Compounds **5k** and **5k-2** were recrystallized by diffusion method from two different polar solvents solution to afford a single crystal suitable for X-ray crystallography determination. Compounds **5k** and **5k-2** were dissolved in CH_2Cl_2 separately, and excess n-hexane was added to the solution. Several days later, crystals were appeared and collected for X-ray diffraction. Compound **5k** and **5k-2** were mounted in inert oil and transferred to the cold gas stream of the diffractometer, respectively. Cell dimensions and intensities were measured using a Rigaku 007 Saturn 70 diffractometer with graphite monochromated Mo Kα radiation. Compound **5k**: orthorhombic, $a = 16.747$ (3) Å, $b = 4.1793$ (8) Å, $c = 21.916$ (4) Å, $U = 1533.9(5)$ Å^3, $F = 680$, space group Pca2(1), $Z = 4$. A total of 16,116 reflections were measured, of which 3637 were unique ($R_{int} = 0.0538$) in the range of $1.858 < 2\Theta < 27.860°$ ($-21 \le h \le 21$, $-5 \le k \le 5$, $-28 \le l \le 28$), and 3276 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F^2. Compound **5k-2**: triclinic, $a = 7.7125(15)$ Å, $b = 7.7471(15)$ Å, $c = 14.847(3)$ Å, $U = 766.3(3)$ Å^3, $F = 340$, space group P-1, $Z = 2$. A total of 9195 reflections were measured, of which 3639 were unique ($R_{int} = 0.0381$) in the range of $1.397 < 2\Theta < 27.904°$ ($-10 \le h \le 9$, $-10 \le k \le 10$, $-19 \le l \le 19$), and 2721 observed reflections with $I > 2\sigma(I)$ were used in the refinement on F^2. The structure of **5k** and **5k-2** were solved by direct method with the SHELXTL-97 program. The absorption correction was according to semiempirical from equivalents. All of the non-H atoms were refined anisotropically by full-matrix least squares on F^2. The atomic coordinates for **5k** and **5k-2** have been deposited at the Cambridge Crystallographic Data Centre. CCDC-1953743 and CCDC-1953744 contain the supplementary crystallographic data for this paper.

Antifungal activity test

The antifungal activities against *Alternaria solani*, *Botrytis cinerea*, *Cercospora arachidicola*, *Gibberella zeae*, *Phytophthora infestans* (Mont) de Bary, *Physalospora piricola*, *Pellicularia sasakii*, *Rhizoctonia cerealis* and *Sclerotinia sclerotiorum* were conducted in vitro at 50 μg/mL by using the mycelium growth-inhibition method according to a reported method [25]. Trifloxystrobin and azoxystrobin which were commercially available fungicides were chose as positive control. The synthesized compounds and controls were dissolved in DMSO to prepare 20 mg/mL stock solutions. The stock solution mixed with molten potato dextrose agar (PDA) and the media containing compounds at a concentration of 50 μg/mL were obtained for the initial antifungal activities screening.

Their relative inhibition ratio (%) was calculated using the following equation:

$$I(\%) = [(C - T)/(C - 4)] \times 100\%$$

I means the inhibition ratio, **C** (mm) means the average growth colony diameter of control and **T** (mm) means the average growth colony diameter of treatment.

Compounds with growth inhibition > 70% at 50 μg/mL and their median effective concentrations (EC_{50}) were determined. A 20 mg/mL stock solution was diluted with PDA to obtain a series of concentrations, repeating the experiments above, and the inhibition rates were calculated separately. The EC_{50} value was calculated by using linear regression equation [26].

Acknowledgements This work was supported in part by the Tianjin Natural Science Foundation (No. 18JCZDJC33500), the National Natural Science Foundation of China (No. 31872007), the International Science and Technology Cooperation Program of China (No. 2014DFR41030), The Fundamental Research Funds for the Central Universities, Nankai University (No. 63191743), The Tianjin Development Program for Innovation and Entrepreneurship and Russian Foundation for Basic Research (No. 18-316-20018). Dedication to the 100th anniversary of Nankai University and the 100th birthday anniversary of Professor Ruyu Chen, special dedication to the 14 Years anniversary of the collaboration with Yeltsin UrFU, Russia.

References

1. Pawlowski R, Stanek F, Stodulski M (2019) Recent advances on metal-free, visible-light-induced catalysis for assembling nitrogen- and oxygen-based heterocyclic scaffolds. Molecules 24:1533. https://doi.org/10.3390/molecules24081533
2. Shaikh AR, Farooqui M, Satpute RH, Abed S (2018) Overview on Nitrogen containing compounds and their assessment based on 'International Regulatory Standards'. J Drug Deliv Ther 8:424–428. https://doi.org/10.22270/jddt.v8i6-s.2156
3. Zhong LL, Hou CH, Zhang L, Zhao JC, Li F, Li WB (2019) Synthesis of deuterium-enriched sorafenib derivatives and evaluation of their biological activities 23:341–350. https://doi.org/10.1007/s11030-018-9875-7
4. Krygowski TM, Krzysztof E, Stepień BT, Cyrański MK, Jordi P, Miquel S (2004) Relation between the substituent effect and aromaticity. J Org Chem 69:6634–6640. https://doi.org/10.1021/jo0492113
5. Wu QF, Zhao B, Fan ZJ, Guo XF, Yang DY, Zhang NR, Yu B, Zhou S, Zhao JB, Fan C (2019) Discovery of novel piperidinylthiazole derivatives as broad-spectrum fungicidal candidates. J Agric Food Chem 67:1360–1370. https://doi.org/10.1021/acs.jafc.8b06054
6. Ozoe Y, Yagi K, Nakamura M, Akamatsu M, Miyake T, Matsumura F (2000) Fipronil-related heterocyclic compounds: structure–activity relationships for interaction with γ-aminobutyric acid- and voltage-gated ion channels and insecticidal action. Pestic Biochem Physiol 66:92–104. https://doi.org/10.1006/pest.1999.2452
7. Kai H, Ichiba T, Takase A, Masuko M (2000) Synthesis and fungicidal activities of heterocyclic compounds having

α-methoxyimino-2-phenoxymethylbenzyl group. J Pestic Sci 25:24–30. https://doi.org/10.1584/jpestics.25.24
8. Kurek J, Kwasniewska-Sip P, Myszkowski K, Cofta G, Barczynski P, Murias M, Kurczab R, Sliwa P, Przybylski P (2019) Antifungal, anticancer, and docking studies of colchiceine complexes with monovalent metal cation salts. Chem Biol Drug Des. https://doi.org/10.1111/cbdd.13583
9. Harris PA, Marinis JM, Lich JD, Berger SB, Chirala A, Cox JA, Eidam PM, Finger JN, Gough PJ, Jeong JU, Kang J, Kasparcova V, Leister LK, Mahajan MK, Miller G, Nagilla R, Ouellette MT, Reilly MA, Rendina AR, Rivera EJ, Sun HH, Thorpe JH, Totoritis RD, Wang W, Wu D, Zhang D, Bertin J, Marquis RW (2019) Identification of a RIP1 kinase inhibitor clinical candidate (GSK3145095) for the treatment of pancreatic cancer. ACS Med Chem Lett 10:857–862. https://doi.org/10.1021/acsmedchemlett.9b00108
10. Brindisi M, Ulivieri C, Alfano G, Gemma S, de Asis Balaguer F, Khan T, Grillo A, Chemi G, Menchon G, Prota AE, Olieric N, Lucena-Agell D, Barasoain I, Diaz JF, Nebbioso A, Conte M, Lopresti L, Magnano S, Amet R, Kinsella P, Zisterer DM, Ibrahim O, O'Sullivan J, Morbidelli L, Spaccapelo R, Baldari C, Butini S, Novellino E, Campiani G, Altucci L, Steinmetz MO, Brogi S (2019) Structure–activity relationships, biological evaluation and structural studies of novel pyrrolonaphthoxazepines as antitumor agents. Eur J Med Chem 162:290–320. https://doi.org/10.1016/j.ejmech.2018.11.004
11. Takeuchi CS, Kim BG, Blazey CM, Ma S, Johnson HWB, Anand NK, Arcalas A, Baik TG, Buhr CA, Cannoy J, Epshteyn S, Joshi A, Lara K, Lee MS, Wang L, Leahy JW, Nuss JM, Aay N, Aoyama R, Foster P, Lee J, Lehoux I, Munagala N, Plonowski A, Rajan S, Woolfrey J, Yamaguchi K, Lamb P, Miller N (2013) Discovery of a novel class of highly potent, selective, ATP-competitive, and orally bioavailable inhibitors of the mammalian target of rapamycin (mTOR). J Med Chem 56:2218–2234. https://doi.org/10.1021/jm3007933
12. Banerji B, Pramanik SK, Sanphui P, Nikhar S, Biswas SC (2013) Synthesis and cytotoxicity studies of novel triazolo-benzoxazepine as new anticancer agents. Chem Biol Drug Des 82:401–409. https://doi.org/10.1111/cbdd.12164
13. Kubota K, Kurebayashi H, Miyachi H, Tobe M, Onishi M, Isobe Y (2011) Synthesis and structure-activity relationship of tricyclic carboxylic acids as novel anti-histamines. Bioorg Med Chem 19:3005–3021. https://doi.org/10.1016/j.bmc.2011.03.003
14. Daya S, Kaye PT, Mphahlele MJ (1996) Benzodiazepine analogs. Part 12. An investigation of substituent and ring-atom effects on receptor binding affinities. Med Sci Res 24:137–141
15. Donnell AF, Michoud C, Rupert KC, Han XC, Aguilar D, Frank KB, Fretland AJ, Gao L, Goggin B, Hogg JH, Hong K, Janson CA, Kester RF, Kong N, Le K, Li S, Liang WL, Lombardo LJ, Lou Y, Lukacs CM, Mischke S, Moliterni JA, Polonskaia A, Schutt AD, Solis DS, Specian A, Taylor RT, Weisel M, Remiszewski SW (2013) Benzazepinones and benzoxazepinones as antagonists of inhibitor of apoptosis proteins (IAPs) selective for the second baculovirus IAP repeat (BIR2) domain. J Med Chem 56:7772–7787. https://doi.org/10.1021/jm400731m
16. Pifferi G, Consonni P, Monguzzi R, Omodei-Sale A (1971) Synthesis of 1,3,4,5-tetrahydro-2,3-benzoxazepines and 1,2,4,5-tetrahydro-3,2-benzoxazepines. J Heterocycl Chem 8:911–918. https://doi.org/10.1002/jhet.5570080605
17. Bailey TS, Bremner JB, Carver JA (1993) [2,3] Sigmatropic rearrangement of 1-vinylic tetrahydroisoquinoline N-ylides and N-oxides. Tetrahedron Lett 34:3331–3334. https://doi.org/10.1016/S0040-4039(00)73696-3
18. Bremner JB, Browne EJ, Davies PE, Van Thuc L (1980) The Meisenheimer rearrangement in heterocyclic synthesis. I. Synthesis of some tetrahydro-2,3-benzoxazepines. Aust J Chem 33:833–841. https://doi.org/10.1071/CH9800833
19. Seomoon D, Lee K, Kim H, Lee PH (2007) Inter- and intramolecular palladium-catalyzed allyl cross-coupling reactions using allylindium generated in situ from allyl acetates, indium, and indium trichloride. Chem Eur J 13:5197–5206. https://doi.org/10.1002/chem.200601338
20. Sauter H, Steglich W, Anke T (1999) Strobilurins: evolution of a new class of active substances. Angew Chem Int Ed 38:1328–1349. https://doi.org/10.1002/(SICI)1521-3773(19990517)38:10%3c1328:AID-ANIE1328%3e3.0.CO;2-1
21. Chen L, Guo XF, Fan ZJ, Zhang NL, Zhu YJ, Zhang ZM, Khazhieva I, Yurievich MY, Belskaya NP, Bakulev VA (2017) Synthesis and fungicidal activity of 3,4-dichloroisothiazole based strobilurins as potent fungicide candidates. RSC Adv 7:3145–3151. https://doi.org/10.1039/C6RA25520E
22. Yang DY, Wan C, He MM, Che CL, Xiao YM, Fu B, Qin ZH (2017) Design, synthesis, crystal structure and fungicidal activity of (*E*)-5-(methoxyimino)-3,5-dihydrobenzo[e][1,2]oxazepin-4(1*H*)-one analogues. MedChemComm 8:1007–1014. https://doi.org/10.1039/C7MD00025A
23. Aicher TD, Bebernitz GR, Bell PA, Brand LJ, Dain JG, Deems R, Fillers WS, Foley JE, Knorr DC, Nadelson J, Otero DA, Simpson R, Strohschein RJ, Young DA (1999) Hypoglycemic prodrugs of 4-(2,2-dimethyl-1-oxopropyl)benzoic acid. J Med Chem 42:153–163. https://doi.org/10.1021/jm980438y
24. Li Y, Zhang HQ, Liu J, Yang XP, Liu ZJ (2006) Stereoselective synthesis and antifungal activities of (*E*)-α-(methoxyimino)benzeneacetate derivatives containing 1,3,5-substituted pyrazole ring. J Agric Food Chem 54:3636–3640. https://doi.org/10.1021/jf060074f
25. Li FY, Guo XF, Fan ZJ, Zhang YQ, Zong GN, Qian XL, Ma LY, Chen L, Zhu YJ, Tatiana K, Morzherin YY, Belskaya NP (2015) Synthesis and biological activities of novel 2-amino-1,3-thiazole-4-carboxylic acid derivatives. Chin Chem Lett 26:1315–1318. https://doi.org/10.1016/j.cclet.2015.05.040
26. Fan ZI, Yang ZK, Zhang HK, Na M, Huan W, Fei C, Xiang Z, Zheng QX, Song HB (2010) Synthesis, crystal structure, and biological activity of 4-methyl-1,2,3-thiadiazole-containing 1,2,4-triazolo[3,4-b][1,3,4]thiadiazoles. J Agric Food Chem 58:2630–2636. https://doi.org/10.1021/jf9029628

Affiliations

Dongyan Yang[1] · Haixia Wang[1] · Zhijin Fan[1] · Zhengming Li[1] · Shuang Zhou[1] · Zesheng Hao[1] · You Lv[1] · Tatiana A. Kalinina[2] · Tatiana V. Glukhareva[2]

✉ Zhijin Fan
fanzj@nankai.edu.cn

✉ Zhengming Li
nkzml@vip.163.com

✉ Tatiana V. Glukhareva
taniagluhareva@yandex.ru

[1] State Key Laboratory of Elemento-Organic Chemistry, College of Chemistry, Nankai University, No. 94, Weijin Road, Nankai District, Tianjin 300071, People's Republic of China

[2] The Ural Federal University Named After the First President of Russia B. N. Yeltsin, Ekaterinburg, Russia 620002