## **RSC** Advances



View Article Online

View Journal | View Issue

## PAPER

Check for updates

Cite this: RSC Adv., 2023, 13, 14631

Received 16th March 2023 Accepted 28th April 2023 DOI: 10.1039/d3ra01721d

rsc.li/rsc-advances

#### 1. Introduction

Thiazinanones, despite their an appropriate term, are very interesting because of their significant role in pharmaceutical chemistry.<sup>1-3</sup> Substituted thiazinanones displayed antitumor,<sup>4</sup> antifungal<sup>5</sup> and antimalarial activity which was assessed by Kumawat *et al.*,<sup>6</sup> as well as anti-oxidant activity.<sup>7</sup> Thiazinanone derivatives were obtained through a multicomponent condensation or a two-step process involving an amine, mercapto acid, and carbonyl compounds.<sup>5</sup> 3-Alkyl-2-aryl-1,3-thiazinan-4-ones with methylsulfonyl pharmacophore exhibited inhibition activity against cyclooxygenase-2-[COX-2].<sup>8</sup> As well, 3-pyridin-2-ylmethyl-1,3-thiazinan-4-ones displayed anti-oxidant

# Novel quinoline/thiazinan-4-one hybrids; design, synthesis, and molecular docking studies as potential anti-bacterial candidates against MRSA\*

Asmaa H. Mohamed,<sup>a</sup> Sara M. Mostafa, <sup>b</sup><sup>a</sup> Ashraf A. Aly, <sup>b</sup>\*<sup>a</sup> Alaa A. Hassan,<sup>a</sup> Esraa M. Osman,<sup>a</sup> AbdElAziz A. Nayl,<sup>b</sup> Alan B. Brown <sup>b</sup><sup>c</sup> and Elshimaa M. N. Abdelhafez <sup>b</sup><sup>d</sup>

In an attempt to develop effective and safe antibacterial agents, we synthesized novel thiazinanones by combining the quinolone scaffold and the 1,3-thiazinan-4-one group by reaction between ((4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazinecarbothioamides and 2,3-diphenylcycloprop-2-enone in refluxing ethanol in the presence of triethyl amine as a catalyst. The structure of the synthesized compounds was characterized by spectral data and elemental analysis, IR, MS, <sup>1</sup>H and <sup>13</sup>C NMR spectroscopy which showed two doublet signals for CH-5 and CH-6 and four sharp singlets for the protons of thiazinane NH, CH=N, quinolone NH and OH, respectively. Also, the <sup>13</sup>C NMR spectrum clearly showed the presence of two quaternary carbon atoms which were assigned to thiazinanone-C-5 and C-6. All the 1,3-thiazinan-4-one/quinolone hybrids were screened for antibacterial activity. Compounds **7a**, **7e** and **7g** showed broad spectrum antibacterial activity against MRSA with the minimum inhibitory concentration against MRSA found to be 48  $\mu$ g mL<sup>-1</sup> compared to the drug ciprofloxacin (96  $\mu$ g mL<sup>-1</sup>). Additionally, a molecular docking study was performed to understand the molecular interaction and binding mode of the compounds on the active site of *S. aureus Murb* protein. *In silico* docking assisted data strongly correlated with the experimental approach of antibacterial activity against MRSA.

activities.<sup>7</sup> 3-(3-(6-Chloro-2-methoxyacridin-9-ylamino)propyl)-2-(thiophen-2-yl)-1,3-thiazinan-4-one (I) showed activity against various cancer cell types, such as prostate cancer, two lung cancer cell lines, and eight breast cancer cell lines with varying genetic background (Fig. 1).<sup>9</sup>

Quinolones are a fascinating class of heterocycles having a nitrogen atom. They are also essential moieties in medicinal chemistry. Scientists around the world have been interested in quinolones' biological applications.<sup>10,11</sup> Quinolone derivatives have revealed anti-cancer,<sup>12</sup> anti-malarial,<sup>13</sup> anti-inflammatory,<sup>14</sup> anti-viral,<sup>15</sup> anti-bacterial and anti-fungal activities.<sup>16</sup> 3-((7-Chloroquinolin-4-ylamino)methyl)-2-phenyl-1,3-thiazinan-4one derivatives **II** (Fig. 1) were screened for their *in vitro* antibacterial activity against a panel of pathogenic bacterial strains,



Fig. 1 Anticancer and antibacterial thiazinanones I and II.

<sup>&</sup>lt;sup>a</sup>Chemistry Department, Faculty of Science, Minia University, El-Minia 61519, Egypt. E-mail: asmaa.hamouda@mu.edu.eg; sara.ahmed@mu.edu.eg; ashrafaly63@yahoo. com; ashraf.shehata@mu.edu.eg; alaahassan2001@mu.edu.eg; esraamah33@gmail. com

<sup>&</sup>lt;sup>b</sup>Department of Chemistry, College of Science, Jouf University, Sakaka 72341, Aljouf, Saudi Arabia. E-mail: aanayel@ju.edu.sa

<sup>&</sup>lt;sup>c</sup>Chemistry Department, Florida Institute of Technology, Melbourne, FL, USA

<sup>&</sup>lt;sup>d</sup>Department of Medicinal Chemistry, Faculty of Pharmacy, Minia University, 61519 Minia, Egypt

<sup>†</sup> Electronic supplementary information (ESI) available. See DOI: https://doi.org/10.1039/d3ra01721d

antitubercular activity against *Mycobacterium tuberculosis* H37Rv and also for their *in vitro* antimalarial activity against *Plasmodium falciparum*. Several of the synthesized compounds exhibited excellent antibacterial activity against *C. tetani*. Some of them showed excellent antitubercular and antimalarial activity.<sup>17</sup>

Many chemists have been interested in the chemistry of cyclopropenones throughout the last three decades,<sup>18,19</sup> with a special emphasis on diphenylcyclopropenone's behavior.20 The formation of aza-cyclopentanones (pyrrolidinones) has been reported, via the reaction of 2,3-diphenylcyclopropenone with compounds containing C=N moieties.<sup>21-24</sup> Triphenylpyrimidinones were obtained through the reaction of amidrazones with 2,3-diphenylcyclopropenone in EtOH/Et<sub>3</sub>N accompanied elimination of ammonia.25 The reaction bv of alkenylidenehydrazine-carbothioamides with cyclopropenone, as well as the presence of nucleophilic sites like azomethine carbon and sulfur atoms, resulted in 3,5-disubstituted 1,3,4thiadiazolyl-2,3-diphenylpropenones.<sup>26</sup> The reaction of cyclopropenone with various aldehyde 4-phenyl thiosemicarbazones in acetic acid afforded pyrrolo[2,1-b]oxadiazoles through [2+3]cycloaddition; H<sub>2</sub>S was eliminated.<sup>27</sup> Moreover, 2,4-disubstituted thiosemicarbazides reacted with cyclopropenone to afford the corresponding pyridazines.<sup>28</sup> 2,3-Diphenylcyclopropenone reacted with N-imidoyl-thiourease accompanied by elimination phenylisothiocyanate; 3-substituted of 2,5,6triphenylpyrimidin-4-ones were obtained.29 The reaction of pyrazolylthiourea with cyclopropenone, followed by oxidation with DDQ, yielded 5,6-diphenyl-1,3-thiazinones via the formation of pyrazolylimino-3,5,6-triphenyl-1,3-thiazinan-4-ones.30 2-((2,4-dinitrophenyl)-hydrazono)-5,6-diphenyl-1,3-Racemic (Z)-N'-(2,4-dinitrophenyl)-2,3thiazinan-4-ones and diphenylacrylo-hydrazides were obtained via the diastereoselective reaction between 2,3-diphenylcyclopropenone and 4-substituted 1-(2,4-dinitrophenyl) thiosemicarbazides.<sup>31</sup>

The serious medical problem of Multi Drug Resistance (MDR) of bacteria leads to increasing levels of resistance to classical antibiotics among Gram-positive organisms such as *pneumococci*, *enterococci*, and *staphylococci*.<sup>32</sup> In communities worldwide, MRSA (methicillin-resistant *Staphylococcus aureus*) is a severe health hazard. The World Health Organization (WHO) has identified MRSA as one of the top threats to people causing developed resistance to almost all classes of antimicrobial agents.<sup>33</sup> Treatments for MRSA infections are limited and thus it has become a leading cause of morbidity and mortality across the globe after cancer.<sup>34</sup> In spite of enormous amounts of research works, these MDR pathogens remain a challenge in developing new drug candidates.

Large amounts of effort towards further research of quinolones are performed to develop new more effective antibacterial agents with broader antimicrobial spectrum and better therapeutic index. The azolylthioether quinolones **III** (Fig. 2) exhibited good antimicrobial activities that displayed remarkable anti-MRSA and anti-*P. aeruginosa* efficacies with low MIC values of 0.25  $\mu$ g mL<sup>-1</sup>, even superior to reference drugs. They induced bacterial resistance more slowly than clinical drugs.<sup>35</sup> Also, compound **IV** (Fig. 2), 3-aminothiazolquinolones, 3-(2-

aminothiazol-4-yl)-7-chloro-6-(pyrrolidin-1-yl)quinolone exhibited potent antibacterial activity, low cytotoxicity to hepatocyte cells, strong inhibitory potency to DNA gyrase and a broad antimicrobial spectrum including against multidrug-resistant strains. This active molecule IV also induced bacterial resistance more slowly than norfloxacin.36 Moreover, thiazinane was taken into consideration in MDR challenge whereas the monoiodinated thiazine derivative V (Fig. 2) showed good antibacterial activity against methicillin-sensitive Staphylococcus aureus (S. aureus, MSSA) ATCC 29213 and methicillin-resistant Staphvlococcus aureus (MRSA) ATCC 43300. Among strategies by which resistance can be achieved, overexpression of efflux pumps such as NorA of Staphylococcus aureus leads to a sublethal concentration of 3-phenyl-1,4-benzothiazine VI (Fig. 2), at the active site that in turn may predispose the organism to the development of high-level target-based resistance. With an aim to improve both the chemical stability and potency of our previously reported 3-phenyl-1,4-benzothiazine.37

In response to the previously mentioned findings, we here designed novel compounds based on the concept of merging more than one scaffold in one compact structure. Hybrids **7a–h** gather two types of anti-MRSA scaffolds; 2-quinolones and 1,3-thiazines in one novel hybrid aims to develop simpler and more efficient antibacterial compounds with synergistic effect and less bacterial resistance. Testing against G +ve and G –ve bacteria align with examining against methicillin-resistant *S. aureus* (MRSA) to investigate the anti-MDR activity as well as anti-bacterial spectrum. This is illustrated in a summarized schematic diagram (Fig. 2).

#### 2. Results and discussion

#### 2.1. Chemistry

The ((E)-((4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl) target methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one derivatives 7a-h were obtained through the route outlined in Scheme 1. The strategy starts by preparing compounds 2a-h, 3a-h and 5a-h according to reported methods. Treating aniline derivatives 1a-h with polyphosphoric acid (PPA), and diethyl malonate (DEM) at 220 °C afforded 2-quinolones 2a-h.38 Gentle heating of 2a-h with CHCl<sub>3</sub> and 15% NaOH gave the corresponding 4hydroxy-2-oxo-1,2-dihydroquinoline-3-carbaldehydes 3a-h. Reaction of 3a-h with thiosemicarbazide (4) gave the corresponding thiosemicarbazones 5a-h (Scheme 1), and their structures were confirmed by comparing their spectral data to those previously published. Accordingly, thiosemicarbazones 5a-h were treated with 2,3-diphenylcyclopropenone (6) in dry EtOH using a few drops of  $Et_3N$  under reflux for 4–6 h to give 1,3thiazinan-4-ones 7a-h as the only products in excellent yields.

Diastereomeric mixtures **7a–h** were formed as a result of the development of two new stereo centers at C-5 and C-6 positions. As a result, most signals in the <sup>1</sup>H and <sup>13</sup>C NMR spectra were duplicated. The expected diastereomeric forms were not separable by column chromatography. In the <sup>1</sup>H NMR spectra, the signals of the respective protons of the synthesized compounds were confirmed based on their chemical shifts and multiplicities. The compounds reported in this study have been



Fig. 2 Design of target compounds 7a-h.



Scheme 1 Synthesis of hydrazono-5,6-diphenyl-1,3-thiazinan-4-ones 7a-h.

thoroughly characterized by elemental analysis and mass spectral data. The <sup>1</sup>H NMR spectrum of 7a showed, in addition to the aromatic protons, two doublet signals for CH-6 and CH-5 at  $\delta_{\rm H} = 4.50$  ppm and 5.44 ppm with coupling constant J =4.0 Hz and four sharp singlets at  $\delta_{\rm H}=$  8.15, 8.55, 11.60 and 12.03 ppm related to the protons of thiazinane NH, CH=N, quinolone NH and OH, respectively. As the saturated thiazinanes belong to the cyclohexane confirmation structure, the coupling constant values of CH-5 and CH-6 = 4 Hz. Moreover, the <sup>13</sup>C NMR spectrum clearly showed the presence of two quaternary carbon atom which resonated at  $\delta_{\rm C} = 43.36$  and 56.06 ppm which were assigned to thiazinanone-CH-6,5. Furthermore, the <sup>13</sup>C NMR spectrum revealed the presence of carbonyl-thiazinanone and carbonyl-quinolone, quinolone C-4, CH=N and C=N at  $\delta_{\rm C}$  = 168.17, 165.88, 163.30, 161.45 and 158.07 ppm, respectively (see the Experimental section).

According to elemental analysis and mass spectrometry, compound 7a has a molecular formula of  $C_{26}H_{20}N_4O_3S$ , resulting from the addition of one molecule of hydrazine-carbothioamide 5a with one molecule of 6 without any elimination.

In case of **7b**, its <sup>1</sup>H NMR spectrum showed triplet and quartet signals for CH<sub>3</sub> and CH<sub>2</sub> groups appeared at  $\delta_{\rm H} = 1.23$  and  $\delta_{\rm H} = 4.28$  ppm. Whereas the OH, CH=N and thiazinanone-NH protons resonated as three singlets at  $\delta_{\rm H} = 12.03$ , 8.83 and 8.03 ppm, respectively. Also, doublet signals for CH-5 and CH-6 at  $\delta_{\rm H} = 4.50$  ppm and  $\delta_{\rm H} = 5.44$  ppm (J = 4.0 Hz). The <sup>13</sup>C NMR spectrum revealed CH<sub>3</sub>, CH<sub>2</sub>, C-6, C-5, C=N, CH=N, C-OH, carbonyl-quinolone and carbonyl-thiazinanone at  $\delta_{\rm C} = 15.09$ , 38.11, 44.19, 56.98, 157.16, 161.34, 164.28, 165.28 and 168.81, respectively (Fig. 3).

The plausible mechanism for the formation of 1,3-thiazinan-4-ones 7**a**–**h** was based upon the conjugate double bond of **6** was attacked by the thione lone pair forming zwitterion salts **8a–h**. Subsequently, a proton was transferred in **8a–h** to give the intermediates **9a–h**, which on rearrangement and ring opening of cyclopropenone would give the intermediate **10a–h**. The carbonyl carbon was then attacked by the lone-pair of nitrogen to form intermediates **11a–h**, which rearranged to give the final products **7a–h** (Scheme 2).



Fig. 3  $~~\delta$  values of some distinctive carbons and protons of compound 7b.

#### **RSC** Advances

Using compound **7a** as an example, we carried out the reaction in various settings after optimizing the reaction conditions. When the reaction was refluxed in DMF/Et<sub>3</sub>N and dioxane/Et<sub>3</sub>N, it was found that the yield of **7a** was reduced to 60% and 64%, respectively. In addition, side products were obtained from the reaction. As a result, utilizing ethanol in the presence of Et<sub>3</sub>N as a catalyst is the best way to get high yields.

#### 2.2. Screening of antibacterial activity

The antibacterial and antifungal activities of compounds **7a–h** were evaluated *in vitro* against three-Gram positive (G +ve) strains; non-resistant *S. aureus* (ATCC 6538), methicillin resistant *Staphylococcus aureus* (MRSA) and *Escherichia coli* (ATCC 25922) and two-Gram negative (G –ve) strains; *Pseudomonas aeruginosa* (ATCC 10145) and *Salmonella*. The tested compounds were assayed against ciprofloxacin as an antibacterial reference using standard agar cup diffusion method. Results of the antibacterial screening are listed in Table 1.

According to the MICs recorded in Table 1, it can be deduced that most of the tested compounds showed a higher antibacterial activity than the reference ciprofloxacin against G +ve bacteria. It was found that compound **7a**, **7e** and **7h** displayed potent activity against non-resistant *S. aureus* compared with the reference with MICs of 12, 48, and 48  $\mu$ M, respectively. Meanwhile, compounds **7e** displayed significant antibacterial activity against MRSA better than the reference with MICs 48 and 96  $\mu$ M, respectively, however **7a** showed remarkable activity of MIC 96  $\mu$ M.

Moreover, compounds 7g exhibited the good activity against *E. coli* with MICs of 24  $\mu$ M when compared to the reference, however, both 7a and 7d showed moderate activity against *E. coli*.

Concerning activity against G –ve strains; compounds 7e and 7g revealed a high potency against *P. aeruginosa* with MICs of 12 and 12  $\mu$ M. On contrast, other compounds displayed moderate to weak activity (Fig. 4). Furthermore, the derivatives 7d–f showed moderate activity against *Salmonella* with MICs of 96  $\mu$ g mL<sup>-1</sup>, respectively (Table 1 and Fig. 4).



Scheme 2 The rationale for the formation of 1,3-thiazinan-4-ones 7a-h.

**2.2.1. Structure–activity relationship.** Based on the aforementioned results, it is obvious that compounds 7a, 7e and 7g showed broad spectrum antibacterial activity against all the tested strains either G +ve or G –ve. In general, the quinolone-based thiazine derivatives 7c and 7f exhibited weak activity almost against most of the tested strains. From the above results, it can be concluded that, there is no specific substituent on the *quinolone nucleus* of tested compounds to enhance the antibacterial activity of some of the tested derivatives may be due to improvement of the physicochemical properties and consequently enhancing permeability to microbial cells.

In summary, compound 7e presented a significant broad spectrum anti-bacterial activity that was probably attributed to when  $(R^1 = CH_3)$ , it would enhance the physicochemical parameters and hence increase cell permeability against either nonresistant or resistant strains.

#### 2.3. Molecular modeling studies

Docking studies have been carried out to elucidate the binding mode of the quinolone/thiazine hybrids **7a–h** with the protein active site of *S. aureus Murb* (PDB ID: IHSK). Prior to the molecular docking studies, the receptor protein was prepared for docking by omitting additional water and co-factors, followed by the addition of polar hydrogens and computing charges fixation. Also, the docking scores of the tested compounds are depicted in Table 2 that used to calculate the inhibition constant ( $K_i$  value) according to the reported equation<sup>7</sup> (see ESI†). Typically, a high potency is implied by a low  $K_i$  value and it has to be in the micromolar range for a molecule to be qualified as a lead compound or hit. Compounds **7b**, **7c**, **7e** and **7h** have the least  $K_i$  value of  $0.62 \times 10^{-6}$ ,  $0.83 \times 10^{-6}$ ,  $0.78 \times 10^{-6}$  and  $0.76 \times 10^{-6} \,\mu$ M, respectively to qualify as a drug and hence, the most potent among the other tested compounds.

Docking results of the known antibacterial reference; ciprofloxacin into active site of *S. aureus Murb* protein (Fig. 5 and Table 2) revealed that ciprofloxacin showed CDOCKER energy of -6.53 kcal mol<sup>-1</sup> and engaged in two hydrogen bonds with amino acid residues SER82 and GLY79.

Most of the tested compounds have high binding affinity to protein of *S. aureus Murb* as the binding free energy ( $\Delta G$ ) values of them range from 0.0 to -2.6 kcal mol<sup>-1</sup>. The docking study results of target 7**b**, 7**c** and 7**f** showed interactions typically as the reference with amino acid residues SER82 and GLY79.

Although, all the tested compounds **7a**–**h** showed interaction with amino acid residues SER82 and TYR149, hybrids **7a**, **7e** and **7h** lack interaction with the last residue.

Moreover, compounds **7e** and **7h** exhibited potential interactions with both amino acid residues ASN80 and ARG255, while the hybrid **7d** interacted with the first residue and the second residue engaged with the **7a**.

Interestingly, compound **7f** showed additional two hydrophobic interactions with ILE140 amino acid residue which is not observed with the others.

Collectively, the docking results were in agreement with the biological study, and we could conclude that hybrid 7e entitled

Table 1	The MICs of antibacteria	l activity of the	tested compounds,	ciprofloxacin (µg	3 mL <sup>-1</sup> )
---------	--------------------------	-------------------	-------------------	-------------------	----------------------

	$\operatorname{MIC}^{a}(\mu M)$							
	Gram +ve			Gram –ve				
Compound	Non-resistant S. aureus	MRSA	E. coli	P. aeruginosa	Salmonella			
7a	48	96	48	48	768			
7b	768	>2000	768	96	>2000			
7 <b>c</b>	>2000	>2000	768	768	>2000			
7 <b>d</b>	48	334	48	24	96			
7e	12	48	96	12	96			
7f	142	>2000	768	320	96			
7g	96	768	24	12	>2000			
7h	48	384	768	96	320			
Ciprofloxacin	12	96	24	12	24			



to be promising as attractive future lead candidate for the development of broad-spectrum antibacterial activity.

### Experimental

#### 3.1. Chemistry

A list of chemicals and instrumentation is provided in the ESI.†

**3.1.1. Starting materials.** Carbaldehydes  $3\mathbf{a}-\mathbf{c}$ ,  $3^{3-41}$   $3\mathbf{e}-\mathbf{h}^{42}$  and thiosemicarbazones  $5\mathbf{a}-\mathbf{c}^{43,44}$  and  $5\mathbf{e}-\mathbf{h}^{45}$  were prepared according to literature methods.

**3.1.2. General procedure.** Equimolar amounts of 2,3diphenylcycloprop-2-enone **6** and the appropriate hydrazinecarbothioamides **5a–e** were mixed in absolute EtOH and a few drops of  $Et_3N$  was added as a catalyst and refluxed for about 4– 6 h, furnished yellow precipitates (*i.e.* the reaction was followed up by TLC analysis). The precipitate was filtered, washed with ethanol, dried and recrystallized from the stated solvents to give the final products **7a–h**.

(*Z*)-2-((*E*)-((*4*-Hydroxy-2-oxo-1,2-dihydroquinolin-3-yl) methylene)-hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7*a*). Yellow crystals (DMF/EtOH), yield: 0.379 g (81%); mp 300–302 ° C;  $R_{\rm f} = 0.22$  (toluene–ethyl acetate, 1:1); IR (KBr):  $\nu = 3392$ (OH), 3230, 3215 (NH), 3066 (Ar-CH), 2934 (aliph-CH), 1662 and 1649 (CO), 1628 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO-*d*<sub>6</sub>):  $\delta_{\rm H}$ = 4.50 (d, 1H, *J* = 4.0 Hz, thiazinanone-H6), 5.44 (d, 1H, *J* = 4.0 Hz, thiazinanone-H5), 6.84 (dd, 2H, J = 8.0 Hz, Ar-H), 6.96 (dd, 2H, J = 8.0 Hz, Ar-H), 7.18–7.30 (m, 5H, Ar-H), 7.58–7.60 (m, 5H, Ar-H), 8.15 (brs, 1H, thiazinanone-NH), 8.55 (s, 1H, CH=N), 11.60 (s, 1H, quinolone-NH), 12.03 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 43.36$  (thiazinanone-CH-6), 56.06 (thiazinanone-CH-5), 109.90 (quinolone-C3), 114.87, 116.49, 117.75, 118.41, 120.03, 122.02, 122.68, 123.27, 125.56, 126.59, 127.55, 128.30, 129.83, 132.05 (Ar-CH), 134.99, 136.98, 139.57, 143.77 (Ar-C), 158.07 (C=N), 161.45 (CH=N), 163.30 (C-OH), 165.88 (quinolone-C=O), 168.17 (thiazinanone-C=O). MS (Fab, 70 eV, %): m/z = 468 (M<sup>+</sup>, 70), 391 (25), 307 (100), 289 (15), 273 (5). Anal. calcd for C<sub>26</sub>H<sub>20</sub>N<sub>4</sub>O<sub>3</sub>S (468.53): C, 66.65; H, 4.30; N, 11.96; S, 6.84. Found: C, 66.80; H, 4.34; N, 12.10; S, 6.98.

(Z)-2-((E)-((1-Ethyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7b). Yellow crystals (DMF/EtOH), yield: 0.412 g (83%); mp 281-283 ° C;  $R_{\rm f} = 0.30$  (toluene-ethyl acetate, 10:8); IR (KBr)  $\nu = 3390$ (OH), 3230 (NH), 3070 (Ar-CH), 2970 (aliph-CH), 1672 and 1668 (CO), 1611 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\rm H} =$ 1.23 (t,  $3H, J = 8.0 Hz, CH_3$ ), 4.28 (q,  $2H, J = 8.0 Hz, CH_2$ ), 4.50 (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.44 (d, 1H, J = 4.0 Hz, thiazinanone-H5), 6.84 (dd, 2H, Ar-H), 6.97 (dd, 2H, Ar-H), 7.28-7.31 (m, 10H, Ar-H), 8.03 (brs, 1H, thiazinanone-NH), 8.83 (s, 1H, CH=N), 12.03 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 15.09$  (CH<sub>3</sub>), 38.11 (CH<sub>2</sub>), 44.19 (thiazinanone-CH-6), 56.98 (thiazinanone-CH-5), 109.89 (quinolone-C3), 115.30, 123.90, 123.99, 127.94, 128.02, 128.59 (Ar-CH), 128.79, 128.90, 129.24, 129.39 (Ar-2CH), 133.50, 133.63, 134.62, 139.80 (Ar-C), 157.16 (C=N), 161.34 (CH=N), 164.28 (C-OH), 165.28 (quinolone-C=O), 168.81 (thiazinanone-C=O); MS (Fab, 70 eV, %):  $m/z = 496 (M^+, 100), 468 (70), 307 (50), 316 (88), 288 (45), 280$ (20), 216 (15), 189 (30). Anal. calcd for C<sub>28</sub>H<sub>24</sub>N<sub>4</sub>O<sub>3</sub>S (496.58): C, 67.72; H, 4.87; N, 11.28; S, 6.46. Found: C, 67.81; H, 4.92; N, 11.15; S, 6.33.

(Z)-2-((E)-((1-Methyl-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7c). Yellow crystals (DMF/H<sub>2</sub>O), yield: 0.405 g (84%); mp 280–282 °C;  $R_{\rm f} = 0.22$  (toluene–ethyl acetate, 10 : 8); IR (KBr)  $\nu = 3308$  (OH), 3276 (NH), 3109 (Ar-CH), 2965 (aliph-CH), 1639 and 1615 (CO), 

 Table 2
 Energy scores for the complexes formed by the optimized structures of tested 7a-h in the active site of the S. aureus Murb (PDB ID: IHSK)

	S score	C-Docker energy (kcal mol <sup>-1</sup> )		Ligand–receptor interaction		
Compound			Inhibition constant, <i>K</i> <sub>i</sub> (µM)	Residue	Туре	Length (Å)
7a	-7.43	-0.7	$3.64\times 10^{-6}$	SER82	H-donor	3.68
		-0.8		ARG225	Pi-cation	4.32
7 <b>b</b>	-8.48	-2.3	$0.62\times 10^{-6}$	SER82	H-donor	2.86
		-2.2		GLY79	H-acceptor	3.00
		-1.4		GLY81	H-acceptor	3.24
		-0.0		<b>TYR149</b>	Pi-Pi	3.94
7 <b>c</b>	-8.27	-2.1	$0.83 imes10^{-6}$	SER82	H-donor	2.94
		-2.2		GLY79	H-acceptor	3.00
		-1.2		GLY81	H-acceptor	3.26
		-0.0		<b>TYR149</b>	Pi-Pi	3.94
7 <b>d</b>	-8.00	-2.1	$1.39\times 10^{-6}$	GLY146	H-donor	3.19
		-2.2		SER82	H-acceptor	3.12
		-1.6		SER82	H-acceptor	2.60
		-0.7		<b>TYR149</b>	H-Pi	4.10
		-2.6		ASN83	Pi–H	4.15
7e	-8.34	-1.7	$0.78\times 10^{-6}$	AS80	H-acceptor	3.30
		-1.9		SER143	H-acceptor	3.28
		-0.7		SER82	Рi-H	4.55
		-0.9		ARG225	Pi-cation	4.36
7 <b>f</b>	-7.95	-2.0	$1.51\times 10^{-6}$	SER82	H-donor	2.99
		-2.1		GLY79	H-acceptor	2.99
		-0.9		GLY81	H-acceptor	3.32
		-0.6		ILE140	Pi-H	4.51
		-0.6		ILE140	Pi–H	4.10
		-0.0		<b>TRY149</b>	Pi–Pi	3.93
7g	-7.69	-0.9	$2.34\times 10^{-6}$	SER82	H-acceptor	3.99
U		-1.5		SER82	H-acceptor	2.86
		-0.7		<b>TRY149</b>	Pi-H	4.08
7h	-8.36	-2.4	$0.76\times 10^{-6}$	ASN80	H-acceptor	3.14
		-1.0		SER143	H-acceptor	3.49
		-0.7		SER80	Pi-H	4.52
		-0.9		ARG225	Pi-cation	4.36
Ciprofloxacin	-6.53	-1.5	$14.49\times 10^{-6}$	SER82	H-acceptor	3.19
1		-2.7		GLY79	H-acceptor	2.74

1584 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H = 3.61$  (s, 3H, CH<sub>3</sub>), 4.51 (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.45 (d, 1H, J = 4.0 Hz, thiazinanone-H5), 6.84–6.86 (m, 2H, Ar-H), 6.97 (dd, 2H, Ar-H), 7.23–7.30 (m, 10H, Ar-H), 7.97 (brs, 1H, thiazinanone-NH), 8.83 (s, 1H, CH=N), 12.03 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 34.48$  (CH<sub>3</sub>), 44.19 (thiazinanone-CH-6), 55.76 (thiazinanone-CH-5), 108.56 (quinolone-C3), 114.11, 122.27, 122.75, 126.61, 126.93, 128.07 (Ar-CH), 128.40, 128.52, 129.47, 129.73 (Ar-2CH), 133.74, 133.77, 134.81, 141.52 (Ar-C), 157.97 (C=N), 161.29 (CH=N), 164.65 (C-OH), 165.69 (quinolone-C=O), 168.38 (thiazinanone-C=O); MS (Fab, 70 eV, %): m/z = 482 (M<sup>+</sup>, 70), 468 (50), 316 (80), 307 (100), 286 (45), 280 (90), 202 (10), 175 (30), 161 (50). Anal. calcd for C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S (482.55): C, 67.20; H, 4.60; N, 11.61; S, 6.64. Found: C, 67.31; H, 4.64; N, 11.55; S, 6.58.

(Z)-2-((E)-((4-Hydroxy-6-methoxy-2-oxo-1,2-dihydroquinolin-3yl)methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7d). Yellow crystals (DMF/H<sub>2</sub>O), yield: 0.403 g (81%); mp 295–297 °C;  $R_{\rm f} = 0.18$  (toluene–ethyl acetate, 1 : 1); IR (KBr):  $\nu = 3334$  (OH), 3276, 3190 (NH), 3110 (Ar-CH), 2865 (aliph-CH), 1661 and 1625 (CO), 1593 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_{\rm H} =$ 3.77 (s, 3H, OCH<sub>3</sub>), 4.48 (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.45 (d, 1H, J = 4.0 Hz, thiazinanone-H5), 6.85–6.86 (m, 2H, Ar-H), 6.95-6.97 (m, 1H, Ar-H), 7.23-7.31 (m, 10H, Ar-H), 7.98 (brs, 1H, thiazinanone-NH), 8.76 (s, 1H, CH=N), 11.48 (s, 1H, quinolone-NH), 12.03 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 44.20$  (thiazinanone-CH-6), 55.36 (OCH<sub>3</sub>), 56.30 (thiazinanone-CH-5), 109.31 (quinolone-C3), 116.61 (Ar-2CH), 125.26, 126.92, 127.15, 127.24 (Ar-CH), 128.06, 128.31 (Ar-2CH), 128.47 (Ar-CH), 130.09 (Ar-2CH), 132.54, 133.10, 136.90, 138.83, 143.80 (Ar-C), 153.64 (C=N), 156.61 (CH=N), 162.78 (C-OH), 164.81 (quinolone-C=O), 167.09 (thiazinanone-C=O); MS (Fab, 70 eV, %): m/z = 498 (M<sup>+</sup>, 30), 468 (60), 307 (100), 280 (85), 218 (14), 191 (20). Anal. calcd for C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>4</sub>S (498.55): C, 65.05; H, 4.45; N, 11.24; S, 6.43. Found: C, 65.17; H, 4.48; N, 11.17; S, 6.53.

(Z)-2-((E)-((4-Hydroxy-6-methyl-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7e). Yellow crystals (DMF/MeOH), yield: 0.314 g (82%); mp = 304– 306 °C;  $R_{\rm f}$  = 0.20 (toluene–ethyl acetate, 10:8); IR (KBr):  $\nu$  =



Ciprofloxacin



Fig. 5 3D diagram illustrating the binding modes of the optimized structures of tested 7a-h in the active site of the S. aureus Murb (PDB ID: IHSK).

3410 (OH), 3215, 3211 (NH), 3062 (Ar-CH), 2925 (aliph-CH), 1668 and 1648 (CO), 1620 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$  = 2.78 (s, 3H, CH<sub>3</sub>), 4.55 (d, 1H, J = 4.0 Hz,

thiazinanone-H6), 5.53 (d, 1H, J = 4.0 Hz, thiazinanone-H5), 7.01 (dd, 2H, J = 8.0 Hz, Ar-H), 7.25–7.54 (m, 10H, Ar-H), 7.89 (s, 1H, Ar-H), 8.10 (brs, 1H, thiazinanone-NH), 8.56 (s, 1H, CH=

3

Paper

N), 11.55 (s, 1H, quinolone-NH), 12.56 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 20.02$  (CH<sub>3</sub>), 51.26 (thiazinanone-CH-6), 54.88 (thiazinanone-CH-5), 109.27, (quinolone-C3), 110.26, 110.35, 114.08, 114.17, 114.94, 115.05, 116.35, 117.17, 118.22, 123.91, 124.93, 125.54, 129.71, (Ar-CH), 131.14, 137.80 (Ar-C), 139.29 (Ar-2C), 140.12 (Ar-C), 160.72 (C=N), 161.45 (CH=N), 164.99 (C-OH), 165.10 (quinolone-C= O), 166.16 (thiazinanone-C=O). MS (Fab, 70 eV, %): m/z = 482(M<sup>+</sup>, 58), 391 (26), 316 (78), 309 (100), 286 (45), 282 (35), 202 (10), 175 (28), 161 (36). Anal. calcd for C<sub>27</sub>H<sub>22</sub>N<sub>4</sub>O<sub>3</sub>S (482.55): C, 67.20; H, 4.60; N, 11.61; S, 6.64. Found: C, 67.36; H, 4.64; N, 11.75; S, 6.73.

(Z)-2-((E)-((7-Chloro-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl) methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7**f**). Yellow crystals (DMF), yield: 0.295 g (79%); mp =  $310-312 \circ C$ ;  $R_f$ = 0.15 (toluene-ethyl acetate, 1:1); IR (KBr):  $\nu$  = 3402 (OH), 3221, 3216 (NH), 3042 (Ar-CH), 2920 (Ali-CH), 1670, 1640 (CO), 1588 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H = 4.54$  (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.49 (d, 1H, J = 4.0 Hz, thiazinanone-H5), 6.81 (dd, 2H, J = 8.0 Hz, Ar-H), 7.19-7.58 (m, 10H, Ar-H), 7.90 (s, 1H, Ar-H), 8.12 (brs, 1H, thiazinanone-NH), 8.76 (s, 1H, CH=N), 12.62 (s, 1H, quinolone-NH), 13.21 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO- $d_6$ ):  $\delta_C = 45.05$ (thiazinanone-CH-6), 56.14 (thiazinanone-CH-5), 100.10 (quinolone-C3), 113.65, 114.91, 115.12, 115.85, 116.20, 122.02, 123.01, 123.27, 125.50 (Ar-CH), 126.05 (Ar-2CH), 128.41, 129.98 (Ar-CH), 131.89, 135.02, 136.98, 138.86, 142.78 (Ar-C), 156.12 (C=N), 161.46 (CH=N), 163.45 (C-OH), 165.35 (quinolone-C= O), 166.24 (thiazinanone-C=O); MS (Fab, 70 eV, %): m/z = 504 $(M + 2, 40), 503 (M + 1, 15), 502 (M^+, 7), 391 (10), 309 (5), 308 (12),$ 307 (40), 289 (17), 260 (5), 154 (100). Anal. calcd for  $C_{26}H_{19}$ -ClN<sub>4</sub>O<sub>3</sub>S (502.97): C, 62.09; H, 3.81; N, 11.14; S, 6.38. Found: C, 62.24; H, 3.85; N, 11.28; S, 6.48.

(Z)-2-((E)-((6-Chloro-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl) methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7g). Yellow crystals (DMF/EtOH), yield: 0.402 g (80%); mp 270-272 ° C;  $R_f = 0.18$  (toluene-ethyl acetate, 1:1); IR (KBr):  $\nu = 3330$ (OH), 3282, 3178 (NH), 3089 (Ar-CH), 2860 (aliph-CH), 1670 and 1652 (CO), 1627 cm<sup>-1</sup> (C=N); <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$ = 4.50 (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.44 (d, 1H, J =4.0 Hz, thiazinanone-H5), 6.85-6.86 (m, 2H, Ar-H), 6.95-6.97 (m, 1H, Ar-H), 7.23-7.30 (m, 10H, Ar-H), 8.03 (brs, 1H, thiazinanone-NH), 8.63 (s, 1H, CH=N), 11.62 (s, 1H, quinolone-NH), 12.03 (s, 1H, quinolone-OH); <sup>13</sup>C NMR (100 MHz, DMSO $d_6$ ):  $\delta_C = 44.19$  (thiazinanone-CH-6), 56.89 (thiazinanone-CH-5), 109.86 (quinolone-C3), 115.32, 122.10, 123.90, 127.92, 128.01, 128.53, 128.95, 129.24, 129.39 (Ar-CH), 133.54, 134.80 (Ar-2CH), 132.40, 133.30, 133.60, 136.32, 143.76 (Ar-C), 157.26 (C=N), 161.32 (CH=N), 162.57 (C-OH), 164.89 (quinolone-C=O), 168.71 (thiazinanone-C=O); MS (Fab, 70 eV, %): m/z = 503 (M + 1, 30), 502 (M<sup>+</sup>, 55), 468 (40), 307 (20), 280 (16), 223/222 (7/50), 196/195 (100/64). Anal. calcd for C<sub>26</sub>H<sub>19</sub>ClN<sub>4</sub>O<sub>3</sub>S (502.97): C, 62.09; H, 3.81; N, 11.14; S, 6.38. Found: C, 62.16; H, 3.86; N, 11.26; S, 6.48.

(Z)-2-((E)-((7-Bromo-4-hydroxy-2-oxo-1,2-dihydroquinolin-3-yl)methylene)hydrazono)-5,6-diphenyl-1,3-thiazinan-4-one (7h). Yellow crystals (DMF/EtOH), yield: 0.325 g (87%); mp = 338-

340 °C;  $R_f = 0.20$  (toluene-ethyl acetate, 1 : 1); IR (KBr):  $\nu = 3390$ (OH), 3219, 3215 (NH), 3072 (Ar-CH), 2914 (aliph-CH), 1661 and 1650 (CO), 1600 cm<sup>-1</sup> (C=N). <sup>1</sup>H NMR (400 MHz, DMSO- $d_6$ ):  $\delta_H$ = 4.54 (d, 1H, J = 4.0 Hz, thiazinanone-H6), 5.55 (d, 1H, J =4.0 Hz, thiazinanone-H5), 6.99 (dd, 2H, J = 8.0 Hz, Ar-H), 7.13-7.33 (m, 10H, Ar-H), 7.90 (m, 1H, Ar-H), 8.12 (brs, 1H, thiazinanone-NH), 8.55 (s, 1H, CH=N), 12.20 (s, 1H, quinolone-NH), 12.91 (s, 1H, quinolone-OH). <sup>13</sup>C NMR (100 MHz, DMSO $d_6$ ):  $\delta_C = 46.14$  (thiazinanone-CH-6), 55.34 (thiazinanone-CH-5), 109.33 (quinolone-C3), 110.50, 112.35, 114.15, 114.98, 115.22, 116.32, 117.22, 119.54, 122.65, 123.34, 125.30 (Ar-CH), 129.80 (Ar-2CH), 131.14 (Ar-2C), 136.89, 138.40, 141.09 (Ar-C), 160.80 (C=N), 161.14 (CH=N), 164.98 (C-OH), 165.24 (quinolone-C= O), 167.23 (thiazinanone-C=O). MS (70 eV, %): *m*/*z* 549 (M + 2, 25), 547 (M<sup>+</sup>, 25), 530 (17), 529 (14), 476 (15), 460 (100), 443 (25), 391 (30), 375 (22), 330 (38), 305 (40), 154 (100). Anal. calcd for C<sub>26</sub>H<sub>19</sub>BrN<sub>4</sub>O<sub>3</sub>S (547.42): C, 57.05; H, 3.50; N, 10.23; S, 5.86. Found: C, 57.23; H, 3.55; N, 10.38; S, 5.96.

#### 3.2. Biology

**3.2.1.** Screening of antibacterial activity. The antibacterial activity was screened according to serial dilution method. Minimal inhibition concentration (MIC) is the lowest concentration of an antimicrobial agent that can inhibit the visible growth of a microorganism after overnight incubation (see ESI<sup>†</sup>).

**3.2.2. Molecular docking study.** The docking simulation study was carried out using Molecular Operating Environment (MOE®) version 2014.09 (Chemical Computing Group Inc., Montreal, QC, Canada). The computational software operated under "Windows XP" installed on an Intel Pentium IV PC with a 1.6 GHz processor and 512 MB memory. The target compounds were constructed into a 3D model using the builder interface of the MOE program and docked into the active site of caspase-3 (PDB: 3GJQ). Checking their structures and the formal charges on atoms by 2D depiction was carried out and the energy, was minimized until an RMSD (root mean square deviations) gradient of 0.01 kcal mol<sup>-1</sup> and RMS (Root Mean Square) distance of 0.1 A with MMFF94X (Merck molecular force field 94X) force-field and the partial charges were automatically calculated (see ESI<sup>†</sup>).

#### 4. Conclusions

In short, a series of 1,3-thiazinanone derivatives have been synthesized in excellent yields *via* nucleophilic attack of thiosemicarbazones on 2,3-diphenylcyclopropenone. The target compounds were identified and characterized using <sup>1</sup>H NMR, <sup>13</sup>C NMR, MS and elemental analysis. The suggested mechanism for the formation of the final products was remembered. The biological results revealed that some target compounds exhibited good antibacterial activity against most of the tested G +ve and G –ve strains, especially compound 7e against MRSA even superior to reference drug. They induced bacterial resistance more slowly than clinical drugs. Molecular docking study indicated strong binding interaction of the tested compounds.

In conclusion, compound **7e** revealed potential broad spectrum anti-bacterial activity that should be taken into consideration as good candidates for further study.

## Author contributions

A. H. M. (writing, editing, and revision); S. M. M. (revision), A. A. A. (concept, writing, edit, revision, and submitting), A. A. H. (editing), E. M. O. (experimental), A. B. B. (editing and revision), E.-S. M. N. A. (biology, writing, and editing). All authors have read and agreed to the published version of the manuscript.

## Conflicts of interest

The authors declare no conflict of interest. The authors declare that they have no known competing interests.

## Acknowledgements

The authors thank DFG for providing Ashraf A. Aly with a onemonth fellowship, enabling him to conduct the compound analysis at the Karlsruhe Institute of Technology, Karlsruhe, Germany, in July and August 2019.

## Notes and references

- 1 R. K. Rawal, R. Tripathi, S. B. Katti, C. Pannecouque and E. De Clercq, *Bioorg. Med. Chem.*, 2007, **15**, 3134–3142, DOI: **10.1016/j.bmc.2007.02.044**.
- 2 R. K. Rawal, R. Tripathi, S. B. Katti, C. Pannecouque and E. De Clercq, *Bioorg. Med. Chem.*, 2007, **15**, 1725–1731, DOI: **10.1016/j.bmc.2006.12.003**.
- 3 A. Verma and S. K. Saraf, *Eur. J. Med. Chem.*, 2008, **43**, 897–905, DOI: **10.1016/j.ejmech.2007.07.017**.
- 4 A. M. Das Neves, G. A. Berwaldt, C. T. Avila, T. B. Goulart,
  B. C. Moreira, T. P. Ferreira and W. Cunico, *J. Enzyme Inhib. Med. Chem.*, 2020, 35, 31–41, DOI: 10.1080/14756366.2019.1680659.
- 5 A. Verma, S. S. Verma and S. K. Saraf, J. Heterocycl. Chem., 2010, 47, 1084–1089, DOI: 10.1002/jhet.429.
- 6 M. K. Kumawat, U. P. Singh, B. Singh, A. Prakash and D. Chetia, *Arab. J. Chem.*, 2016, 9, 643–647, DOI: 10.1016/ j.arabjc.2011.07.007.
- 7 C. W. Murray, D. A. Erlanson, A. L. Hopkins, G. R. M. Keseru, P. D. Leeson, D. C. Rees, C. H. Reynolds and N. J. Richmond, *ACS Med. Chem. Lett.*, 2014, 5, 616–618, DOI: 10.1021/ ml500146d.
- 8 J. Bosenbecker, V. D. Bareño, R. Difabio, F. A. Vasconcellos,
  F. S. Dutra, P. S. Oliveira and W. Cunico, *J. Biochem. Mol. Toxicol.*, 2014, 28, 425–432, DOI: 10.1002/jbt.21581.
- 9 T. Zebardast, A. Zarghi, B. Daraie, M. Hedayati and O. G. Dadrass, *Bioorg. Med. Chem. Lett.*, 2009, **19**, 3162– 3165, DOI: **10.1016/j.bmcl.2009.04.125**.
- 10 V. R. Solomon, S. Pundir, H. T. Le and H. Lee, *Eur. J. Med. Chem.*, 2018, 143, 1028–1038, DOI: 10.1016/j.ejmech.2017.11.097.

- 11 S. M. Prajapati, K. D. Patel, R. H. Vekariya, S. N. Panchal and
  H. D. Patel, *RSC Adv.*, 2014, 4, 24463–24476, DOI: 10.1039/ C4RA01814A.
- 12 O. Navneetha, K. Deepthi, A. M. Rao and T. S. Jyostna, *Int. J. Pharm. Chem. Biol. Sci.*, 2017, 7, 364–372.
- 13 M. A. Elbastawesy, A. A. Aly, M. Ramadan, Y. A. Elshaier, B. G. Youssif, A. B. Brown and G. E. D. A. Abuo-Rahma, *Bioorg. Chem.*, 2019, **90**, 103045, DOI: **10.1016**/ **j.bioorg.2019.103045**.
- 14 Y. L. Fan, X. W. Cheng, J. B. Wu, M. Liu, F. Z. Zhang, Z. Xu and L. S. Feng, *Eur. J. Med. Chem.*, 2018, **146**, 1–14, DOI: **10.1016/j.ejmech.2018.01.039**.
- 15 P. Gao, L. Wang, L. Zhao, Q. Y. Zhang, K. W. Zeng, M. B. Zhao and X. Y. Guo, *J. Phytochem.*, 2020, **172**, 112260, DOI: **10.1016/j.phytochem.2020.112260**.
- 16 P. N. Batalha, L. Da SM Forezi, N. M. D. C. Tolentino, F. S. Sagrillo, V. G. de Oliveira, M. C. B. de Souza and F. Da CS Boechat, *Curr. Top. Med. Chem.*, 2020, **20**, 244–255, DOI: **10.1016/j.molstruc.2021.130845**.
- 17 T. M. Rawson, L. S. Moore, N. Zhu, N. Ranganathan, K. Skolimowska, M. Gilchrist and A. Holmes, *Clin. Infect. Dis.*, 2020, **71**, 2459–2468, DOI: **10.1093/cid/ciaa530**.
- 18 M. K. Kumawat, U. P. Singh, B. Singh, A. Prakash and D. Chetia, *Arab. J. Chem.*, 2016, 9, 643–647, DOI: 10.1016/ j.arabjc.2011.07.007.
- 19 T. Eicher and J. L. Weber, *Cycl. Compd.*, 1975, 57, 1–109, DOI: 10.1007/BFb0048013.
- 20 M. L. Deem, Synthesis, 1982, 1982, 701–716, DOI: 10.1055/s-1982-29909.
- 21 B. Musicki, J. Org. Chem., 1991, 56, 110-118, DOI: 10.1021/ j000001a023.
- 22 T. Eicher and G. Franke, *Justus Liebigs Ann. Chem.*, 1981, 1981, 1337–1353, DOI: 10.1002/jlac.198119810802.
- 23 M. Takahashi, T. Funaki, H. Honda, Y. Yokoyama and H. Takimoto, *Heterocycles*, 1982, **19**, 1921–1924.
- 24 M. A. M. Gomaa and D. Döpp, *Synthesis*, 2003, **10**, 1545–1548, DOI: **10.1055/s-2003-40522**.
- 25 M. A. M. Gomaa, J. Chem. Soc., Perkin Trans. 1, 2002, 1, 341– 344, DOI: 10.1039/B109711N.
- 26 A. A. Aly, M. Ramadan, M. A. Al-Aziz, H. M. Fathy, S. Bräse,
  A. B. Brown and M. Nieger, *J. Chem. Res.*, 2016, 40, 637–639, DOI: 10.3184/174751916X14743924874916.
- 27 A. A. Hassan, F. F. Abdel-Latif, A. M. N. El-Din, S. M. Mostafa, M. Nieger and S. Bräse, *Tetrahedron*, 2012, 68, 8487–8492, DOI: 10.1016/j.tet.2012.07.063.
- 28 A. A. Aly, A. A. Hassan, M. A. Ameen and A. B. Brown, *Tetrahedron Lett.*, 2008, 49, 4060–4062, DOI: 10.1016/ j.tetlet.2008.04.066.
- 29 A. A. Aly, A. A. Hassan, M. A. M. Gomaa and E. M. El-Sheref, *ARKIVOC*, 2007, **14**, 1–11.
- 30 A. A. Aly, A. M. Nour El-Din, M. A. M. Gomaa, A. B. Brown and M. S. Fahmi, *J. Chem. Res.*, 2007, 8, 439–441, DOI: 10.24820/ ark.5550190.p010.607.
- 31 E. M. El-Sheref, J. Sulfur Chem., 2017, 38, 625–634, DOI: 10.1080/17415993.2017.1337121.
- 32 H. N. Prasad, A. Ananda, S. Najundaswamy, S. Nagashree, L. Mallesha, B. Dayananda, H. Jayanth and P. Mallu, *J.*

*Mol. Struct.*, 2021, **1232**, 130047, DOI: **10.1016**/ **j.molstruc.2021.130047**.

- 33 W. H. Organization, *The evolving threat of antimicrobial resistance: options for action*, World Health Organization, 2012.
- 34 V. Kumar, P. Shetty, H. S. Arunodaya, K. S. Chandra, R. Ramu, S. M. Patil, A. Baliga, V. M. Rai, M. S. Shenoy, V. Udupi, V. Poojary and B. Poojary, *Chem. Biodiversity*, 2022, 19, e20210053, DOI: 10.1002/cbdv.202100532.
- 35 L. Zhang, K. V. Kumar, S. Rasheed, S. L. Zhang, R. X. Geng and C. H Zhou, *MedChemComm*, 2015, 6, 1303–1310, DOI: 10.1039/C5MD00186B.
- 36 S. F. Cui, D. Addla and C. H. Zhou, *J. Med. Chem.*, 2016, **59**, 4488–4510, DOI: **10.1021/acs.jmedchem.5b01678**.
- 37 T. Felicetti, R. Cannalire, M. S. Burali, S. Massari, G. Manfroni, M. L. Barreca, O. Tabarrini, B. D. Schindler, S. Sabatini and G. W. Kaatz, *ChemMedChem*, 2017, 12, 1293–1302, DOI: 10.1002/cmdc.201700286.

- 38 A. A. Hassan, N. K. Mohamed, A. A. Aly, H. N. Tawfeek, H. Hopf, S. Bräse and M. Nieger, *Mol. Diversity*, 2019, 23, 821–828, DOI: 10.1007/s11030-018-09912-5.
- 39 M. A. Moaz, Arab. J. Chem., 2017, 10, 3324-3337, DOI: 10.1016/j.arabjc.2014.01.012.
- 40 B. Bhudevi, P. V. Ramana, A. Mudiraj and A. R. Reddy, *Indian J. Chem., Sect. B: Org. Chem. Incl. Med. Chem.*, 2009, 48, 255–260.
- 41 A. Jayashree and M. Darbarwar, *J. Indian Chem. Soc.*, 2010, **87**, 325–330, DOI: **10.5281/zenodo.5779020**.
- 42 E. A. Mohamed, M. M. Ismail, Y. Gabr and M. Abass, *Chem. Pap.*, 1994, **48**, 285–292. ISSN print edition: 0366-6352.
- 43 A. A. Aly, A. H. Mohamed and M. Ramadan, *J. Mol. Struct.*, 2020, **1207**, 127798, DOI: **10.1016/j.molstruc.2020.127798**.
- 44 B. Bonev, J. Hooper and J. Parisot, *J. Antimicrob. Chemother.*, 2008, **61**, 1295–1301, DOI: **10.1093/jac/dkn090**.
- 45 M. F. Lin, Y. Y. Lin, H. W. Yeh and C. Y. Lan, *BMC Microbiol.*, 2014, 14, 119, DOI: 10.1186/1471-2180-14-119.