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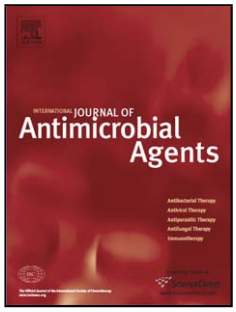

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A study of the antimicrobial activity of selected synthetic and naturally occurring quinolines

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ABSTRACT

The antimicrobial activities of 60 naturally occurring and synthetic quinolines were studied. The quinolines were organised into seven structural subgroups and, using an in-house microtitre assay, were tested against a range of Gram-positive and Gram-negative bacteria, including a hospital isolate of meticillin-resistant *Staphylococcus aureus* (MRSA). The quinolines exhibiting good bioactivity [i.e. low minimum inhibitory concentration (MIC)] against two *S. aureus* strains were then assessed for their antimicrobial activity against a range of eight clinically isolated MRSA strains. The study showed that 30 of the tested compounds displayed antimicrobial activity, mostly against Gram-positive bacteria. The effects of substituent groups on the bioactivity of these quinolines have also been discussed. The quinoline 4-hydroxy-3-iodo-quinol-2-one (**11**) exhibited significant antimicrobial activity, being active against the MRSA clinical isolates with MIC values comparable with the antibiotic vancomycin used in the treatment of MRSA infections. In particular, 4-hydroxy-3-iodo-quinol-2-one (**11**) showed MIC values of 0.097 μg/mL against an Irish hospital MRSA-1 strain and 0.049 μg/mL against a distinct MRSA strain as well as a non-typeable MRSA strain.

1. Introduction

The rise in antibiotic-resistant microorganisms in recent years has led to an increasing search for new antibiotics. Plant secondary metabolites have been used for centuries in traditional medicines and therefore represent a source of potentially active compounds [1]. Naturally occurring and synthetic quinoline derivatives have been studied for many years for their pharmacological activity, but only a few of these compounds have been developed for clinical use.

Mitscher et al. [2] found that the quaternary alkaloid pteleatinium chloride and the *O*-methylptelefolonium salt isolated from *Ptelea trifoliata* showed antimicrobial activity towards *Staphylococcus aureus* and *Mycobacterium tuberculosis*. A study by Fournet et al. [3] showed that the bioactivity of the plant *Galipea longiflora* against *Leishmania amazonensis* was due to 2-substituted quinoline alkaloids present in the plant, namely 2-propylquinoline and chimanine D.

Hanawa et al. [4] investigated the photo-activated antimicrobial activity of several furoquinoline derivatives such as skimmianine, kokusaginine, haplopine and flindersine against *S. aureus*. Towers et al. [5] carried out studies on the phototoxic effects of furoquinoline alkaloids. Five of the twelve compounds tested were active against *Escherichia coli* and *Saccharomyces cerevisiae*, namely isodictamnine, 7-desmethylskimmianine, maculosidine, maculine and dictamnine [5].

Skimmianine and kokusaginine have also shown good bioactivity against the fungus *Leucoagaricus gongylophorus* [6].

Use of quinoline antimalarials such as quinine, chloroquine and amodiaquine in the treatment of malaria is well known. Many other synthetic quinoline derivatives have pharmaceutical significance. One group of synthetic quinolines that has significant use as antimicrobials in the treatment of many infections is the quinolones [7]. Nalidixic acid was the first of this group of compounds to be introduced and was used for the treatment of urinary tract infections in the 1960s. In the 1980s a succession of quinolone antimicrobials were introduced that differed from nalidixic acid by having a fluorine substituent in the 6-position and a piperazinyl derivative in the 7-position. These compounds are often referred to as fluoroquinolones. They are broad-spectrum antimicrobials and are used to treat sexually transmitted diseases and infections of the urinary tract, gastrointestinal tract, respiratory tract, skin, and bones and joints [8].

This study reports the results of an investigation into the bioactivities of 60 quinoline derivatives against six different microorganisms by in-house microtitre assay. The minimum inhibitory concentration (MIC) of each quinoline derivative is reported. Quinolines that initially showed a low MIC against meticillin-resistant *S. aureus* (MRSA) and/or *S. aureus* were further tested against eight clinically isolated MRSA.

2. Materials and methods

2.1. Quinolines

The quinoline derivatives investigated were available either from previous isolation from plant sources or from previous synthetic studies carried out in The University of Ulster, Coleraine, Northern Ireland [9–11]. Edulitine (**7**), lunacridine (**24**), veprisine (**29**), vepridimerine A (**37**), platydesmine (**39**), balfouridine (**41**), lemobiline (**42**), dictamnine (**44**), γ-fagarine (**45**), skimmianine (**46**), evoxine (**49**), choisyine (**50**) and ribalinine (**60**) were all obtained from plant sources. The remainder of the quinolines were prepared synthetically in the laboratory, for example the synthesis of pyrano(3,2-c)quinol-5-one alkaloids [12]. Some of the quinoline derivatives were intermediates in the synthesis of naturally occurring quinolines. The names of the quinolines used are given in Tables 1–4 and their corresponding structures are illustrated in Figures 1–7. All samples were dissolved in acetone and prepared at a concentration of 6.67 mg/mL.

2.2. Microtitre assay

The MIC values of the quinoline derivatives were estimated according to a previously reported microtitre method [13]. Lane 1 contained a blank, i.e. 100 μL of Mueller–Hinton broth (MHB). Lane 2 comprised of the positive control (acetone), containing the initial concentration of acetone (15 μL) along the lane with 10 μL of sterile water and 25 μL of sterile MHB. The negative control was in lane 3, with each well containing 25 μL of sterile water and 25 μL of the antibiotic added to Well 1 of the lane followed by

serial double dilutions down to Well 12 of the lane. The final concentration range for oxacillin started at 21.6 μg/mL at Well 1 followed by serial dilution to 0.0105 μg/mL at Well 12. The concentration of vancomycin and trimethoprim antibiotics started at 25 μg/mL for Well 1 down to 0.0122 μg/mL at Well 12. Lanes 4–8 contained the pure quinolines to be tested for antibacterial activity, which were made up in acetone from a stock solution of 6.67 mg/mL. To each well of these lanes, 25 μL of sterile water was added, apart from the first two wells. In Well 1, 20 μL of sterile water was added followed by 30 μL of the test compound (final starting concentration in Well 1 was 1000 μg/mL), which was then serially diluted down every second well to Well 11 of each lane. In Well 2, 30 μL of sterile water was added followed by 20 μL of the test compound (final starting concentration in Well 2 was 666 μg/mL), which was serially diluted every second well down to Well 12. In this way, two concentration ranges were on the one plate with a starting concentration in Well 1 of 1000 μg/mL and a final concentration of 20.8 μg/mL in Well 12. The highly active compound 4-hydroxy-3-iodo-quinol-2-one (**11**) required a different concentration range starting at 100 μg/mL in Well 1 followed by double dilution down each well to a final concentration of 0.049 μg/mL in Well 12. All the microorganisms, which were grown overnight in MHB, were adjusted to 10^6 cells/mL before use, according to their optical density at 650 nm in MHB. Apart from Lane 1, all the wells of the microtitre plate were inoculated with 50 μL of bacterial suspension and were sealed with Parafilm™ and incubated at 37 °C for 24 h in a Stuart orbital incubator (SI 50; Rhys International Ltd.,

Bolton, UK) at 50 rpm. Iodonitrotetrazolium chloride (INT) has been shown to the best indicator for determining microbial growth, producing a stable pink colour when there is microbial activity [14]. Following addition of INT (Sigma-Aldrich Co. Ltd., Poole, UK) and incubation, the MIC was determined as the lowest sample concentration at which no pink colour appeared. For each compound, the assay was performed in triplicate to ensure reproducible results.

2.3. Bacteria and antibiotics

The antimicrobial activities of the compounds were tested against the following bacteria: *Bacillus subtilis* ATCC 6051; *Micrococcus luteus* (University of Ulster, Coleraine, culture collection); *S. aureus* ATCC 12600; MRSA clinical isolate (Coleraine hospital); and the Gram-negative bacteria *E. coli* ATCC 11775 and *Salmonella enterica* serovar Typhimurium ATCC 14028. Quinolines that were particularly active against MRSA and/or *S. aureus* were further tested against eight hospital strains of MRSA: epidemic MRSA-15 (EMRSA-15); epidemic MRSA-16 (EMRSA-16); Irish hospital MRSA-1 (IMRSA-1); Irish hospital MRSA-2 (IMRSA-2); a non-typeable MRSA strain (NTMRSA); a distinct MRSA strain (DMRSA); community-acquired Hodgkin MRSA (HMRSA); and community-acquired Charles–Worth MRSA (CWMRSA). Vancomycin was used as the antibiotic control against these clinical MRSA isolates.

The antibiotics oxacillin, vancomycin and trimethoprim were obtained from Sigma-Aldrich (Poole, UK). Stock solutions of 0.173 mg/mL oxacillin and

0.2 mg/mL vancomycin and trimethoprim were prepared. The indicator *p*-INT was purchased from Sigma-Aldrich.

3. Results and discussion

The results are discussed under the different structural subgroups, comprising the quinol-2-ones, 3-*C*-dimethylallylquinol-2-ones, flindersine derivatives, quinoline dimers, dihydrofuroquinolines, linear and angular furoquinolines, and other quinolines. In this study, no bioactivity was defined as an MIC >1000 μg/mL, mild bioactivity as an MIC in the range 501–1000 μg/mL, moderate bioactivity as an MIC in the range 126–500 μg/mL, good bioactivity as an MIC in the range 26–125 μg/mL, strong bioactivity as an MIC in the range 10–25 μg/mL and very strong bioactivity as an MIC <10 μg/mL.

3.1. Quinol-2-ones

The MICs of the 16 quinol-2-ones and the antibiotic controls are given in Table 1 and the structures of the quinol-2-ones are shown in Fig. 1. 4-Hydroxy-1-methyl-quinol-2-one (**1**) and 4-methoxy-1-methyl-quinol-2-one (**2**) were found to be inactive against the six microorganisms. However, 1,3-dimethyl-4-hydroxy-quinol-2-one (**3**), with an extra methyl group compared with (**1**), showed mild bioactivity (MIC = 1000 μg/mL) against MRSA, *B. subtilis* and *E. coli* and moderate activity (MIC = 500 μg/mL) against *S. aureus and M. luteus*. The presence of the extra methyl group in the 3-position of (**3**) in comparison with (**1**) may contribute to its activity

among this group of compounds. 7,8-Dimethoxy-4-hydroxy-quinol-2-one (**5**) had moderate activity against the Gram-negative microorganism *E. coli* with an MIC of 500 μg/mL but was not active against the other microorganisms. When a methoxyl group was not present at the 7-position, as for 8-methoxy-4-hydroxy-quinol-2-one (**6**), the compound was no longer active against *E. coli* but showed mild activity against MRSA, *S. aureus* and *M. luteus*. When the 4-hydroxy group in (**6**) was replaced with a methoxyl group or an ethoxyl group, there was no activity against the microorganisms, as seen with edulitine (**7**) and 4-ethyloxy-8-methoxy-quinol-2-one (**8**). It can be tentatively suggested that a 4-hydroxy substituent may contribute towards bioactivity.

4-Hydroxy-3-iodo-7,8-dimethoxy-quinol-2-one (**9**) had an MIC of 250 μg/mL against MRSA and *M. luteus* and an MIC of 166.5 μg/mL against *S. aureus*. 4,7,8-Trimethoxy-3-iodo-quinol-2-one (**10**) was more active than (**9**) against *S. aureus* (MIC = 125 μg/mL), *M. luteus* (MIC = 125 μg/mL) and *E. coli* (1000 μg/mL) but was less active against MRSA (MIC = 500 μg/mL). 4-Hydroxy-3-iodo-quinol-2-one (**11**) had very strong activity against all six microorganisms, with an MIC of 0.39 μg/mL against MRSA, *M. luteus* and *B. subtilis*, an MIC of 0.195 μg/mL against *E. coli* and *S.* Typhimurium and an MIC of 6.25 μg/mL against *S. aureus.* Regarding these three compounds, it appears that iodine at position 3 and the absence of substitution in the benzene ring significantly enhances the bioactivity of these quinol-2-ones.

4-Geranyloxy-quinol-2-one (**13**) had an MIC of 250 μg/mL against MRSA and *S. aureus* and an MIC of 1000 μg/mL against *M. luteus*. Quinol-2-ones with relatively long side chains in the 3-position, i.e. compounds (**14**), (**15**) and (**16**), did not show bioactivity.

3.2. 3-C-dimethylallylquinol-2-ones

The MICs of the 3-*C*-dimethylallylquinol-2-ones are given in Table 2 and the structures of the compounds in this group can be seen in Fig. 2. The compounds in this group did not show activity against *S.* Typhimurium and only one compound (**26**) showed mild activity against *E. coli* and *B. subtilis.* 4-Hydroxy-3-(3'-methylbut-2'-enyl)-quinol-2-one (**17**) showed mild activity against *M. luteus* but was not active against any of the other microorganisms. 4-Hydroxy-6-methoxy-3-(3'-methylbut-2'-enyl)-quinol-2-one (**18**) differs from 4,6-dimethoxy-3-(3'-methylbut-2'-enyl)-quinol-2-one (**19**) by having a hydroxy group in the 4-position instead of a methoxyl group. They both showed very mild activity against MRSA and *M. luteus* (MIC = 1000 μg/mL), but (**18**) was active against *S. aureus* (MIC = 500 μg/mL). This suggests that the 4-hydroxy group may play a part in the bioactivity of (**18**) against *S. aureus*. It was tentatively suggested in the last section that a 4-hydroxy substituent for quinol-2-ones may contribute towards their bioactivity. When an *N*-methyl group is present in this group of compounds, as for compound (**20**), bioactivity is lost.

4-Hydroxy-8-methoxy-3-(3'-methyl-2'-hydroxybutyl)-1-methyl-quinol-2-one (**22**) had MICs of 500 μg/mL against MRSA and 250 μg/mL against *S. aureus* and *M. luteus*. This is an increase in bioactivity compared with 4-hydroxy-8-methoxy-3-(3'-methylbut-2'-enyl)-1-methyl-quinol-2-one (**23**), which has only mild activity against *M. luteus* (MIC = 1000 μg/mL), suggesting that the double bond in the pentyl side chain may minimise the compound's activity. Lunacridine (**24**), with methylation of the 4-hydroxy group compared with (**22**), showed a decrease in activity and was only mildly active against *S. aureus* (MIC = 1000 μg/mL). This again supports the 4-hydroxy group enhancing bioactivity, as with compound (**18**). 4-Hydroxy-7,8-methylenedioxy-3-(3'methylbut-2'-enyl)-quinol-2-one (**26**) had an MIC of 1000 μg/mL against MRSA, *E. coli* and *B. subtilis*, an MIC of 500 μg/mL against *S. aureus* and an MIC of 333 μg/mL against *M. luteus*. Compound (**26**) was more bioactive than (**17**), possibly due to the presence of the 7,8-methylenedioxy group.

3.3. Flindersine derivatives

The MICs of the flindersine derivatives are given in Table 3 and the structures of these compounds can be seen in Fig. 3. The compounds in this group did not show any activity against *B. subtilis* or the Gram-negative microorganisms *S.* Typhimurium and *E. coli*. Veprisine (**29**) showed good bioactivity against *S. aureus* (MIC = 125 μg/mL) but had no activity against the other microorganisms. Veprisine (**29**) differs from 7,8-dimethoxyflindersine (**28**) only by having an *N*-methyl group. Flindersine

(**27**) had no activity at all, whereas *N*-methylflindersine (**30**) showed good activity against MRSA, *S. aureus* and *M. luteus* (MICs = 125 μg/mL). This suggests that the presence of the *N*-methyl group for this group of compounds may contribute to the activity of (**29**) and (**30**). 7-Hydroxyflindersine (**31**) showed good activity against MRSA, *S. aureus* and *M. luteus*, with an MIC of 125 μg/mL against all three microorganisms, which is identical to the bioactivity shown by (**30**). This suggests that the presence of an *N*-methyl group or a hydroxy group in the 7-position may increase the bioactivity of the basic flindersine molecule. However, when both groups are present in the same compound, as with 7-hydroxy-1-methylflindersine (**32**), the bioactivity is marginally decreased.

The presence of side chains may increase the bioactivity of the basic flindersine molecule as with 7-tetrahydropyranyloxyflindersine (**33**) and 7-dimethylallyloxy-*N*-methylflindersine (**34**). Compound (**33**) showed moderate activity against MRSA and *M. luteus* and good activity against *S. aureus*, with MIC values of 250 μg/mL and 125 μg/mL respectively. Compound (**34**) showed mild activity against MRSA (MIC = 1000 μg/mL) and moderate activity against *S. aureus* (MIC = 500 μg/mL) and *M. luteus* (MIC = 250 μg/mL).

3.4. Quinoline dimers

Compounds in this group (Fig. 4) showed no bioactivity against any of the microorganisms (Table 3).

3.5. Dihydrofuroquinolines

The five dihydrofuroquinolines (Fig. 5) tested showed no bioactivity (Table 3).

3.6. Linear and angular furoquinolines

Ten linear and angular furoquinolines were investigated. Their MICs are given in Table 4 and their structures are presented in Fig. 6. 5-Methylfuro-(3,2-c)-quinol-4-one (**43**) showed the greatest bioactivity against all six microorganisms. It had good activity against *M. luteus* (MIC = 125 μg/mL) and moderate activity against the other microorganisms, with MICs of 250 μg/mL for *S. aureus*, 333 μg/mL for MRSA and 500 μg/mL for *B. subtilis*, *E. coli* and *S.* Typhimurium. Compound (**43**) is the only one in this group that has an angular furan ring in the 3,2-c position, suggesting it may be significant in the compound's bioactivity.

Dictamnine (**44**) is a direct biosynthetic precursor to γ-fagarine (**45**) and skimmianine (**46**). Dictamnine (**44**) was not active against any of the microorganisms, but γ-fagarine (**45**) showed moderate activity against MRSA, *S. aureus* and *M. luteus* (MICs = 500 μg/mL). γ-Fagarine (**45**) has a similar structure to dictamnine with an extra methoxyl group in the 8-position, suggesting that the presence of this methoxyl group could contribute to its activity. Skimmianine (**46**) has extra methoxyl groups in the 7- and 8-positions. However, (**46**) is only mildly active against *M.*

luteus (MIC = 1000 μg/mL) and showed no activity against the other microorganisms. Thus, having a third methoxyl group in the 7-position appears to reduce the bioactivity of the molecule. 4-Methoxy-2-isopropyl-furoquinoline (**47**) showed moderate activity towards MRSA and *S. aureus* and mild activity towards *M. luteus*. This also suggests that the presence of the isopropyl side chain increases bioactivity compared with (**44**).

3.7. Other quinolines

The MICs of the compounds in this group are shown in Table 4 and their structures are given in Fig. 7. 2,4-Quinolinediol (**53**) showed mild activity against *S. aureus* (MIC = 1000 μg/mL). 2,4-Dichloroquinoline (**54**), 2,4-dimethoxyquinoline (**55**) and 2,4,8-trimethoxyquinoline (**56**) showed no activity against any of the microorganisms. This suggests that replacing the hydroxy groups with Cl or OCH_3 reduces the little bioactivity seen with (**53**). Orixine (**57**) showed moderate activity towards MRSA (MIC = 250 μg/mL). 5-Methoxy-2,2-dimethyldihydropyrano-(2,3-b)-quinoline (**58**) showed moderate activity against MRSA (MIC = 500 μg/mL), *S. aureus* (MIC = 333 μg/mL) and *M. luteus* (MIC = 500 μg/mL) and mild activity against *B. subtilis* (MIC = 1000 μg/mL).

3.8. Bioactivity of selected quinolines against different strains of MRSA

Quinolines that showed an MIC of ≤125 μg/mL against MRSA and/or *S. aureus* were further tested against eight hospital isolates of MRSA. The results are shown in Table 5. The microtitre assay for some of the

compounds (**10**, **29**, **30**, **31** and **33**) tested against IMRSA-1 is shown in Fig. 8.

As stated earlier, (**10**) was active against MRSA (MIC = 500 μg/mL) and *S. aureus* (MIC = 125 μg/mL). Compound (**10**) also showed good activity against the eight other strains of MRSA. It was most active against EMRSA-16 with an MIC of 62.5 μg/mL. It had an MIC of 125 μg/mL against EMRSA-15, IMRSA-1, IMRSA-2, NTMRSA, CWMRSA and HMRSA but was less active against DMRSA (MIC = 250 μg/mL). In the original testing, veprisine (**29**) was not active against MRSA but had good activity against *S. aureus* (MIC = 125 μg/mL). Therefore, (**29**) was tested further and it showed good to moderate activity towards all eight MRSA strains.

N-Methylflindersine (**30**) originally had an MIC value of 125 μg/mL against MRSA, *S. aureus* and *M. luteus*. It also has an MIC value of 125 μg/mL against all eight strains of MRSA. 7-Hydroxyflindersine (**31**) had an MIC of 125 μg/mL against IMRSA-1, DMRSA and CWMRSA, an MIC of 166.5 μg/mL against HMRSA, EMRSA-15 and EMRSA-16, and an MIC of 250 μg/mL against IMRSA-2 and NTMRSA. Compound (**33**) had an MIC of 250 μg/mL against IMRSA-1, IMRSA-2, DMRSA, CWMRSA, EMRSA-15 and EMRSA-16 but showed slightly more activity against NTMRSA and HMRSA (MIC = 166.5 μg/mL).

Compound (**11**) was noticeably the most active quinoline derivative against MRSA and all other microorganisms. It was most active against DMRSA and NTMRSA with MICs of 0.049 μg/mL. It had MICs of 0.097 μg/mL against IMRSA-1, 0.39 μg/mL against IMRSA-2 and EMRSA-15, 1.56 μg/mL against CWMRSA and HMRSA and 25 μg/mL against EMRSA-16. The MICs of the antibiotic vancomycin, commonly employed in the treatment of MRSA infections, are also given in Table 5. Compound (**11**) had an identical bioactivity to vancomycin against CWMRSA and HMRSA, whilst for the remaining MRSA strains, except EMRSA-16, it displayed a greater antimicrobial effect than vancomycin.

4. Conclusions

Sixty quinolines grouped in seven structural subdivisions were investigated for their bioactivities against a number of microorganisms. Thirty of the sixty quinolines showed bioactivity against the microorganisms investigated. The quinolines (**26**), (**3**), (**10**), (**5**), (**43**) and (**11**) showed activity against the Gram-negative bacterium *E. coli*. Unfortunately, the activity of these compounds against the two Gram-negative bacteria only ranged from mild to moderate, with the exception of (**11**) that had very strong bioactivity. The characteristic protective outer membrane of Gram-negative bacteria may play a role in the inactivity of many of the quinolines against them. In this study, many of the other quinolines demonstrated activity against one or more Gram-positive bacteria, with varying MIC values. The effects of the substituent groups on

the bioactivity of these quinolines have also been studied. Substituents such as iodo, hydroxy, methyl and methoxy, in general, can enhance bioactivity but this can depend on the number of substituents and their relative position in the quinolone structure.

Of all the quinoline derivatives, 4-hydroxy-3-iodo-quinol-2-one (**11**) showed very strong activity, with MICs of 0.195 μg/mL against *S.* Typhimurium and *E. coli*, 0.39 μg/mL against MRSA, *M. luteus* and *B. subtilis* and 6.25 μg/mL against *S. aureus*. When tested against eight clinical MRSA strains, (**11**) also showed strong to very strong bioactivity. Against the majority of clinical isolates the MICs for (11) were equal to or lower than those for the antibiotic vancomycin used in the treatment of MRSA infections. The MIC against both EMRSA-15 and IMRSA-2 was 0.39 μg/mL compared with 0.78 μg/mL for vancomycin. Very strong activity was seen against IMRSA-1 (0.097 μg/mL), DMRSA and NTMRSA (both MICs = 0.049 μg/mL) compared with vancomycin with MICs ranging from 0.78 μg/mL to 1.56 μg/mL for the three hospital strains. Through further investigation into the mode of action of these quinolines and the testing of compounds of similar structure, in particular iodinated quinolines such as (**11**), it is possible that new therapeutic compounds active against MRSA could be discovered.

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Fig. 1. Structures of the quinol-2-ones.

Fig. 2. Structures of the 3-*C*-dimethylallylquinol-2-ones.

Fig. 3. Structures of the flindersine derivatives.

Fig. 4. Structures of the quinoline dimers.

Fig. 5. Structures of the dihydrofuroquinolines.

Fig. 6. Structures of the linear and angular furoquinolines.

Fig. 7. Structures of the other quinoline derivatives.

Fig. 8. Microtitre assay for selected quinolines against Irish hospital MRSA-1 (IMRSA-1). Row 1 (R1) is the blank, R2 is the acetone control, R3 is the antibiotic vancomycin and R4–R8 are the quinolines (**30**), (**31**), (**29**), (**33**) and (**10**).

Table 1

Minimum inhibitory concentrations (μg/mL) of quinol-2-ones and the antibiotic controls (oxacillin, vancomycin and trimethoprim)

Quinol-2-one	MRSA	*S. aureus*	*Micrococcus luteus*	*Bacillus subtilis*	*Escherichia coli*	*Salmonella* Typhimurium
4-Hydroxy-1-methyl-quinol-2-one (**1**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Methoxy-1-methyl-quinol-2-one (**2**)	>1000	>1000	>1000	>1000	>1000	>1000
1,3-Dimethyl-4-hydroxy-quinol-2-one (**3**)	1000	500	500	1000	1000	>1000
7,8-Dimethoxy-1,3-dimethyl-4-hydroxy-quinol-2-one (**4**)	>1000	1000	>1000	>1000	>1000	>1000
7,8-Dimethoxy-4-hydroxy-quinol-2-one (**5**)	>1000	>1000	>1000	>1000	500	>1000
8-Methoxy-4-hydroxy-quinol-2-one (**6**)	1000	1000	1000	>1000	>1000	>1000
Edulitine (**7**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
4-Ethyloxy-8-methoxy-quinol-2-one (**8**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Hydroxy-3-iodo-7,8-dimethoxy-quinol-2-one (**9**)	250	166.5	250	>1000	>1000	>1000
4,7,8-Trimethoxy-3-iodo-quinol-2-one (**10**)	500	125	125	>1000	1000	>1000
4-Hydroxy-3-iodo-quinol-2-one (**11**)	0.39	6.25	0.39	0.39	0.195	0.195
4-Epoxygeranyloxy-quinol-2-one (**12**)	>1000	>1000	>1000	>1000	>1000	>1000

4-Geranyloxy-quinol-2-one (**13**)	250	250	1000	>1000	>1000	>1000
3-(2'-Hydroxy-3'-methylbut-3'-enyl)-4-methoxy-1-methyl-quinol-2-one (**14**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Keto-3,3-di-(3'-methylbut-2-enyl)-quinol-2-one (**15**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Acetyloxy-3-(1',1'-dimethylallyl)-1-methyl-quinol-2-one (**16**)	>1000	>1000	>1000	>1000	>1000	>1000
Oxacillin	>21.6	0.17	>21.6	21.6	>21.6	>21.6
Vancomycin	0.79	0.4	>25	>25	>25	>25
Trimethoprim	>25	0.79	0.4	>25	1.57	1.57

MRSA, meticillin-resistant *Staphylococcus aureus*.

[a] [NS] indicates isolated from natural sources.

Table 2

Minimum inhibitory concentrations (μg/mL) of 3-*C*-dimethylallylquinol-2-ones

3-*C*-dimethylallylquinol-2-one	MRSA	*S. aureus*	*Micrococcus luteus*	*Bacillus subtilis*	*Escherichia coli*	*Salmonella* Typhimurium
4-Hydroxy-3-(3'-methylbut-2-enyl)-quinol-2-one (**17**)	>1000	>1000	1000	>1000	>1000	>1000
4-Hydroxy-6-methoxy-3-(3'-methylbut-2-enyl)-quinol-2-one (**18**)	1000	500	1000	>1000	>1000	>1000
4,6-Dimethoxy-3-(3'-methylbut-2-enyl)-quinol-2-one (**19**)	1000	>1000	1000	>1000	>1000	>1000
4-Hydroxy-6-methoxy-3-(3'-methylbut-2-enyl)-1-methyl-quinol-2-one (**20**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Hydroxy-6,8-dimethoxy-3-(3'-methylbut-2-enyl)-1-methyl-quinol-2-one (**21**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Hydroxy-8-methoxy-3-(3'-methyl-2'-hydroxybutyl)-1-methyl-quinol-2-one (**22**)	500	250	250	>1000	>1000	>1000
4-Hydroxy-8-methoxy-3-(3'-methylbut-2'-enyl)-1-methyl-quinol-2-one (**23**)	>1000	>1000	1000	>1000	>1000	>1000

Lunacridine (**24**) [NS] [a]	>1000	1000	>1000	>1000	>1000	>1000
4,6-Dimethoxy-3-(3'-methyl-2'-oxobutyl)-1-methyl-quinol-2-one (**25**)	>1000	>1000	>1000	>1000	>1000	>1000
4-Hydroxy-7,8-methylenedioxy-3-(3'-methylbut-2-enyl)-quinol-2-one (**26**)	1000	500	333	1000	1000	>1000

MRSA, meticillin-resistant *Staphylococcus aureus*.

[a] [NS] indicates isolated from natural sources.

Table 3

Minimum inhibitory concentrations (μg/mL) of flindersine derivatives, quinoline dimers and dihydrofuroquinolines

	MRSA	*S. aureus*	*Micrococcus luteus*	*Bacillus subtilis*	*Escherichia coli*	*Salmonella* Typhimurium
Flindersine compound						
Flindersine (**27**)	>1000	>1000	>1000	>1000	>1000	>1000
7,8-Dimethoxyflindersine (**28**)	>1000	>1000	>1000	>1000	>1000	>1000
Veprisine (**29**) [NS] [a]	>1000	125	>1000	>1000	>1000	>1000
N-Methylflindersine (**30**)	125	125	125	>1000	>1000	>1000
7-Hydroxyflindersine (**31**)	125	125	125	>1000	>1000	>1000
7-Hydroxy-*N*-methylflindersine (**32**)	250	250	250	>1000	>1000	>1000
7-Tetrahydropyranyloxyflindersine (**33**)	250	125	250	>1000	>1000	>1000
7-Dimethylallyloxy-*N*-methylflindersine (**34**)	1000	500	250	>1000	>1000	>1000
Quinoline dimers						
Quinolone dimer (**35**)	>1000	>1000	>1000	>1000	>1000	>1000
Ketoquinoline dimer (**36**)	>1000	>1000	>1000	>1000	>1000	>1000
Vepridimerine A (**37**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
Dihydrofuroquinolines						

4-Chloro-6-methoxydihydrofuro-(3,2-c)-quinoline (**38**)	>1000	>1000	>1000	>1000	>1000	>1000
Platydesmine (**39**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
2-Hydroxyisopropyl-6-methoxy-5-methyldihydro-furo-(3,2-c)-quinol-4-one (**40**)	>1000	>1000	>1000	>1000	>1000	>1000
Balfouridine (**41**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
Lemobiline (**42**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000

MRSA, meticillin-resistant *Staphylococcus aureus*.

[a] [NS] indicates isolated from natural sources.

Table 4

Minimum inhibitory concentrations (μg/mL) of linear and angular furoquinolines and other quinoline compounds

	MRSA	*S. aureus*	*Micrococcus luteus*	*Bacillus subtilis*	*Escherichia coli*	*Salmonella* Typhimurium
Linear or angular furoquinoline						
5-Methylfuro-(3,2-c)-quinol-4-one (**43**)	333	250	125	500	500	500
Dictamnine (**44**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
γ-Fagarine (**45**) [NS] [a]	500	500	500	>1000	>1000	>1000
Skimmianine (**46**) [NS] [a]	>1000	>1000	1000	>1000	>1000	>1000
4-Methoxy-2-isopropyl-furoquinoline (**47**)	500	500	1000	>1000	>1000	>1000
Dehydroplatydesmine (**48**)	>1000	500	>1000	>1000	>1000	>1000
Evoxine (**49**) [NS] [a]	>1000	1000	>1000	>1000	>1000	>1000
Choisyine (**50**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000
4-Chloro-6,7-methylenedioxy-furoquinoline (**51**)	>1000	>1000	>1000	>1000	>1000	>1000
6,7-Methylenedioxyfuro-(2,3-b)-quinol-4-one (**52**)	>1000	>1000	>1000	>1000	>1000	>1000
Other quinolines						

2,4-Quinolinediol (**53**)	>1000	1000	>1000	>1000	>1000	>1000
2,4-Dichloroquinoline (**54**)	>1000	>1000	>1000	>1000	>1000	>1000
2,4-Dimethoxyquinoline (**55**)	>1000	>1000	>1000	>1000	>1000	>1000
2,4,8-Trimethoxyquinoline (**56**)	>1000	>1000	>1000	>1000	>1000	>1000
Orixine (**57**)	250	>1000	>1000	>1000	>1000	1000
5-Methoxy-2,2-dimethyldihydropyrano-(2,3-b)-quinoline (**58**)	500	333	500	1000	>1000	>1000
3,5-Diacetyloxy-2,2-dimethyldihydropyrano-(2,3-b)-quinoline (**59**)	>1000	>1000	>1000	>1000	>1000	>1000
Ribalinine (**60**) [NS] [a]	>1000	>1000	>1000	>1000	>1000	>1000

MRSA, meticillin-resistant *Staphylococcus aureus*.

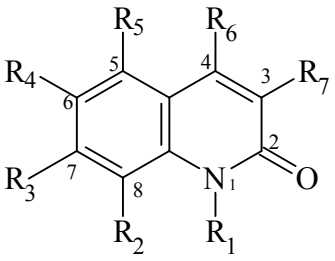
[a] [NS] indicates isolated from natural sources.

Table 5

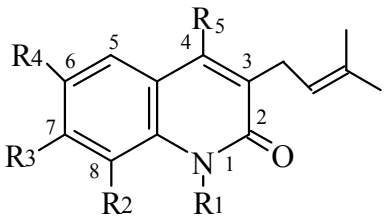
Minimum inhibitory concentrations (μg/mL) of selected quinolines against different strains of meticillin-resistant *Staphylococcus aureus* (MRSA)

Compound	EMRSA-15	EMRSA-16	IMRSA-1	IMRSA-2	DMRSA	NTMRSA	CWMRSA	HMRSA
4,7,8-Trimethoxy-3-iodo-quinol-2-one (**10**)	125	62.5	125	125	250	125	125	125
4-Hydroxy-3-iodo-quinol-2-one (**11**)	0.39	25	0.097	0.39	0.049	0.049	1.56	1.56
Veprisine (**29**)	250	125	333	250	333	166.5	125	500
N-Methylflindersine (**30**)	125	125	125	125	125	125	125	125
7-Hydroxyflindersine (**31**)	166.5	166.5	125	250	125	250	125	166.5
7-Tetrahydro-pyranyloxyflindersine (**33**)	250	250	250	250	250	166.5	250	166.5
Vancomycin	0.78	0.78	1.56	0.78	1.56	0.78	1.56	1.56

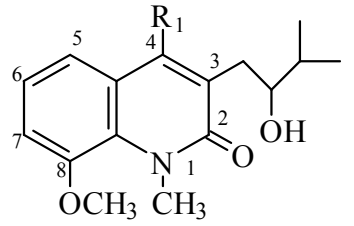
EMRSA-15, epidemic MRSA-15; EMRSA-16, epidemic MRSA-16; IMRSA-1, Irish hospital MRSA-1; IMRSA-2; Irish hospital MRSA-2; DMRSA, distinct MRSA strain; NTMRSA, non-typeable MRSA strain; CWMRSA, community-acquired Charles–Worth MRSA; HMRSA, community-acquired Hodgkin MRSA.



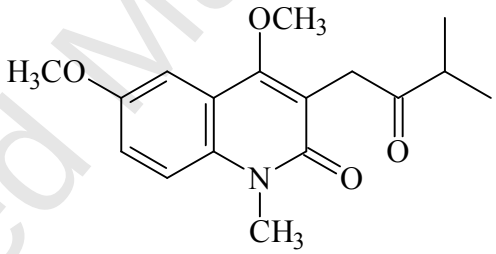
Quinol-2-one	R1	R2	R3	R4	R5	R6	R7
(1)	CH_3	H	H	H	H	OH	H
(2)	CH_3	H	H	H	H	OCH_3	H
(3)	CH_3	H	H	H	H	OH	CH_3
(4)	CH_3	OCH_3	OCH_3	H	H	OH	CH_3
(5)	H	OCH_3	OCH_3	H	H	OH	H
(6)	H	OCH_3	H	H	H	OH	H
(7)	H	OCH_3	H	H	H	OCH_3	H
(8)	H	OCH_3	H	H	H	OC_2H_5	H
(9)	H	OCH_3	OCH_3	H	H	OH	I
(10)	H	OCH_3	OCH_3	H	H	OCH_3	I
(11)	H	H	H	H	H	OH	I
(12)	H	H	H	H	H	Epoxygeranyloxy	H
(13)	H	H	H	H	H	Geranyloxy	H
(14)	CH_3	H	H	H	H	OCH_3	2’-hydroxy-3’-methylbutyl-3’-enyl
(15)	H	H	H	H	H	Keto	di-3’-methylbut-2’-enyl
(16)	CH_3	H	H	H	H	$OCOCH_3$	1’,1’-dimethylallyl



3-*C*-dimethylallyl-quinol-2-ones	R_1	R_2	R_3	R_4	R_5
(17)	H	H	H	H	OH
(18)	H	H	H	OCH_3	OH
(19)	H	H	H	OCH_3	OCH_3
(20)	CH_3	H	H	OCH_3	OH
(21)	CH_3	OCH_3	H	OCH_3	OH
(23)	CH_3	OCH_3	H	H	OH



(22)R_1=OH, **(24)**R_1=OCH_3



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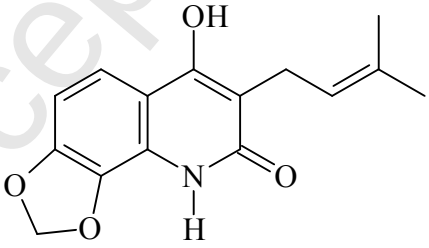

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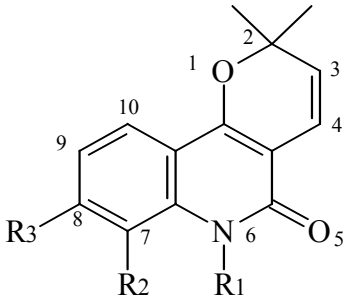
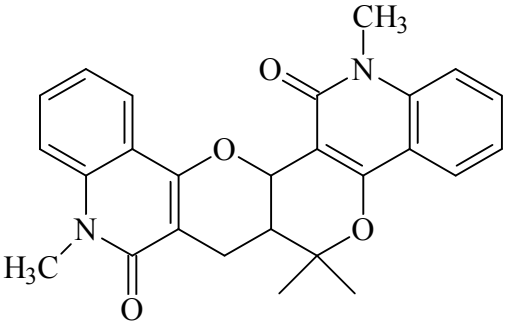


Flindersine compound	R_1	R_2	R_3
(27)	H	H	H
(28)	H	OCH_3	OCH_3
(29)	CH_3	OCH_3	OCH_3
(30)	CH_3	H	H
(31)	H	OH	H
(32)	CH_3	OH	H
(33)	H	Tetrahydropyranyloxy	H
(34)	CH_3	Dimethylallyloxy	H



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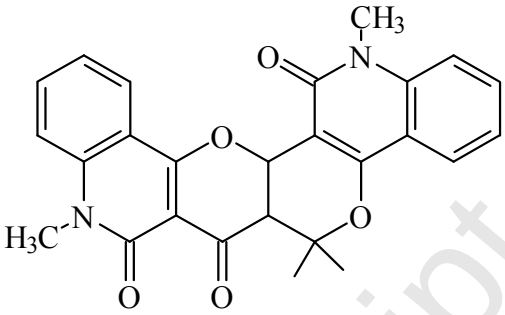

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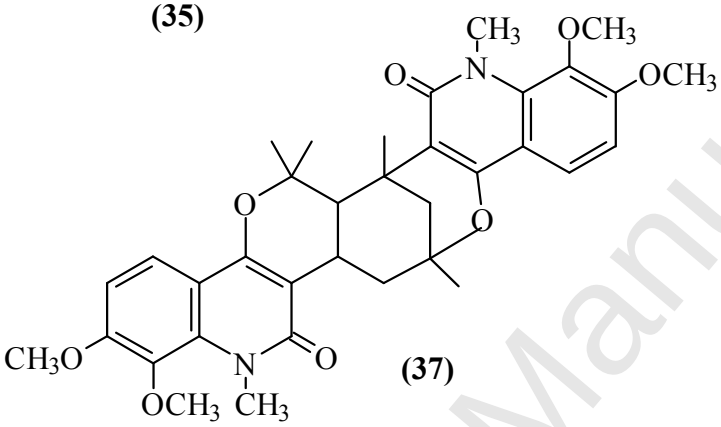

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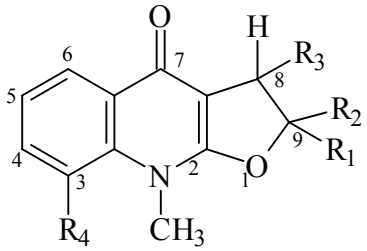
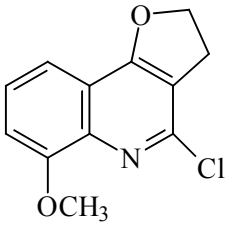


Dihydrofuroquinoline Compound	R_1	R_2	R_3	R_4
(41)	$C(OH)(CH_3)_2$	H	H	OCH_3
(42)	CH_3	CH_3	CH_3	H



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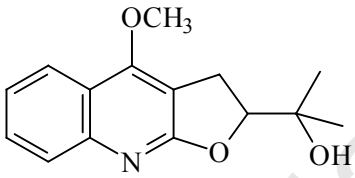

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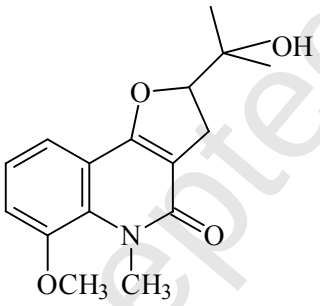

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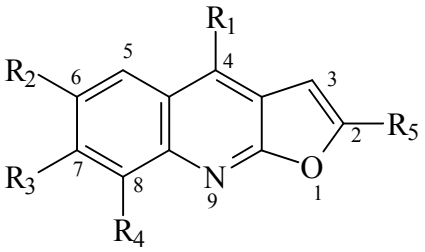
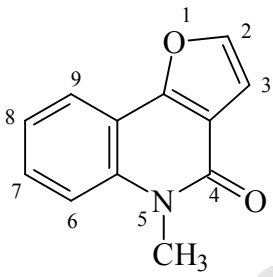


Linear and augular Furoquinolines	R_1	R_2	R_3	R_4	R_5
(44)	OCH_3	H	H	H	H
(45)	OCH_3	H	H	OCH_3	H
(46)	OCH_3	H	OCH_3	OCH_3	H
(47)	OCH_3	H	H	H	$C(CH_3)CH_3$
(48)	OCH_3	H	H	H	$C(CH_3)(OH)CH_3$
(49)	OCH_3	H	$OCH_2CH(OH)C(OH)(CH_3)_2$	OCH_3	H
(51)	Cl	*	R_2-R_3 = OCH_2O	H	H
(52)	Oxo	*	R_2-R_3 = OCH_2O	H	H

* Methylenedioxy ring between position R_2 and R_3 for compounds **(51)** and **(52)**.



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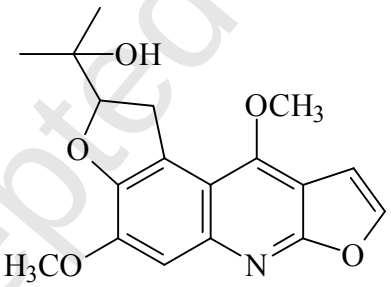

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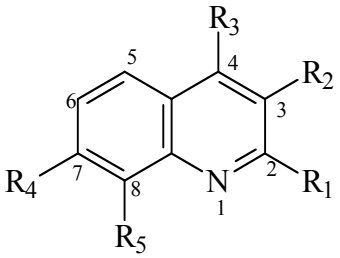
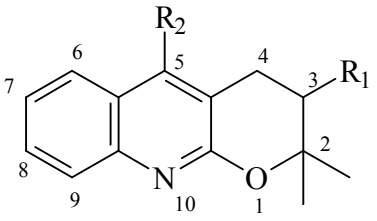
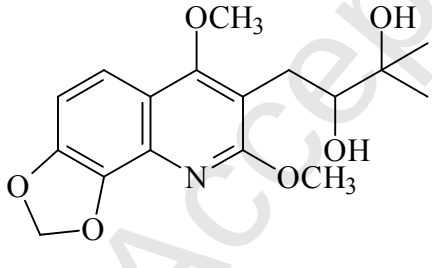


Quinolines	R_1	R_2	R_3	R_4	R_5
(53)	OH	H	OH	H	H
(54)	Cl	H	Cl	H	H
(55)	OCH_3	H	OCH_3	H	H
(56)	OCH_3	H	OCH_3	H	OCH_3



Quinolines	R_1	R_2
(58)	H	OCH_3
(59)	$OCOCH_3$	$OCOCH_3$



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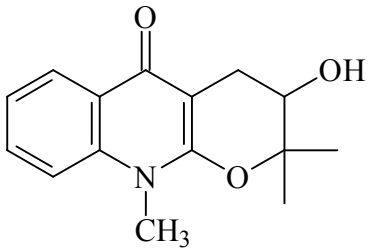

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