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Discovery of 4-nitro-3-phenylisoxazole derivatives as potent antibacterial agents derived from the studies of [3 + 2] cycloaddition[†]

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Polysubstituted phenylisoxazoles were designed and synthesized to discover new antibacterial agents *via* [3 + 2] cycloaddition. Thirty-five compounds with a phenylisoxazole scaffold were characterized by NMR, HRMS, and X-ray techniques. After being evaluated against *Xanthomonas oryzae* (*Xoo*), *Pseudomonas syringae* (*Psa*), and *Xanthomonas axonopodis* (*Xac*), 4-nitro-3-phenylisoxazole derivatives were found to better antibacterial activities. Further studies have shown that the EC₅₀ values of these compounds were much better than that of the positive control, bismerthiazol.

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Introduction

Plant diseases have been one of the main factors restricting food security.1 These diseases not only affect the yield of crops but also hamper the quality of food. The use of antibacterial agents and fungicides has greatly reduced the economic losses caused by plant diseases.² However, there are also some negative effects along with the social benefits. Due to the unreasonable application of these agents, the resistance of pathogens has become increasingly serious, which also has a tremendous impact on non-target organisms.3 Additionally, these effects bring great pressure to the environment. With the extensive attention to health and increasing environmental awareness, the development of efficient, low toxic, and green antibacterial agents or fungicides has become a hot topic in the field of pesticide research.⁴ A large number of pesticides have been found in the market.5 For example, fluopyram (Fig. 1) was developed and applied to control the plant pathogens in crops such as rice, citrus, and kiwi fruit.6 Bismerthiazol (Fig. 1) was used to control the effect of rice bacterial blight and bacterial leaf streak.7 In 2012, fluxapyroxad (Fig. 1) was developed as a new pesticide for corresponding plant diseases.8

Isoxazole derivatives are important heterocyclic compounds that are widely used in pesticides.⁹ For instance, 5methylisoxazol-3-ol (hymexazol in Fig. 1) is considered as a soil disinfectant and plant growth regulator.¹⁰ Isouron (Fig. 1), a selective herbicide, is mostly employed to control the weeds such as paspalum and white grass.¹¹ Isoxaflutole (Fig. 1) belongs to early sulfone herbicides, and are mainly applied in corn and sugarcane fields.¹² Benzamizole, a herbicide cell division inhibitor (Fig. 1), is usually used in broad-leaved plants including cereal crops, broad beans, peas, trees, and grapes.¹³ Based on the characteristics and wide application of isoxazole derivatives, the rapid and efficient construction of various isoxazole derivatives has become the focus of researchers.¹⁴ Among the synthetic methods of isoxazole compounds, the most efficient strategy is [3 + 2] cycloaddition.¹⁵ Therefore, many chemists have used this method to synthesize isoxazole compounds and apply them to develop new pesticides.¹⁶

Our group has focused on the development of small molecules with various biological activities for several years.¹⁷ Considering the urgent need for novel pesticides containing isoxazole rings and our previous research on heterocyclic compounds,¹⁸ we designed and synthesized phenylisoxazole derivatives as a novel pesticide in agriculture. Furthermore, there are only a few reports on phenylisoxazoles as antibacterial agents in literature. In this study, we first developed a new synthetic method for constructing a phenylisoxazole ring with diverse substituent groups. Subsequently, we screened the biological activities of these compounds to obtain novel pesticides.



Fig. 1 Important antibacterial agents in market.

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r	Table 1Reactionphenylacetylenea,b	optimization	of	(E)-benza	ldehyde	oxime	and
	N-OH	+ =-{>	Ad Base	ditive / Solvent			

	1a	2a		3a			
Entry	Additive	Base	Solvent	$T(^{\circ}C)$	Yield (%)		
1	NCS	DBU	DMF	25	65 (63) ^c c		
2	NCS	DBU	CH_2Cl_2	25	38		
3	NCS	DBU	THF	25	31		
4	NCS	DBU	Dioxane	25	None		
5	NBS	DBU	DMF	25	17		
6	NIS	DBU	DMF	25	19		
7	PIFA	DBU	DMF	25	39		
8	Chloramine	DBU	DMF	25	37		
9	NCS	Cs_2CO_3	DMF	25	43		
10	NCS	K ₂ CO ₃	DMF	25	51		
11	NCS	NaO ^t Bu	DMF	25	51		
12	NCS	Na_2CO_3	DMF	25	53		
13	NCS	Pyrrolidine	DMF	25	47		
14	NCS	NaOH	DMF	25	52		
15	NCS	DMAP	DMF	25	55		
16	NCS	DIEA	DMF	25	80		
17	NCS	DABCO	DMF	25	63		
18	NCS	TEA	DMF	25	85		
19	NCS	TEA	DMF	50	84		
20	NCS	TEA	DMF	75	79		
21	NCS	TEA	DMF	100	74		

^a Reagents and conditions: 1a (1 mmol), 2a (1.2 mmol), additive (2 mmol), base (1 mmol), solvent (6 mL), 6 h. ^b Isolated yields. ^c Reagents and conditions: 1a (1 mmol), 2a (1.2 mmol), NCS (1.2 mmol), DBU (1 mmol), DMF (6 mL), 6 h.

Results and discussion

Mohammed et al. reported benzaldehyde oxime (1a) reacted with phenylacetylene (2a) to afford compound 3a in the presence of NCS and DBU in 2015.19 Initially, we repeated the reaction and obtained the isolated yield of 63%. When the additive NCS was increased to two equivalents, the yield still remained at 65% (Table 1, entry 1). Later, we screened different solvents to improve the yield and identified that DMF is still the best solvent (Table 1, entries 1-4). The different additives such as NBS, NIS, PIFA, chloramine-T were also used to accelerate the reaction.²⁰ Unfortunately, these additives were all ineffective in improving the yield (Table 1, entries 5-8). Subsequently, we found that different bases could severely influence the reaction rate (Table 1, entries 9-18). When triethylamine was used as the base, the separated yield reached 85% (Table 1, entry 18), indicating that the weak organic base was ideal for accelerating the yield. Interestingly, the yield decreased slowly with the increase in temperature (Table 1, entries 19-21). This may be due to the substrate side effects accompanied with the increase in temperature, which reduced the reaction yield. Finally, the optimal condition was determined in the presence of TEA and DMF at room temperature (Table 1, entry 18).

Table 2 Reaction examples of 1 and 2^{4}



^a Reagents and conditions: 1 (1 mmol), 2 (1.2 mmol), NCS (2 mmol), TEA (1 mmol), DMF (6 mL), 25 °C, 6 h.

Table 3 Reaction examples of 1 and 4^a



^a Reagents and conditions: 1 (1 mmol), 4 (1.2 mmol), NCS (2 mmol), TEA (1 mmol), DMF (6 mL), 25 °C, 6 h.



Fig. 2 X-ray structures of $\mathbf{5p},\,\mathbf{5q},\,and\,\mathbf{5r}.$

Having the optimal condition in hand (Table 1, entry 18), the scope was explored in different substituted phenyloxime derivatives and phenylacetylene derivatives (Table 2). Phenyloximes with electron-donating groups $-CH_3$ and $-OCH_3$ resulted in lower yields than 2a, while electron-withdrawing groups -F and $-CF_3$ resulted in higher yields than 2a (3a-3g). Furthermore, the steric effect of substituents on the phenyl ring also decreased the yield of this [3 + 2] cycloaddition (3c-3e). In addition, phenyloxime derivatives such as 3methyl (2h), 4-methyl (2i), 4-methoxy (2j), 3-chloro (2k) benzaldehyde oximes produced the desired products in 65-76% yield (**3h-3l**).

Structural diversity is very crucial for screening new antibacterial agents.²¹ To ensure molecular diversity, 3,4-disubstituted isoxazoles were synthesized (Table 3), and benzaldehyde oxime (1a) and commercially available 4dimethylamino-but-3-en-2-one (4a) were chosen as the starting materials. Under the identical conditions as mentioned previously, compound 5a was isolated with 61% yield (Table 3). The structure of 5a was confirmed by NMR and HRMS, which was consistent with that obtained from other cycloadditions using hypervalent iodine reagent as the catalyst.20 Subsequently, a phenyl ring with electron-donating groups -CH₃ (5b) and -OCH₃ (5c) produced lower yields, while electron-withdrawing groups $-CF_3$ (5e) and $-NO_2$ (5h) produced higher yields than 5a. The steric effect of substituents on the phenyl ring significantly decreased the yield of this cycloaddition (5f, 5g and 5h). Besides, 3-dimethylamino-

		compound					
	Cpd	$Xoo (\mu g m L^{-1})$		$Xac (\mu g m L^{-1})$		Psa (µg mL ⁻¹)	
Entry		100	50	100	50	100	50
1	3a	_	_	_	_	9.6 ± 2.1	_
2	3b	_	_	_	_	10.7 ± 3.8	_
3	3c	_	_	38.2 ± 3.7	15.0 ± 2.4	15.8 ± 1.4	_
4	3d	_	_	35.5 ± 2.8	12.9 ± 1.7	12.6 ± 1.1	_
5	3e	_	_	36.1 ± 3.2	14.6 ± 2.5	14.9 ± 0.8	_
6	3f	_	_	_	_	14.5 ± 4.5	_
7	3g	_	_	43.5 ± 5.9	38.1 ± 2.1	19.6 ± 1.5	_
8	3h	_	_	35.1 ± 3.7	20.3 ± 5.0	18.6 ± 5.8	_
9	3i	_	_	44.8 ± 3.6	21.6 ± 2.5	19.3 ± 4.5	18.3 ± 7.4
10	3j	_	_	14.4 ± 2.7	_	16.8 ± 4.9	9.3 ± 4.1
11	3k	_	_	46.7 ± 3.6	36.1 ± 4.1	19.2 ± 4.2	_
12	31	_	_	72.8 ± 2.5	35.1 ± 1.3	16.0 ± 0.9	5.8 ± 2.2
13	5a	29.6 ± 0.9	22.4 ± 3.6	34.4 ± 3.5	25.3 ± 2.6	27.4 ± 0.4	17.7 ± 0.2
14	5b	41.1 ± 5.7	28.7 ± 3.1	45.8 ± 1.7	29.5 ± 4.3	27.0 ± 5.7	14.9 ± 2.8
15	5c	32.9 ± 4.1	31.5 ± 2.2	39.0 ± 8.2	12.3 ± 6.0	27.6 ± 4.9	16.5 ± 2.0
16	5 d	42.4 ± 5.2	27.6 ± 3.4	46.7 ± 1.8	28.6 ± 4.1	26.8 ± 5.3	13.7 ± 2.5
17	5e	42.2 ± 1.7	10.4 ± 5.9	64.0 ± 4.6	56.8 ± 5.1	29.6 ± 2.2	16.0 ± 3.0
18	5 f	33.5 ± 1.1	24.1 ± 1.6	60.6 ± 7.4	46.2 ± 4.2	26.8 ± 2.7	14.3 ± 2.6
19	5g	37.9 ± 6.9	26.8 ± 8.3	51.9 ± 8.4	29.3 ± 6.6	25.3 ± 1.9	12.0 ± 1.4
20	5h	48.4 ± 2.8	19.3 ± 4.7	51.3 ± 2.5	26.0 ± 6.5	25.7 ± 1.5	13.4 ± 1.6
21	5i	34.9 ± 1.6	26.5 ± 5.1	70.4 ± 5.0	51.6 ± 3.4	26.0 ± 0.7	14.8 ± 5.1
22	5j	37.7 ± 1.4	28.9 ± 4.3	63.7 ± 4.5	46.2 ± 2.8	28.2 ± 0.5	16.4 ± 5.8
23	5k	36.8 ± 1.9	28.7 ± 6.7	72.9 ± 6.1	53.7 ± 4.9	27.1 ± 0.8	15.3 ± 6.6
24	51	42.2 ± 1.7	10.4 ± 5.9	74.0 ± 4.6	56.8 ± 7.1	26.5 ± 0.7	16.6 ± 4.5
25	5m	33.5 ± 1.1	24.1 ± 1.6	60.6 ± 2.4	46.2 ± 5.2	27.1 ± 0.8	15.3 ± 3.6
26	5n	41.2 ± 1.8	26.7 ± 1.5	62.1 ± 2.1	42.0 ± 4.8	28.8 ± 1.2	16.8 ± 3.4
27	50	97.7 ± 0.2	93.6 ± 0.3	99.5 ± 0.4	98.5 ± 0.1	60.8 ± 3.2	55.6 ± 6.5
28	5p	97.7 ± 1.0	96.8 ± 0.0	97.9 ± 1.0	96.4 ± 0.6	66.3 ± 5.6	63.7 ± 5.2
29	5q	97.7 ± 0.1	94.0 ± 0.3	97.8 ± 0.7	95.6 ± 0.1	65.4 ± 4.5	57.0 ± 4.6
30	5r	96.4 ± 0.1	93.5 ± 0.1	99.2 ± 0.2	97.7 ± 0.2	58.4 ± 1.4	41.7 ± 1.3
31	5s	97.8 ± 0.1	97.6 ± 0.1	97.9 ± 0.3	97.5 ± 0.0	55.0 ± 4.1	51.7 ± 5.3
32	5t	97.9 ± 0.1	96.6 ± 0.1	99.8 ± 0.4	97.6 ± 0.6	53.3 ± 0.5	48.0 ± 1.9
33	5u	96.0 ± 0.3	69.4 ± 6.5	99.6 ± 0.2	95.4 ± 0.0	42.7 ± 4.5	21.7 ± 0.7
34	5 v	97.5 ± 0.1	94.1 ± 0.5	98.9 ± 0.0	98.7 ± 0.1	44.2 ± 5.0	40.8 ± 1.6
35	5w	97.5 ± 0.1	94.1 ± 0.5	98.9 ± 0.0	98.7 ± 0.1	44.2 ± 5.0	40.8 ± 1.6
Bismerthia	loz	73.9 ± 1.1	29.3 ± 1.7	78.8 ± 6.6	46.7 ± 2.3	39.0 ± 3.5	15.6 ± 4.1

^{*a*} The average of three trials.

Table 5 EC₅₀ values of compounds 50–5w against Xoo, Xac, and Psa⁴

		Correlation coefficient	
Compound	Regression equation	(<i>r</i>)	EC_{50} (µg mL ⁻¹
Xanthomonas oryzae (Xoo	<i>b)</i>		
Bismerthiazol	y = 0.5792x + 2.3536	0.9595	82.3 ± 5.1
50	y = 3.2815x + 0.658	0.9856	15.0 ± 0.8
5p	y = 3.6552x + 7.277	0.9683	11.7 ± 0.4
5 q	y = 3.7164x + 3.068	0.9883	12.6 ± 0.5
5r	y = 3.5643x + 2.158	0.9835	13.4 ± 0.4
5s	y = 6.55167x + 0.248	0.9530	7.6 ± 0.3
5t	y = 5.3958x + 0.8359	0.9838	9.1 ± 0.3
5u	y = 3.1172x + 0.4496	0.9667	15.9 ± 0.8
5 v	y = 1.6916x + 0.0594	0.9870	29.5 ± 1.4
5w	y = 6.0038x + 2.4873	0.9861	7.9 ± 0.4
Xanthomonas axonopodis	s (Xac)		
Bismerthiazol	y = 0.8141x + 0.3426	0.9599	61.0 ± 4.4
50	y = 19.477x + 1.2731	0.9394	2.5 ± 0.1
5p	y = 15.73x + 6.1445	0.9082	2.8 ± 0.2
5q	y = 9.3762x + 5.5612	0.9371	4.7 ± 0.2
5r	y = 6.8912x + 5.5944	0.9804	6.4 ± 0.3
5s	y = 10.836x + 18.611	0.9176	2.9 ± 0.2
5t	y = 13.73x + 10.154	0.9309	2.9 ± 0.2
5u	y = 7.3972x + 5.8451	0.9466	6.0 ± 0.3
5 v	y = 6.922x + 5.6802	0.9762	6.4 ± 0.4
5w	y = 12.884x + 14.465	0.9782	2.8 ± 0.2
Pseudomonas syringae (Psa	1)		
Bismerthiazol			>100
50	y = 0.6055x + 23.34	0.9104	44.0 ± 3.8
5p	y = 1.1501x + 19.741	0.9581	26.3 ± 2.2
5q	y = 0.9974x + 13.765	0.9199	36.3 ± 2.7
5r	y = 0.6203x + 14.995	0.9779	56.4 ± 5.1
5s	y = 0.699x + 6.2785	0.9784	62.6 ± 5.3
5t	y = 0.9171x + 6.8663	0.9650	47.0 ± 3.7
5u	y = 0.6372x + 14.585	0.9821	55.6 ± 4.6
5v	-		>100
5w			>100
a The average of three tria	ble		

acrylic acid ethyl ester (4b) was also used in this reaction instead of compound 4a. Fortunately, the final targets 5i-5nwere successfully synthesized with 44–67% yields. The effect of substituents on the yield was similar to 5a-5h. Nitroisoxazole derivatives have a wide range of biological activities, such as antitumor, antibacterial, and anti-inflammatory.²² To investigate the antibacterial activities of nitroisoxazoles, 4-nitro-3phenylisoxazole derivatives were prepared. Dimethyl-(2nitrovinyl)-amine (4c) reacted with corresponding phenyloximes (1) to give the products 5o-5w. The yield was moderate from 36% to 63%.

In addition, the NMR spectra of compound **50** was consistent with the data in the literature.²³ However, the test result of HRMS was inconsistent with the actual values. This phenomenon was observed in all the 4-nitro-3-phenylisoxazole derivatives. To ensure the structures of this series of products, compounds **5p**, **5q**, and **5r** were characterized by X-ray diffraction analysis. As shown in Fig. 2, the deposition numbers in CCDC (Cambridge Crystallographic Data Centre) were 2130131 (**5p**), 2130134 (**5q**), and 2153382 (**5r**). These results indirectly

indicate that the structures of compounds **50–5w** were appropriate.

To investigate the mechanism, the benzaldehyde oxime **1a** and compound **4c** were subjected to undergo [3 + 2] cycloaddition. Based on the observed results and the reports in the literature,²⁴ the regioselectivity of the [3 + 2] cycloaddition reaction between nitrile *N*-oxides and conjugated nitroalkenes was determined by the nucleophilic attack of oxygen atom from the CNO moiety on the activated electrophilic 2-position of nitroalkene. Considering several mechanisms related to the 32CA reaction,²⁵ we described a plausible mechanism in Scheme **1**. Initially, the NCS chlorinated oxime **1a** afforded an intermediate **6**. Then, compound **6** was dechlorinated under base DIEA to form nitrile oxide **7**. Finally, it was reacted with compound **4c** to afford the isoxazole compound **50** through [3 + 2] cycloaddition with 55% yield.

In order to explain the pathway of this mechanism, we conducted two complementary experiments. As shown in Scheme 2, under the optimized conditions, the benzaldehyde oxime **1a** was converted to compound **6** with 85% yield in the



Scheme 1 Proposed mechanism.



presence of NCS. The NMR spectra of **6** was consistent with the literature.²⁶ At last, compound **6** reacted with (E)-N,N-dimethyl-2-nitroethen-1-amine **4c** at 25 °C to afford the required product **50** in 55% yield. These complementary experiments successfully proved our proposed mechanism in Scheme **1**.

With the target compounds 3a-3l and 5a-5w in hand, we screened *in vitro* screening of antibacterial activities against representative plant diseases including *Xanthomonas oryzae* (*Xoo*), *Xanthomonas axonopodis* (*Xac*), and *Pseudomonas syringae* (*Psa*) at 100 µg mL⁻¹ and 50 µg mL⁻¹ according to the previous report.²⁷ The results are listed in Table 4. The activities of compounds **3a–3l** and **5a–5n** were lower than those of bismerthiazol and fluopyram.²⁸ It was interesting to note that the activities of compounds **5o–5w** were much better than the positive controls. Surprisingly, the inhibitions against *Xoo* and *Xac* were more than 90% at the concentration of 100 µg mL⁻¹ and 50 µg mL⁻¹. Therefore, compounds **5o–5w** were selected for further studies as novel antibacterial agents.

As shown in Table 5, compounds **50–5w** exhibited much better EC_{50} values against *Xoo*, *Xac*, and *Psa* than bismerthiazol and fluopyram.²⁸ Preliminary structure–activity relationship can also be found in Table 5. The *ortho*-substituted derivatives (**5p**, **5s**) have better activities than *meso*-substituted derivatives (**5q**, **5t**) and *para*-substituted derivatives (**5r**, **5u**, and **5v**). Against *Xoo*, the large-steric substituted compounds **5t** (–Br, 9.1 µg mL⁻¹) and **5w** (–NO₂, 7.9 µg mL⁻¹) have lower EC₅₀ than small-steric substituted compound **5q** (–F, 12.6 µg mL⁻¹). A similar phenomenon was observed against *Xac*. However, against *Psa*, small-steric substituted compound **5q** (12.6 µg $mL^{-1})$ showed a better effect than large-steric substituted compound $5t~(47.0~\mu g~mL^{-1}).$

Conclusions

In summary, an efficient method was developed to prepare polysubstituted phenylisoxazoles *via* [3 + 2] cycloaddition. This series of phenylisoxazole derivatives were characterized and evaluated at 100 μ g mL⁻¹ and 50 μ g mL⁻¹ against *Xoo*, *Xac*, and *Psa*. The results suggested that 4-nitro-3-phenylisoxazole derivatives performed excellent antibacterial activities. Further studies on the EC₅₀ values have shown that these compounds were much better than bismerthiazol. However, the antibacterial mechanism of these 4-nitro-3-phenylisoxazole derivatives is ongoing in our lab.

Author contributions

Yan Zhang and Zhiwu Long synthesized the compounds and performed the spectral studies; Longjia Yan and Li Liu contributed to the design and implementation of the research; Lan Yang and Yi Le tested bioactive activities, and wrote the manuscript with input from all authors.

Conflicts of interest

The authors declare no conflicts of interest.

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