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ARTICLE

Drug repurposing strategy part 1: from approved drugs to agri-bactericides leads

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Abstract

Phytopathogenic bacteria are a major cause of crop mortality and yield reduction, especially in field cultivation. The lack of effective chemistry agri-bactericides is responsible for challenging field prevention and treatment, prompting the development of long-lasting solutions to prevent, reduce, or manage some of the most devastating plant diseases facing modern agriculture today and in the future. Therefore, there is an urgent need to find lead drugs preventing and treating phytopathogenic bacterial infection. Drug repurposing, a strategy used to identify novel uses for existing approved drugs outside of their original indication, takes less time and investment than Traditional R&D Strategies in the process of drug development. Based on this method, we conduct a screen of 700 chemically diverse and potentially safe drugs against *Xanthomonas oryzae* PV. *oryzae* ACCC 11602 (*Xoo*), *Xanthomonas axonopodis* PV. *citri* (*Xac*), and *Pectobacterium atrosepticum ACCC* 19901 (*Pa*). Furthermore, the structure-activity relationship and structural similarity analysis of active drugs classify potent agri-bactericides into 8 lead series: salicylanilides, cationic nitrogen-containing drugs, azole antifungals, *N*-containing group, hydroxyquinolines, piperazine, kinase inhibitor and miscellaneous groups. MIC values were evaluated as antibacterial activities in this study. Identifying highly active lead compounds from the screening of approved drugs and comparison with the currently applied plant pathogenic bactericide to validate the bactericidal activity of the best candidates and assess if selected molecules or scaffolds lead to develop new antibacterial agents in the future. In conclusion, this study provides a possibility for the development of potent and highly selective agri-bactericides leads.

Introduction

The development of human agricultural civilization has a history of nearly 10,000 years [1]. However, a sharply increased demand in food production has attracted unprecedented attention as the growing world population makes it an important responsibility to protect crops from phytopathogenic bacteria [2–4]. Phytopathogenic bacteria cause enormous yield loss in various crops worldwide every year, particularly *Xanthomonas oryzae* PV. *Oryzae* (*Xoo*), *Xanthomonas axonopodis* PV. *citri* (*Xac*), and *Pectobacterium atrosepticum* (*Pa*) [5–8]. Taking *Xoo* as an example, as the staple food of more than half of the world' s population, rice is frequently exposed to the infections of phytopathogenic bacteria [9, 10]. This bacterial infection will seriously reduce crop yield and directly lead to enormous losses of the agricultural economy [11]. The wide application of agribactericides has contributed to inhibiting phytopathogenic bacteria infection, and the number of bactericides used to control plant bacterial diseases is limited. Currently, only a few traditional agri-bactericides, such as bismerthiazol (BT), thiodiazole copper (TC), streptomycin (banned for putative risk in China), and zhongshengmycin [12, 13]. However, the current situation is exacerbated by

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the multidrug-resistant caused by the long-term and frequent use of these agribactericides [14, 15]. Therefore, there is an urgent need to discover and develop new agribactericides to control phytopathogenic bacteria.

In the area of drug discovery and development, despite the urgent requirement for efficient anti-phytopathogenic bacteria alternatives, the available anti-phytopathogenic bacteria drugs are few and the targets are limited. Agrochemicals play an important role in agricultural production by protecting crops from phytopathogenic bacteria. Given the increasing demands of food and exploding phytopathogenic bacteria resistance, it is necessary to development of new agrochemicals urgently [16]. However, the development of agrochemicals faces serious challenges traditionally [17]. The development of new agrochemical is expensive and long-term, with an average cost of US$ 286 million, and taking 10–12 years to bring the drugs to the field [18–20]. Due to the high cost, long time-consuming, and low success rate of new drug research and development, private pharmaceutical enterprises withdraw from agribactericides research and development [21]. In response, novel or non-traditional approaches focusing on the discovery of agribactericides have increased. One approach is to discover potential uses of approved drugs besides their original indications, also known as "drug repositioning" or "drug repurposing" [22–25].

This repurposing approach has several advantages. First, the main advantage of using approved drugs is that the investment in research and development and the risk of failure is low. The second this strategy also has a shorter timeline of drug discovery and development, the discovery and development of new agrochemicals from the beginning is a process of 10 to 12 years [18]. In contrast, drug repurposing provides the possibility of reducing this process to 3–12 years [26–28]. In addition, in the process of agribactericides discovery, the number of screening new active compounds increased significantly. Searching for active lead compounds from approved drugs and then carrying out structural modification or derivatization has been proved to be a successful way to find agribactericides with new action modes [29–31]. However, the discovery of lead compound remains a major challenge, The number of compounds rose from 52,500 in 1995 to 140,000 in 2005 to discover a new agrochemical lead compound [16, 32]. Thus, the lead compound is a prerequisite for the discovery of agrochemicals.

To this extent, we screened 700 approved drugs against *Xoo*, *Xac* and *Pa*. Among them, the structure-activity relationship and structural similarity analysis of active drugs classify potent agri-bactericides into 8 lead series: salicylanilides, cationic nitrogen-containing drugs, azole antifungals, *N*-containing group, hydroxyquinolines, piperazine, kinase inhibitor, and miscellaneous groups.

Materials and methods

Bacterial Strains and growth conditions

Xoo ACCC 11602 and *Pa* ACCC 19901 were purchased from the Agricultural Culture Collection of China (ACCC). *Xac* was provided by Professor Song Yang's research group from Guizhou University. The bacteria were experienced the 16 S ribosome gene series alignment, the comparison results are provided in the Supporting Information.

The above strains containing 30% glycerol were frozen at – 80 °C in the laboratory. The frozen strains were taken out, scribed on nutrient broth (NB) solid media, culturing at 28 °C until a single colony grew. Then, a single colony was picked from the solid media to the nutrient broth (NB) media and cultured to the logarithmic growth phase at 28 °C on a shaker incubator at 180 rotations per min (rpm). The strain in the logarithmic growth phase was diluted with nutrient broth (NB) media to about 10^6 CFU ml^{-1} for later use.

The nutrient broth (NB) media: 3.0 g of beef extract, 5.0 g of peptone, 1.0 g of yeast extract, 10.0 g of sucrose, 8.0 g of sodium chloride, 1 L of distilled water, pH = 7.0 − 7.2.

Chemicals and compounds

All drugs or compounds were purchased from commercial suppliers and available without purification (unless stated otherwise). The above-tested drugs were dissolved in DMSO at concentrations of 100,000 μg ml^{-1} and stored at −4 °C or −20 °C. Then, to a 2 ml tube, 998 μl of nutrient broth (NB) media, 2 μl of the compounds dissolved in DMSO were added so that the final concentration is 200 μg ml^{-1} for later use.

In vitro antibacterial assay

Antibacterial activities of target drugs and compounds were tested against three phytopathogenic bacteria (*Xoo, Xac, and Pa*) using the turbidimetric method [33–35]. In addition, minimum inhibitory concentration (MIC) was determined by the two-fold dilution method [36, 37]. Commercial agricultural bactericides were positive controls. The same concentration of DMSO without compounds was dissolved in nutrient broth (NB) media as a blank control [38]. To the 96-well plate, 50 μl of drug-containing medium and 50 μl of phytopathogenic bacteria (*Xoo*, *Xac*, and *Pa*) culture containing about 10^6 CFU ml^{-1} were added. Then, the test 96-well plates were incubated in a shaker incubator for 24−48 h at 28 °C. The optical density (OD_{600}) of NB media in each test 96-well plate was measured on a microplate reader until the phytopathogenic bacteria in the

no drugs NB media grew logarithmically. The calculation formula of corrected OD and inhibition rates is as follows, where C represents the corrected optical density value (OD_{600}) of the no drugs NB media; T represents the corrected optical density value (OD_{600}) of the treated NB media.

$OD_{corrected} = OD_{contain\ bacteria} - OD_{sterile\ culture}$;

Inhibition rates = (C-T)/C × 100%.

Molecular docking

The crystal structure of *ftsZ* was used for the homology modeling as the template by SwissModel. The FASTA information of *X. oryzae ftsZ* was retrieved from the NCBI Gene Bank. After the model was built, the Ramachandran plot was used to evaluate the rationality of the model, the detailed information could be found in the Supporting Information. Finally, the QuickPrep Panel was used for docking by AutoDockTools version 1.5.7.

Results and discussion

In this study, the activity of 800 marketed drugs were evaluated against phytopathogenic bacteria, all drugs were initially tested at 100 μg ml^{-1} to determine their anti-agribacterial activity. The queries of toxicity for highly active antibacterial compounds are shown in supporting information.

Among them, 300 drugs show antibacterial activity against the tested strains. In order to further determine the antibacterial activity of these active drugs, the MICs of these active drugs were evaluated. The MIC values of the confirmed active drugs were between 0.01 and 100 μg ml^{-1}. Based on our finding that there is a specific relationship between the backbones of these test drugs and their antibacterial activity is closely related, we divided the drugs into 8 lead series for discussion.

Phytopathogenic bacteria antibiotics

To date, it remains a great challenge to control plant pathogen infection in the field of agricultural production. Besides, there are only a few types of antibacterial agents for the management of plant pathogenic bacteria on the market, such as meconazole, thiophanate copper, neutropin, streptomycin, and so on. Herein, the activity of these commercially available specific drugs were evaluated against three plant pathogens (*Xoo*, *Xac*, and *Pa*), with MICs ranging from 1.56 to 100 μg ml^{-1}. Among them, most of the positive drugs showed the average vitro antibacterial activities, while some drugs exhibited excellent activities, such as zhongshengmycin and streptomycin (MIC = 1.56–3.12 μg ml^{-1}), which may be related to the broad-spectrum bactericidal properties of antibiotics. It is worth mentioning that streptomycin is banned for the risk of toxicity and resistance and in China while it has been used widely for the control of plant pathogenic bacteria for 50 years. Although these positive drugs (including antibiotics and agricultural fungicides) show excellent antibacterial activities in this study, their applications in agriculture are limited to putative risks. Other antibacterial activities of positive drugs were shown in Fig. 1.

Salicylic acid and Salicylanilides

Salicylic acid is produced in plants and is an important substance of plant immune response to defend against infection by various phytopathogenic bacteria. In addition, salicylic acid is essential for the establishment of systemic resistance [39]. Salicylanilide structural drugs have rich biological activities, take an oxyclozanide example, used in veterinary medicine for treating fluke infections, which shows activity against *staphylococcus aureus*, *helicobacter pylori*, and *clostridioides difficile* because of disruption of their cell envelope. In addition, niclosamide, the prodrug of oxyclozanide, has also been identified as a potent antibacterial drug against gram-positive bacteria [40].

As shown in Table 1 and Fig. 2, the results of the antibacterial activity of salicylic acid derivatives (lead series 1) are not enough to determine whether substituted or unsubstituted benzene rings affect the good antibacterial activity of those salicylic acid drugs. However, the antibacterial activity of salicylanilide (lead series 2) is much higher than that of salicylic acid. Among them, oxyclozanide has the potent antibacterial activity against *Xoo* with a minimum inhibitory concentration (MIC) of 0.78 μg ml^{-1}. The introduction of halogen atoms and hydroxyl in the benzene ring, drugs nicldrugsde, oxyclozanide, rafoxanide, closantel sodiumor which contains backbones salicylanilides, has a positive effect on activity against all three phytopathogenic bacteria. In addition, the introduction of an thiazole ring such as nitazoxanide (the MIC value was 3.12 μg ml^{-1} against *Xoo*) retains the antibacterial activity.

In order to better explore the antibacterial mechanism of the lead compound, we preliminarily carried out molecular docking for oxyclozanide, the details of molecular docking are provided in the supporting information. Also, we will verifiy antibacterial mechanism of the other lead compound in our forthcoming work.

Cationic nitrogen-containing drugs

Cationic nitrogen-containing drugs are widely used and have biological activities in insecticidal, antibacterial, anti-inflammatory, antidepressant, and antitumor aspects. It is

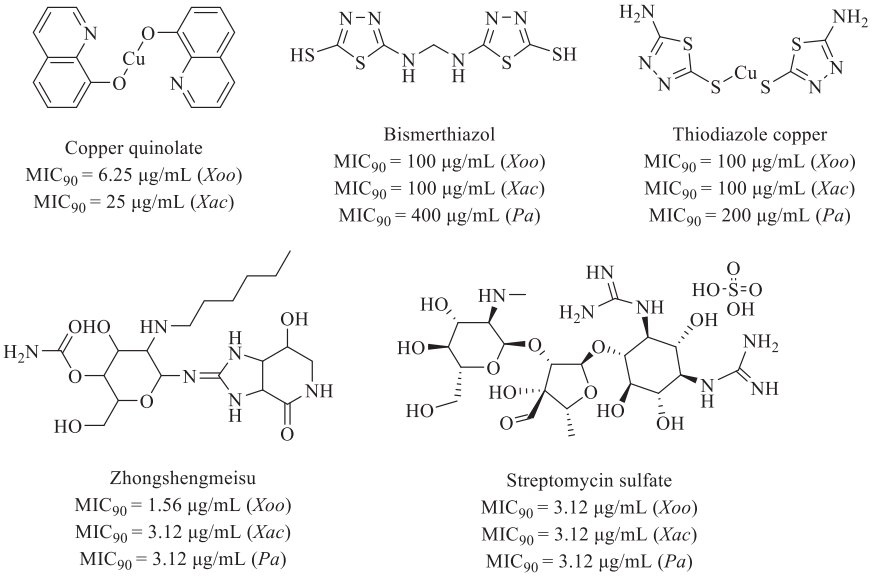


Fig. 1 The MICs of positive drugs against phytopathogenic bacteria

Table 1 In vitro antibacterial activities (Inhibition rate/%) of the salicylic acid and salicylanilides against phytopathogenic bacteria

Compounds	concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Salicylic acid	800	98.05 ± 0.49	51.67 ± 2.26	98.28 ± 0.11
2,4-Dihydroxybenzoic acid	100	44.48 ± 2.44	7.74 ± 3.51	36.02 ± 1.14
4-Methoxysalicylic acid	100	96.59 ± 0.49	23.18 ± 2.01	19.65 ± 0.8
4-Aminosalicylic acid	100	92.21 ± 0	14.27 ± 5.02	47.35 ± 3.55
4-Fluorosalicyclic acid	100	97.08 ± 0.97	27.7 ± 3.26	62.91 ± 3.39
Ethyl 2-hydroxybenzoate	100	21.59 ± 3.9	10.25 ± 2.89	11.87 ± 6.64
Salicylamide	100	17.21 ± 4.87	39.5 ± 5.02	13.47 ± 4.01
Salicylanilide	100	79.03 ± 4.4	41.58 ± 0	0 ± 0
Acetylsalicylic acid	100	91.23 ± 0.49	18.41 ± 0.25	13.01 ± 5.15
Diflunisal	100	89.03 ± 4.54	73.66 ± 1.28	0 ± 0
Salicylhydroxamic acid	100	85.39 ± 0.49	46.03 ± 1.13	31.44 ± 1.76
auxobil	100	95.62 ± 1.46	59.96 ± 0.75	34.19 ± 5.72
Sasapyrine	100	95.62 ± 0.49	11.26 ± 4.02	14.73 ± 5.49
Benorilate	100	17.69 ± 5.36	29.96 ± 4.9	15.41 ± 3.89
Labetalol hydrochloride	100	39.61 ± 1.46	70 ± 9.29	14.96 ± 2.75
Mosapride	100	24.51 ± 3.9	11.76 ± 1.13	12.55 ± 3.78
Sanatol ITR	100	36.69 ± 5.36	28.58 ± 4.81	13.01 ± 4.01
Xipamide	100	48.86 ± 2.44	2.97 ± 5.77	0 ± 0
Otilonium bromide	100	100 ± 0	100 ± 0	92.18 ± 0.28
Niclosamide	100	100 ± 0	100 ± 0	15.19 ± 7.1
Sulfasalazine	100	16.83 ± 4.65	48.5 ± 2.82	7.04 ± 8.52
Nitazoxanide	100	100 ± 0	100 ± 0	100 ± 0
Closantel	100	78.39 ± 5.2	66.04 ± 0.54	0 ± 0
Closantel sodium	100	100 ± 0	99.3 ± 1.76	29.09 ± 4.3
Rafoxanide	100	100 ± 0	54.1 ± 1.83	0 ± 0
Oxyclozanide	100	100 ± 0	100 ± 0	100 ± 0

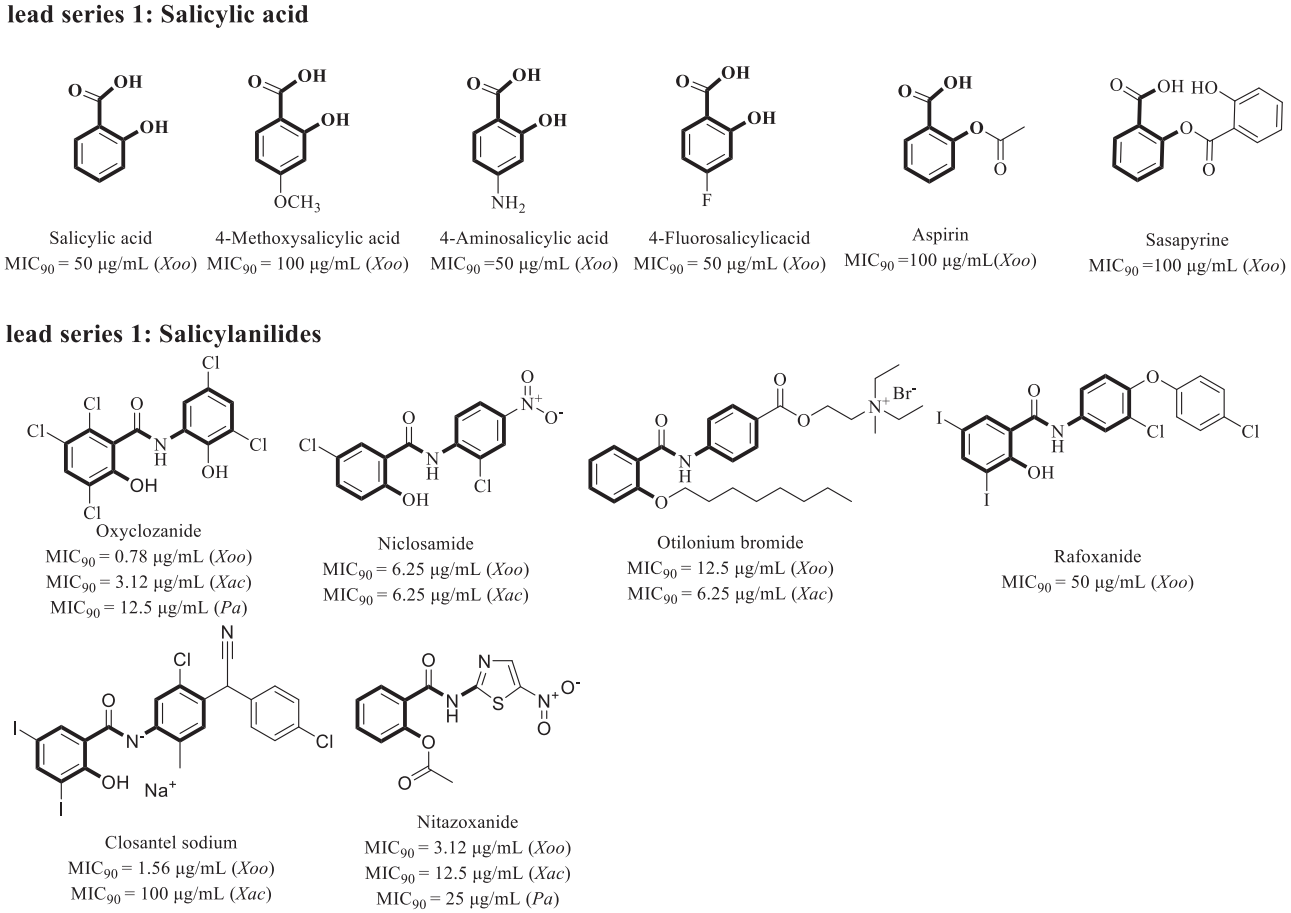


Fig. 2 The MICs of salicylic (lead series 1) acid and salicylanilides (lead series 2) against phytopathogenic bacteria

mainly divided into aliphatic long-chain quaternary ammonium salt ionic drugs and mesoionic drugs with six- or five-membered heterocyclic dipoles. Those drugs exhibited potent antibacterial activities through the electrostatic absorption to negatively charged bacterial cell walls via the cationic nitrogen-containing.

As shown in Table 2 and Fig. 3, cationic nitrogen-containing drugs exhibit excellent activity against phytopathogenic bacteria (MICs ranged from 0.78 to 100 μg ml^{-1}). Structure-activity relationship studies have demonstrated that the number of cationic nitrogen-containing and the substitution pattern on the nitrogen atom are decisive to the activity of the drugs. Comparing the activity data, the activity relationship of these drugs against phytopathogenic bacteria is long chain > pyridine ring > imidazole ring (lead series 3–5). Moreover, we cleared that by increasing the carbon chain length in cationic nitrogen-containing, their antibacterial activity increases, the presence of 16 carbon atoms results in the most potent antibacterial activity. From the screen of these cationic nitrogen-containing drugs we seem to have drawn up an antibacterial structural model of aromatic ring-cation-long chains.

Azole antifungals drugs

Azole compounds are commonly been used as treating fungal infections in clinics. Considering the structure and biological antibacterial activity, azole, as a backbone, not only provides antibacterial potential active fragments with broad antibacterial activity but also as a modification group for various derivatization, showing its activity synergism for developing new drugs. According to the relationship between structure and activity, azoles were divided into three lead series, namely 1-(phenylethyl)imidazole derivatives, imidazole, thiazole.

As shown in Table 3 and Fig. 4, the first azole series we investigated was 1-(phenylethyl)imidazole derivatives (lead series 6), active drugs of this lead series contained fenticonazole nitrate, miconazole, econazole, butoconazole nitrate (MIC_{90} ranged from 3.12 to 12.5 μg ml^{-1}). The preliminary structure-activity relationships indicated that the substitution of benzyl contributed to increaseing the antibacterial activity, introduction of oxygen and sulfur atoms to form ethers could cause a more potent antibacterial effect. Among the 1-(phenylethyl)imidazole derivatives, the

Table 2 In vitro antibacterial activities (Inhibition rate/%) of the Nitrogen-containing ionic drugs against phytopathogenic bacteria

Compounds	concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
1-Butylpyridinium bromide	100	30.77 ± 1.91	2.17 ± 0.93	0 ± 0
N-butyl-4-methylpyridinium chloride	100	14.53 ± 1.11	0 ± 0	0 ± 0
1-Hexadecylpyridinium bromide	100	100 ± 0	100 ± 0	100 ± 0
1-Dodecylpyridinium bromide	100	100 ± 0	100 ± 0	100 ± 0
1-Methyl-3-n-octylimidazolium tetrafluoroborate	100	98.58 ± 0	91.33 ± 0.31	5.3 ± 2.15
1,1'-Di-n-heptyl-4,4'-Bipyridinium dibromide	100	98.91 ± 1.09	98.45 ± 0	0 ± 0
N-N-octadecyl-4-stilbazole bromide	100	0 ± 0	9.03 ± 1.66	0 ± 0
1-Tetradecylpyridinium chloride	100	96.72 ± 1.91	100 ± 0	0 ± 0
1-Hexyl-3-methylimidazolium bromide	100	0 ± 0	0 ± 0	92.56 ± 0.19
1-Butyl-3-methylimidazolium chloride	100	0 ± 0	0 ± 0	9.22 ± 3.05
1-propyl-3-Methyl iMidazoliuM	100	0 ± 0	0 ± 0	0 ± 0
3-Methyl-1-octylimidazolium chloride	100	99.45 ± 0.55	40 ± 2.35	6.17 ± 7.63
1-Hexyl-3-methylimidazolium chloride	100	99.18 ± 0	0 ± 0	29.24 ± 14.3
1-Decyl-3-methylimidazolium chloride	100	98.64 ± 0.55	98.53 ± 0	72.92 ± 8.39
1-Dodecyl-3-methylimidazolium chloride	100	98.36 ± 0.27	100 ± 0	98.66 ± 0.76
1-Hexadecyl-3-methylimidazolium chloride monohydrate	100	100 ± 0	100 ± 0	98.09 ± 0.19
1-Decyl-3-methylimidazolium bromide	100	100 ± 0	99.41 ± 0.29	0 ± 0
BenzyldodecyldiMethy	100	100 ± 0	100 ± 0	100 ± 0
Benzyldimethylhexadecylammonium chloride	100	100 ± 0	100 ± 0	98.28 ± 0.19
Tetradecyldimethylbenzylammonium chloride	100	93.99 ± 0.55	100 ± 0	100 ± 0
Stearyldimethylbenzylammonium chloride	100	100 ± 0	100 ± 0	91.04 ± 6.87
Dodecyldimethylbenzylammonium chloride	100	100 ± 0	100 ± 0	25.62 ± 1.91
Octenidine dihydrochloride	100	100 ± 0	100 ± 0	100 ± 0
Miltefosine	100	99.18 ± 0.27	99.46 ± 0.18	34.54 ± 2.32
Hexadecyl trimethyl ammonium bromide	100	100 ± 0	100 ± 0	100 ± 0
Benzyldimethylhexadecylammonium chloride	100	100 ± 0	100 ± 0	100 ± 0
Domiphen bromide	100	95.81 ± 0.22	94.03 ± 1.05	96.69 ± 0.5
Cetylpyridinium chloride	100	77.76 ± 0.29	87.66 ± 0	93.25 ± 3.37

position of the halogen substituent on the benzene ring seemed to greatly improve the antibacterial activity, especially with 2,6-dichloro-substituted. Miconazole and econazole, a broad-spectrum imidazole fungicide, inhibit synthesis in fungal cell membranes and RNA, the screening and further confirmation revealed that miconazole and econazole were found to exhibit a considerable activity against *Xoo* ($MIC_{90} = 12.5\ \mu g\ ml^{-1}$). Nitroimidazoles and benzimidazoles are our second lead series of azoles (lead series 7), with triclabendazole being the standout for antibacterial activity(the MIC value was $6.25\ \mu g\ ml^{-1}$ against *Xoo* and *Xac*). Interestingly, our screening identified the third azole series (lead series 8), simple-structured thiazolinones exhibit strong antibacterial activity. The substituent of thiazolinone affects the activity of drugs, methyl and chlorine decreased the activity 4-time (5-chloro-2-methylisothiazol-3(2*H*)-one), as compared to the unsubstituted thiazol-3-one. In addition, the introduction of a long chain into the nitrogen atom of thiazolinone does not indicate an increase or decrease in activity compared with thiazol-3-one. Therefore, nitrogen may not be the key factor affecting the anti-agribacterial activity. The benzothiazoles, 1,2-benzisothiazol-3(2*H*)-one, 2-methyl-1,2-benzothiazol-3(2*H*)-one, and 6-fluoro-1,2-benzisothiazol-3(2*H*)-one, show considerable activities, especially 6-fluoro-1,2-benzisothiazol-3(2*H*)-one with the substitution of fluorine on its phenyl rings, which may be accountable for the higher activity as a functional group.

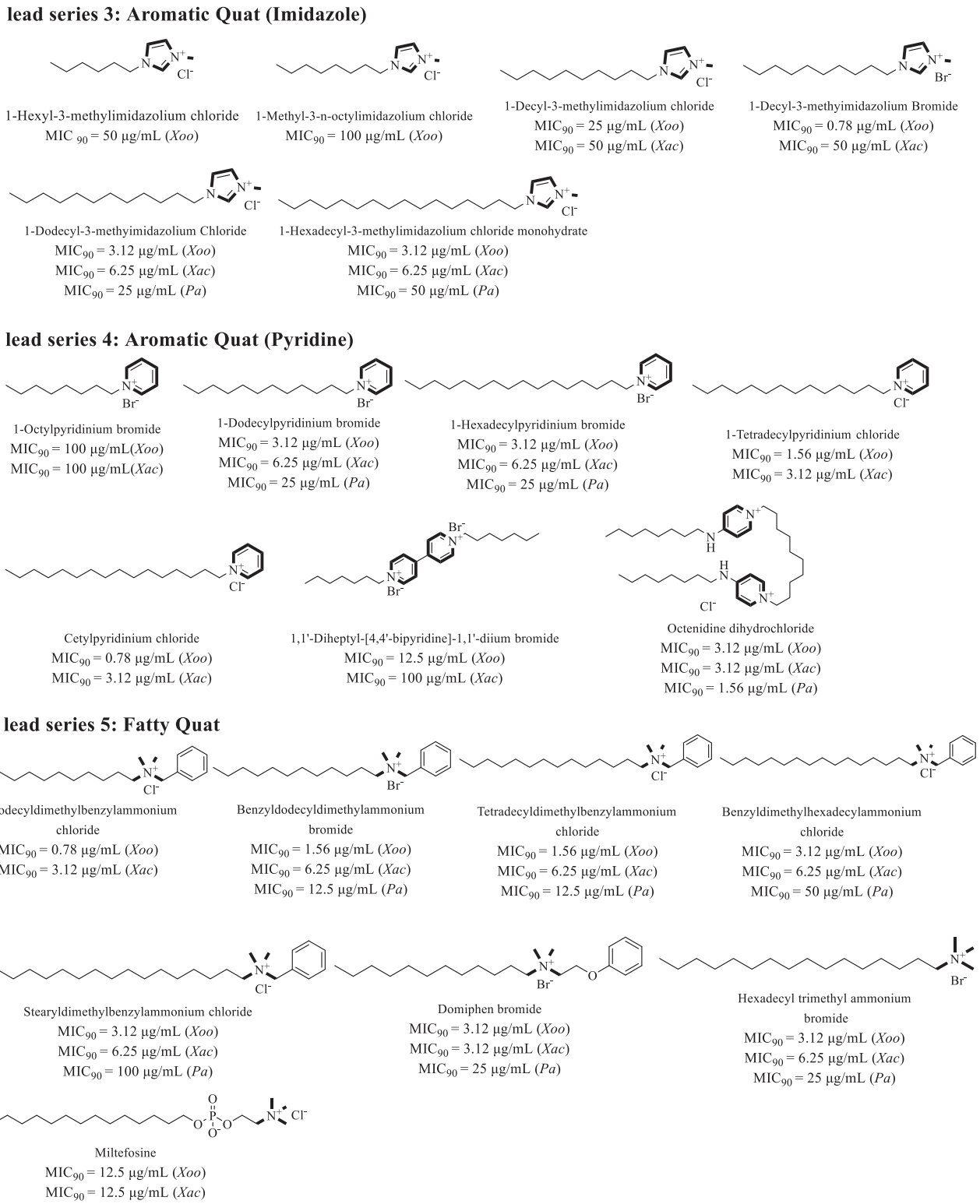


Fig. 3 The MICs of cationic nitrogen-containing drugs (lead series 3–5) against phytopathogenic bacteria

Table 3 In vitro antibacterial activities (Inhibition rate/%) of the azole antifungals drugs against phytopathogenic bacteria

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Ketoconazole	100	15.95 ± 6.27	13.31 ± 0.31	0 ± 0
Bifonazole	100	96.58 ± 2.28	8.67 ± 2.79	13.46 ± 3.44
Clotrimazole	100	100 ± 0	97.83 ± 0	13.46 ± 3.44
Fluconazole	100	0 ± 0	0 ± 0	0 ± 0
Voriconazole	100	0 ± 0	0 ± 0	0 ± 0
Sulconazle Nitrate	100	100 ± 0	97.52 ± 0.62	83.04 ± 0.64
Vagistat	100	97.72 ± 0.57	97.21 ± 0.31	0 ± 0
Butoconazole nitrate	100	100 ± 0	99.07 ± 0.31	0 ± 0
Terconazole	100	78.63 ± 4.84	43.65 ± 3.41	4.65 ± 1.5
Efinaconazole	100	71.51 ± 0	50.46 ± 0.31	10.88 ± 3.22
Isoconazole nitrate	100	97.72 ± 1.71	92.57 ± 0.31	8.95 ± 2.03
Fenticonazole nitrate	100	98.86 ± 5.98	86.69 ± 0.62	46.96 ± 5.46
Elubiol	100	92.59 ± 3.99	62.54 ± 8.67	0 ± 0
Miconazole	100	97.48 ± 0.13	63.72 ± 2.12	7.09 ± 2.12
Itraconazole	100	26.68 ± 1.92	21 ± 9.99	29.5 ± 13.94
Econazole	100	100 ± 0	100 ± 0	50.11 ± 2.12
Posaconazole	100	14.64 ± 4.92	0.48 ± 12.53	16.72 ± 3.87
Isavuconazole	100	100 ± 0	55.89 ± 2.58	86.47 ± 5.15
Luliconazole	100	95.62 ± 2.79	36.29 ± 1.03	6.6 ± 10.63
letrozole	100	25.6 ± 3.98	15.65 ± 11.61	67.79 ± 4.35
Atipamezole hydrochloride	100	92.1 ± 0.29	96.52 ± 0.95	0 ± 0
Anastrozole	100	27.59 ± 6.76	7.91 ± 2.84	6.92 ± 2.74
InterMediate of Linezolid	100	0 ± 0	15.01 ± 1.45	0 ± 0
(*R*)-[3-(3-Fluoro-4-morpholinophenyl)-2-oxo-5-oxazolidinyl]methyl methanesulfonate	100	100 ± 0	20.82 ± 0.73	0 ± 0
Rivaroxaban	100	12.01 ± 9.67	20.1 ± 6.54	0 ± 0
Methazolamide	100	0 ± 0	0 ± 0	0 ± 0
Valsartan	100	0 ± 0	23.02 ± 5.32	0 ± 0
Deracoxib	100	9.73 ± 1.92	92.44 ± 0.56	29.25 ± 5.18
Benzydamine hydrochloride	100	45.84 ± 0.19	76.75 ± 0.28	13.04 ± 0
2-Benzoxazolinone	100	3.01 ± 4.99	29.69 ± 0.28	100 ± 0
Deferasirox	100	81.27 ± 1.46	68.99 ± 3.48	0 ± 0
Cilostazol	100	9.23 ± 2.8	0 ± 0	0.67 ± 0.84
topiroxostat	100	68.57 ± 4.38	25.71 ± 8.83	0 ± 0
Levamisole hydrochloride	100	34.7 ± 1.99	35.92 ± 11.65	15.25 ± 7.51
Temozolomide	100	25.06 ± 5.32	17.92 ± 3.63	0 ± 0
Celecoxib	100	85.01 ± 0	0 ± 0	0 ± 0
Flubendazole	100	86.87 ± 1.09	16.65 ± 7.99	79.08 ± 8.52
Mebendazole	100	100 ± 0	1.8 ± 21.35	19.41 ± 11.66
Oxibendazole	100	100 ± 0	65.69 ± 3.81	13.68 ± 0.64
Fenbendazole	100	99.44 ± 0.28	54.05 ± 4.62	0.44 ± 19.53
Albendazole	100	68.26 ± 1.95	15.12 ± 1.34	3.35 ± 2.92
Omeprazole	100	33.57 ± 2.13	48.95 ± 22.17	31.29 ± 1.86
Esomeprazole magnesium	100	32.15 ± 2.84	52.56 ± 1.29	63.87 ± 4.22
Ufiprazole	100	18.29 ± 0	38.12 ± 4.38	39.05 ± 2.36
Lansoprazole	100	54.53 ± 0.36	78.34 ± 0.52	61.51 ± 3.04
lansoprazole sulfide	100	16.87 ± 1.78	11.82 ± 1.29	18.46 ± 2.7
R-(+)-Lansoprazole	100	75.49 ± 2.84	84.01 ± 0.77	75.86 ± 0.34
Ilaprazole(IY 81149)	100	38.9 ± 26.64	54.1 ± 22.95	30.95 ± 3.71
Pantoprazole Sodium	100	30.73 ± 1.42	68.03 ± 1.03	46.82 ± 1.01
pantoprazole sulfide	100	22.91 ± 3.2	63.9 ± 4.9	18.29 ± 2.19
Abeprazole Sulfide	100	28.24 ± 1.07	53.33 ± 2.58	17.28 ± 4.05
Azilsartan	100	0 ± 0	6.4 ± 0.77	30.28 ± 2.7
Telmisartan	100	0 ± 0	47.4 ± 4.38	42.09 ± 1.69
Candesartan cilexetil	100	4.44 ± 2.13	81.95 ± 0.52	11.37 ± 0.34

Table 3 (continued)

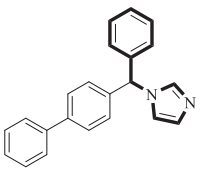
Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Dabigatran etexilate	100	5.63 ± 4.07	0 ± 0	12.52 ± 2.19
Pimobendan	100	18.24 ± 4.07	2.59 ± 7.47	13.46 ± 0.47
Astemizole	100	100 ± 0	100 ± 0	40.17 ± 0
Parbendazole	100	71.12 ± 17.9	45.92 ± 2.99	17.52 ± 5.62
Thiabendazole	100	73.97 ± 11.8	66.24 ± 5.08	36.27 ± 3.44
Carbendazim	100	26.78 ± 7.73	24.1 ± 26.29	14.4 ± 4.22
Oxfendazole	100	100 ± 0	100 ± 0	43.07 ± 0.85
Theophylline	100	14.57 ± 1.96	23.32 ± 0.67	17.46 ± 3.42
Imidurea	100	97.31 ± 0.19	98.04 ± 0	14.07 ± 5.66
Imiquimod	100	4.86 ± 0.44	49.06 ± 5.27	8.43 ± 7.44
Daclatasvir	100	13.81 ± 3.36	41.58 ± 2.63	37.88 ± 1.65
Atipamezole hydrochloride	100	92.1 ± 0.29	96.52 ± 0.95	0 ± 0
Albendazole S-oxide	100	0 ± 0	8.6 ± 3.69	0 ± 0
Benzoylmetronildazole	100	37.62 ± 3.15	20.72 ± 1.05	0 ± 0
(+)-Pilocarpine hydrochloride	100	5.02 ± 3.86	12.55 ± 1.84	0 ± 0
Triclabendazole	100	100 ± 0	100 ± 0	20.86 ± 0.27
Metronidazole	100	1.86 ± 11.14	21.97 ± 2.02	76.27 ± 9.58
Ornidazole	100	11.65 ± 15.94	13.9 ± 3.36	93.91 ± 1.52
Tinidazole	100	78.68 ± 1.34	21.3 ± 0.67	96.5 ± 0.15
Ronidazole	100	77.34 ± 1.34	15.92 ± 0	97.41 ± 0
4,5-Dichloro-2-octyl-isothiazolone	100	100 ± 0	100 ± 0	100 ± 0
2-Octyl-2*H*-isothiazol-3-one	100	100 ± 0	100 ± 0	100 ± 0
Methylisothiazolinone	100	55.00 ± 2.00	99.14 ± 0.08	98.54 ± 0.78
1,2-Benzisothiazol-3(2*H*)-one	100	100 ± 0	100 ± 0	100 ± 0
2-Methyl-1,2-benzothiazol-3(2*H*)-one	100	100 ± 0	100 ± 0	100 ± 0
6-Fluoro-1,2-benzoisothiazol-3(2*H*)-one	100	100 ± 0	100 ± 0	100 ± 0
Thiazol-3-one	100	100 ± 0	100 ± 0	99.23 ± 0.19
5-chloro-3-hydroxyisothiazole	100	100 ± 0	100 ± 0	100 ± 0
5-Chloro-2-Methylisothiazol-3(2*H*)-one	100	100 ± 0	100 ± 0	100 ± 0
3-(1-Piperazinyl)-1,2-benzisothiazole	100	65.1 ± 9.69	94.17 ± 2.91	68.22 ± 0.58
6-Ethoxy-2-benzothiazolesulfonamide	100	66.91 ± 12.98	31.54 ± 3.2	74.97 ± 3.82
2-(4-chloro-phenyl)-thiazolidine-4-carboxylic acid	100	20.45 ± 0	24.16 ± 2.19	33.11 ± 3.7
Ethyl 2-(2-aminothiazol-4-yl)glyoxylate	100	0 ± 0	52.33 ± 0.18	0 ± 0
Ethyl 2-(2-aminothiazole-4-yl)-2-(1-tert-butoxycarbonyl-1-methylethoxyimino) acetate	100	100 ± 0	79.27 ± 1.95	52.92 ± 2.92
1,3-Thiazol-2-amine	100	1.11 ± 0.9	26.28 ± 0.36	11.58 ± 4.39
Thiabendazole	100	73.97 ± 11.8	66.24 ± 5.08	36.27 ± 3.44
Ethyl 2-(2-aminothiazol-4-yl)-2-methoxyiminoacetate	100	28.94 ± 0.77	33.33 ± 4.48	6.6 ± 7.46
Acotiamide hydrochloride trihydrate	100	0 ± 0	1.64 ± 0.35	0 ± 0
Febuxostat	100	61.41 ± 13.53	22.1 ± 2.84	24.8 ± 4.03
isavuconazole	100	100 ± 0	55.89 ± 2.58	86.47 ± 5.15
Riluzole	100	98.44 ± 0.45	62.52 ± 0.17	59.5 ± 2.45

Hydroxyquinolines

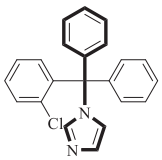
Hydroxyquinolines are established to own wealthy biological activities and can be used as herbicides, disinfectants, preservatives, chemical intermediates, etc, that determines their wide application within the field of medication. Our research group previously conducted research on 8-hydroxyquinoline as metal chelators against agricultural fungi, and the results showed that this kind of compounds has excellent antifungal activity, revealing great potential as agricultural fungicides [41].

As shown in Table 4 and Fig. 5, the results of the screening experiments indicated that the quinoline derivatives with 8-hydroxyl group exhibited increased antibacterial activity at primary screening of 100 μg ml^{-1}, compared with other positions of hydroxyl substitution, such as the 2, 5, 6 hydroxyl groups. With 8-hydroxyquinoline (lead series 9) as the skeleton, different

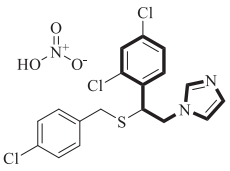
lead series 6: pyrithione



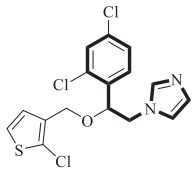
Bifonazole
MIC_{90} = 100 μg/mL (*Xoo*)



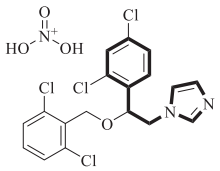
Clotrimazole
MIC_{90} = 12.5 μg/mL (*Xoo*)
MIC_{90} = 100 μg/mL (*Xac*)



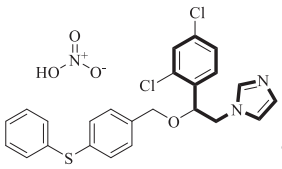
Sulconazle Nitrate
MIC_{90} = 100 μg/mL (*Xoo*)
MIC_{90} = 100 μg/mL (*Xac*)



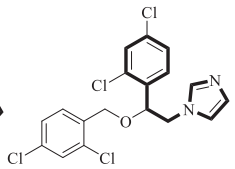
Vagistat
MIC_{90} = 25 μg/mL (*Xoo*)
MIC_{90} = 100 μg/mL (*Xac*)



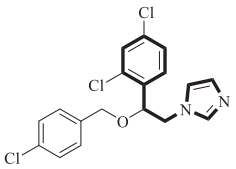
Isoconazole nitrate
MIC_{90} = 50 μg/mL (*Xoo*)
MIC_{90} = 100 μg/mL (*Xac*)



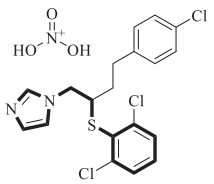
Fenticonazole nitrate
MIC_{90} = 3.12 μg/mL (*Xoo*)



Miconazole
MIC_{90} = 12.5 μg/mL (*Xoo*)

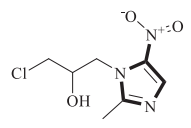


Econazole
MIC_{90} = 12.5 μg/mL (*Xoo*)
MIC_{90} =12.5 μg/mL (*Xac*)

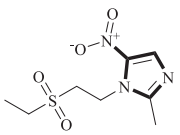


Butoconazole nitrate
MIC_{90} = 3.12 μg/mL (*Xoo*)
MIC_{90} = 12.5 μg/mL (*Xac*)

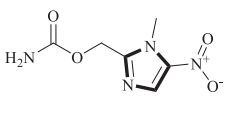
lead series 7: pyrithione



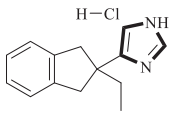
Ornidazole
MIC_{90} = 50 μg/mL (*Pa*)



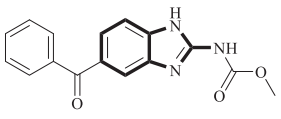
Tinidazole
MIC_{90} = 12.5 μg/mL (*Pa*)



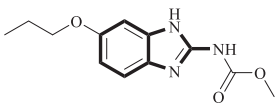
Ridazole
MIC_{90} = 50 μg/mL (*Pa*)



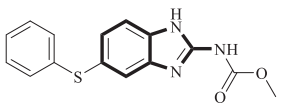
Atipamezole hydrochloride
MIC_{90} = 100 μg/mL (*Xoo*)
MIC_{90} = 50 μg/mL (*Xac*)



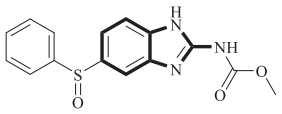
Mebendazole
MIC_{90} = 100 μg/mL (*Xoo*)



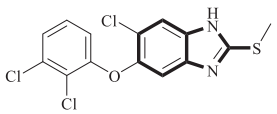
Oxibendazole
MIC_{90} = 100 μg/mL (*Xoo*)



Fenbendazole
MIC_{90} = 100 μg/mL (*Xoo*)



Oxfendazole
MIC_{90} = 50 μg/mL (*Xoo*)
MIC_{90} = 100 μg/mL (*Xac*)

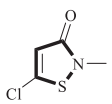


Triclabendazole
MIC_{90} = 6.25 μg/mL (*Xoo*)
MIC_{90} = 6.25 μg/mL (*Xac*)

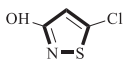
lead series 8: pyrithione

Thiazol-3-one
MIC_{90} = 6.25 μg/mL (*Xoo*)
MIC_{90} = 12.5 μg/mL (*Xac*)
MIC_{90} =25 μg/mL (*Pa*)

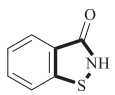
Methylisothiazolinone
MIC_{90} = 25 μg/mL (*Xac*)
MIC_{90} = 50 μg/mL (*Pa*)



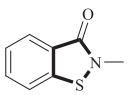
5-Chloro-2-methylisothiazol-3(2*H*)-one
MIC_{90} = 25 μg/mL (*Xac*)
MIC_{90} = 50 μg/mL (*Pa*)



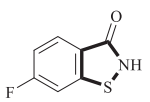
5-Chloro-3-hydroxyisothiazole
MIC_{90} = 3.12 μg/mL (*Xoo*)
MIC_{90} = 3.12 μg/mL (*Xac*)
MIC_{90} = 3.12 μg/mL (*Pa*)



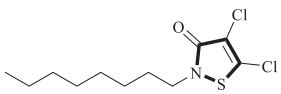
1,2-Benzisothiazol-3(2H)-one
MIC_{90} = 6.25 μg/mL (*Xoo*)
MIC_{90} = 3.12 μg/mL (*Xac*)
MIC_{90} = 12.5 μg/mL (*Pa*)



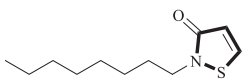
2-Methyl-1,2-benzothiazol-3(2H)-one
MIC_{90} = 6.25 μg/mL (*Xoo*)
MIC_{90} = 3.12 μg/mL (*Xac*)
MIC_{90} = 12.5 μg/mL (*Pa*)



6-Fluoro-1,2-benzisothiazol-3(2H)-one
MIC_{90} = 3.12 μg/mL (*Xoo*)
MIC_{90} = 3.12 μg/mL (*Xac*)
MIC_{90} = 12.5 μg/mL (*Pa*)



4,5-Dichloro-2-octyl-isothiazolone
MIC_{90} = 12.5 μg/mL (*Xoo*)
MIC_{90} = 3.12 μg/mL (*Xac*)
MIC_{90} = 50 μg/mL (*Pa*)



2-Octyl-2H-isothiazol-3-one
MIC_{90} = 50 μg/mL (*Xoo*)
MIC_{90} = 25 μg/mL (*Xac*)
MIC_{90} =50 μg/mL (*Pa*)

Fig. 4 The MICs of azole antifungals drugs (lead series 6–8) against phytopathogenic bacteria

Table 4 In vitro antibacterial activities (Inhibition rate/%) of the hydroxyquinolines against phytopathogenic bacteria

Compounds	Concentration ($\mu g\ ml^{-1}$)	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
8-Hydroxyquinoline	100	96.19 ± 0.00	98.47 ± 0.31	96.87 ± 0.00
8-Hydroxyquinaldine	100	97.92 ± 0.69	99.08 ± 0.31	96.87 ± 0.2
5-Chloro-8-hydroxyquinoline	100	100.00 ± 0.00	100.00 ± 0.00	95.69 ± 0.59
5-bromoquinolin-8-ol	100	100.00 ± 0.00	100.00 ± 0.00	89.23 ± 0.98
Nitroxoline	100	100.00 ± 0.00	94.51 ± 1.22	93.54 ± 2.94
5,7-Dichloro-8-hydroxyquinoline	100	100.00 ± 0.00	100.00 ± 0.00	99.8 ± 2.94
5,7-Dibromo-8-hydroxyquinoline	100	100.00 ± 0.00	100.00 ± 0.00	85.7 ± 5.09
5,7-Diiodo-8-quinolinol	100	100.00 ± 0.00	81.99 ± 0.92	97.65 ± 1.76
Clioquinol	100	90.31 ± 2.42	92.07 ± 0.31	94.91 ± 3.13
8-Hydroxyquinoline-5-sulfonic acid	100	31.83 ± 1.04	22.18 ± 7.93	0.00 ± 0.00
Chlorquinalol	100	100.00 ± 0.00	98.62 ± 0.23	74.49 ± 0.2
2-Quinolinol	100	96.19 ± 0.35	86.88 ± 9.77	29.70 ± 9.99
6-Aminoquinoline	100	92.39 ± 2.08	83.83 ± 9.16	53.00 ± 5.29
5-Hydroxyquinoline	100	96.19 ± 1.73	86.88 ± 9.46	40.47 ± 1.37
7-Hydroxyquinoline	100	100.00 ± 0.00	67.96 ± 1.83	44.78 ± 7.25
3-Hydroxyquinoline	100	94.12 ± 3.11	75.28 ± 5.49	18.54 ± 5.87
6-Hydroxyquinoline	100	82.01 ± 5.88	63.07 ± 0.92	10.51 ± 2.15
6-Hydroxyquinoline	100	37.72 ± 2.42	31.94 ± 6.1	45.17 ± 0.98
2,4-Quinolinediol	100	44.98 ± 1.38	2.34 ± 6.71	31.27 ± 0.2
6-Methoxy-8-nitroquinoline	100	100.00 ± 0.00	55.75 ± 5.49	63.19 ± 2.15

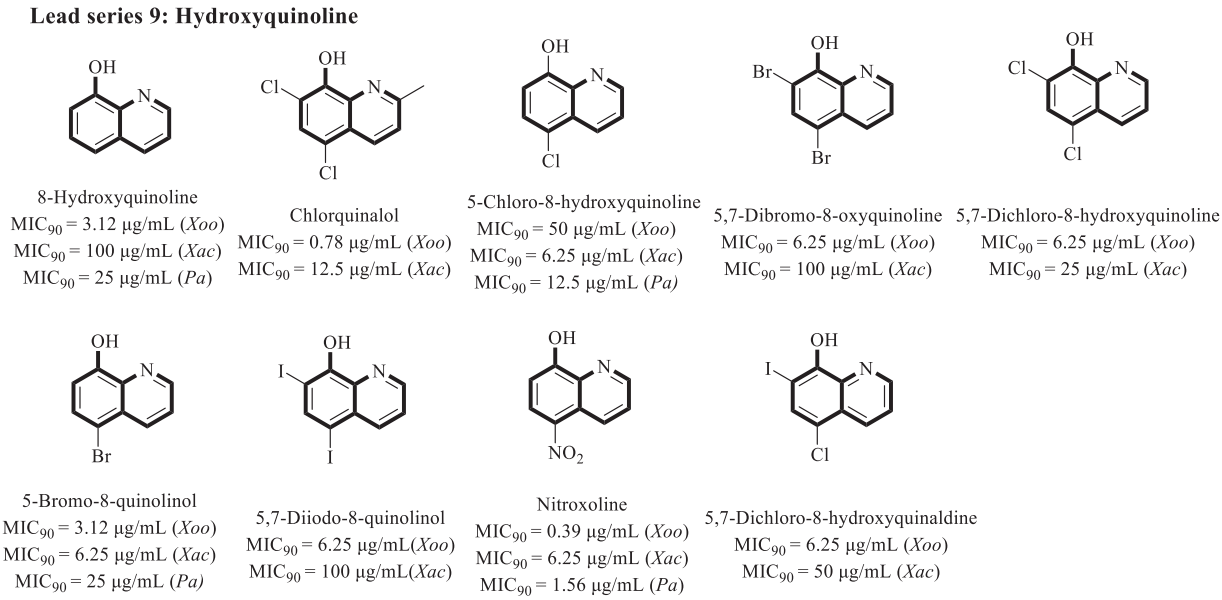


Fig. 5 The MICs of Hydroxyquinoline (lead series 9) against phytopathogenic bacteria

group substitutions even have different antibacterial effects. When the NO_2 on the 5-position is substituted, the activity of 8-hydroxyquinoline against three pathogenic bacteria is greatly improved, with the increased bactericide result against *Xoo*, *Xac*, *Pa* by 4, 16 and 8 times respectively (the MICs are 0.39, 6.25, 1.56). Substitution of Cl and Br at the 5-position produces a similar effect either. However, CH_3 substitution did not appear to have a positive effect, even reduced activity against *Xoo*. In addition, 8-hydroxyquinoline bears two groups substituents at the 5

Table 5 In vitro antibacterial activities (Inhibition rate/%) of the N-containing group against phytopathogenic bacteria

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Xinjunan	100	95.41 ± 0.19	100 ± 0	97.56 ± 0.41
2-Aminoethyl(ethyl)amine	100	19.2 ± 2.11	37.59 ± 3.65	9.68 ± 2.3
1,4-Diaminobutane	100	52.06 ± 3.62	56.2 ± 1.09	56.99 ± 1.8
Diethylenetriamine	100	24.92 ± 0.3	31.02 ± 1.46	8.68 ± 3.99
Tetraethyenepentamine	100	54.77 ± 2.11	44.16 ± 1.82	7.58 ± 1.9
1,6-Diaminohexane	100	32.46 ± 3.92	37.59 ± 0.36	5.99 ± 2.59
Triethylenetetramine	100	46.63 ± 0.6	41.61 ± 4.01	9.38 ± 0.4
4-Methyl-1-piperazineethanamine	100	10.45 ± 3.92	15.69 ± 0.36	9.68 ± 2.4
Cyclen	100	18.29 ± 1.51	8.39 ± 0	63.87 ± 3.99
Hexacyclen	100	6.53 ± 0.9	8.76 ± 2.92	50.3 ± 0.9
N,*N*'-bis(3-aminopropyl) ethylenediamine	100	65.33 ± 3.32	27.37 ± 1.46	23.35 ± 5.49
N-Aminoethylpiperazine	100	32.76 ± 1.21	49.27 ± 0	2.69 ± 2.3
1,5-Diaminopentane	100	11.36 ± 1.51	22.26 ± 6.57	0.6 ± 0.2
*N*1,*N*1'-(butane-1,4-diyl)bis(ethane-1,2-diamine)	100	57.79 ± 5.73	32.48 ± 1.09	23.55 ± 0.2
1,3-Diaminopropane	100	29.45 ± 6.93	46.35 ± 1.46	6.69 ± 4.09
Tris(2-aminoethyl)amine	100	19.2 ± 3.32	6.93 ± 4.38	3.49 ± 5.29
Ethylenediamine	100	1.66 ± 7.81	0.47 ± 0.47	0 ± 0
1,7-Diaminoheptane	100	65.27 ± 3.89	4.5 ± 2.95	0 ± 0
Dmapapa	100	19.03 ± 7.38	14.11 ± 3.57	1.19 ± 0.74
Piperazine	100	0 ± 0	15.04 ± 4.5	0 ± 0
Ethambutol	100	0 ± 0	0 ± 0	23.63 ± 1.22
Diethylenetriaminepentaacetic acid	100	56.87 ± 1.51	70.33 ± 2.81	0 ± 0
Khimcoecid	100	28.86 ± 4.18	100 ± 0	99.42 ± 0
Moroxydine hydrochloride	100	1.47 ± 1.92	15.97 ± 5.32	0 ± 0
Febantel	100	0 ± 0	35.32 ± 12.06	19.52 ± 0.14
1,1-Dimethylbiguanide Hydrochloride-D6	100	78.39 ± 2.07	80.57 ± 0	4.33 ± 12.78
Enebicyanog	100	100 ± 0	100 ± 0	100 ± 0
Chlorhexidine diacetate	100	100 ± 0	100 ± 0	100 ± 0
Chlorhexidine hydrochloride	100	90.85 ± 0.4	94.84 ± 0	96.62 ± 0.16
Olsalazine sodium	100	1.47 ± 2.3	17.37 ± 3.36	0 ± 0
Isoniazid	100	12.07 ± 4.29	23.8 ± 2.3	3.22 ± 0.29
Cyanoacetohydrazide	100	0 ± 0	15.97 ± 1.96	30.53 ± 8.23
Nifuroxazide	100	54.97 ± 3.53	43.44 ± 0.7	60.33 ± 0.17
Iproniazid	100	0 ± 0	17.35 ± 2.55	69.47 ± 1.99
Diminazene aceturate	100	71.08 ± 6.15	100 ± 0	53.87 ± 4.65
Diminazene	100	88.27 ± 0.31	77.29 ± 0.37	55.4 ± 0.86
Pentamidine	100	100 ± 0	100 ± 0	100 ± 0
Thiacetazone	100	3.02 ± 7.15	65.45 ± 6.38	27.19 ± 7.89
Imidurea	100	97.31 ± 0.19	98.04 ± 0	14.07 ± 5.66
Imidocarb dipropionate	100	57.94 ± 3.84	94.68 ± 0.28	0 ± 0
Glimepiride	100	0 ± 0	28.07 ± 1.28	0 ± 0
Triclocarban	100	100 ± 0	100 ± 0	11.78 ± 7.53
Enzalutamide	100	78.51 ± 1.14	14.62 ± 3.1	0 ± 0

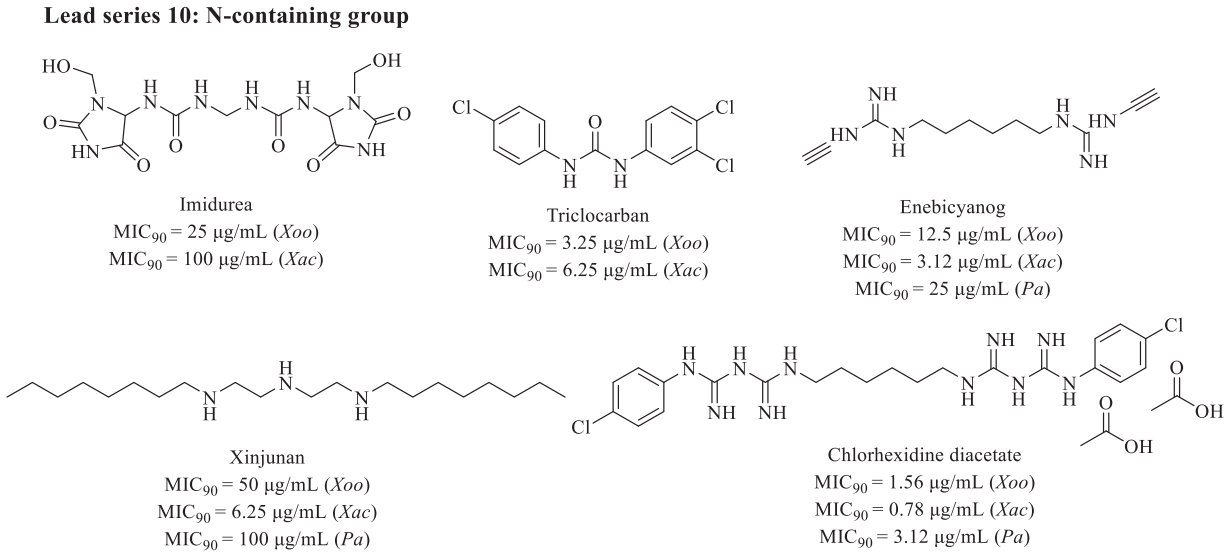


Fig. 6 The MICs of N-containing group (lead series 10) against phytopathogenic bacteria

and 7 positions have less potential, especially 5,7-dibromo-8-hydroxyquinoline. Studies have shown that the ability of the 8-hydroxyquinoline scaffold to chelate divalent ions make this molecule an important fragment to interact with metalloproteins in microorganisms as targets, which may be the main reason for its antibacterial activities.

It is worth mentioning that the commercialized chloroquinadol, as one of the main components of the clinically used drug Kejingbao, is well known for its anti-Candida albicans effect. In fact, our experiments show that its in vitro antibacterial activity against *Xoo* is even better than that against *Candida albicans*, with MIC of 0.39 μg ml^{-1} against *Xoo* and 0.12 μg ml^{-1} against Ca (The data were measured by us simultaneously). Overall, our repurposing of the commercially available drugs, 8-hydroxyquinoline, endows it with a broader application, is warrant further investigation within the area of controling phytopathogenic pathogens.

N-containing group

As shown in Table 5 and Fig. 6, *N*-containing group drugs were screened as lead series 10. The pharmacophore of these compounds includes amines, ureas and guanidines. Amines are nitrogenous aliphatic or heterocyclic substances with biological functions. Xinjunan is a precursor in the synthesis of Junduqing, a broad-spectrum bactericide which was successfully developed by China Shandong Chemical Development Center in 1989. It has been used for various crops to control agricultural diseases caused by fungi, bacteria and viruses for many years. Xinjunan has good antibacterial activity against three phytopathogenic bacteria in this screening experiment. In order to investigate the impact of amino groups on antibacterial activity, the activity of commercial fatty amines was tested, but these fatty amines have no antibacterial activity. which shows that the exposed amino group is not the active center. Xinjunan to a reasonable improvement of activity only when the bilateral amino groups are connected by a long aliphatic chain. In addition, compounds with urea and guanidine groups such as triclocarban and chlorhexidine acetate have been widely used in the field of medical sterilization and disinfection, which have broad-spectrum antimicrobial activity and are harmless in direct contact with the human skin. These *N*-containing groups as the hydrophilic head of these molecules contain strong positive charges and adsorb negatively charged bacterial cell membranes by electrostatic interaction. Our results suggest that these drugs have equal effect against plant bacteria.

Piperazine

As shown in Table 6 and Fig. 7, the category discussion of lead series 11 was based on the presence of a central heterocyclic ring system containing at least one nitrogen atom (piperazine and piperidine groups). From the structure-activity point of view, the nature and position of the electron donating functional groups on the piperazine and piperidine core may contribute to the antibacterial activity. It is worth mentioning that Penfluridol, a commercial long-acting antipsychotic indicated for the maintenance treatment of chronic schizophrenia, has high antibacterial activity against *Xoo* and *Xac* with the MICs of 3.12 μg ml^{-1}, providing a basis again for the strategy of drug-repurposing.

Table 6 In vitro antibacterial activities (Inhibition rate/%) of the piperazine against phytopathogenic bacteria

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Prochlorperazine maleate	100	99.18 ± 0.27	98.53 ± 0.29	96.19 ± 0.19
Perphenazine	100	98.64 ± 0.27	98.24 ± 0.29	92.94 ± 5.53
Clozapine	100	98.91 ± 0.55	99.41 ± 0.00	0 ± 0
Olanzapine	100	33.45 ± 5.12	7.65 ± 1.18	15.61 ± 2.62
Aripiprazole	100	98.72 ± 0.26	99.12 ± 0	18.23 ± 3.67
Ziprasidone HCL	100	22.7 ± 1.79	15.86 ± 1.9	0 ± 0
Buclizine, dihydrochloride	100	100 ± 0	58.88 ± 0.38	0 ± 0
Cinnarizine	100	88.23 ± 4.1	94.29 ± 1.14	75.54 ± 2.27
Cetirizine	100	0.94 ± 2.82	7.87 ± 0.38	0 ± 0
Ranolazine	100	10.67 ± 4.1	26.14 ± 4.95	65.75 ± 1.88
Amoxapine	100	100 ± 0	100 ± 0	100 ± 0
Quetiapine fumarate	100	85.67 ± 5.12	58.88 ± 0.76	59.99 ± 0.7
Mirtazapine	100	64.68 ± 5.63	0 ± 0	70.47 ± 2.8
Sitagliptin	100	0 ± 0	0 ± 0	41.99 ± 3.67
Brexpiprazole	100	77.22 ± 0.77	13.2 ± 0.76	0 ± 0
Terfenadine	100	100 ± 0	100 ± 0	98.3 ± 0.64
Thioridazine hydrochloride	100	38.05 ± 0.84	0.94 ± 1.94	94.17 ± 11.81
Pimozide	100	93.61 ± 0.36	99.23 ± 1.03	30.95 ± 17.39
Astemizole	100	100 ± 0	100 ± 0	40.17 ± 0
Penfluridol	100	100 ± 0	100 ± 0	88.05 ± 1.42
Loperamide hydrochloride	100	100 ± 0	100 ± 0	12.33 ± 1.99
Trifluoperazine dihydrochloride	100	69.42 ± 0	33.89 ± 1.96	99.49 ± 0.26
Benzhexol hydrochloride	100	95.14 ± 1.1	5.15 ± 1.05	0 ± 0
Paroxetine HCL	100	96.92 ± 0	95.63 ± 0.36	99.34 ± 0.17
Ebastine	100	96.31 ± 0.31	76.7 ± 3.28	2.1 ± 6.97
Haloperidol	100	79.38 ± 2.55	7.45 ± 3.96	13.89 ± 1.06
Mizolastine	100	100 ± 0	67.73 ± 3.59	20.02 ± 0.16
Vortioxetine	100	100 ± 0	85.17 ± 2.56	100 ± 0
Sildenafil	100	10.98 ± 2.1	6.76 ± 3.69	0 ± 0
Imatinib	100	18.57 ± 0.58	61.06 ± 1.4	30.02 ± 2.9
3-(1-Piperazinyl)-1,2-benzisothiazole	100	65.1 ± 9.69	94.17 ± 2.91	68.22 ± 0.58
Domperidone	100	33.21 ± 3.2	0 ± 0	30.28 ± 7.43
Flibaserin	100	16.52 ± 14.92	14.4 ± 30.94	24.87 ± 0.34
Bilastin	100	19.05 ± 5.69	0.2 ± 1.79	18.15 ± 0.16
Abemaciclib	100	88.2 ± 2.44	36.65 ± 1.49	29.55 ± 17.34
Risperidone	100	91.05 ± 1.22	62.95 ± 1.49	1.43 ± 9.06
Terazosin hydrochloride	100	27.17 ± 3.64	15.92 ± 3.7	16.89 ± 0.85
Donepezil	100	12.14 ± 3.46	9.72 ± 0.35	0 ± 0
Piperaquine phosphate	100	64.94 ± 0.95	57.95 ± 2.36	52.13 ± 4.47
Desloratadine	100	96.38 ± 0.52	97.05 ± 0.33	99.41 ± 0.12
Loratadine	100	9.54 ± 15.08	27.91 ± 0.73	5.75 ± 4.48
Fexofenadine	100	0 ± 0	21.36 ± 0.36	13.05 ± 3.48
Posaconazole	100	14.64 ± 4.92	0.48 ± 12.53	16.72 ± 3.87
Itraconazole	100	26.68 ± 1.92	21 ± 9.99	29.5 ± 13.94
Vardenafil hydrochloride	100	17.96 ± 0	6.53 ± 2.82	0 ± 0

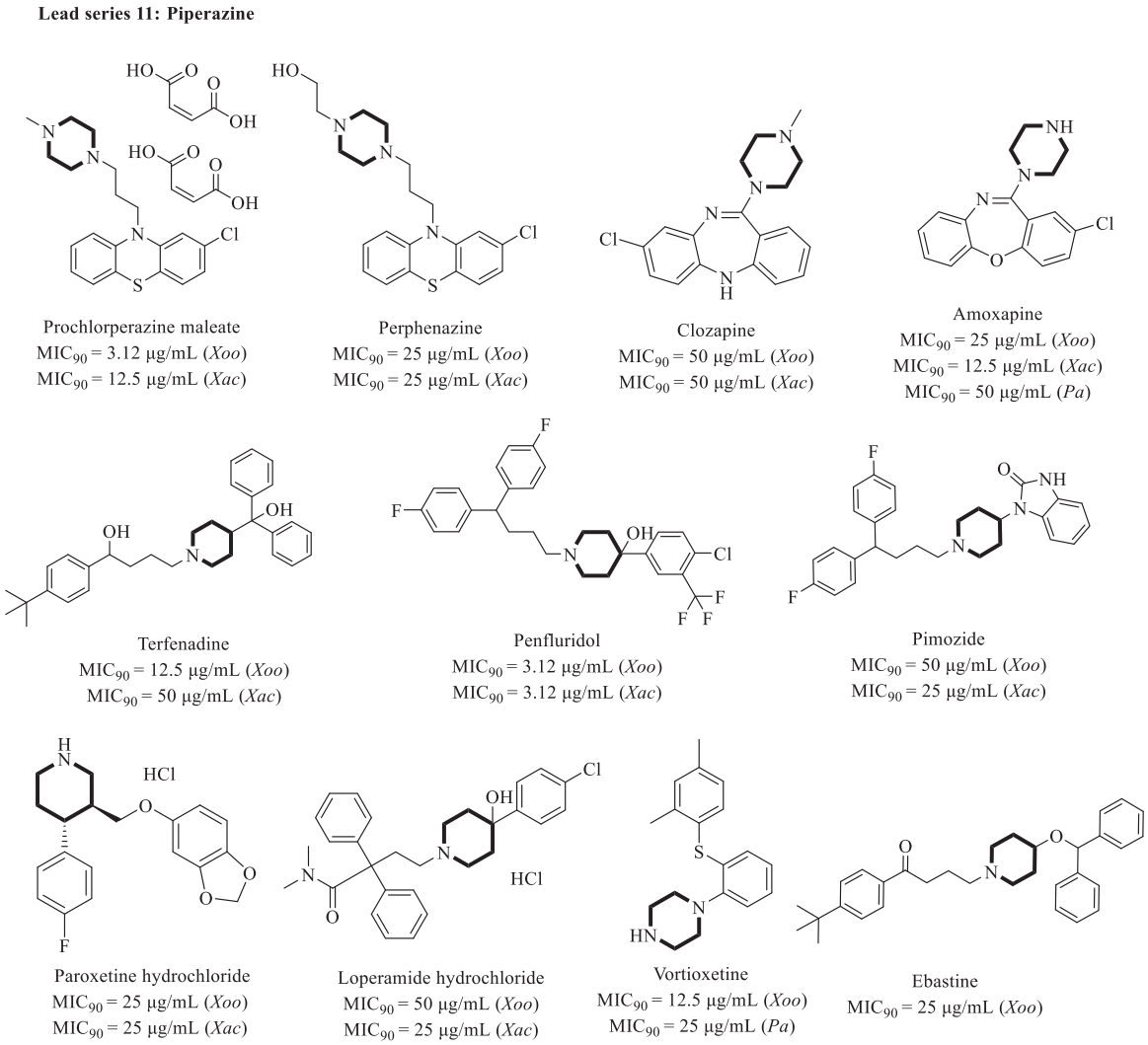


Fig. 7 The MICs of piperazine (lead series 11) against phytopathogenic bacteria

Kinase inhibitors

Kinase inhibitors attracted much attention for a long time, owing to their significant role in the field of anti-tumor. However, bacterial growth processes are also affected by signal pathways. Hence, many studies have focused on the application of kinase inhibitors to the antibacterial field recently. For instance, Philipp Le found the anti-cancer drug Sorafenib showed high anti-bacterial activity against MRSA strains and did not induce in vitro resistance.

As shown in Table 7 and Fig. 8, among this established series (lead series 12), 4,4' -(dithiodicarbonothioyl)dimorpholine (JX06) is well known as a PDK inhibitor, which usually binds covalently to cysteine residues in an irreversible manner resulting in antitumor activity. In this study, we screened the 53 key kinase inhibitors led to the discovery of JX06 as a outstanding hit effectively killing the two specific plant pathogenic strains at concentrations of micromoles per milliliter. The MICs of JX06 were 6.25 and 12.5 μg ml^{-1} against *Xoo* and *Xac* respectively. Besides, Perifosine also has a similar effect (the MICs of 6.25 and 25 μg ml^{-1} against *Xoo* and *Xac* respectively), which may be the result of the combined effect of cation membranes permeability and certain signaling pathway regulation. Taken together, these results support the potential application of these kinase inhibitors with antibacterial activity for bacterial disease control in plants.

Miscellaneous groups

As shown in Table 8 and Fig. 9, the last series (lead series 13) is some chemically dispersed drugs. Drugs which are conducted in this screen category are quinine, sulfa anti-inflammatory, nucleoside anticancer, cephalosporin antimicrobial and *S*-containing drugs which include thioether, mercaptan, disulfide drugs. Highly active anti-agribacterial

Table 7 In vitro antibacterial activities (Inhibition rate/%) of the kinase inhibitors against phytopathogenic bacteria

Compounds	concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Gefitinib	100	20.77 ± 2.48	45.22 ± 0.26	0 ± 0
Erlotinib	100	33.63 ± 7.22	61.02 ± 7.64	11.07 ± 9.06
Sorafenib tosylate	100	60.95 ± 1.35	100 ± 0	8.56 ± 5.87
Dasatinib	100	100 ± 0	99.21 ± 0	46.48 ± 5.7
Sunitinib	100	100 ± 0	26.78 ± 1.58	0 ± 0
Lapatinib	100	32.96 ± 0	69.18 ± 1.32	16.61 ± 1.68
Nilotinib	100	18.96 ± 0.9	98.42 ± 0.26	40.77 ± 5.54
Vandetanib	100	99.77 ± 0.23	45.22 ± 0.26	73.83 ± 2.18
Axitinib	100	0 ± 0	2.19 ± 1.88	0 ± 0
Vemurafenib	100	0 ± 0	2.5 ± 22.5	0 ± 0
Bosutinib	100	100 ± 0	90.25 ± 3.17	0 ± 0
Tofacitinib	100	0 ± 0	1.88 ± 3.75	8.38 ± 3.68
Trametinib	100	0 ± 0	0.31 ± 3.12	75.94 ± 2.45
Nintedanib	100	23.95 ± 2.21	21.25 ± 2.5	91.73 ± 7.2
Lenvatinib	100	0 ± 0	0.62 ± 5.94	21.86 ± 0.46
Mereletinib	100	100 ± 0	100 ± 0	0 ± 0
Palbociclib	100	3.77 ± 3.22	46.56 ± 29.69	59.55 ± 1.84
Baricitinib	100	0 ± 0	0 ± 0	13.43 ± 0.15
Brigatinib	100	43.64 ± 5.26	12.5 ± 7.5	1.63 ± 8.58
Venclexta	100	0 ± 0	35 ± 3.44	0 ± 0
Ponatinib	100	96.31 ± 1.48	100 ± 0	0 ± 0
Sonidegib	100	43.15 ± 2.46	77.19 ± 4.69	44.54 ± 1.84
Olaparib	100	0 ± 0	0 ± 0	0 ± 0
Niraparib	100	100 ± 0	98.75 ± 0	4.24 ± 3.52
Rucaparib phosphate	100	98.77 ± 0	97.81 ± 0.31	0.87 ± 12.72
Pazopanib hydrochloride	100	16.25 ± 3.13	3.81 ± 2.7	8.73 ± 2
Cabozantinib	100	53.54 ± 6.25	53.25 ± 4.99	20.89 ± 6.95
Regorafenib	100	36.67 ± 2.29	26.87 ± 3.95	0 ± 0
Afatinib	100	100 ± 0	98.34 ± 0.21	0.45 ± 4.14
Ibrutinib	100	24.17 ± 7.71	76.11 ± 1.87	0 ± 0
Idelalisib	100	26.46 ± 5.21	8.17 ± 9.35	7.93 ± 10.82
Acalabrutinib	100	20.63 ± 2.29	10.04 ± 7.06	0 ± 0
Ribociclib	100	94.58 ± 0.21	84.83 ± 0.83	16.35 ± 2.14
Ripretinib	100	0 ± 0	0 ± 0	0 ± 0
Upadacitinib	100	15 ± 2.92	8.59 ± 0.21	0 ± 0
Dabrafenib	100	37.5 ± 6.67	69.25 ± 3.32	0 ± 0
Ruxolitinib	100	16.46 ± 0.63	9.42 ± 2.08	7.93 ± 0.27
JX06	100	100 ± 0	100 ± 0	100 ± 0
Nilotinib Hydrochloride Monohydrate	100	0 ± 0	17.11 ± 3.95	19.42 ± 1.74
Perifosine	100	100 ± 0	99.38 ± 0.21	29.04 ± 0.4
Tandutinib	100	32.29 ± 0	34.56 ± 4.78	3.92 ± 3.21
Phenformin hydrochloride	100	99.38 ± 0.21	10.66 ± 3.32	5.52 ± 5.88
Phenformin hydrochloride	100	94.79 ± 1.67	98.75 ± 2.08	77.02 ± 0.13
Selumetinib	100	18.13 ± 3.75	16.69 ± 0.62	11.27 ± 1.87
Nilvadipine	100	9.79 ± 7.92	16.69 ± 0.83	1.11 ± 3.47

Table 7 (continued)

Compounds	concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Sulfatinib	100	100 ± 0	100 ± 0	15.21 ± 0.26
Imatinib	100	18.57 ± 0.58	61.06 ± 1.4	30.02 ± 2.9
Fasudil hydrochloride	100	0 ± 0	17.72 ± 1.09	0 ± 0
Crizotinib	100	94.74 ± 0.35	98.42 ± 0.79	98.49 ± 0
Alectinib	100	13.58 ± 4.63	0 ± 0	0 ± 0
Ceritinib	100	98.46 ± 1.23	41.39 ± 8.79	0 ± 0
Regorafenib hydrate	100	8.33 ± 3.7	74.18 ± 1.47	0 ± 0

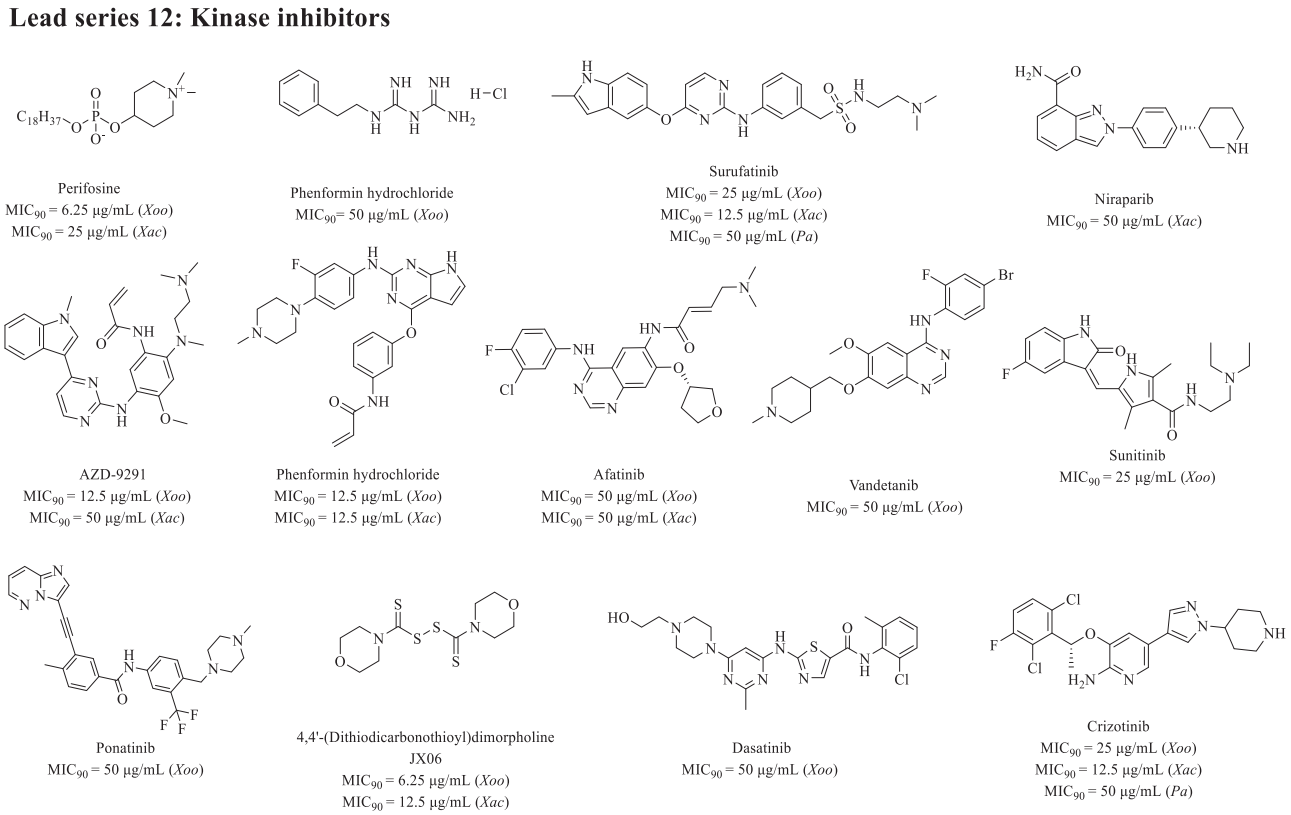


Fig. 8 The MICs of kinase inhibitors (lead series 12) against phytopathogenic bacteria

drugs identified in the screening are listed by class. It was also attracted that the derivative of pyrithione (Zinc pyrithione, Sodium omadine, Copper pyritione, and Pyrion disulfide) has reasonable anti-phytopathogenic bacteria activity. In previous reports, Zinc pyrithione passed the increase in cellular zinc levels, decrease in lipase expression, and inhibition of mitochondrial function against *M. restricta*[42]; Bithionol exhibits bactericidal activity against both antibiotic-resistant *S. aureus* with its ability to pass through and embed in bacterial membranes lipid bilayers [43]. The anti-phytopathogenic bacteria activities of double phenol-containing drugs (Dichlorophen, Triclosan, and Bithionol) might be attributed to the anti-corrosion and weak acidity of the phenolic part. Among them, triclosan and dichlorophen have the strongest antibacterial activity, both drugs contain similar structure, the MIC_{90} ranged from 3.12 to 25 μg ml^{-1}; Abafungin was found to have potentiality antifungal activity whether the pathogens are growing or resting [44]. The anti-phytopathogenic bacteria activity of these five drugs against *Xoo, Xac*, and *Pa* has never been reported and therefore is worth further exploration; Pleuromutilin is a broad-spectrum diterpene antibiotic produced

Table 8 In vitro antibacterial activities (Inhibition rate/%) of the miscellaneous groups against phytopathogenic bacteria

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Brinzolamide	100	0 ± 0	0 ± 0	7.91 ± 5.73
Rivaroxaban intermediate	100	48.51 ± 41.1	0 ± 0	0 ± 0
Gemcitabine	100	72.44 ± 1.45	0 ± 0	0 ± 0
Ethyl bromopyruvate	100	91.52 ± 0.27	97.82 ± 0.36	98.84 ± 0.39
Alibendol	100	48.29 ± 0.55	0 ± 0	22.92 ± 8.13
Synephrine	100	80.47 ± 2.03	53.69 ± 6.57	21.11 ± 7.97
Atovaquone	100	100 ± 0	33.98 ± 1.74	21.95 ± 7.39
Clorprenaline hydrochloride	100	0 ± 0	9.58 ± 0	5.83 ± 6.36
Nifuratel	100	100 ± 0	100 ± 0	100 ± 0
Nimodipine	100	24.65 ± 9.78	22.39 ± 1.52	9.23 ± 3.39
Amlodipine	100	99.86 ± 0.14	100 ± 0	98.25 ± 1.02
Droperidol	100	67.32 ± 1.42	0 ± 0	25.04 ± 2.7
Simvastatin	100	4 ± 7.32	0 ± 0	16.9 ± 27.02
Nimesulide	100	21.49 ± 4.07	35.46 ± 0.9	10.49 ± 3.44
Clomipramine hydrochloride	100	96.75 ± 0.41	94.92 ± 0.3	99.06 ± 0.16
Benzbromarone	100	95.08 ± 0.76	91.82 ± 0.26	0 ± 0
Nortriptyline hydrochloride	100	98.11 ± 0	96.16 ± 1.02	84.92 ± 1.12
Atorvastatin	100	0.88 ± 3.4	0 ± 0	0 ± 0
Fluvastatin sodium salt	100	18.66 ± 2.65	51.15 ± 1.28	0 ± 0
Tamoxifen	100	90.92 ± 1.13	90.03 ± 1.79	78.77 ± 3.07
Fluoxetine hydrochloride	100	100 ± 0	100 ± 0	100 ± 0
Tulobuterol hydrochloride	100	25.49 ± 1.68	62 ± 7.74	19.17 ± 7.4
Tilorone dihydrochloride	100	55.18 ± 1.12	20.12 ± 0.17	18.88 ± 4.27
Indometacin	100	29.69 ± 1.4	85.37 ± 8.58	53.61 ± 0.28
Dichlorophen	100	100 ± 0	100 ± 0	100 ± 0
Avobenzone	100	15.69 ± 2.24	19.96 ± 3.36	32.26 ± 0.57
L-Cycloserine	100	100 ± 0	100 ± 0	50.47 ± 4.55
Clofazimine	100	100 ± 0	100 ± 0	31.12 ± 1.71
Bedaquiline	100	91.04 ± 0.84	69.73 ± 0.17	0 ± 0
Ethionamide	100	100 ± 0	78.74 ± 4.78	37.43 ± 3.22
Protionamide	100	65.69 ± 0.24	100 ± 0	42.98 ± 0.88
Diclazuril	100	26.85 ± 10.01	100 ± 0	23.39 ± 0.29
Decoquinate	100	17.79 ± 6.67	46.84 ± 2.84	18.13 ± 4.09
Amprolium	100	13.26 ± 5.48	76.08 ± 5.32	12.87 ± 0.58
Clopidol	100	21.13 ± 4.77	78.38 ± 8.68	48.54 ± 3.8
Ethopabate	100	13.5 ± 6.2	77.67 ± 3.01	41.81 ± 1.17
Arprinocide	100	0 ± 0	52.66 ± 2.52	0 ± 0
(*E*,*E*)-Farnesol	100	11.27 ± 0.38	24.37 ± 1.68	65.01 ± 8.23
Trimethobenzamide hydrochloride	100	2.62 ± 0.19	17.93 ± 0.28	73.24 ± 0.51
Orphenadrine citrate	100	18.57 ± 4.23	57.42 ± 1.4	0 ± 0
Chlorphenesin	100	35.66 ± 9.03	47.34 ± 0.28	0 ± 0
Triacetin	100	0 ± 0	5.5 ± 0	0 ± 0
Bronopol	100	100 ± 0	96.84 ± 0	99.34 ± 0.17
Etravirine	100	0 ± 0	10.42 ± 2.11	6.28 ± 9.09
Diphenhydramine Hydrochloride	100	15.67 ± 2.21	5.15 ± 1.05	0 ± 0
Levetiracetam	100	0 ± 0	61.01 ± 1.76	0 ± 0
Tropicamide	100	0 ± 0	95.08 ± 1.76	16.53 ± 7.19
Benztropine mesylate	100	98.01 ± 0.22	77.17 ± 2.11	5.95 ± 3.64
Pyrantel pamoate	100	0 ± 0	64.17 ± 2.46	0 ± 0
Flufenamic acid	100	3.53 ± 12.36	93.68 ± 0.35	0 ± 0
Furazolidone	100	100 ± 0	100 ± 0	100 ± 0
Furaltadone hydrochloride	100	98.3 ± 0.34	99.27 ± 0	94.59 ± 1
Monomyristin	100	0 ± 0	45.19 ± 2.92	46.72 ± 1.28
Revaprazan HCL	100	58.21 ± 1.7	34.96 ± 1.83	0 ± 0
Taurolidine	100	98.64 ± 0.68	97.81 ± 0	17.66 ± 9.69
Aprepitant	100	0 ± 0	69.67 ± 10.23	28.49 ± 0.85
Beaprine	100	40.78 ± 5.21	64.09 ± 4.72	38.09 ± 2.77

Table 8 (continued)

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Pyrantel tartrate salt	100	6.44 ± 0.95	0 ± 0	22.13 ± 2.55
Carbonyl Cyanide	100	97.87 ± 0.24	98.11 ± 0.94	96.6 ± 0.21
Pyrimethamine	100	90.53 ± 0.71	76.85 ± 1.42	54.68 ± 4.04
Artemether	100	11.65 ± 1.42	0 ± 0	32.34 ± 8.3
Artesunate	100	11.41 ± 2.84	2.2 ± 8.5	64.68 ± 5.53
Itopride hydrochloride	100	0 ± 0	0 ± 0	6.38 ± 7.87
Atropine sulfate monohydrate	100	6.91 ± 1.18	2.68 ± 2.36	16.38 ± 5.11
Dihydroarteminisin	100	28.23 ± 0.24	22.99 ± 2.83	26.17 ± 7.87
Lumefantrine	100	5.33 ± 9.05	39.78 ± 1.09	16.77 ± 6.49
Cetylpyridinium chloride monohydrate	100	80.4 ± 1.81	78.47 ± 0.36	95.51 ± 0.3
Thiamine chloride	100	0 ± 0	8.76 ± 1.82	9.88 ± 3.69
1-Adamantanamine hydrochloride	100	41.51 ± 6.63	21.53 ± 1.46	3.29 ± 1
1,3-Thiazol-2-amine	100	1.11 ± 0.9	26.28 ± 0.36	11.58 ± 4.39
4-(2-Aminoethyl)benzenesulfonylfluoride hydrochloride	100	88.61 ± 0.52	91.79 ± 2.63	0 ± 0
Diphenhydramine	100	64.28 ± 1.29	55.69 ± 0.33	38.12 ± 1.41
Bufexamac	100	57.81 ± 2.33	69.15 ± 0.66	0 ± 0
Acrivastine	100	0 ± 0	15.65 ± 1.31	0 ± 0
Metoclopramide hydrochloride	100	1.64 ± 4.92	21.23 ± 3.61	0 ± 0
5-Phenylpenta-2,4-dienoic acid	100	38.4 ± 1.81	40.92 ± 0.66	17.18 ± 10.12
Roflumilast	100	0.49 ± 2.34	33.54 ± 0.32	49.22 ± 10.12
Hydroxyurea	100	21.56 ± 1.46	40.19 ± 4.75	0 ± 0
Thiamine chloride	100	0 ± 0	15.51 ± 3.8	62.34 ± 6.56
Acetylcysteine	100	0 ± 0	14.87 ± 0.63	62.52 ± 15.74
Escitalopram oxalate	100	44.1 ± 3.22	56.96 ± 0.95	18.68 ± 7.12
Rimantadine hydrochloride	100	81.27 ± 0.88	60.76 ± 0.95	0 ± 0
Amantadine	100	59.61 ± 1.17	44.94 ± 0.32	27.86 ± 6.93
Ezetimibe	100	12.78 ± 3.51	30.7 ± 14.56	0 ± 0
Thalidomide	100	0 ± 0	17.41 ± 4.75	0 ± 0
Primidone	100	0 ± 0	25.95 ± 7.59	0 ± 0
Venlafaxine hydrochloride	100	5.76 ± 6.73	29.11 ± 0.95	0 ± 0
Cinacalcet	100	0 ± 0	18.45 ± 1.46	66.32 ± 2.16
Propranolol hydrochloride	100	93.23 ± 2.77	83.98 ± 5.83	38.27 ± 0.33
Vorinostat	100	15.69 ± 0	34.83 ± 0.73	15.54 ± 1.49
(+/−)-Verapamil hydrochloride	100	55.38 ± 5.85	47.21 ± 1.82	21.52 ± 2.99
Mecarbinate	100	10.77 ± 8.92	19.9 ± 16.02	10.9 ± 4.31
Efavirenz	100	57.23 ± 0.62	43.2 ± 0.73	6.42 ± 0.33
Bazedoxifene acetate	100	40.31 ± 5.69	79.25 ± 3.64	0 ± 0
Fasudil hydrochloride	100	0 ± 0	17.72 ± 1.09	0 ± 0
Pitavastatin calcium	100	0 ± 0	13.35 ± 3.28	1.6 ± 1
Dronedarone hydrochloride	100	96.01 ± 0	97.23 ± 0.25	3.08 ± 7.22
Ticlopidine	100	42.27 ± 3.38	19.78 ± 2.51	21.64 ± 6.52
Ipratropium bromide	100	19.39 ± 7.36	38.63 ± 10.54	0 ± 0
Ketotifen fumarate	100	67.76 ± 3.86	58.65 ± 3.69	0 ± 0
Rolipram	100	25.35 ± 0.35	15.98 ± 2.11	0 ± 0
Avanafil	100	9.58 ± 0.7	8.34 ± 1.05	76.34 ± 3.36
Milrinone	100	23.6 ± 4.56	21.77 ± 0.53	18.79 ± 1.68
Tadalafil	100	24.01 ± 11.14	10.49 ± 14.19	4.35 ± 5.31
Verapamil	100	23.21 ± 2.79	17.45 ± 0.52	0 ± 0
Bicalutamide	100	36.74 ± 4.77	18.49 ± 3.35	62.8 ± 4.35
Vildagliptin	100	14.46 ± 5.97	11.26 ± 7.74	77.78 ± 2.9
Leflunomide	100	69.36 ± 5.17	47.12 ± 4.9	4.99 ± 0
Entacapone	100	24.8 ± 0	0 ± 0	50.08 ± 0.32
RU-58841	100	24.01 ± 1.19	9.46 ± 2.32	39.45 ± 4.99
strontium ranelate	100	0 ± 0	0 ± 0	0 ± 0
teriflunomide	100	59.42 ± 14.72	39.64 ± 8.25	20.93 ± 5.31
Mupirocin	100	96.42 ± 0.4	94.07 ± 0.52	96.46 ± 0.16

Table 8 (continued)

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Levosimendan	100	16.9 ± 1.06	24.87 ± 2.12	0 ± 0
Mupirocin	100	93.63 ± 0	91.53 ± 0.18	96.65 ± 0
Pralidoxime Chloride	100	0 ± 0	0 ± 0	9.83 ± 0.69
Teriflunomide	100	25.4 ± 2.12	14.64 ± 2.82	24.51 ± 3.99
Bephenium hydroxynaphthoate	100	94.96 ± 0.8	89.59 ± 0	22.31 ± 3.53
Thiamine nitrate	100	33.99 ± 8.46	11.18 ± 5.89	0 ± 0
ApreMilast	100	0 ± 0	17.83 ± 3.07	0 ± 0
Procaine	100	7.38 ± 2.84	2.68 ± 6.14	23.19 ± 5.96
Amylmetacresol	100	99.07 ± 0.31	6.23 ± 12.27	1.24 ± 5.59
Trajenta	100	12.35 ± 1.23	0 ± 0	7.7 ± 3.44
Azelastine hydrochloride	100	83.02 ± 2.35	38.46 ± 1.28	8.08 ± 14.91
Pyributicarb	100	14.81 ± 2.65	0 ± 0	38.48 ± 0.29
Florfenicol	100	100 ± 0	100 ± 0	96.08 ± 0.51
Piroctone olamine	100	95.01 ± 1.15	98.65 ± 0.67	100 ± 0
Ciclopirox ethanolamine	100	96.93 ± 0.77	99.33 ± 0	100 ± 0
Caprylohydroxamic acid	100	76.57 ± 1.54	89.91 ± 2.02	70.15 ± 1.00
Triclosan	100	100 ± 0	100 ± 0	100 ± 0
Mefloquine hydrochloride	100	99.07 ± 0.13	90.23 ± 0	96.73 ± 1.93
Linezolid	100	79.27 ± 5.18	0 ± 0	48.59 ± 4.5
Acetazolamide	100	0 ± 0	100 ± 0	91.65 ± 0.64
Promethazine hydrochloride	100	96.76 ± 0	100 ± 0	60.03 ± 7.99
4-Carboxy-2,2,6,6-tetramethylpiperidine 1-oxyl	100	0 ± 0	0 ± 0	10.93 ± 5.28
3-Carboxy-2,2,5,5-tetraMethylpyrrolidine 1-Oxyl Free Radical	100	0 ± 0	0 ± 0	15.19 ± 2.21
Nitrofurantoin	100	93.55 ± 0	99 ± 0.33	96.42 ± 0.17
Ibuprofen	100	53.43 ± 5.79	24.62 ± 9.01	0 ± 0
Diciofenac	100	63.1 ± 7.16	21.62 ± 4.34	0 ± 0
Ebselen	100	74.57 ± 5.91	100 ± 0	100 ± 0
Trimethoprim	100	77.25 ± 0.36	41.3 ± 1	93.87 ± 0.68
Florfenicol	100	100 ± 0	100 ± 0	96.08 ± 0.51
Methotrexate	100	57.73 ± 8.78	23.96 ± 1.33	0.54 ± 5.62
Tolnaftate	100	11.46 ± 3.83	0 ± 0	12.07 ± 8.22
Liranaftate	100	25.48 ± 9.8	27.35 ± 2.69	57.1 ± 4.26
Tranilast	100	7.04 ± 4.99	12.56 ± 2.69	0 ± 0
Lappaconitine	100	0 ± 0	24.66 ± 1.35	30.32 ± 2.54
Fluoxetine	100	100 ± 0	100 ± 0	99.49 ± 1.02
Iodopropynyl butylcarbamate	100	71.29 ± 9.57	100 ± 0	99.26 ± 0.25
Sodium dehydroacetate	400	78.39 ± 21.07	19.55 ± 0.36	77.82 ± 0.35
Potassium sorbate	100	4.56 ± 6.75	69.54 ± 0.2	34.51 ± 4.61
Silver	100	96.75 ± 0.24	5.58 ± 0.00	0 ± 0
Bortezomib	100	64.66 ± 6.53	66.37 ± 0.67	30.02 ± 1.37
Tavaborole	100	100 ± 0	100 ± 0	97.03 ± 0.52
Crisaborole	50	58.59 ± 4.82	0 ± 0	0 ± 0
3,5-Dihydroxy-4-isopropylstilbene	100	97.62 ± 1.79	99.49 ± 0.51	55.21 ± 5.35
Stanozolol	100	6.56 ± 4.16	19.18 ± 0.51	0 ± 0
Megestrol acetate	100	0 ± 0	4.09 ± 3.32	0 ± 0
Dexamethasone	100	14.5 ± 0.38	24.81 ± 0.51	24.58 ± 6.42
Spironolactone	100	11.73 ± 2.33	30.42 ± 3.94	56 ± 2.35
Triamcinolone acetonide	100	1.64 ± 3.11	30.42 ± 0.66	66.12 ± 9.18
Betamethasone	100	7.08 ± 4.14	38.29 ± 3.61	60.59 ± 10.35
Hydrocortisone	100	13.03 ± 2.85	30.74 ± 0.33	59.76 ± 0.59
Prednisolone	100	3.71 ± 11.39	34.35 ± 1.64	0 ± 0
Fluticasone propionate	100	0 ± 0	17.72 ± 7.28	15.87 ± 1.33
Bardoxolone methyl	100	78.81 ± 1.84	27.07 ± 4.53	20.94 ± 1.4
Megestrol	100	97.54 ± 0	34.87 ± 1.56	0 ± 0
Trilostane	100	56.23 ± 6.37	8.94 ± 2.32	0 ± 0
6-Aminopenicillanic acid	100	24.88 ± 0.13	33.98 ± 2.91	98.84 ± 0.19

Table 8 (continued)

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
7-Aminodesacetoxycephalosporanic acid	100	13.6 ± 3.72	0.97 ± 3.88	0 ± 0
Aztreonam nucleus	100	22.23 ± 1.46	0 ± 0	22.76 ± 11.94
Ceftazidime intermediate	100	0 ± 0	14.24 ± 9.04	0 ± 0
Ethyl 2-(2-aminothiazol-4-yl)glyoxylate	100	0 ± 0	52.33 ± 0.18	0 ± 0
Ceftazidime intermediate	100	100 ± 0	100 ± 0	27.19 ± 1.17
5-Fluorouridine	100	92.85 ± 2.38	23.53 ± 2.53	87.71 ± 1.96
Doxifluridine	100	0 ± 0	33.25 ± 3.48	3.35 ± 4.19
Uridine	100	0 ± 0	71.1 ± 3.07	0 ± 0
2'-Fluoro-2'-deoxyuridine	100	0 ± 0	7.93 ± 0.51	0 ± 0
1-(2-Deoxy-2-fluoro-beta-D-arabinofuranosyl)uracil	100	0 ± 0	2.81 ± 2.81	4.19 ± 1.96
1-beta-D-Arabinofuranosyluracil	100	11.66 ± 1.1	15.53 ± 9.63	13.2 ± 9.9
Trifluorothymine	100	26.01 ± 0.37	22.03 ± 7.39	19.88 ± 7.6
Broxuridine	100	47.73 ± 1.47	10.16 ± 2.69	7.67 ± 2.76
5-Bromouridine	100	2.82 ± 0.74	22.93 ± 0.45	20.8 ± 0.46
5-Iodouridine	100	0 ± 0	0 ± 0	0 ± 0
Carmofur	100	100 ± 0	100 ± 0	94.7 ± 0.23
Tegafur	100	18.28 ± 1.1	39.73 ± 0.45	38.07 ± 0.46
Cytidine	100	0 ± 0	7.69 ± 10.31	5.14 ± 10.59
5-Fluorocytidine	100	76.07 ± 0.74	34.58 ± 4.71	32.77 ± 4.83
5-Azacytidine	100	81.23 ± 0.37	15.31 ± 1.12	12.97 ± 1.15
Lamivudine	100	43.31 ± 4.79	4.11 ± 1.79	1.46 ± 1.84
Trifluridine	100	81.23 ± 0.74	5.45 ± 11.2	45.43 ± 11.51
Guanosine	100	10.92 ± 3.31	24.72 ± 3.14	22.64 ± 3.22
2'-Deoxyuridine	100	0 ± 0	39.28 ± 5.15	37.61 ± 5.3
Dideoxyinosine	100	0 ± 0	38.83 ± 5.15	37.15 ± 5.3
Stavudine	100	6.87 ± 2.21	42.42 ± 1.12	40.83 ± 1.15
Abacavir	100	12.02 ± 0	9.26 ± 2.46	6.75 ± 2.53
Acyclovir	100	0 ± 0	19.79 ± 0.9	17.57 ± 0.92
Famciclovir	100	8.71 ± 3.31	41.3 ± 5.38	39.68 ± 5.53
Penciclovir	100	0 ± 0	2.09 ± 1.34	0 ± 0
Ganciclovir	100	0 ± 0	0 ± 0	0 ± 0
Flavopiridol	100	61.11 ± 0.43	82.8 ± 3.82	11.68 ± 0.27
Brivudine	100	13.03 ± 0.21	14.56 ± 7.77	0 ± 0
Cytarabine	100	2.56 ± 0.64	21.36 ± 5.83	0.88 ± 0.81
Ribavirin	100	8.12 ± 0.64	14.56 ± 6.8	0 ± 0
(Vidarabine,Ara-A)	100	3.42 ± 3.21	10.68 ± 5.83	46.25 ± 2.7
5-iodo-2'-deoxyuridine	100	66.24 ± 1.5	11.65 ± 0.97	0 ± 0
Thymidine	100	0 ± 0	41.4 ± 4.19	0 ± 0
Floxuridine	100	81.01 ± 0	100 ± 0	97.62 ± 0.17
5-Fluorouracil	100	86.39 ± 3.4	75.99 ± 4	97.45 ± 0
Fluorocytosine	100	29.96 ± 8.48	55.51 ± 0	0 ± 0
Emtricitabine	100	0.78 ± 0.59	18.35 ± 0.95	0 ± 0
Favipiravir	100	0 ± 0	30.38 ± 0.32	3.31 ± 5.25
6-Thioguanine	100	5.85 ± 3.69	30.83 ± 1.09	0 ± 0
Zidovudine	100	75.34 ± 2.18	2.66 ± 6.54	45.16 ± 2.74
Capecitabine	100	5.46 ± 2.93	26.9 ± 2.22	0 ± 0
Quinine	100	45.81 ± 0.69	39.84 ± 1.06	7.59 ± 5.88
Quinidine	100	53.22 ± 0.23	41.44 ± 0.53	0 ± 0
Cinchonidine	100	44.65 ± 11.58	37.18 ± 2.13	0.5 ± 2.71
Cinchonine	100	35.16 ± 0.93	36.11 ± 2.66	9.4 ± 8.14
N-Benzylcinchoninium chloride	100	30.82 ± 0.21	5.96 ± 1.68	0.63 ± 4.97
N-Benzylquininium chloride	100	21 ± 2.99	6.3 ± 0.67	0 ± 0
Hydroquinine	100	26.76 ± 9.82	22.08 ± 1.18	0 ± 0
N-Benzylcinchonidinium chloride	100	26.76 ± 9.82	22.08 ± 1.18	0 ± 0
Cinchonine hydrochloride	100	11.81 ± 2.56	5.96 ± 3.86	18.14 ± 1.66
Quinine HCL	100	57.94 ± 0.21	0 ± 0	29.97 ± 7.1
Quinine dihydrochloride	100	50.89 ± 3.63	5.63 ± 1.18	2.52 ± 3.55

Table 8 (continued)

Compounds	Concentration (μg ml^{-1})	Inhibition rate/%		
		Xoo	*Xac*	*Pa*
Quinine sulfate dihydrate	100	30.25 ± 0.76	0 ± 0	4.56 ± 0.64
Quinine hydrochloride dihydrate	100	64.87 ± 0.25	0.28 ± 0.46	4.56 ± 1.91
Hydroquinidine 4-chlorobenzoate	100	63.6 ± 32.58	19.34 ± 10.06	0 ± 0
Hydroquinidine	100	64.11 ± 0.76	3.48 ± 5.34	0 ± 0
Hydroquinidine hydrochloride	100	100 ± 0	3.02 ± 4.42	79 ± 19.94
(9 S)- 10,11-dihydro-Cinchonan-6',9-diol	100	100 ± 0	54.26 ± 2.52	12.05 ± 3.42
Hydroxychloroquine	100	12.83 ± 2.84	14.02 ± 0.47	27.02 ± 8.09
Pheniramine maleate	100	0 ± 0	24.18 ± 1.31	0 ± 0
Chlorpheniramine maleate	100	38.14 ± 3.88	40.92 ± 1.31	0 ± 0
Amlodipine maleate	100	95.34 ± 0.26	95.73 ± 0.33	98.94 ± 0.24
Fluvoxamine maleate	100	96 ± 0.31	88.71 ± 0.73	7.08 ± 3.48
Naftifine	100	0 ± 0	0 ± 0	0 ± 0
Terbinafine	100	0 ± 0	0 ± 0	0 ± 0
Butenafine	100	10.50 ± 8.84	0 ± 0	4.56 ± 1.18
Sulfasalazine	100	16.83 ± 4.65	96.91 ± 1.82	7.04 ± 8.52
Sulfaquinoxaline sodium	100	53.53 ± 1.67	57.83 ± 0.35	19.01 ± 0.88
Sulfaclozine sodium monohydrate	100	74.27 ± 2.14	61.9 ± 1.59	36.55 ± 2.05
Sulfamethazine	100	60.44 ± 0.95	68.1 ± 11.87	2.63 ± 3.51
Sulfamonomethoxine	100	71.88 ± 1.43	51.27 ± 5.14	10.82 ± 4.09
Sulfachloropyridazine	100	52.37 ± 6.33	64.71 ± 1.68	100 ± 0
Sodium *N*-(5-methylisoxazol-3-yl)sulphanilamidate	100	54.76 ± 0.24	47.09 ± 1.89	40 ± 7.45
Sulfamethoxypyridazine	100	39.6 ± 1.89	50.39 ± 6.14	18.09 ± 9.15
Sulfisoxazole	100	13.95 ± 2.63	50.32 ± 3.16	39.29 ± 0.56
Dichloro-1,2-dithiacyclopentenone	100	99.07 ± 0.13	100 ± 0	100 ± 0
Anethole trithione	100	26.74 ± 14.33	14.56 ± 0.97	66.1 ± 0.39
Levamisole hydrochloride	100	34.7 ± 1.99	35.92 ± 11.65	15.25 ± 7.51
Bithionol	100	100 ± 0	64.08 ± 4.85	82.09 ± 0.19
Famotidine	100	24.49 ± 1.37	0 ± 0	100 ± 0
Nizatidine	100	14.09 ± 0.55	0 ± 0	97.68 ± 0.77
3*H*-1,2-Benzodithiol-3-one	100	44.73 ± 4.92	0 ± 0	7.81 ± 8.13
Ufiprazole	100	18.29 ± 0	38.12 ± 4.38	39.05 ± 2.36
Lansoprazole intermediates	100	16.87 ± 1.78	11.82 ± 1.29	18.46 ± 2.7
Pantoprazole Thioether	100	22.91 ± 3.2	63.9 ± 4.9	18.29 ± 2.19
Rabeprazole sulfide	100	28.24 ± 1.07	53.33 ± 2.58	17.28 ± 4.05
2-(4-Chloro-phenyl)-thiazolidine-4-carboxylic acid	100	20.45 ± 0	24.16 ± 2.19	33.11 ± 3.7
Toltrazuril	100	42.57 ± 0.48	42.41 ± 4.25	25.73 ± 4.39
5,5′-Dithiobis(2-nitrobenzoic acid)	100	0 ± 0	17.93 ± 1.96	0 ± 0
Arbidol hydrochloride	100	99.56 ± 0	44.15 ± 1.41	78.02 ± 0.66
2,3-Dimercapto-1-propanol	100	84.99 ± 2.33	67.83 ± 3.94	10.24 ± 1.88
Probucol	100	0 ± 0	24.05 ± 2.53	9.31 ± 3.19
Oltipraz	100	70.83 ± 2.15	37.89 ± 2.77	0 ± 0
Sertraline hydrochloride	100	94.45 ± 1.25	99.33 ± 0.67	100 ± 0
Rosiglitazone	100	33.55 ± 7.87	31.39 ± 2.02	17.24 ± 0.76
Pioglitazone hydrochloride	100	53.16 ± 1.54	100 ± 0	0 ± 0
Disulfiram	100	89.68 ± 0.99	58.09 ± 3.58	18.31 ± 0.91
Abafungin	100	100 ± 0	100 ± 0	46.31 ± 5.57

by *Pleurotus mutilus*. It inhibits bacterial growth by disturbing bacterial protein synthesis. Retapamulin and valnemulin hydrochloride are based on pleuromutilin antibiotics. In this study, retapamulin and valnemulin show excellent anti-phytopathogenic bacterial activities against *Xoo* with a MIC of 6.25 and 0.78 μg ml^{-1}. Although there is no necessary connection between the activity and structure of this group of drugs, these results provide a approach based structure screening for the repurposing of commercially available drugs, expecting to quicken the discovery of drugs against phytopathogenic bacteria.

Risk

Although drug repurposing provides a rapid and efficient method to screen antibacterial leads from approved drugs,

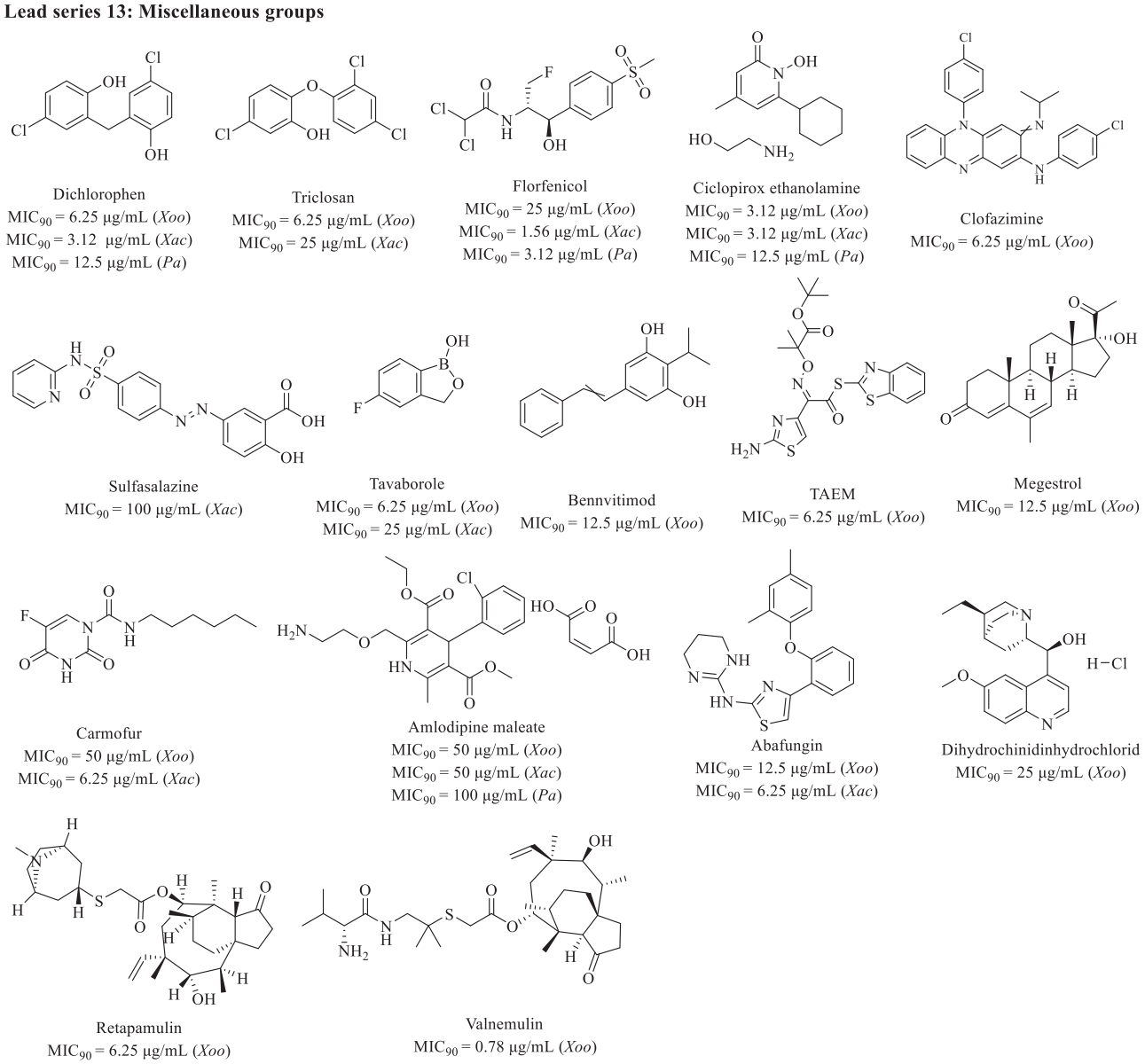


Fig. 9 The MICs of miscellaneous groups (lead series 13) against phytopathogenic bacteria

which are making a significant impact on the development of antimicrobial resistance (AMR) [45, 46]. When clinical drugs or other drugs are used as agrichemicals, it may provide new resistant strains and accelerate the development of AMR. The clinical drugs or other antimicrobial agents use in agriculture practice, particularly as agrichemicals used in the field, are one of the causes of the development of AMR. However, this risk is extending to humans through the food chain, the use of antimicrobial agents in food and agriculture has a direct or indirect impact on the development of antimicrobial resistance (AMR) in plant-associated bacteria [47]. For those reasons, alternative antimicrobials are also needed to combat the phenomenon of AMR in clinical settings and agricultural practices, such as in farms and food premises. To reduce or replace the use of common antibiotics, drug repurposing provides new lead compounds from the antibacterial screening of approved drugs, while also paying attention to the risks that exist in drug repurposing.

Conclusion

Our work provides a basis for drug discovery that enables the discovery of agricultural bacterial drugs superior to current traditional methods. Hopefully, we will enable the development of repurposed approved drugs to be effective against phytopathogenic bacteria. In addition to drug repurposing, approved drugs-with known well-documented

safety, stability, and toxicological effects-can be used as new lead compounds.

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Compliance with ethical standards

Conflict of interest The authors declare no competing interests.

References

1. Doebley JF, Gaut BS, Smith BD. The molecular genetics of crop domestication. Cell. 2006;127:1309–21.
2. Oerke EC, Dehne HW. Safeguarding production—losses in major crops and the role of crop protection. Crop Prot. 2004;23:275–85.
3. Atkinson D, Litterick AM, Walker KC, Walker R, Watson CA. Crop protection–what will shape the future picture? Pest Manag Sci. 2004;60:105–12.
4. Quintana-Rodriguez E, Duran-Flores D, Heil M, Camacho-Coronel X. Damage-associated molecular patterns (DAMPs) as future plant vaccines that protect crops from pests. Sci horticulturae. 2018;237:207–20.
5. Mansfield J, Genin S, Magori S, Citovsky V, Sriariyanum M, Ronald P, et al. Top 10 plant pathogenic bacteria in molecular plant pathology: Top 10 plant pathogenic bacteria. Mol plant Pathol. 2012;13:614–29.
6. Mattinen L, Nissinen R, Riipi T, Kalkkinen N, Pirhonen M. Host-extract induced changes in the secretome of the plant pathogenic bacterium Pectobacterium atrosepticum. Proteom (Weinh). 2007;7:3527–37.
7. Ke Y, Wu M, Zhang Q, Li X, Xiao J, Wang S. Hd3a and OsFD1 negatively regulate rice resistance to Xanthomonas oryzae pv. oryzae and Xanthomonas oryzae pv. oryzicola. Biochemical biophysical Res Commun. 2019;513:775–80.
8. Cernadas RAS, Camillo LR, Benedetti CE. Transcriptional analysis of the sweet orange interaction with the citrus canker pathogens Xanthomonas axonopodis pv. citri and Xanthomonas axonopodis pv. aurantifolii. Mol plant Pathol. 2008;9:609–31.
9. Seck PA, Diagne A, Mohanty S, Wopereis MCS. Crops that feed the world 7: Rice. Food Security. 2012;4:7–24.
10. Li C, Zhang J, Ren Z, Xie R, Yin C, Ma W, et al. Development of 'multiresistance rice' by an assembly of herbicide, insect and disease resistance genes with a transgene stacking system. Pest Manag Sci. 2021;77:1536–47.
11. Le Dang Q, Shin TS, Park MS, Choi YH, Choi GJ, Jang KS, et al. Antimicrobial activities of novel mannosyl lipids isolated from the biocontrol fungus Simplicillium lamellicola BCP against phytopathogenic bacteria. J Agric Food Chem. 2014;62:3363–70.
12. Xiang M, Song YL, Ji J, Zhou X, Liu LW, Wang PY, et al. Synthesis of novel 18beta-glycyrrhetinic piperazine amides displaying significant in vitro and in vivo antibacterial activities against intractable plant bacterial diseases. Pest Manag Sci. 2020;76:2959–71.
13. Wang P, Gao M, Zhou L, Wu Z, Hu D, Hu J, et al. Synthesis and antibacterial activity of pyridinium-tailored aromatic amphiphiles. Bioorg Med Chem Lett. 2016;26:1136–9.
14. Pan X, Xu S, Wu J, Luo J, Duan Y, Wang J, et al. Screening and characterization of Xanthomonas oryzae pv. oryzae strains with resistance to pheazine-1-carboxylic acid. Pestic Biochem Physiol. 2018;145:8–14.
15. Dai X, Zhao Y, Li J, Li S, Lei R, Chen X, et al. Thiazolium-derivative functionalized silver nanocomposites for suppressing bacterial resistance and eradicating biofilms. N. J Chem. 2018;42:1316–25.
16. Hao G-F, Yang S-G, Huang W, Wang L, Shen Y-Q, Tu W-L et al. Rational design of highly potent and slow-binding cytochrome bc(1) inhibitor as fungicide by computational substitution optimization. Sci Rep. 2015;5:1–10.
17. Lamberth C, Jeanmart S, Luksch T, Plant A. Current Challenges and Trends in the Discovery of Agrochemicals. Sci (Am Assoc Advancement Sci). 2013;341:742–6.
18. Demarque DP, Espindola LS. Challenges, advances and opportunities in exploring natural products to control arboviral disease vectors. Front Chem. 2021;9:1–10.
19. Sparks TC, Lorsbach BA. Perspectives on the agrochemical industry and agrochemical discovery. Pest Manag Sci. 2017;73:672–7.
20. Sparks TC, Wessels FJ, Lorsbach BA, Nugent BM, Watson GB. The new age of insecticide discovery-the crop protection industry and the impact of natural products. Pestic Biochem Physiol. 2019;161:12–22.
21. Torres NS, Abercrombie JJ, Srinivasan A, Lopez-Ribot JL, Ramasubramanian AK, Leung KP. Screening a commercial library of pharmacologically active small molecules against Staphylococcus aureus biofilms. Antimicrobial agents Chemother. 2016;60:5663–72.
22. Wilkinson GF, Pritchard K. In vitro screening for drug repositioning. 20. Los Angeles, CA: SAGE Publications; 2015. p. 167–79.
23. Dudley JT, Deshpande T, Butte AJ. Exploiting drug-disease relationships for computational drug repositioning. Brief Bioinforma. 2011;12:303–11.
24. Kaiser M, Maser P, Tadoori LP, Ioset J-R, Brun R. Antiprotozoal activity profiling of approved drugs: a starting point toward drug repositioning. PloS One. 2015;10:e0135556–e0135556.
25. Novac N. Challenges and opportunities of drug repositioning. Trends Pharmacol Sci (Regul ed). 2013;34:267–72.
26. Oliveira IM, Borges A, Simões M The potential of drug repurposing to face bacterial and fungal biofilm infections. *Recent Trends in Biofilm Science and Technology*, 2020, pp 307-28.
27. Ashburn TT, Thor KB. Drug repositioning: identifying and developing new uses for existing drugs. Nat Rev Drug Disco. 2004;3:673–83.
28. Munos B. Lessons from 60 years of pharmaceutical innovation. Nat Rev Drug Discov. 2009;8:959–68.
29. Gu J, Gui Y, Chen L, Yuan G, Lu HZ, Xu X. Use of natural products as chemical library for drug discovery and network pharmacology. PloS One 2013;8:e6283.
30. Ohlson S, Duong-Thi M-D. Fragment screening for drug leads by weak affinity chromatography (WAC-MS). Methods (San Diego, Calif). 2018;146:26–38.
31. Nosengo N. New tricks for old drugs. Nat (Lond). 2016;534:314–6.
32. Delaney J, Clarke E, Hughes D, Rice M. Modern agrochemical research: a missed opportunity for drug discovery? Drug Discov today. 2006;11:839–45.
33. Li P, Hu D, Xie D, Chen J, Jin L, Song B. Design, Synthesis, and Evaluation of New Sulfone Derivatives Containing a 1,3,4-Oxadiazole Moiety as Active Antibacterial Agents. J Agric Food Chem. 2018;66:3093–3100.
34. Fan Z, Shi J, Luo N, Ding M, Bao X. Synthesis, crystal structure, and agricultural antimicrobial evaluation of novel quinazoline thioether derivatives incorporating the 1,2,4-triazolo[4,3-a]pyridine moiety. J Agric Food Chem. 2019;67:11598–606.

35. Guo T, Xia R, Chen M, He J, Su S, Liu L, et al. Biological activity evaluation and action mechanism of chalcone derivatives containing thiophene sulfonate. RSC Adv. 2019;9:24942–50.
36. Luo HZ, Guan Y, Yang R, Qian GL, Yang XH, Wang JS, et al. Growth inhibition and metabolomic analysis of Xanthomonas oryzae pv. oryzae treated with resveratrol. BMC Microbiol. 2020;20:117.
37. Chen J, Wang X, Han H. A new function of graphene oxide emerges: inactivating phytopathogenic bacterium Xanthomonas oryzae pv. Oryzae. J Nanoparticle Res. 2013;15:1–14.
38. Wu S, Shi J, Chen J, Hu D, Zang L, Song B. Synthesis, Antibacterial Activity, and Mechanisms of Novel 6-Sulfonyl-1,2,4-triazolo[3,4-b][1,3,4]thiadiazole Derivatives. J Agric Food Chem. 2021;69:4645–54.
39. Lefevere H, Bauters L, Gheysen G. Salicylic acid biosynthesis in plants. Front Plant Sci. 2020;11:1–7.
40. Kratky M, Stepankova S, Houngbedji N-H, Vosatka R, Vorcakova K, Vinsova J. 2-Hydroxy-N-phenylbenzamides and Their Esters Inhibit Acetylcholinesterase and Butyrylcholinesterase. Biomolecules (Basel, Switzerland). 2019;9:698–714.
41. Yin X-D, Sun Y, Lawoe RK, Yang G-Z, Liu Y-Q, Shang X-F, et al. Synthesis and anti-phytopathogenic activity of 8-hydroxyquinoline derivatives. RSC Adv. 2019;9:387–99.
42. Park M, Cho Y-J, Lee YW, Jung WH. Understanding the mechanism of action of the anti-dandruff agent zinc pyrithione against Malassezia restricta. Sci Rep. 2018;8:12086–97.
43. Kim W, Zou G, Hari TPA, Wilt IK, Zhu W, Galle N, et al. A selective membrane-targeting repurposed antibiotic with activity against persistent methicillin-resistant Staphylococcus aureus. Proc Natl Acad Sci. 2019;116:16529–34.
44. Borelli C, Schaller M, Niewerth M, Nocker K, Baasner B, Berg D, et al. Modes of action of the new arylguanidine abafungin beyond interference with ergosterol biosynthesis and in vitro activity against medically important fungi. Chemother (Basel). 2008;54:245–59.
45. Srivastava J, Chandra H, Nautiyal AR, Kalra SJS. Antimicrobial resistance (AMR) and plant-derived antimicrobials (PDA(m)s) as an alternative drug line to control infections. 3 Biotech. 2014;4:451–60.
46. Cheng G, Ning J, Ahmed S, Huang J, Ullah R, An B et al. Selection and dissemination of antimicrobial resistance in Agri-food production. Antimicrobial Resistance Infection Control. 2019;8:158–71.
47. Compri M, Mader R, Mazzolini E, de Angelis G, Mutters NT, Rajendran NB, et al. White Paper: Bridging the gap between surveillance data and antimicrobial stewardship in the animal sector-practical guidance from the JPIAMR ARCH and COMBACTE-MAGNET EPI-Net networks. J Antimicrobial Chemother. 2020;75:52–66.