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 bis-methiazol (BT), thiodiazole copper (TC), streptomycin (banned for putative risk in China), and zhongshengmycin [12, 13]. However, the current situation is exacerbated by...
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 develop 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 16S 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.

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\text{OD}_{\text{corrected}} = \frac{\text{OD}_{\text{contain bacteria}} - \text{OD}_{\text{sterile culture}}}{C} \times 100%.
\]

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 antibacterial 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, neotopin, 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, rafonaxide, 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 verify 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

![Copper quinolate](image)
MIC$_{90}$ = 6.25 μg/mL (Xoo)
MIC$_{90}$ = 25 μg/mL (Xac)

![Bismerthiazol](image)
MIC$_{90}$ = 100 μg/mL (Xoo)
MIC$_{90}$ = 100 μg/mL (Xac)

![Thiodiazole copper](image)
MIC$_{90}$ = 100 μg/mL (Xoo)
MIC$_{90}$ = 200 μg/mL (Pa)

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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      |
| Labelatol 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           |
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). 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 fenchonazole nitrate, miconazole, econazole, butoconazole nitrate (MIC90 ranged from 3.12 to 12.5 μg/ml⁻¹). The preliminary structure-activity relationships indicated that the substitution of benzyl contributed to increasing 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...
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 μg 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 μg 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 thiazoline affects the activity of drugs, methyl and chlorine decreased the activity 4-time (5-chloro-2-methylthiazol-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-benzisothiazol-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.

### 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-Hexadecylypyridinium 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′-Bipyrindinum 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-Tetradecylypyridinium 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 iMidazolU M              | 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   | 100                          | 100 ± 0        | 100 ± 0  | 98.09 ± 0.19 |
| 1-Decyl-3-methylimidazolium bromide        | 100                          | 100 ± 0        | 99.41 ± 0.29 | 0 ± 0  |
| Benzyldecylidimethy                         | 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 |

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**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 |
| Sulconazole 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 |
| Isoavuconazole nitrate    | 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 | 12.01 ± 9.67 | 20.1 ± 6.54 | 0 ± 0 |
| Rivaroxaban               | 100                     | 0 ± 0            | 0 ± 0         | 0 ± 0 |
| Methazolamide             | 100                     | 0 ± 0            | 23.02 ± 5.32  | 0 ± 0 |
| Valsartan                 | 100                     | 9.73 ± 1.92      | 92.44 ± 0.56  | 29.25 ± 5.18 |
| Deracoxib                 | 100                     | 45.84 ± 0.19     | 76.75 ± 0.28  | 13.04 ± 0 |
| Benzylamine hydrochloride | 100                     | 3.01 ± 4.99      | 29.69 ± 0.28  | 100 ± 0 |
| 2-Benzoxazolinone         | 100                     | 81.27 ± 1.46     | 68.99 ± 3.48  | 0 ± 0 |
| Deferasirox               | 100                     | 9.23 ± 2.8       | 0 ± 0        | 0.67 ± 0.84 |
| Cilostazol                | 100                     | 68.57 ± 4.38     | 25.71 ± 8.83  | 0 ± 0 |
| topiroxostat              | 100                     | 34.7 ± 1.99      | 35.92 ± 11.65 | 15.25 ± 7.51 |
| Levamisole hydrochloride  | 100                     | 25.06 ± 5.32     | 17.92 ± 3.63  | 0 ± 0 |
| Temozolomide              | 100                     | 85.01 ± 1.9      | 16.65 ± 7.99  | 79.08 ± 8.52 |
| Celecoxib                 | 100                     | 86.87 ± 1.09     | 16.65 ± 7.99  | 79.08 ± 8.52 |
| Mebendazole               | 100                     | 45.84 ± 0.19     | 76.75 ± 0.28  | 13.04 ± 0 |
| Oxibendazole              | 100                     | 3.01 ± 4.99      | 29.69 ± 0.28  | 100 ± 0 |
| Fenbendazole              | 100                     | 81.27 ± 1.46     | 68.99 ± 3.48  | 0 ± 0 |
| Albendazole               | 100                     | 9.23 ± 2.8       | 0 ± 0        | 0.67 ± 0.84 |
| Omeprazole                | 100                     | 68.57 ± 4.38     | 25.71 ± 8.83  | 0 ± 0 |
| Esomeprazole magnesium    | 100                     | 34.7 ± 1.99      | 35.92 ± 11.65 | 15.25 ± 7.51 |
| Ufiprazole                | 100                     | 25.06 ± 5.32     | 17.92 ± 3.63  | 0 ± 0 |
| Lansoprazole              | 100                     | 85.01 ± 1.9      | 16.65 ± 7.99  | 79.08 ± 8.52 |
| Lansoprazole sulfide      | 100                     | 45.84 ± 0.19     | 76.75 ± 0.28  | 13.04 ± 0 |
| R-(-)-Lansoprazole        | 100                     | 3.01 ± 4.99      | 29.69 ± 0.28  | 100 ± 0 |
| Ilaprazole(IV 81149)      | 100                     | 81.27 ± 1.46     | 68.99 ± 3.48  | 0 ± 0 |
| Pantoprazole Sodium       | 100                     | 9.23 ± 2.8       | 0 ± 0        | 0.67 ± 0.84 |
| pantoprazole sulfide      | 100                     | 68.57 ± 4.38     | 25.71 ± 8.83  | 0 ± 0 |
| Abeprazole Sulfide        | 100                     | 34.7 ± 1.99      | 35.92 ± 11.65 | 15.25 ± 7.51 |
| Azilsartan                | 100                     | 25.06 ± 5.32     | 17.92 ± 3.63  | 0 ± 0 |
| Telmisartan               | 100                     | 85.01 ± 1.9      | 16.65 ± 7.99  | 79.08 ± 8.52 |
| Candesartan cilexetil     | 100                     | 44.4 ± 2.13      | 81.95 ± 0.52  | 11.37 ± 0.34 |
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
Fig. 4 The MICs of azole antifungals drugs (lead series 6–8) 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. 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-position.

### Table 4

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

| Compounds                      | Concentration (μg ml$^{-1}$) | Inhibition rate/%  |
|--------------------------------|------------------------------|--------------------|
| 8-Hydroxyquinoline             | 100                          | 96.19 ± 0.00       |
| 5-Chloro-8-hydroxyquinoline    | 100                          | 97.92 ± 0.69       |
| 5-bromoquinoline-8-ol          | 100                          | 100.00 ± 0.00      |
| Nitroxoline                    | 100                          | 100.00 ± 0.00      |
| 5,7-Dichloro-8-hydroxyquinoline| 100                          | 100.00 ± 0.00      |
| 5,7-Dibromo-8-hydroxyquinoline| 100                          | 100.00 ± 0.00      |
| 5,7-Diiodo-8-quinolinol        | 100                          | 100.00 ± 0.00      |
| Clioquinol                     | 100                          | 31.83 ± 1.04       |
| 5-Chloro-8-hydroxyquinoline    | 100                          | 90.31 ± 2.42       |
| 2-Quinolinol                   | 100                          | 96.19 ± 0.35       |
| 6-Aminoquinoline               | 100                          | 96.19 ± 0.78       |
| 5-Hydroxyquinoline             | 100                          | 96.19 ± 1.73       |
| 7-Hydroxyquinoline             | 100                          | 96.19 ± 0.00       |
| 3-Hydroxyquinoline             | 100                          | 94.12 ± 3.11       |
| 6-Hydroxyquinoline             | 100                          | 82.01 ± 5.88       |
| 6-Hydroxyquinoline             | 100                          | 37.72 ± 2.42       |
| 2,4-Quinolinediol              | 100                          | 44.98 ± 1.38       |
| 6-Methoxy-8-nitroquinoline     | 100                          | 100.00 ± 0.00      |

### Lead series 9: Hydroxyquinoline

![Lead series 9: Hydroxyquinoline](image)

**Fig. 5** The MICs of Hydroxyquinoline (lead series 9) against phytopathogenic bacteria
### 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      | 6.68 ± 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      |
| Tetraethylenepentamine                         | 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                      | 32.76 ± 1.21      | 49.27 ± 0         | 2.69 ± 2.3       |
| N-Aminoethylpiperazine                         | 100                      | 11.36 ± 1.51      | 22.26 ± 6.57      | 0.6 ± 0.2        |
| 1,5-Diaminopentane                             | 100                      | 57.79 ± 5.73      | 32.48 ± 1.09      | 23.55 ± 0.2      |
| N1,N’1-(butane-1,4-diyl)bis(ethane-1,2-diamine)| 100                      | 29.45 ± 6.93      | 46.35 ± 1.46      | 6.69 ± 4.09      |
| 1,3-Diaminopropane                             | 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            |
| Ethenbutol                                     | 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                      | 78.40 ± 2.07      | 80.57 ± 0         | 4.33 ± 12.78     |
| Enebicynan                                     | 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            |
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 \textit{Xoo} is even better than that against \textit{Candida albicans}, with MIC of 0.39 \( \mu \text{gm l}^{-1} \) against \textit{Xoo} and 0.12 \( \mu \text{gm l}^{-1} \) against \textit{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 controlling phytopathogenic pathogens.

N-containing group

As shown in Table 5 and Fig. 6, \textit{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 \textit{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 \textit{Xoo} and \textit{Xac} with the MICs of 3.12 \( \mu \text{gm l}^{-1} \), 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) | \(X_{\text{oo}}\)          | \(X_{\text{ac}}\)          | \(P_{\text{a}}\)          |
|-----------------------------------|-------------------------|-----------------------------|-----------------------------|-----------------------------|
| 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                |
| Brexipiprazole                    | 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                     | 100 ± 0                     | 20.02 ± 0.16                |
| Vortioxetine                      | 100                     | 100 ± 0                     | 100 ± 0                     | 100 ± 0                     |
| Sildenafil                        | 100                     | 100 ± 0                     | 100 ± 0                     | 61.06 ± 1.4                 |
| Imatinib                          | 100                     | 18.57 ± 0.58                | 0 ± 0                       | 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                       |
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 against Xoo and Xac respectively. Besides, Perifosine also has a similar effect (the MICs of 6.25 and 25 μg/mL 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 ± 0                 | 99.21 ± 0.26      | 46.48 ± 5.7  |
| Sunitinib                 | 100 ± 0                 | 26.78 ± 1.58      | 0 ± 0  |
| Lapatinib                 | 100                     | 32.96 ± 0.26      | 69.18 ± 1.32 | 16.61 ± 1.68 |
| Nilotinib                 | 100 ± 0                 | 18.96 ± 0.9       | 98.42 ± 0.26 | 40.77 ± 5.54 |
| Vandetanib                | 100 ± 0                 | 99.77 ± 0.23      | 45.22 ± 0.26 | 73.83 ± 2.18 |
| Axitinib                  | 0 ± 0                   | 2.19 ± 1.88       | 0 ± 0  |
| Vemurafenib               | 0 ± 0                   | 2.5 ± 22.5        | 0 ± 0  |
| Bosutinib                 | 100 ± 0                 | 90.25 ± 3.17      | 0 ± 0  |
| Tofacitinib               | 100 ± 0                 | 1.88 ± 3.75       | 8.38 ± 3.68 |
| Trametinib                | 100 ± 0                 | 0.31 ± 3.12       | 75.94 ± 2.45 |
| Nintedanib                | 100 ± 0                 | 23.95 ± 2.21      | 21.25 ± 2.5 | 91.73 ± 7.2  |
| Lenvatinib                | 100 ± 0                 | 0.62 ± 5.94       | 21.86 ± 0.46 |
| Merelititinib             | 100 ± 0                 | 100 ± 0           | 0 ± 0  |
| Palbociclib               | 100 ± 0                 | 3.77 ± 3.22       | 46.56 ± 29.69 | 59.55 ± 1.84 |
| Baricitinib               | 0 ± 0                   | 0 ± 0             | 13.43 ± 0.15 |
| Brigatinib                | 100 ± 0                 | 43.64 ± 5.26      | 12.5 ± 7.5 | 1.63 ± 8.58 |
| Vencelexta                | 100 ± 0                 | 0 ± 0             | 35 ± 3.44 | 0 ± 0 |
| Ponatinib                 | 100 ± 0                 | 96.31 ± 1.48      | 100 ± 0 | 0 ± 0 |
| Sonidegib                 | 100 ± 0                 | 43.15 ± 2.46      | 77.19 ± 4.69 | 44.54 ± 1.84 |
| Olaparib                  | 0 ± 0                   | 0 ± 0             | 0 ± 0  |
| Niraparib                 | 100 ± 0                 | 98.75 ± 0.0       | 4.24 ± 3.52 |
| Rucparib phosphate        | 100 ± 0                 | 98.77 ± 0.0       | 0.87 ± 12.72 |
| Pazopanib hydrochloride   | 100 ± 0                 | 16.25 ± 3.13      | 3.81 ± 2.7 | 8.73 ± 2  |
| Cabozantinib              | 100 ± 0                 | 53.54 ± 6.25      | 53.25 ± 4.99 | 20.89 ± 6.95 |
| Regorafenib               | 100 ± 0                 | 36.67 ± 2.29      | 26.87 ± 3.95 | 0 ± 0 |
| Aflatinib                 | 100 ± 0                 | 98.34 ± 0.21      | 0.45 ± 4.14 |
| Ibrutinib                 | 100 ± 0                 | 24.17 ± 7.71      | 76.11 ± 1.87 | 0 ± 0 |
| Idelalisib                | 100 ± 0                 | 26.46 ± 5.21      | 8.17 ± 9.35 | 7.93 ± 10.82 |
| Acalabrutinib             | 100 ± 0                 | 20.63 ± 2.29      | 10.04 ± 7.06 | 0 ± 0 |
| Ribociclib                | 100 ± 0                 | 94.58 ± 0.21      | 84.83 ± 0.83 | 16.35 ± 2.14 |
| Ripretinib                | 0 ± 0                   | 0 ± 0             | 0 ± 0  |
| Upadacitinib              | 100 ± 0                 | 15.29 ± 2.96      | 8.59 ± 0.21 | 0 ± 0 |
| Dabrafenib                | 100 ± 0                 | 37.5 ± 6.67       | 69.25 ± 3.32 | 0 ± 0 |
| Ruxolitinib               | 100 ± 0                 | 16.46 ± 0.63      | 9.42 ± 2.08 | 7.93 ± 0.27 |
| JX06                      | 100 ± 0                 | 100 ± 0           | 100 ± 0 | 0 ± 0 |
| Nilotinib Hydrochloride   | 100 ± 0                 | 0 ± 0             | 17.11 ± 3.95 | 19.42 ± 1.74 |
| Monohydrate               | 100 ± 0                 | 100 ± 0           | 99.38 ± 0.21 | 29.04 ± 0.4 |
| Perifosine                | 100 ± 0                 | 32.29 ± 0.0       | 34.56 ± 4.78 | 3.92 ± 3.21 |
| Tandutinib                | 100 ± 0                 | 99.38 ± 0.21      | 10.66 ± 3.32 | 5.52 ± 5.88 |
| Phenformin hydrochloride  | 100 ± 0                 | 94.79 ± 1.67      | 98.75 ± 2.08 | 77.02 ± 0.13 |
| Phenformin hydrochloride  | 100 ± 0                 | 18.13 ± 3.75      | 16.69 ± 0.62 | 11.27 ± 1.87 |
| Selumetinib               | 100 ± 0                 | 9.79 ± 7.92       | 16.69 ± 0.83 | 1.11 ± 3.47 |
drugs identified in the screening are listed by class. It was also attracted that the derivative of pyrithione (Zinc pyrithione, Sodium omadin, 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 MIC90 ranged from 3.12 to 25 μg ml⁻¹; Abafungin was found to have potential 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; Pleuroomutilin is a broad-spectrum diterpene antibiotic produced.

Table 7 (continued)

| Compounds        | concentration (μg ml⁻¹) | Inhibition rate/% |
|------------------|------------------------|-------------------|
|                  |                        | Xoo   | Xac   | Pu    |
| 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 |

**Lead series 12: Kinase inhibitors**

Fig. 8 The MICs of kinase inhibitors (lead series 12) 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|
| Syneprine                         | 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|
| Cloprenaline hydrochloride        | 100                     | 0 ± 0              | 9.58 ± 0    | 5.83 ± 6.36 |
| Nifurtel                          | 100                     | 100 ± 0            | 100 ± 0     | 100 ± 0     |
| Nimesulide                        | 100                     | 24.65 ± 9.78       | 22.39 ± 5.22| 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|
| Nortriptyline hydrochloride       | 100                     | 98.11 ± 0.0        | 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     |
| Tuloxylerol 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|
| Dichloroferon                     | 100                     | 100 ± 0            | 100 ± 0     | 100 ± 0     |
| Avobenzone                        | 100                     | 15.69 ± 2.24       | 19.96 ± 3.36| 32.26 ± 0.57|
| i-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|
| Protonamide                       | 100                     | 65.69 ± 0.24       | 100 ± 0     | 42.98 ± 0.88|
| Diclofenuril                      | 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 ± 3.52| 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|
| Arpinocide                        | 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 ± 4.1  | 0 ± 0       |
| Chlorphenesin                     | 100                     | 35.66 ± 9.03       | 47.34 ± 0.28| 0 ± 0       |
| Triacetin                         | 100                     | 0 ± 0              | 5.5 ± 0     | 0 ± 0       |
| Bromopol                          | 100                     | 100 ± 0            | 96.84 ± 0   | 99.34 ± 0.17|
| Envirine                          | 100                     | 0 ± 0              | 10.42 ± 2.11| 6.28 ± 9.09 |
| Diphenydramine Hydrochloride      | 100                     | 15.67 ± 2.21       | 5.15 ± 1.05 | 0 ± 0       |
| Levetiracetam                     | 100                     | 0 ± 0              | 61.01 ± 1.76| 0 ± 0       |
| Tropicamid                        | 100                     | 0 ± 0              | 95.08 ± 1.76| 16.53 ± 7.19|
| Benzetropine mesylate             | 100                     | 98.01 ± 0.22       | 77.17 ± 2.11| 5.95 ± 3.64 |
| Pyranet 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   |
| Mometorystin                     | 100                     | 0 ± 0              | 45.19 ± 2.92| 46.72 ± 1.28|
| Revparazan HCL                    | 100                     | 58.21 ± 1.7        | 34.96 ± 1.83| 0 ± 0       |
| Tauradoline                       | 100                     | 98.64 ± 0.68       | 97.81 ± 0   | 17.66 ± 9.69|
| Aprepitant                        | 100                     | 0 ± 0              | 69.67 ± 10.23| 28.49 ± 0.85|
| Beiprine                          | 100                     | 40.78 ± 5.21       | 64.09 ± 4.72| 38.09 ± 2.77|
| Compounds                                      | Concentration (μg ml$^{-1}$) | $X_{oo}$       | $X_{ac}$       | $P$      |
|-----------------------------------------------|------------------------------|---------------|---------------|---------|
| 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  |
| Artemisin                                     | 100                          | 11.41 ± 2.84  | 2 ± 8.5       | 64.68 ± 5.53 |
| Iopride 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 |
| Lumezantrine                                  | 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  |
| Thiamine chlorate                             | 100                          | 41.51 ± 6.63  | 21.53 ± 1.46  | 3.29 ± 1     |
| 1-Adamantanamine hydrochloride                | 100                          | 1.11 ± 0.9    | 26.28 ± 0.36  | 39.8 ± 4.39  |
| 1,3-Thiazol-2-amine                           | 100                          | 88.61 ± 0.52  | 91.79 ± 0.24  | 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                          | 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 |
| Rosfumilast                                   | 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 |
| Escalopram 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 ± 0.09  | 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 acetalet                         | 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 ± 0.08  | 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  |
| Vildaglipin                                   | 100                          | 14.46 ± 5.97  | 11.26 ± 7.74  | 77.88 ± 2.9  |
| Lefunomide                                    | 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       |
| terriflunomide                                | 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 |
| Compounds                        | Concentration (μg ml<sup>−1</sup>) | Inhibition rate/%<br>\(Xoo\) | Inhibition rate/%<br>\(Xac\) | Inhibition rate/%<br>\(Pu\) |
|---------------------------------|-------------------------------------|------------------------------|------------------------------|------------------------------|
| 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                  |
| Terriflunomide                 | 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                  |
| Teriflunomide                  | 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                 |
| Pyrbuticarb                    | 100                                 | 14.81 ± 2.65              | 0 ± 0                        | 38.48 ± 0.29                 |
| Florfenicol                    | 100                                 | 95.01 ± 0.15              | 98.65 ± 0.67                 | 100 ± 0                      |
| Picrotox tolamine             | 100                                 | 76.57 ± 1.54              | 89.91 ± 2.02                 | 70.15 ± 1.00                 |
| Mefloquine hydrochloride       | 100                                 | 99.07 ± 0.13              | 90.23 ± 0.40                 | 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 ± 0.00              | 96.03 ± 7.99                 | 10.93 ± 5.28                 |
| 4-Carboxy-2,2,6,6-tetramethylpiperidine 1-oxyl | 100                                 | 0 ± 0                       | 0 ± 0                        | 15.19 ± 2.21                 |
| 3-Carboxy-2,2,5,5-tetramethylpyrrolidine 1-Oxyl Free Radical | 100                                 | 0 ± 0                       | 0 ± 0                        | 15.19 ± 2.21                 |
| Nitrofurantoim                 | 100                                 | 93.55 ± 0                  | 99 ± 0.33                    | 96.42 ± 0.17                 |
| Ibuprofen                      | 100                                 | 53.43 ± 5.79              | 24.62 ± 9.01                 | 0 ± 0                        |
| Diclofenac                     | 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                 |
| Liranafate                     | 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                 |
| Tavaborol                      | 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                 |
| Stanoxol                       | 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                    |
| Trimcinolone acetone           | 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 ± 11.29              | 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               | Pu                |
| 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     |
| Cefazolin 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             |
| Cefazolin intermediate                        | 100                     | 100 ± 0           | 100 ± 0           | 22.76 ± 11.94     |
| 5-Fluoorouridine                              | 100                     | 92.85 ± 2.38      | 23.53 ± 2.53      | 87.71 ± 1.96      |
| Doxifluoruridine                              | 100                     | 0 ± 0             | 33.25 ± 3.48      | 3.35 ± 4.19       |
| Uracil                                        | 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                     | 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       |
| 3'-Deoxyinosine                               | 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 ± 0.0       | 9.26 ± 2.46       | 6.75 ± 2.53       |
| Acyclovir                                     | 100                     | 0 ± 0             | 19.79 ± 0.9       | 17.57 ± 0.92      |
| Famiclovir                                    | 100                     | 8.71 ± 3.31       | 41.3 ± 5.38       | 39.68 ± 5.53      |
| Penclovir                                     | 100                     | 0 ± 0             | 2.93 ± 1.34       | 0 ± 0             |
| Ganclovir                                     | 100                     | 0 ± 0             | 0 ± 0             | 0 ± 0             |
| Flavopiridol                                  | 100                     | 61.11 ± 0.43      | 82.8 ± 3.82       | 11.68 ± 0.27      |
| Brividine                                      | 100                     | 13.05 ± 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             |
| Flouxuridine                                  | 100                     | 81.01 ± 0.0       | 100 ± 0           | 97.62 ± 0.17      |
| 5-Fluourouracil                               | 100                     | 86.39 ± 3.4       | 75.99 ± 4         | 97.45 ± 0.0       |
| Fluorocytoine                                 | 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 ± 0.64       | 45.16 ± 2.74      |
| Capicitabine                                  | 100                     | 5.46 ± 2.93       | 26.9 ± 2.22       | 0 ± 0             |
| Quimine                                       | 100                     | 45.81 ± 0.69      | 39.84 ± 1.06      | 7.59 ± 5.88       |
| Quimidine                                     | 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             |
| Hydorquinim                                   | 100                     | 26.76 ± 9.82      | 22.08 ± 1.18      | 0 ± 0             |
| N-Benzylcinchoninium 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      |
| Quimine HCL                                   | 100                     | 57.94 ± 0.21      | 0 ± 0             | 29.97 ± 7.1       |
| Quimine dihydrochloride                       | 100                     | 50.89 ± 3.63      | 5.63 ± 1.18       | 2.52 ± 3.55       |
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.

**Table 8 (continued)**

| Compounds                                      | Concentration (μg ml⁻¹) | Inhibition rate/% |
|------------------------------------------------|-------------------------|-------------------|
| Quinine sulfate dihydrate                      | 100                     | 30.25 ± 0.76      |
| Quinine hydrochloride dihydrate                | 100                     | 64.87 ± 0.25      |
| Hydroquinidine 4-chlorobenzamide                | 100                     | 63.6 ± 32.58      |
| Hydroquinidine                                   | 100                     | 64.11 ± 0.76      |
| Hydroquinidine hydrochloride                    | 100                     | 100 ± 0           |
| (9 S)-10,11-dihydro-Cinchonan-6',9-diol          | 100                     | 100 ± 0           |
| Hydroxycylocline                                 | 100                     | 12.83 ± 2.84      |
| Pheniramine maleate                             | 100                     | 0 ± 0             |
| Chlorpheniramine maleate                        | 100                     | 38.14 ± 3.88      |
| Amodipine maleate                               | 100                     | 95.34 ± 0.26      |
| Fluvonaxine maleate                             | 100                     | 96 ± 0.31         |
| Naltifene                                       | 100                     | 0 ± 0             |
| Terminafine                                     | 100                     | 0 ± 0             |
| Butenafine                                      | 100                     | 10.50 ± 8.84      |
| Sulfasalazine                                   | 100                     | 16.83 ± 4.65      |
| Sulfafurinoxaline sodium                        | 100                     | 53.53 ± 1.67      |
| Sulfadiazine Sodium monohydrate                 | 100                     | 74.27 ± 2.14      |
| Sulfamethazine                                  | 100                     | 60.44 ± 0.95      |
| Sulfamonomethoxime                              | 100                     | 71.88 ± 1.43      |
| Sulfachloropyridazine                           | 100                     | 52.37 ± 6.33      |
| Sodium N-(5-methylisoxazol-3-yl)sulphanilamide  | 100                     | 54.76 ± 0.24      |
| Sulfamethoxypyridazine                          | 100                     | 39.6 ± 1.89       |
| Sulfoxazole                                     | 100                     | 13.95 ± 2.63      |
| Dichloro-1,2-dihydrocyclopentone                | 100                     | 99.07 ± 0.13      |
| Anethole trithione                              | 100                     | 26.74 ± 14.33     |
| Levamisole hydrochloride                        | 100                     | 34.7 ± 1.99       |
| Bithionol                                       | 100                     | 100 ± 0           |
| Famotidine                                      | 100                     | 24.49 ± 1.37      |
| Nizatidine                                      | 100                     | 14.09 ± 0.55      |
| 3H-1,2-Benzodithiol-3-one                       | 100                     | 44.73 ± 4.92      |
| Ufpirezole                                      | 100                     | 18.29 ± 2.65      |
| Lansoprazole intermediates                      | 100                     | 16.87 ± 1.78      |
| Pantoprazole Thioether                          | 100                     | 22.91 ± 3.2       |
| Rabeprazole sulfide                             | 100                     | 28.24 ± 1.07      |
| 2-(4-Chloro-phenyl)-thiazolidine-4-carboxylic acid | 100                     | 20.45 ± 0.45      |
| Toltrazuril                                     | 100                     | 42.57 ± 0.48      |
| 5,5'-Dithiobis(2-nitrobenzoic acid)             | 100                     | 0 ± 0             |
| Arbidol hydrochloride                           | 100                     | 99.56 ± 0.45      |
| 2,3-Dimercapto-1-propanol                       | 100                     | 84.99 ± 2.33      |
| Probufol                                        | 100                     | 0 ± 0             |
| Olipraz                                         | 100                     | 70.83 ± 2.15      |
| Serratine hydrochloride                         | 100                     | 94.45 ± 1.25      |
| Rosiglitazone                                   | 100                     | 33.55 ± 7.87      |
| Pioglitazone hydrochloride                      | 100                     | 53.16 ± 1.54      |
| Disulfiram                                      | 100                     | 89.68 ± 0.99      |
| Abafungin                                       | 100                     | 100 ± 0           |

**Risk**

Although drug repurposing provides a rapid and efficient method to screen antibacterial leads from approved drugs,
which are making a significant impact on the development of antimicrobial resistance (AMR) [45, 46]. When clinical drugs or other drugs are used as agrochemicals, 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 agrochemicals 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.

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