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# Synthesis of 2-alkenyl-3-hydroxyquinolin-4(1*H*)-ones as promising antimicrobial and fluorescent agents

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ABSTRACT

2-Alkenyl-3-hydroxyquinolin-4(1*H*)-ones were prepared by the rearrangement of anthranilic acid esters synthesized by two alternative methods. The prepared derivatives were screened for their antimicrobial activities against representative Gram-positive and Gram-negative bacteria, displaying notable minimum inhibitory concentration values against specific strains. The emission spectra of the target quinolines exhibited two well-separated emission bands, and the maximum excitation wavelengths of the selected compounds were detected at relatively high values.



## 1. Introduction

Quinolin-4(1*H*)-ones are pharmacologically attractive compounds with a wide range of biological effects. In this regard, quinolin-4(1*H*)-one-3-carboxylic acids are particularly attractive due to their highly potent antimicrobial activities.[1] A report on the synthesis and screening of oxolinic acid and pefloxacin analogues, which bear 3-hydroxy groups instead of carboxylic groups, toward different bacterial strains revealed only negligible activity.[2] This indicated the negative influence of such structural modification, and therefore, 3-hydroxy-4(1*H*)-quinolines (3HQs) have not been considered promising antimicrobial agents for a long period. Nevertheless, the discovery of a simple synthetic route for the routine preparation of 2-phenyl-3HQs[2,3] as flavonol isosteres initiated a detailed investigation of their biological properties. To date, a number of different 2-phenyl-3HQs with significant cytotoxic[4–6] and immunosuppressive effects[7] have been reported. Regarding their biomolecular targets, 2-phenyl-3HQs have been shown to act as topoisomerase and microtubule polymerization inhibitors with a resulting effect on mitosis.[8] These specific 3HQs also inhibited inosine monophosphate dehydrogenase (IMPDH)[9] and reverse transcriptase of human immunodeficiency viruses.[10] In contrast, significant antibacterial properties of 3HQs have not been reported to date.

In addition to biological effects, 2-aryl-3HQs exhibit interesting fluorescent properties and have been suggested as compounds for the labeling of molecules.[6,11–14] This presumption was supported by the fact that 3HQs typically exhibit two well-separated emission bands, resulting in dual fluorescence. Dual fluorescent labels are not dependent on concentration because the ratio of the intensities of the two bands can be applied as a signal. This is advantageous in complex biological systems, such as cells or tissues, in which the local concentration of the label cannot be controlled easily because of its inhomogeneous distribution.[15,16] On the other hand, the excitation of previously reported 2-aryl-3HQs requires relatively low-wavelength light (usually approximately 350 nm),[12,13] which is not beneficial due to the interfering fluorescence of intrinsic fluorophores as well as harmful effects of UV radiation. For this reason, excitation with higher-wavelength light is considerably more advantageous with respect to possible biological applications.

In this paper, we focus on the preparation of novel 3HQs bearing an alkenyl or alkyl moiety in the 2 position. The introduction of an

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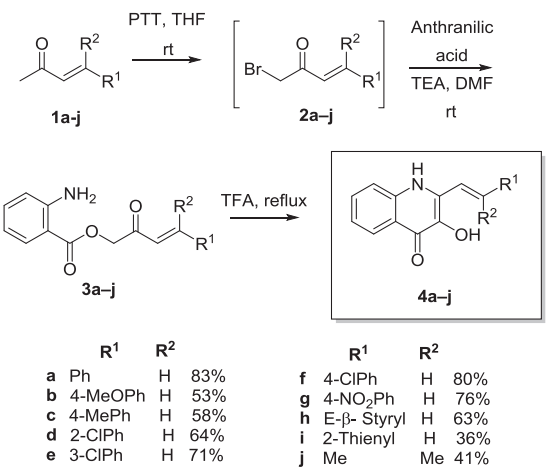
alkene conjugated with an additional aromatic ring was suggested to produce a bathochromic shift of the absorption, thus possibly increasing the excitation wavelength energy. Furthermore, 2-alkyl-3HQs represent biologically relevant compounds, with 2-heptyl-3-hydroxyquinolin-4(1*H*)-one (PQS, Pseudomonas quinolone signal) being the most important derivative. PQS acts as a signaling molecule used by resistant bacteria *Pseudomonas aeruginosa* in the virulence regulatory system,[17–19] which is one of the possible targets for treating diseases caused by resistant bacteria.[20–22]

## 2. Results and discussion

### 2.1. Synthesis

The synthetic approach leading to target compounds **4** was inspired by a previously reported method for 2-aryl-3HQs.[2] Nevertheless, the limited availability and stability of unsaturated intermediates **2** or **7** in comparison to analogous α-haloacetophenones required substantial modification. In the first stage, the synthesis of key intermediates **3a**–**o** was performed. These esters were prepared by the alkylation of anthranilic acid with α-haloketones. Two alternative methods were developed depending on the resulting substitution pattern. Method A (Scheme 1) was applicable for aryl ($R^1$ = Ar) or dialkyl ($R^{1,2}$ = $CH_3$) intermediates. It was based on the condensation of commercially available aldehydes with acetone[23] and subsequent bromination of the resulting α,β-unsaturated ketones **1a**–**i** with phenyl trimethylammonium tribromide (PTT).[24] Haloketone **2j** was prepared from commercially available mesityl oxide **1j** using a similar procedure. In contrast, the bromination of monoalkyl or pyridyl unsaturated ketones prepared from aldehydes **6k-o**, **6s**, and **6t** (see the structure of aldehydes in Scheme 2) by method A was unsuccessful.

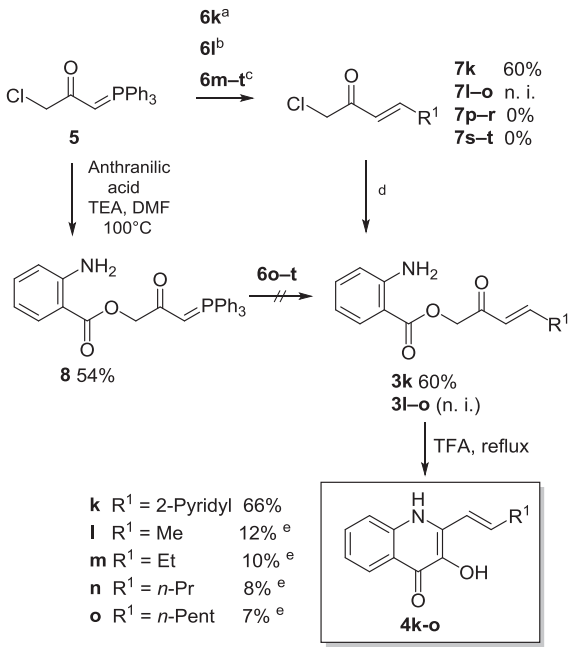
For this reason, intermediates **7k-o** were synthesized by Method B based on a Wittig reaction of phosphorane **5** with pyridine 2-carboxaldehyde **6k**[25] or aliphatic aldehydes **6l**–**o** (Scheme 2). However, reaction conditions to react α-branched aldehydes **6p**–**r** (pivaloyl aldehyde, isobutyraldehyde or cyclohexanecarboxaldehyde) or pyridyl aldehydes **4s** and **4t** with **5** were not found. In contrast to stable compounds **3a**–**k**, anthranilates **3l-o** were prone to spontaneous dimerization during their preparation. We managed to suppress this side-reaction by decreasing the reaction temperature from 25 °C to −5 °C and changing the base ($K_2CO_3$ was used instead of triethylamine). Despite this fact, esters **3l**–**o** were obtained in limited purity (~70%, LCMS) and used immediately in the next reaction step without purification and characterization.




| | $R^1$ | $R^2$ | |
|---|---|---|---|
| **a** | Ph | H | 83% |
| **b** | 4-MeOPh | H | 53% |
| **c** | 4-MePh | H | 58% |
| **d** | 2-ClPh | H | 64% |
| **e** | 3-ClPh | H | 71% |
| **f** | 4-ClPh | H | 80% |
| **g** | 4-$NO_2$Ph | H | 76% |
| **h** | E-β- Styryl | H | 63% |
| **i** | 2-Thienyl | H | 36% |
| **j** | Me | Me | 41% |

Displayed yields of **4a-j** were calculated after 3 reaction steps (based on ketones **1**).

**Scheme 1.** Synthesis of 3HQs **4a**–**j** by method A.




[a]Dichloromethane, rt. [b] Excess aldehyde **6l** was used as the solvent, 35°C, sealed tube. [c]1,2-Dichloroethane, reflux, inert atmosphere. [d]For **7k**: anthranilic acid, TEA, DMF, rt; for **7l–o**: anthranilic acid, $K_2CO_3$, DMF, -5°C. [e] Yield was calculated after 3 reaction steps (based on ylide **5**). n. i.: Not isolated.

**Scheme 2.** Synthesis of hydroxyquinolones **4k**–**o** by method B.

The use of anthranilate **8** as an alternative intermediate for the preparation of anthranilates **3** was also tested (Scheme 2). Nevertheless, its reaction with various aliphatic, aromatic or heteroaromatic aldehydes under the Wittig reaction conditions was unsuccessful. To prepare the target 3HQs, the original conditions[2] (using PPA or solvent-free cyclization) were initially applied. However, the cyclization of anthranilates **3a**–**o** failed or led to the formation of inseparable impurities. On the other hand, 3HQs **4a-k** were prepared in good yields by the cyclization of the corresponding anthranilates using trifluoroacetic acid.[6] This method was also applicable for products **4l-o**, however with limited yields 7–12% (calculated after 3 steps).

To test the applicability of the reaction sequence for the preparation of 2-alkyl-3HQs, two representative compounds **4a** and **4h** were reduced using catalytic hydrogenation (Scheme 3). In both cases, the hydrogenation yielded the corresponding target compounds **9a** and **9h**.

### 2.2. Antibacterial activity

The prepared 3HQs were screened for antibiotic activity against representative Gram-positive (*B. subtilis*, ATCC 6633; *M. luteus*,

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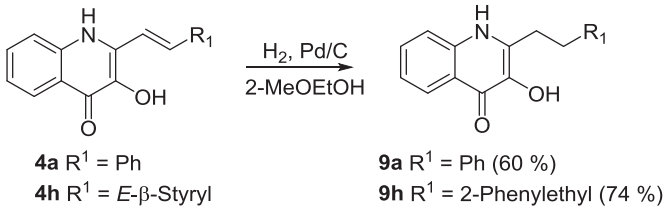


**Scheme 3.** Preparation of 2-alkyl-3HQs.

ATCC 10240; *M. vaccae*, DSM 43514; *S. aureus*, CCM 2524) and Gram-negative (*P. aeruginosa*, CCM 3955; *E. coli*, CCM 3954) bacteria using agar diffusion assays.[26] Derivatives **4a**, **4i**, **4k** and **4m** displayed noticeable antibacterial activities against *M. luteus* when tested at 2 mM, as indicated by the large inhibition zones (Table 1) they induced. *M. vaccae* was susceptible to derivatives **4i** and **4k**, and *S. aureus* was susceptible to **4i**. Derivatives with inhibition zones ≥20 mm were subjected to further assays[27] to determine their minimum inhibitory concentrations (MIC). Notable MIC values were observed for **4a**, **4i** and **4k** (3.13, 12.5 and 25.0 μmol $L^{-1}$ against *M. luteus*, respectively). Additionally, compound **4i** exhibited promising inhibition of *S. Aureus* (25.0 μmol $L^{-1}$). The most active derivatives possessed a similar structural motif – an unsubstituted aromatic scaffold (phenyl, thiophene and pyridine) bonded to the 3-hydroxyquinolin-4(1*H*)-one skeleton through an ethenyl group.

2-Alkyl 3HQs **9** were also tested for their antibiotic activities. The reduction of the double bond in **4a** led to derivative **9a** with noticeable activity against *S. Aureus*. In contrast, the activity against *M. luteus* was diminished by the hydrogenation of derivative **4a**. Compound **4h** with an elongated alkyl chain was inactive against all tested strains.

### 2.3. Fluorescence properties

To determine the detailed fluorescence properties of the studied compounds, the excitation and emission spectra, as well as quantum yields, were measured. The excitation spectra (Table 2, Fig. 1) showed that the maximum excitation wavelengths were obtained in the range from 346 to 470 nm and exhibited several relatively narrow distinct local maxima (Fig. 1). In contrast to 2-aryl-3HQs that are excited by relatively low-wavelength light (usually approximately 350 nm),[11,12] it was evident that excitation was possible in a wider excitation wavelength range. Moreover, some derivatives could be excited by light with relatively high wavelengths of approximately 450 nm. The difference (Stokes shift) between the longer excitation wavelength and the closer emission maximum wavelength remained sufficient to measure the fluorescence intensity at the lower wavelength maximum of the emission spectrum. The emission spectra primarily exhibited two well-separated emission bands with various ratios of fluorescence maximum intensities $I_1/I_2$ (Table 2). For derivatives **4d**, **4h** and **4i**, the emission spectra lost the dual fluorescence character, and only emission spectra with one maximum or only a hint of the second maximum were observed (Fig. 1). The quantum yields were detected in units of percent. Higher quantum yields (20%) were observed for derivatives with branched (**4j**) or linear alkenyl chains (**4l**, **4m**, **4n**, and **4o**) in the position 2 (see Table 2). To investigate the effect of the double bond in the alkenyl chain on the

**Table 1**
Antibacterial activities of hydroxyquinolones **4** and **9**.

| Cmpd | Diameter of inhibition zone in agar diffusion assay (mm)/(MIC) (μmol $L^{-1}$) | | | | | |
|---|---|---|---|---|---|---|
| | *B. subtilis* | *M. luteus* | *M. vaccae* | *S. aureus* | *P. aeruginosa* | *E. coli* |
| **4a** | 14 | 22/(3.13) | 0 | 0 | 15 | 15 |
| **4b** | 14 | 15 | 17 | 0 | 16 | 0 |
| **4c** | 0 | 12 | 0 | 0 | 0 | 0 |
| **4d** | 12 | 18 | 0 | 0 | 0 | 0 |
| **4e** | 0 | 17 | 0 | 0 | 0 | 0 |
| **4f** | 0 | 13 | 0 | 0 | 0 | 0 |
| **4g** | 0 | 0 | 0 | 0 | 0 | 0 |
| **4h** | 0 | 13 | 0 | 0 | 0 | 0 |
| **4i** | 13 | 21/(12.5) | 21/(25.0) | 22/(25.0) | 14 | 18 |
| **4j** | 0 | 0 | 0 | 18 | 0 | 0 |
| **4k** | 15 | 26/(25.0) | 25/(50.0) | 0 | 0 | 21/(>200) |
| **4l** | 0 | 14 | 0 | 0 | 0 | 17 |
| **4m** | 12 | 22/(200) | 17 | 18 | 20/(>200) | 20/(>200) |
| **4n** | 13 | 15 | 15 | 17 | 0 | 16 |
| **4o** | 0 | 13 | 13 | 0 | 0 | 0 |
| **9a** | 15 | 18 | 17 | 20/(100) | 0 | 18 |
| **9h** | 0 | 0 | 0 | 0 | 0 | 0 |
| **Std**[a] | 20/(7.5) | 18/(0.26) | 27/(0.26) | 20/(15.0) | 15/(3.75) | 18-20/(7.5) |

[a] Ciprofloxacin used as a standard.

**Table 2**
Spectroscopic properties of the studied 3HQs in MeOH.

| Entry | Compound | $\lambda_{ex}$[a] | $\lambda_{em,1}$ (nm)[b] | $\lambda_{em,2}$ (nm)[c] | $I_1/I_2$[d] | φ (%)[e] |
|---|---|---|---|---|---|---|
| 1 | **4a** | 444 | 484 | 563 | 0.14 | 8.24 |
| 2 | **4b** | 446 | 482 | 561 | 2.01 | 8.50 |
| 3 | **4c** | 445 | 482 | 553 | 0.15 | 9.34 |
| 4 | **4d** | 446 | 492 | – | – | 8.28 |
| 5 | **4e** | 454 | 494 | 570 | 1.67 | 3.81 |
| 6 | **4f** | 449 | 490 | 574 | 1.92 | 8.81 |
| 7 | **4g** | – | – | – | – | – |
| 8 | **4h** | 470 | 512 | – | – | 5.26 |
| 9 | **4i** | 457 | 503 | – | – | 5.05 |
| 10 | **4j** | 392 | 438 | 530 | 0.39 | 19.49 |
| 11 | **4k** | 456 | 501 | 594 | 2.21 | 6.81 |
| 12 | **4l** | 407 | 436 | 520 | 0.36 | 22.96 |
| 13 | **4m** | 411 | 439 | 528 | 0.30 | 24.06 |
| 14 | **4n** | 409 | 438 | 529 | 0.31 | 22.09 |
| 15 | **4o** | 407 | 439 | 532 | 0.27 | 24.13 |

[a] $\lambda_{ex}$, Excitation wavelength.
[b] $\lambda_{em,1}$, Fluorescence emission maximum at lower wavelengths.
[c] $\lambda_{em,2}$, Fluorescence emission maximum at higher wavelengths.
[d] $I_1/I_2$, ratio of fluorescence maximum intensities.
[e] φ, Fluorescence quantum yield (determined with quinine sulfate in 0.5 M sulfuric acid (φ = 0.577[26]), used as a reference fluorescence standard).

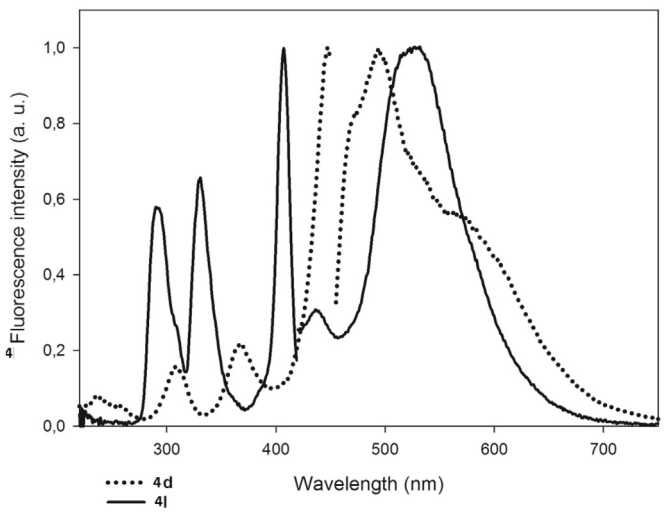


**Fig. 1.** Normalized fluorescence excitation and emission spectra of compounds **4d** and **4l**.

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fluorescence properties of 2-alkenyl-3HQs, the quantum yields of alkyl derivatives **9a** and **9h** were also determined. The quantum yields of **9a** and **9h** were 64.18 and 69.84%, respectively. It was apparent that the introduction of the alkenyl double bond led to a substantially decreased quantum yield.

It has been previously reported that the fluorescence activities of 3-hydroxyquinolin-4(1*H*)-ones are highly dependent on the pH.[11–14] For this reason, the effect of pH on the fluorescence properties of derivatives **4** in phosphate buffer was also investigated. Derivatives **4l**, **4m** and **4n** were chosen because of their high fluorescence quantum yields. In the pH range from 2 to 8, the fluorescence intensity was almost constant or increased slightly (Fig. 2). However, in alkaline solution (pH 8–11), the fluorescence intensity increased dramatically and then reached a plateau at pH 11–12. From the relationship between pH and fluorescence intensity, it can be concluded that the studied compounds possessed two forms in aqueous solution. A neutral form (that exhibited a lower fluorescence intensity) of 2-alkenyl-3-hydroxyquinolin-4(1*H*)-ones is expected under acidic and neutral conditions, and a deprotonated anionic form is formed in strong alkaline solution. The shape of the curve indicated that this transition occurred at pKa values in the range from 9 to 10. The independence of fluorescence intensity on pH in neutral conditions is an advantage for the possible application of these compounds in biological systems.

## 3. Conclusion

To conclude, we have developed a simple synthetic strategy for the preparation of 2-alkenyl- and 2-alkyl-3-hydroxyquinolin-4(1*H*)-ones using readily available starting materials. In contrast to 2-phenyl-3HQs that have been extensively studied, the 2-alkenyl derivatives exhibited noticeable antibacterial activities, indicating that 3HQs with specific substitution patterns are promising antibacterial agents. Although a detailed structure-activity relationship was not observed, two compounds exhibited high or medium MICs against *Micrococcus luteus* and *Staphylococcus aureus*, and they can be used as structural templates to further improve the inhibition values. In contrast to previously reported 2-aryl-3HQs, the bathochromic shifts of 2-alkenyl-3HQs resulted in their excitation by light with higher wavelengths. On the other hand, the quantum yields of 2-alkenyl-3HQs were lower in comparison to the quantum yields of the previously described 3-hydroxyquinolin-4(1*H*)-one derivatives. Despite this fact, the fluorescence intensities of the studied compounds were still sufficient for their potential application as fluorescence probes.

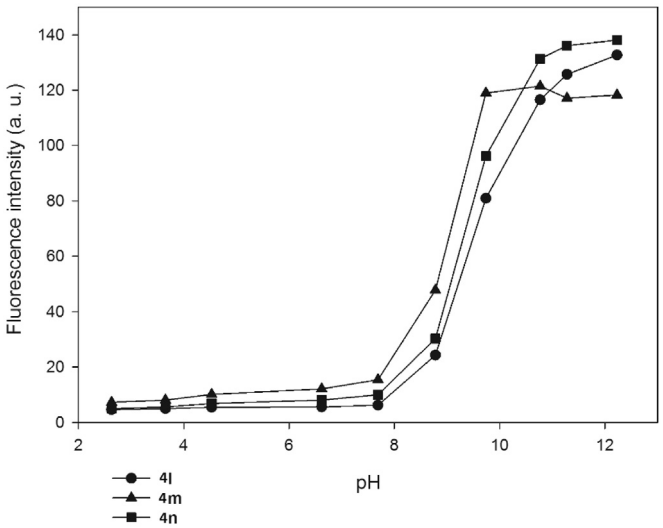


**Fig. 2.** Dependence of the fluorescence intensity on pH for **4l**, **4m** and **4n** (for excitation and emission wavelengths, see Table 2; measured for the emission maxima at higher wavelengths).

## 4. Experimental

### 4.1. General

1,2-Dichloroethane for Wittig reactions was distilled from $P_2O_5$ and stored over molecular sieves. Other solvents were used in common grade. Mesityl oxide **1j**, benzylidene acetone **1a,** aldehydes **6** and anthranilic acid were used commercially. Substituted benzylidene acetones **1b**–**i** were prepared from commercially available aromatic aldehydes and acetone according to the literature.[23] Ylide **5** was prepared from commercially available 1,3-dichloroacetone and triphenylphosphine according to the literature.[25] Phenyl trimethylammonium tribromide was prepared according to the literature[24] from dimethyl aniline, dimethyl sulfate, bromine, and hydrobromic acid.

### 4.2. Analytical methods

High resolution mass spectrometry (HRMS) analyses were measured with a Thermo Exactive instrument (Thermo Scientific, USA). The injection was performed by an apparatus Accela 1250 autosampler. The chromatographic separation parameters include column Luna C18, 3 μm, 50 × 2mm i.d. column (Phenomenex, USA), mobile phase acetonitrile/water 70/30 with 0.1% formic acid, flow rate of 200 μL/min, and column temperature of 30 °C. Sample preparation was obtained using the following procedure: 1 mg of sample was dissolved in 10 mL of a mixture of acetonitrile/water (7:3) with 0.1% of formic acid (1 min sonication) and then 50 μL of this solution and 950 μL of the same solution were added into vial and mixed before injection of 5 μl. High-resolution mass spectrometer Exactive based on orbitrap mass analyser was equipped with heated electrospray ionization (HESI). The spectrometer was tuned to obtain the maximum response for 75–700 m/z. The source parameters were set to the following values: HESI temperature 50 °C, spray voltage +3.0 kV (positive mode), transfer capillary temperature 300 °C, and sheath gas/aux gas (nitrogen) flow rates 35/10.$^1$H NMR, $^{13}$C NMR and $^{31}$P spectra were recorded at 23 °C with a Varian spectrometer (399.90 MHz for $^1$H, 100.56 MHz for $^{13}$C, 161.92 for $^{31}$P) in DMSO. The $^1$H and $^{13}$C chemical shifts were referenced to the central signal of the solvent DMSO ($\delta = 2.50$ $^1$H and $\delta = 39.43$ $^{13}$C). The assignment of resonances in the $^1$H and $^{13}$C NMR spectra was made by two-dimensional homonuclear and heteronuclear shift correlation experiments. Melting points were measured on a Kofler hot-stage microscope VEB Analytik Dresden PHMK 76/1586 and were not corrected. IR spectra (4000 – 400 cm$^{-1}$) were collected using Nicolet Avatar 370 FTIR spectrometer.

### 4.3. Procedure for the preparation of anthranilates *3a–j*

Benzylidenacetone **1a**–**j** (0.05 mol) was dissolved in tetrahydrofuran (30 mL). Phenyl trimethyl ammonium tribromide (0.05 mol, 11.3 g) was charged into the solution at 25 °C. After starting materials were consumed (45 min), the reaction mixture was poured into ice-cold water (300 mL). The product was extracted with diethylether (3 × 50 mL), and the combined organic layers were washed with water, brine and dried over $Na_2SO_4$ and evaporated under reduced pressure at room temperature. The residue was dissolved in DMF (5 mL) and added drop wise over 5 min to a solution of anthranilic acid (0.05 mol; 6.9 g) and

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triethylamine (0.05 mol; 7 mL) in DMF (50 mL). After starting materials were consumed (TLC monitoring), the reaction mixture was poured into water with crushed ice (500 mL), the resulting suspension was filtered and the cake was thoroughly washed with water and dried. Crude anthranilate was purified by the crystallization process.

### 4.4. (E)-2-Oxo-4-phenylbut-3-en-1-yl 2-aminobenzoate (**3a**)

Reaction time 1 h. Yield 3.4 g (24%), beige solid, mp 128–130 °C (EtOH). $\nu_{max}$ (neat) 3482, 3361 3056, 2942, 1703, 1683, 1613, 1583, 1559, 1296, 1246, 1069 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.28 (2H, s), 6.58 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, brs), 6.80 (1H, dd, $J$ = 8.4, 1.0 Hz), 7.03 (1H, d, $J$ = 16.5 Hz), 7.29 (1H, ddd, $J$ = 8.6, 7.0, 1.7 Hz), 7.44–7.48 (3H, m), 7.74–7.77 (3H, m), 7.81 (1H, dd, $J$ = 8.1, 1.6 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.2, 108.1, 114.7, 116.5, 122.6, 128.5, 129.0, 130.7, 130.8, 134.1, 134.3, 143.0, 151.5, 166.6, 193.1 ppm. HRMS (HESI) calcd for ($C_{17}H_{16}NO_3^+$) $[M+H]^+$ 282.11247, found 282.11266.

### 4.5. (E)-4-(4-Methoxyphenyl)-2-oxobut-3-en-1-yl 2-amino-benzoate (**3b**)

Reaction time 18 h. Yield 3.6 g (23%), beige solid, mp 125–127 °C (EtOH). $\nu_{max}$ (neat) 3471, 3367, 2962, 1701, 1683, 1613, 1586, $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 3.81 (3H, s), 5.24 (2H, s), 6.57 (1H, ddd, $J$ = 8.1, 7.0, 1.2 Hz), 6.65 (1H, s), 6.80 (2H, dd, $J$ = 8.4, 0.9 Hz), 6.89 (1H, d, $J$ = 16.4 Hz), 7.02 (2H, d, $J$ = 8.8 Hz), 7.28 (1H, ddd, $J$ = 8.6, 7.0, 1.7 Hz), 7.69–7.73 (3H, m), 7.80 (1H, dd, $J$ = 8.1, 1.6 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 55.3, 67.1, 108.2, 114.5, 114.7, 116.5, 120.1, 126.6, 130.4, 130.7, 134.2, 143.0, 151.4, 161.4, 166.6, 192.8 ppm. HRMS (HESI) calcd for ($C_{18}H_{18}NO_4$)$^+$) $[M+H]^+$ 312.12303, found 312.12299.

### 4.6. (E)-2-Oxo-4-(p-tolyl)but-3-en-1-yl 2-aminobenzoate (**3c**)

Reaction time 18 h. Yield 4 g (27%), beige solid, mp 137–141 °C (toluene). $\nu_{max}$ (neat) 3480, 3359, 3023, 2942, 1701, 1684, 1614, 1584, 1560, 1245 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 2.34 (3H, s), 5.26 (2H, s), 6.56 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.8 Hz), 6.97 (1H, d, $J$ = 16.4 Hz), 7.26–7.31 (3H, m), 7.64 (2H, d, $J$ = 8.2 Hz), 7.71 (1H, d, $J$ = 16.4 Hz), 7.80 (1H, dd, $J$ = 8.1, 1.6 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 21.0, 67.2, 108.1, 114.7, 116.5, 121.6, 128.5, 128.5, 129.6, 130.7, 131.3, 134.3, 140.9, 143.1, 151.5, 166.6, 193.0 ppm. HRMS (HESI) calcd for ($C_{18}H_{18}NO_3^+$) $[M+H]^+$ 296.12812, found 296.12777.

### 4.7. (E)-4-(2-Chlorophenyl)-2-oxobut-3-en-1-yl 2-amino-benzoate (**3d**)

Reaction time 18 h. Yield 3.6 g (23%), yellow solid, mp 125–127 °C (toluene). $\nu_{max}$ (neat) 3483, 3370, 3063, 2917, 1708, 1689, 1608, 1593, 1296, 1246 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.27 (2H, s), 6.56 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.66 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.9 Hz), 7.15 (1H, d, $J$ = 16.2 Hz), 7.29 (1H, ddd, $J$ = 8.5, 7.0, 1.6 Hz), 7.43 (1H, dt, $J$ = 7.5, 1.4 Hz), 7.48 (1H, dt, $J$ = 7.8, 1.9 Hz), 7.57 (1H, dd, $J$ = 7.9, 1.4 Hz), 7.81 (1H, dd, $J$ = 8.1, 1.6 Hz), 7.93 (1H, d, $J$ = 16.2 Hz), 7.94–7.96 (1H, m) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.7, 108.0, 114.7, 116.5, 124.9, 127.8, 128.2, 130.1, 130.7, 131.7, 132.1, 134.2, 134.3, 137.2, 151.5, 166.5, 193.0 ppm. HRMS (HESI) calcd for ($C_{17}H_{15}ClNO_3^+$) $[M+H]^+$ 316.07350, found 316.07354.

### 4.8. (E)-4-(3-Chlorophenyl)-2-oxobut-3-en-1-yl 2-amino-benzoate (**3e**)

Reaction time 18 h. Yield 3.6 g (23%), yellow solid, mp 117–120 °C (toluene). $\nu_{max}$ (neat) 3456, 3357, 2938, 1694, 1607, 15866, 1560, 1375, 1290, 1242 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.27 (2H, s), 6.56 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.8 Hz), 7.13 (1H, d, $J$ = 16.4 Hz), 7.29 (1H, ddd, $J$ = 8.6, 7.0, 1.7 Hz), 7.46–7.53 (2H, m), 7.72 (2H, m), 7.80 (1H, dd, $J$ = 8.1, 1.6 Hz), 7.87 (1H, t, $J$ = 1.7 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.3, 108.1, 114.7, 116.5, 124.0, 127.1, 128.0, 130.3, 130.7, 133.7, 134.3, 136.4, 141.3, 151.5, 166.5, 193.0. HRMS (HESI) calcd for ($C_{17}H_{15}ClNO_3^+$) $[M+H]^+$ 316.07350, found 316.07345.

### 4.9. (E)-4-(4-Chlorophenyl)-2-oxobut-3-en-1-yl 2-amino-benzoate (**3f**)

Reaction time 5 h. Yield 4.1 g (26%), beige solid, mp 171–174 °C (toluene). $\nu_{max}$ (neat) 3480, 3359, 2944, 1702, 1683, 1612, 1584, 1560, 1485, 1382, 1292, 1244, 1067 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.25 (2H, s), 6.56 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.9 Hz), 7.05 (1H, d, $J$ = 16.4 Hz), 7.29 (1H, ddd, $J$ = 8.5, 7.0, 1.7 Hz), 7.52 (1H, d, $J$ = 8.5 Hz), 7.74 (2H, d, $J$ = 16.4 Hz), 7.77–7.81 (3H, m). $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.3, 108.1, 114.7, 116.5, 123.3, 129.0, 130.2, 130.7, 133.1, 134.3, 135.3, 141.6, 151.5, 166.5, 193.0 ppm. HRMS (HESI) calcd for ($C_{17}H_{15}ClNO_3^+$) $[M+H]^+$ 316.07350, found 316.07365.

### 4.10. (E)-4-(4-Nitrophenyl)-2-oxobut-3-en-1-yl 2-aminobenzoate (**3g**)

Reaction time 1 h. Yield 5.2 g (23%), orange solid, mp 176–179 °C (2-methoxyethanol). $\nu_{max}$ (neat) 3483, 3373, 2914, 1688, 1616, 1592, 1567, 1343, 1234, 1104 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.31 (2H, s), 6.57 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.8 Hz), 7.22 (1H, d, $J$ = 16.5 Hz), 7.29 (1H, ddd, $J$ = 8.5, 7.0, 1.7 Hz), 7.80 (1H, dd, $J$ = 8.1, 1.6 Hz), 7.85 (1H, d, $J$ = 16.5 Hz), 8.03 (2H, d, $J$ = 8.8 Hz), 8.29 (2H, d, $J$ = 8.9 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.4, 108.0, 114.7, 116.5, 124.0, 126.3, 129.5, 130.7, 134.3, 140.2, 140.6, 148.2, 151.5, 166.5, 193.2 ppm. HRMS (HESI) calcd for ($C_{17}H_{15}N_2O_5^+$) $[M+H]^+$ 327.09729, found 327.09755.

### 4.11. (3E,5E)-2-Oxo-6-phenylhexa-3,5-dien-1-yl 2-amino-benzoate (**3h**)

Reaction time 5 h. Yield 5.2 g (34%), yellow solid, mp 137–139 °C (toluene/EtOH). $\nu_{max}$ (neat) 3458, 3352, 2947, 1698, 1680, 1611, 1600, 1588, 1567, 1461, 1324, 1268, 1072 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.19 (2H, s), 6.46 (1H, d, $J$ = 15.6 Hz), 6.57 (1H, ddd, $J$ = 8.1, 7.0, 1.2 Hz), 6.66 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.8 Hz), 7.13–7.22 (2H, m), 7.29 (1H, ddd, $J$ = 8.5, 7.0, 1.7 Hz), 7.33–7.43 (3H, m), 7.52 (1H, ddd, $J$ = 15.6, 7.6, 2.6 Hz), 7.55–7.62 (2H, m), 7.80 (1H, dd, $J$ = 8.1, 1.6 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 67.1, 108.1, 114.7, 116.5, 125.5, 126.9, 127.3, 128.8, 129.3, 130.7, 134.3, 135.7, 142.0, 143.7, 151.5, 166.6, 193,0 ppm. HRMS (HESI) calcd for ($C_{19}H_{18}NO_3^+$) $[M+H]^+$ 308.12812, found 308.12828.

### 4.12. (E)-2-Oxo-4-(thiophen-2-yl)but-3-en-1-yl 2-amino-benzoate (**3i**)

Reaction time 4 h. Yield 5.7 g (40%), beige solid, mp 127–130 °C (EtOH). $\nu_{max}$ (neat) 3484, 3365, 2944, 1698, 1681, 1600, 1581, 1558, 1412, 1243, 1160 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 5.22 (2H, s), 6.56 (1H, ddd, $J$ = 8.1, 7.0, 1.1 Hz), 6.65 (2H, s), 6.70 (1H, d, $J$ = 16.0 Hz), 6.79 (1H, dd, $J$ = 8.4, 0.8 Hz), 7.19 (1H, dd, $J$ = 5.1,

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3.6 Hz), 7.28 (1H, ddd, $J$ = 8.5, 7.0, 1.7 Hz), 7.61 (1H, ddd, $J$ = 3.7, 0.6, 0.5 Hz), 7.78–7.80 (2H, m), 7.91 (1H, d, $J$ = 16.0 Hz) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 67.2, 108.1, 114.7, 116.5, 120.7, 128.7, 130.6, 130.7, 133.1, 134.3, 135.8, 139.1, 151.5, 166.5, 192.5 ppm. HRMS (HESI) calcd for ($C_{15}H_{14}NO_3S^+$) $[M+H]^+$ 288.06889, found 288.06920.

### 4.13. 4-Methyl-2-oxopent-3-en-1-yl 2-aminobenzoate (**3j**)

Reaction time 3 h. Yield 1.2 g (10%), beige solid, mp 56–59 °C ($Et_2O$/cyclohexane). $\nu_{max}$ (neat) 3458, 3347, 2924, 1689, 1615, 1584, 1565, 1239, 1102 cm$^{-1}$; 1H NMR (399.9 MHz, DMSO-$d_6$) δ: 1.91 (3H, d, $J$ = 1.1 Hz), 2.11 (3H, d, $J$ = 1.0 Hz), 4.92 (2H, s), 6.21–6.22 (1H, m), 6.55 (1H, ddd, $J$ = 8.1, 7.0, 1.2 Hz), 6.63 (2H, s), 6.78 (1H, dd, $J$ = 8.4, 0.8 Hz), 7.27 (1H, ddd, $J$ = 8.5, 7.0, 1.7 Hz), 7.77 (1H, dd, $J$ = 8.1, 1.6 Hz) ppm. 13C NMR (100.56 MHz, DMSO-$d_6$) δ: 20.6, 27.3, 68.6, 108.2, 114.7, 116.5, 119.2, 130.7, 134.2, 151.4, 157.4, 166.5, 193.0 ppm. HRMS (HESI) calcd for ($C_{13}H_{16}NO_3^+$) $[M+H]^+$ 234.11247, found 216.10191.

### 4.14. Procedure for the preparation of chloroketone **7k**

Chloroketone **7k** was prepared according to the literature:[25] Ylide **5** and pyridine-2-carbaldehyde (15.1 mmol, 1.44 mL) were stirred at room temperature in $CH_2Cl_2$ (30 mL). The reaction mixture was concentrated, and the residue was dissolved in hot EtOAc. Solution was filtered and cooled down to 0 °C. The resulting white crystalline solid was filtered off and the filtrate was concentrated. The obtained residue was purified by column chromatography (petroleum ether: EtOAc 4:1). Yield 1.64 g, 60%, pale yellow solid, mp 46–48 °C (ref.[25] gave 48–49 °C).

### 4.15. Procedure for the preparation of (E)-2-oxo-4-(pyridin-2-yl) but-3-en-1-yl 2-aminobenzoate (**3k**)

Chloroketone **7k** (1.35 g, 7.25 mmol) was dissolved in DMF (5 mL) and added drop wise over 5 min to the solution of anthranilic acid (7.25 mmol; 1.00 g) and triethylamine (7.25 mmol; 1 mL) in DMF (10 mL) at room temperature. The resulting mixture was stirred at room temperature for 24 h. The reaction mixture was poured into water with crushed ice (150 mL), the resulting suspension was filtered, and the cake was thoroughly washed with water and dried. Crude anthranilate was purified by crystallization with MeOH. Yield 1.23 g (60%), beige solid, mp 110 °C. $\nu_{max}$ (neat) 3472, 3361, 2934, 1689, 1669, 1614, 1580, 1562, 1372, 1214, 1106 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 5.31 (2H, s), 6.57 (1H, ddd, $J$ = 7.7, 7.4, 1.0 Hz), 6.66 (2H, s), 6.80 (1H, dd, $J$ = 8.4, 0.6 Hz), 7.27–7.31 (1H, m), 7.30 (1H, d, $J$ = 16.0 Hz), 7.44 (1H, ddd, $J$ = 7.6, 4.8, 1.0 Hz), 7.72–7.81 (3H, m), 7.90 (1H, dt, $J$ = 7.7, 1.8 Hz), 8.68 (1H, dd, $J$ = 4.7, 1.0 Hz) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 67.5, 108.0, 114.7, 116.5, 125.0, 125.3 (2×), 130.7, 134.3, 137.3, 141.9, 150.1, 151.5, 152.1, 166.5, 193.5 ppm. HRMS (HESI) calcd for ($C_{16}H_{15}N_2O_3^+$) $[M+H]^+$ 283.10772, found 283.10788.

### 4.16. Procedure for the preparation of 2-oxo-3-(triphenyl-λ5-phosphanylidene)propyl 2-amino-benzoate (**8**)

Ylide **5** (0.172 mol, 60.6 g) was added into a solution of anthranilic acid (0.183 mol, 25.1 g) and triethylamine (0.183 mol, 25.2 mL) in DMF (400 mL). After stirring for 3.5 h at 95–100 °C, the reaction mixture was slowly poured into the water (2 L). After 30 min of stirring, the suspension was filtered and washed with water and then thoroughly washed with EtOH (3×100 mL). Crystallization from DMF gave pure anthranilate **8**. Yield 42 g (54%), beige solid, mp 224 °C. $\nu_{max}$ (neat) 3465, 3333, 2930, 1695, 1613, 1569, 1540, 1462, 1319, 1232, 1102 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 3.80 (1H, d, $J$ = 23.7 Hz), 4.65 (2H, s), 6.52 (1H, dt, $J$ = 7.6, 1.1 Hz), 6.66 (2H, s), 6.76 (1H, dd, $J$ = 8.3, 0.9 Hz), 7.24 (1H, dt, $J$ = 7.8, 1.8 Hz), 7.54–7.68 (15H, m), 7.77 (1H, dd, $J$ = 8.1, 1.8 Hz) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 46.8 (d, $J$ = 110.2 Hz), 66.6 (d, $J$ = 16.9 Hz), 109.0, 114.7, 116.4, 126.2 (d, $J$ = 90.7 Hz), 129.0 (d, $J$ = 11.9 Hz), 130.6, 132.0, 132.6 (d, $J$ = 10.2 Hz), 133.9 (d, $J$ = 10.2 Hz), 151.2, 166.9, 185.0 ppm. $^{31}$P NMR (161.92 MHz, DMSO-$d_6$) δ: 15.13 ppm. HRMS (HESI) calcd for ($C_{28}H_{25}NO_3P^+$) $[M+H]^+$ 454.15666, found 454.15633.

### 4.17. Procedure for the preparation of quinolones **4a–k**

Anthranilates **3a–k** (0.01 mol) was refluxed in trifluoroacetic acid (25 mL) until initial anthranilates were consumed (TLC monitoring). The reaction mixture was concentrated, and thick residue was poured into ice-cold water (50 mL). The suspension was filtered; filtration cake was thoroughly washed with water and purified by crystallization.

### 4.18. (E)-3-Hydroxy-2-styrylquinolin-4(1H)-one (**4a**)

Reaction time 14 h. Yield 2.2 g (83%), yellow solid, mp 281–284 °C (DMF). $\nu_{max}$ (neat) 3061, 2935, 1636, 1625, 1582, 1542, 1467, 1400, 1370, 1221 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.23 (dt, 1H, $J$ = 7.5, 0.8 Hz), 7.36 (1H, tt, $J$ = 7.3, 1.9 Hz), 7.42–7.47 (m, 3H), 7.59 (1H, ddd, $J$ = 8.4, 6.9, 1.5 Hz), 7.64–7.68 (3H, m), 7.71 (1H, d, $J$ = 8.4 Hz), 8.12 (1H, dd, $J$ = 8.2, 1.3). 8.85 (1H, brs), 11.30 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.9 (2×), 121.5, 121.8, 124.4, 126.8, 128.7, 128.8, 129.0, 130.8, 133.0, 136.1, 137.9, 138.9, 169.7. HRMS (HESI) calcd for ($C_{17}H_{14}NO_2^+$) $[M+H]^+$ 264.10245, found 264.10202.

### 4.19. (E)-3-Hydroxy-2-(4-methoxystyryl)quinolin-4(1H)-one (**4b**)

Reaction time 28 h. Yield 1.6 g (53%), solid, mp 285–289 °C (2-methoxyethanol). $\nu_{max}$ (neat) 3306, 2776, 1648, 1626, 1587, 1544, 1509, 1484, 1469, 1368, 1297, 1245 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 3.8 (3H, s), 7.01 (2H, d, $J$ = 8.8 Hz), 7.20–7.24 (1H, m), 7.27 (1H, d, $J$ = 16.8 Hz), 7.56–7.62 (4H, m), 7.70 (1H, d, $J$ = 8.4 Hz), 8.10 (1H, dd, $J$ = 8.2, 1.3 Hz), 8.74 (1H, brs), 11.23 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 55.2, 114.5, 115.5, 117.8, 121.4, 121.8, 124.3, 128.3, 128.7, 129.3, 130.6, 132.8, 137.8, 138.5, 159.8, 169.5 ppm. HRMS (HESI) calcd for ($C_{18}H_{16}NO_3^+$) $[M+H]^+$ 294.11247, found 294.11263.

### 4.20. (E)-3-Hydroxy-2-(4-methylstyryl)quinolin-4(1H)-one (**4c**)

Reaction time 8 h. Yield 1.6 g (58%), yellow solid, mp 287–291 °C (DMF/EtOH). $\nu_{max}$ (neat) 3373, 2840, 1646, 1625, 1593, 1542, 1511, 1447, 1327, 1237, 1209 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 2.33 (3H, s), 7.21–7.25 (1H, m), 7.25–7.27 (2H, m), 7.37 (1H, d, $J$ = 16.8 Hz), 7.54 (2H, d, $J$ = 8.1 Hz), 7.56–7.61 (1H, m), 7.62 (1H, d, $J$ = 16.8 Hz), 7.70 (1H, d, $J$ = 8.3 Hz), 8.08 (1H, brs), 8.11 (1H, dd, $J$ = 8.2, 1.4 Hz), 11.26 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 20.8, 116.9, 117.9, 121.4, 121.8, 124.3, 126.8, 126.8, 129.0, 129.6, 130.7, 133.0, 133.4, 137.8, 138.4, 138.7, 169.6 ppm. HRMS (HESI) calcd for ($C_{18}H_{16}NO_2^+$) $[M+H]^+$ 278.11756, found 278.11803.

### 4.21. (E)-2-(2-Chlorostyryl)-3-hydroxyquinolin-4(1H)-one (**4d**)

Reaction time 8 h. Yield 1.9 g (64%), yellow solid, mp 283–288 °C (2-Methoxyethanol). $\nu_{max}$ (neat) 3297, 2770, 1646, 1621, 1583, 1562, 1541, 1472, 1482 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.24 (1H, ddd, $J$ = 8.0, 6.8, 1.0 Hz), 7.37–7.46 (2H, m), 7.43 (1H, d, $J$ = 16.6 Hz), 7.55 (1H, dd, $J$ = 7.8, 1.5 Hz), 7.60 (1H, ddd, $J$ = 8.5, 6.8, 1.5 Hz), 7.72

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(1H, d, $J$ = 8.4 Hz), 7.88 (1H, dd, $J$ = 7.7, 1.8 Hz), 7.97 (1H, d, $J$ = 16.6 Hz), 8.12 (1H, dd, $J$ = 8.2, 1.4 Hz), 9.00 (1H, brs), 11.41 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 118.0, 121.4, 121.6, 121.8, 124.4, 127.1, 127.8, 128.2, 128.8, 129.9, 130.1, 130.9, 132.6, 134.3, 137.9, 139.4, 169.9 ppm. HRMS (HESI) calcd for ($C_{17}H_{13}ClNO_2^+$) $[M+H]^+$ 298.06293, found 298.06277.

### 4.22. (E)-2-(3-Chlorostyryl)-3-hydroxyquinolin-4(1H)-one (**4e**)

Reaction time 8 h. Yield 2.1 g (71%), yellow solid, mp 290–294 °C (2-Methoxyethanol). $\nu_{max}$ (neat) 3350, 2897, 1646, 1626, 1549, 1509, 1482, 1466, 1421, 1263, 1238, 1205 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.23 (1H, dd, $J$ = 7.6, 7.4 Hz), 7.40–7.50 (3H, m), 7.57–7.63 (3H, m), 7.66–7.72 (2H, m), 8.11 (1H, dd, $J$ = 8.2, 1.4 Hz), 8.96 (1H, brs), 11.28 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.9, 119.8, 121.6, 121.8, 124.4, 125.6, 126.2, 128.3 (2×), 130.8, 130.9, 131.5, 133.8, 137.9, 138.4, 139.2, 169.8. HRMS (HESI) calcd for ($C_{17}H_{13}ClNO_2^+$) $[M+H]^+$ 298.06293, found 298.06298.

### 4.23. (E)-2-(4-Chlorostyryl)-3-hydroxyquinolin-4(1H)-one (**4f**)

Reaction time 8 h. Yield 2.4 g (80%), yellow solid, mp 315–319 °C (2-Methoxyethanol). $\nu_{max}$ (neat) 3276, 2784, 1651, 1625, 1585, 1567, 1452, 1477, 1435, 1319, 1205, 1089, 1008 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.23 (1H, ddd, $J$ = 7.8, 7.2, 0.8 Hz), 7.43 (1H, d, $J$ = 16.7 Hz), 7.49 (2H, d, $J$ = 8.5 Hz), 7.57–7.70 (5H, m), 8.11 (1H, dd, $J$ = 8.2, 1.3 Hz), 8.90 (1H, brs), 11.28 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.9, 118.8, 121.5, 121.8, 124.4, 128.5 (2×), 129.0, 130.8, 131.6, 133.0, 135.1, 137.9, 139.1, 169.8. HRMS (HESI) calcd for ($C_{17}H_{13}ClNO_2^+$) $[M+H]^+$ 298.06293, found 298.06303.

### 4.24. (E)-3-Hydroxy-2-(4-nitrostyryl)quinolin-4(1H)-one (**4g**)

Reaction time 4 h. Yield 1.3 g (76%), orange solid, mp 326–331 °C (DMF). $\nu_{max}$ (neat) 3111, 1592, 1542, 1509, 1483, 1470, 1420, 1333, 1276, 1232, 1207, 1104 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.24 (1H, ddd, $J$ = 8.1, 6.8, 1.1 Hz), 7.60–7.71 (3H, m), 7.74 (1H, d, $J$ = 16.8 Hz), 7.91 (2H, d, $J$ = 8.9 Hz), 8.11 (1H, dd, $J$ = 8.2, 1.4 Hz), 8.28 (2H, d, $J$ = 8.9 Hz), 11.32 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.9, 121.6, 121.8, 122.4, 124.2 (2×), 124.4, 127.8, 127.8, 127.8, 130.5, 131.1, 138.0, 139.8, 142.7, 146.8, 170.0 ppm. HRMS (HESI) calcd for ($C_{17}H_{13}N_2O_4^+$) $[M+H]^+$ 309.08698, found 309.08728.

### 4.25. 3-Hydroxy-2-((1E,3E)-4-phenylbuta-1,3-dien-1-yl)-quinolin-4(1H)-one (**4h**)

Reaction time 24 h. Yield 1.8 g (63%), yellow solid, mp 284–288 °C (2-Methoxyethanol). $\nu_{max}$ (neat) 3346, 2836, 1635, 1613, 1545, 1477, 1448, 1421, 1370, 1246 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 6.88 (1H, d, $J$ = 16.6 Hz), 7.01 (1H, d, $J$ = 15.8 Hz), 7.2–7.31 (3H, m), 7.38 (2H, t, $J$ = 7.5 Hz), 7.52 (1H, dd, $J$ = 15.8, 10.7 Hz), 7.55–7.61 (3H, m), 7.69 (1H, d, $J$ = 8.4 Hz), 8.09 (1H, dd, $J$ = 8.2, 1.3 Hz), 8.80 (1H, brs), 11.21 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.8, 121.4, 121.7, 121.8, 124.3, 126.7 (2×), 128.2, 128.7 (2×), 128.9, 130.7, 134.2, 136.6, 137.9, 138.8, 169.5 ppm. HRMS (HESI) calcd for ($C_{19}H_{16}NO_2^+$) $[M+H]^+$ 290.11756, found 290.11741.

### 4.26. (E)-3-Hydroxy-2-(2-(thiophen-2-yl)vinyl)quinolin-4(1H)-one (**4i**)

Reaction time 18 h. Yield 1.0 g (36%), orange solid, mp 285–288 °C (2-Methoxyethanol/EtOH). $\nu_{max}$ (neat) 3332, 2787, 1630, 1613, 1583, 1542, 1468, 1445, 1428, 1400, 1233, 1207 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.11–7.15 (2H, m), 7.22 (1H, dd, $J$ = 7.7, 7.3 Hz), 7.36 (1H, d, $J$ = 3.3 Hz), 7.58 (1H, ddd, $J$ = 7.6, 6.9, 1.4 Hz), 7.62–7.67 (2H, m), 7.87 (1H, d, $J$ = 16.4 Hz), 8.10 (1H, dd, $J$ = 8.2, 1.4 Hz), 8.88 (1H, brs), 11.27 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.0,117.8, 121.5, 121.7, 124.4, 126.7, 127.1, 128.4 (2×), 128.5, 130.8, 137.8, 138.8, 141.5, 169.5 ppm. HRMS (HESI) calcd for ($C_{15}H_{12}NO_2S^+$) $[M+H]^+$ 270.05833, found 270.05817.

### 4.27. 3-Hydroxy-2-(2-methylprop-1-en-1-yl)quinolin-4(1H)-one (**4j**)

Reaction time 17 h. Yield 0.9 g (41%), almost white solid, mp 211–215 °C (MeOH/$Et_2O$). $\nu_{max}$ (neat) 3281, 2913, 1634, 1583, 1547, 1486, 1459, 1442, 1418, 1366, 1244, 1099 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 1.76 (3H, d, $J$ = 0.9 Hz), 1.95 (3H, d, $J$ = 1.2 Hz), 6.19–6.21 (1H, m), 7.21 (1H, ddd, $J$ = 6.4, 6.0, 1.5 Hz), 7.49–7.58 (2H, m), 8.10 (1H, dd, $J$ = 7.9, 1.1 Hz), 8.13 (1H, brs), 11.26 (1H, brs) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 20.4, 25.7, 115.9, 117.9, 121.4, 121.8, 124.3, 130.1, 130.2, 137.4, 137.8, 142.1, 169.3 ppm. HRMS (HESI) calcd for ($C_{13}H_{14}NO_2^+$) $[M+H]^+$ 216.10191, found 216.10191.

### 4.28. (E)-3-Hydroxy-2-(2-(pyridin-2-yl)vinyl)quinolin-4(1H)-one (**4k**)

Reaction time 7 h. Yield 1.74 g (66%), orange solid, mp 290–295 °C (2-Methoxyethanol). $\nu_{max}$ (neat) 3061, 2936, 1640, 1624, 1588, 1545, 1493, 1480, 1470, 1443, 1426, 1405, 1375, 1244, 1202 cm$^{-1}$; $^1$H NMR (399.9 MHz, DMSO-$d_6$) δ: 7.24 (1H, ddd, $J$ = 8.0, 6.8, 1.0 Hz), 7.34 (1H, ddd, 7.6, 4.8, 1.0 Hz), 7.57–7.62 (2H, m), 7.70–7.75 (2H, m), 7.85 (1H, dt, $J$ = 7.7, 1.8 Hz), 7.97 (1H, d, $J$ = 16.3 Hz), 8.11 (1H, dd, $J$ = 8.2, 1.3 Hz), 8.65 (1H, ddd, $J$ = 4.7, 0.9, 0.6 Hz), 11.38 (1H, s) ppm. $^{13}$C NMR (100.56 MHz, DMSO-$d_6$) δ: 117.9, 121.6, 121.7, 121.8, 123.2, 123.2, 124.4, 128.1, 130.9, 132.3, 137.2, 138.0, 139.7, 149.8, 153.9, 169.9 ppm. HRMS (HESI) calcd for ($C_{16}H_{13}N_2O_3^+$) $[M+H]^+$ 265.09715, found 265.09727.

### 4.29. Procedure for the preparation of quinolones **4l**–**o**

Ylide **5** (14.2 mmol, 5 g) and aldehyde **6m**–**o** (28.4 mmol) were refluxed in dry 1,2-dichloroethane (25 mL) under a nitrogen atmosphere until the disappearance of **5** (TLC monitoring). In the case of **6l**, excess of **6l** (15 mL) was used as the solvent and the reaction mixture was heated in a glass sealed tube at 35 °C until complete dissolution of **5** (11 h). The reaction mixture was concentrated, and the obtained residue was dissolved in hot EtOAc. The solution was filtered and cooled to 0 °C. The resulting white crystalline solid was filtered off, and the filtrate was concentrated. The residue was vacuum distilled yielding chloroketone **7l**–**m**, which was used immediately in the next reaction step.

Crude chloroketone **7l**–**m** was dissolved in DMF (5 mL), and the solution was added drop wise over 30 min to the cold (−5 °C) suspension of potassium anthranilate (9.8 mmol) in DMF (10 mL) prepared according to the literature.[3] The reaction mixture was further stirred at −5 °C. After starting materials were consumed (TLC monitoring), the reaction mixture was poured into ice-cold water (150 mL) and extracted with diethylether (2 × 50 mL). The combined organic layers were washed with cold water (2 × 50 mL) and dried over $Na_2SO_4$ and rotavaped at 20 °C. The residue was immediately dissolved in trifluoroacetic acid (20 mL) and refluxed until the disappearance of intermediate **3** (TLC monitoring). The reaction mixture was concentrated, and the residue was diluted with EtOAc and cooled to −15 °C. The resulting suspension was filtered and washed with cold EtOAc. Crude product was purified by crystallization.

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### 4.30. (E)-3-Hydroxy-2-(prop-1-en-1-yl)quinolin-4(1H)-one (**4l**)

Reaction time 11 h. Yield 343 mg (12%), pale yellow solid, mp 284–288 °C (MeOH). $\nu_{max}$ (neat) 3300, 3054, 2967, 1652, 1626, 1579, 1544, 1466, 1407, 1368, 1237 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 1.97 (3H, dd, $J$ = 6.4, 1.3 Hz), 6.69 (1H, dd, $J$ = 16.2, 1.4 Hz), 6.80 (1H, dq, $J$ = 16.2, 6.4 Hz), 7.20 (1H, ddd, $J$ = 8.1, 6.9, 1.0 Hz), 7.55 (1H, ddd, $J$ = 8.5, 6.8, 1.5 Hz), 7.66 (1H, d, $J$ = 8.4 Hz), 8.08 (1H, dd, $J$ = 8.2, 1.4 Hz), 11.09 (1H, s) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 18.8, 117.9, 121.0, 121.4, 121.7, 124.3, 129.0, 130.5, 132.2, 137.6 (2×), 169.6 ppm. HRMS (HESI) calcd for ($C_{12}H_{12}NO_2^+$) $[M+H]^+$ 202.08626, found 202.08630.

### 4.31. (E)-2-(But-1-en-1-yl)-3-hydroxyquinolin-4(1H)-one (**4m**)

Reaction time 8 h. Yield 306 mg (10%), pale yellow solid, mp 274–276 °C (MeOH). $\nu_{max}$ (neat) 3259, 2970, 1652, 1626, 1580, 1544, 1466, 1400, 1368, 1233 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 1.11 (3H, t, $J$ = 7.4 Hz), 2.29–2.37 (2H, m), 6.67 (1H, td, $J$ = 16.3, 1.5 Hz), 6.85 (1H, td, $J$ = 16.3, 6.4 Hz), 7.21 (1H, ddd, $J$ = 8.0, 7.0, 1.0 Hz), 7.55 (1H, ddd, $J$ = 8.5, 6.9, 1.5 Hz), 7.67 (1H, d, $J$ = 8.3 Hz), 8.49 (1H, brs), 11.08 (1H, s) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 13.0, 25.9, 117.9, 118.8, 121.4, 121.7, 124.3, 128.9, 130.5, 137.7 (2×), 138.5, 169.6 ppm. HRMS (HESI) calcd for ($C_{13}H_{14}NO_2^+$) $[M+H]^+$ 216.10191, found 216.10186.

### 4.32. (E)-3-Hydroxy-2-(pent-1-en-1-yl)quinolin-4(1H)-one (**4n**)

Reaction time 6 h. Yield 260 mg (8%), pale yellow solid, mp 244–248 °C (MeOH/EtOAc). $\nu_{max}$ (neat) 3239, 2951, 2865, 1655, 1627, 1581, 1547, 1476, 1401, 1369, 1233 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 0.96 (3H, t, $J$ = 7.4 Hz), 1.48–1.57 (2H, m), 2.26–2.32 (2H, m), 6.68 (1H, td, $J$ = 16.3, 1.2 Hz), 6.80 (1H, td, $J$ = 16.3, 6.7 Hz), 7.21 (1H, ddd, $J$ = 8.0, 6.9, 1.0 Hz), 7.55 (1H, ddd, $J$ = 8.5, 6.8, 1.5 Hz), 7.67 (1H, d, $J$ = 8.3 Hz), 8.08 (1H, dd, $J$ = 8.2, 1.3 Hz) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 13.6, 21.6, 34.9, 117.8, 119.9, 121.4, 121.7, 124.3, 128.8, 130.5, 136.8, 137.7 (2X), 169.6. HRMS (HESI) calcd for ($C_{14}H_{16}NO_2^+$) $[M+H]^+$ 230.11756, found 230.11759.

### 4.33. (E)-2-(Hept-1-en-1-yl)-3-hydroxyquinolin-4(1H)-one (**4o**)

Reaction time 5 h. Yield 256 mg (7%), pale yellow solid, mp 208–212 °C (EtOAc). $\nu_{max}$ (neat) 3067, 2950, 2922, 2852, 1655, 1640, 1583, 1548, 1488, 1426, 1431, 1369, 1228 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 0.89 (3H, t, $J$ = 7.0 Hz), 1.29–1.37 (4H, m), 1.50 (2H, p, $J$ = 7.1 Hz), 2.30 (2H, q, $J$ = 6.9 Hz), 6.67 (1H, d, $J$ = 16.3 Hz), 6.80 (1H, td, $J$ = 16.1, 6.7 Hz), 7.20 (1H, dd, $J$ = 7.6, 7.4 Hz), 7.55 (1H, ddd, $J$ = 7.7, 7.6, 1.2 Hz), 7.67 (1H, d, $J$ = 8.4 Hz), 8.49 (1H, brs), 11.06 (1H, s) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 13.8, 21.9, 28.0, 30.7, 32.8, 117.8, 119.7, 121.4, 121.7, 124.3, 128.8, 130.5, 137.1, 137.6, 137.7, 169.6 ppm. HRMS (HESI) calcd for ($C_{16}H_{20}NO_2^+$) $[M+H]^+$ 258.14886, found 258.14900.

### 4.34. Procedure for the preparation of 2-alkyl quinolones **9**

A suspension of quinolone **4a** or **4h** (75 mmol) and 10% Pd/C (50 mg) in 2-methoxyethanol (30 mL) was stirred vigorously under hydrogen atmosphere at 40 °C for 5 h. The reaction mixture was filtered, and most of the solvent was evaporated. The resulting suspension was diluted with EtOH and left in refrigerator overnight. White crystals of **9** were filtered off, washed with small amount of cold EtOH and dried in vacuum.

### 4.35. 3-Hydroxy-2-phenethylquinolin-4(1H)-one (**9a**)

Yield 120 mg (60%), almost white solid, mp 249–253 °C. $\nu_{max}$ (neat) 3064, 2980, 1632, 1593, 1533, 1482, 1468, 1437, 1403, 1371, 1251 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 2.95–3.05 (4H, m), 7.18–7.32 (6H, m), 7.51–7.57 (2H, m), 8.10 (1H, d, $J$ = 8.1 Hz), 8.18 (1H, brs), 11.48 (1H, s) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 30.1, 33.4, 117.7, 121.5, 122.2, 124.4, 126.0, 128.1, 128.3, 130.0, 134.4, 137.3, 137.9, 140.7, 168.9 ppm. HRMS (HESI) calcd for ($C_{17}H_{16}NO_2^+$) $[M+H]^+$ 266.11756, found 266.11769.

### 4.36. 3-Hydroxy-2-(4-phenylbutyl)quinolin-4(1H)-one (**9h**)

Yield 163 mg (74%), almost white solid, mp 255–259 °C. $\nu_{max}$ (neat) 3287, 3023, 2791, 1638, 1599, 1557, 1488, 1448, 1414, 1368, 1237 $cm^{-1}$; $^1H$ NMR (399.9 MHz, DMSO-$d_6$) δ: 1.58–1.74 (4H, m), 2.62 (2H, t, $J$ = 7.5 Hz), 2.77 (2H, t, $J$ = 7.2 Hz), 7.13–7.27 (6H, m), 7.51–7.55 (2H, m), 8.09 (1H, d, $J$ = 7.9 Hz), 8.09 (1H, brs), 11.44 (1H, s) ppm. $^{13}C$ NMR (100.56 MHz, DMSO-$d_6$) δ: 27.4, 27.8, 30.8, 34.9, 117.7, 121.4, 122.1, 124.4, 125.6, 128.2 (2×), 129.9, 135.2, 137.3, 137.8, 142.0 ppm. HRMS (HESI) calcd for ($C_{19}H_{20}NO_2^+$) $[M+H]^+$ 294.14886, found 294.14859.

### 4.37. Fluorescence properties

The absorbance, excitation and emission fluorescence spectra of the studied compounds were measured with a UV–vis spectrophotometer Cary 300 (Agilent Technologies) and a fluorescence spectrometer Cary Eclipse (Varian). The methanolic solution of an individual compound at a concentration of 100 μg/mL were measured.

### 4.38. Agar diffusion test

Overnight cultures of test organisms were grown in LB broth for 18–24 h, and standard suspensions of ~1.5 × 108 cfu/mL were prepared in sterile saline solution (0.9% NaCl) according to a $BaSO_4$ 0.5 McFarland Standard. Of this standardized suspension, 0.1 mL was added to 34 mL of sterile, melted, and tempered (47–50 °C) Mueller-Hinton No. 2 agar. After gentle mixing, the inoculated melted agar was poured into a sterile petri dish (145 mm × 20 mm, Greiner Bio-One) and allowed to solidify next to the flame with lids slightly ajar. The wells of 9 mm diameter were cut from the petri dish agar and filled with 50 μL of the test sample solution. The test solutions were made at 20 mM in DMSO and diluted in MeOH to obtain a final concentration of 2 mM. The petri dish was incubated at 37 °C for 18–24 h, and the inhibition zone diameters were measured (mm) with an electronic caliper after 24–48 h.

### 4.39. MIC determination

Antibacterial activity of the compounds was determined by measuring their MIC using the broth microdilution method. Each well of a 96-well microtiter plate was filled with 50 μL of sterile iron deficient MH2 broth. Each test compound was dissolved in DMSO making a 10 mM solution, and then diluted with sterile MH2 broth to 800 μM. Exactly 50 μL of the compound solution was added to the first well of the microtiter plate, and 2-fold serial dilutions were made down each row of the plate. A pre culture of bacteria was grown in Luria-Bertani broth overnight at 37 °C. This was diluted to McFarland standard 0.5 (1.5 × 108 CFU) with saline. 100 μL of the bacterial suspension was further diluted with 14.9 mL of MH2 broth. Exactly 50 μL of bacterial (IN BROTH) inoculum (1 × 106 CFU/mL) was added to each well giving a total volume of 100 μL/well, 5 × 105 CFU/mL and a compound concentration gradient of

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200–0.1 μM. The plate was incubated at 37 °C. After 18 h, each well was examined visually for bacterial growth. The MIC was recorded as the lowest compound concentration required to inhibit bacterial growth as judged by turbidity relative to a row of wells diluted with the solvent DMSO as a growth control. Ciprofloxacin was included in a control row at a concentration gradient of 5 μg/mL-0.0025 μg/L.

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## Appendix A. Supplementary data

Supplementary data related to this article can be found at https://doi.org/10.1016/j.tet.2017.12.010.

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