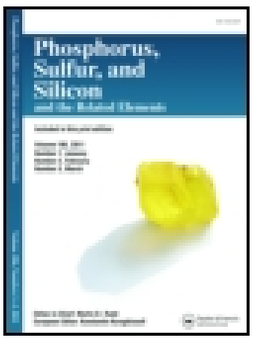

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Synthesis, antibacterial activity and docking studies of substituted quinolone thiosemicarbazones

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ABSTRACT

Fifteen 2-quinolone thiosemicarbazone derivatives of which eleven were new, were synthesized at room temperature. The key intermediate was the quinolone carbaldehyde, from which thiosemicarbazones were formed by the reaction of thiosemicarbazides with the aldehyde moiety. The structures of the synthesized compounds were elucidated by 1D and 2D-NMR spectroscopy and mass spectrometry. The synthesized compounds showed antibacterial activity with MBCs in the range 0.80 to 36.49 mM against *Staphylococcus aureus*, *Staphylococcus aureus* Rosenbach (MRSA), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*, *Escherichia coli* and *Salmonella typhimurium*. The best activity was seen when a larger halogen such as chlorine and bromine were substituted at C-6 on the quinolone scaffold and when a planar phenyl group was present on the thiosemicarbazone moiety. Activity was reduced when a smaller fluorine atom was present at C-6 or when a methyl group was attached to the thiosemicarbazone. This group of compounds showed a high negative binding affinity, which suggested promising antimcrobial activity. The 6-chloro derivative with a phenyl group on the thiosemicarbazone had the greatest negative binding affinity.

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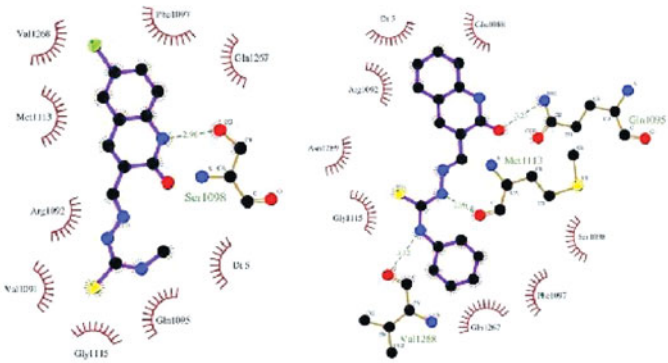
Quinolone; thiosemicarbazone; N-methylthiosemicarbazones; phenylthiosemicarbazones; antibacterial activity

GRAPHICAL ABSTRACT



Introduction

Quinolones are derived from hydroxyquinolines, heterocyclic molecules containing pyridine fused to a benzene ring. These quinolines are synthesized by a variety of methods including the Skraup, Combes, Doebner-von Miller, Knorr and Pfitzinger syntheses.[1] Quinolones are usually formed by the Conrad-Limpach synthesis.[2] Fluoroquinolones in particular are important antibiotics currently prescribed for bacterial infections.[3] They are used in the treatment of respiratory, gastrointestinal, gynaecologic and skin infections, and pneumonia[4,5] and act by interfering with DNA replication.[6] Drugs such as ciprofloxacin and levofloxacin have broad spectrum activity and are drugs of choice against bacterial infections.[7,8] Other derivatives of quinoline have also shown good antimicrobial activity.[9,10]

Thiosemicarbazones belong to a class of Schiff based ligands usually synthesized by condensing aldehydes or ketones with thiosemicarbazide.[11] They can also be prepared by first forming the imine between the aldehyde and hydrazine and then reacting this with isothiocyanate.[12] Thiosemicarbazone derivatives have various pharmacological activities, including antibacterial,[13,14] antioxidant,[15] antimalarial,[16] antitumor,[17] antiviral,[18] anticancer,[19,20] anti-HIV[21] and antitubercular activity.[21]

The combination of two structural scaffolds, each having pharmacological activity of their own could lead to molecules with enhanced therapeutic effects.[22] These molecules

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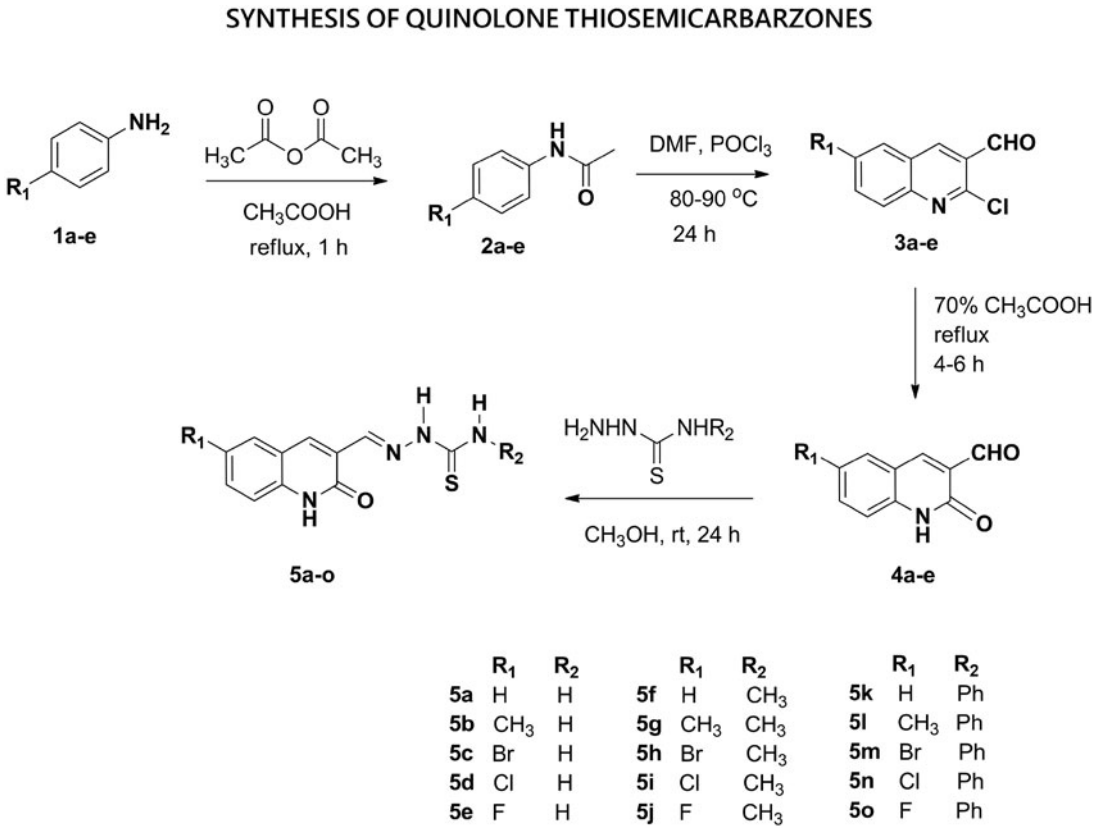

Scheme 1. Synthetic route to the quinoline thiosemicarbazones **5a–o**.

are often referred to as 'molecular hybrids' and extensive work has recently been carried out on quinoline hybrids.[23] Quinoline-thiosemicarbazone hybrids have been prepared by reacting quinoline carbaldehydes with substituted thiosemicarbazides and have shown antibacterial,[24] antifungal,[24] antitubercular,[25] antioxidant,[26–28] anti-inflammatory,[29] and anticancer activity.[27,30,31]

Although similar compounds have been synthesized previously,[27,28] a range of these derivatives halogenated at C-6 have not been synthesized and investigated for their antibacterial activity. Similar compounds have only shown cytotoxic and antioxidant activity.[27,28] Due to the emergence of antibacterial resistance, alternatives to commonly used antibiotics are needed.[32,33] Thus, a small library of quinolone thiosemicarbazones were synthesized and tested for antibacterial activity in order to identify hit compounds to be used as leads in the fight against antibacterial resistance.

Results and discussion

Chemistry

Fifteen derivatives of quinolone-thiosemicarbazone hybrids were prepared, starting with the acetylation of anilines (**1a–e**) with acetic anhydride (forming acetanilides **2a–e**) and then forming the 3-formyl-2-quinolines **3a–e** using the Vilsmeier-Haack reaction with dimethyl formamide and phosphoryl chloride,[34] which under acidic conditions formed the quinolines **4a–e**. Reaction of the quinoline-3-carbaldehydes with methyl or phenylhydrazides **4a–e** with thiosemicarbazide, 4-methyl- or 4-phenylthiosemicarbazide, produced the final quinolone thiosemicarbazone derivatives **5a–o**[31] (Scheme 1). The yields obtained for the final compounds were between 69 and 96%. The synthesized compounds contained electron donating hydrogen and methyl groups and electron withdrawing halogens at C-6 on the quinolone scaffold and the thiosemicarbazone was varied with methyl and phenyl groups to determine the best possible functionalities for antibacterial activity.

Of the 15 derivatives synthesized, only **5a**, **5b**, **5f** and **5k** were previously reported.[27,28] All quinolones containing a halogen at C-6 and two of the quinolones containing a methyl at C-6 were new.

The synthesized compounds were characterized using ^{1}H, ^{13}C, 2D NMR spectroscopy and mass spectrometry. For example, the ^{1}H NMR spectrum of **5d**, the 6-chloro derivative, showed the presence of the quinoline ring with two doublets at δ_H 7.67 (2.3 Hz, H-5) and δ_H 7.31 (8.8 Hz, H-8) and a double doublet at δ_H 7.53 (8.8, 2.3 Hz, H-7). H-4 occurred as a singlet at δ_H 8.70 and NH-1 occurred at δ_H 12.12. J^3 HMBC correlations of H-8 with C-6 and C-4a allowed both these carbon singlets to be assigned to δ_C 126.5 and 120.3 respectively, while H-4, H-5 and H-7 all showed J^3 HMBC correlations to C-8a at δ_C 137.5. The quinolone carbonyl resonance was present at δ_C 178.1

The thiosemicarbazone moiety was characterized by the H-9 (imine) proton occurring as a singlet at δ_H 8.25. The NH-11 proton resonance occurred at δ_H 11.69 and two broadened singlets at δ_H 8.35 and 8.04 were attributed to NH-13a and NH-13b. The thiosemicarbazone carbon, C-12 occurred at δ_C160.7.

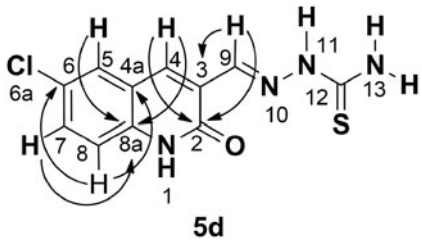

Figure 1. Key HMBC correlations for **5d**.

Table 1. Antibacterial activity of the quinolone-thiosemicarbazone hybrids (MBC in mM).

Compound			Gram positive		Gram negative			
No.	R_1	R_2	MRSA	*S.a*	*P.a*	*S.t*	*E.c*	*K.p*
5g	CH_3	CH_3	18	9.1	9.1	9.1	4.6	37
5l	CH_3	Phenyl	0.93	3.7	1.9	0.93	30	7.4
5m	Br	Phenyl	0.80	3.1	25	6.3	6.3	25
5n	Cl	Phenyl	0.88	1.8	7.0	7.0	7.0	28
5o	F	Phenyl	15	1.8	29	15	15	29
Levofloxacin			0.087	0.022	0.35	0.0216	0.00034	0.022
Ciprofloxacin			0.19	0.094	0.19	0.0030	0.0030	0.0030

Confirmation that the thiosemicarbazone fragment was linked to the quinolone core was indicated by the J^2 HMBC correlation of H-9 to C-3 at δ_C 126.1 and the J^3 HMBC correlation of H-9 to C-2. Important HMBC correlations are depicted in Figure 1.

Antibacterial study

The synthesized quinolone thiosemicarbazones were tested for their antibacterial activity against two Gram positive bacteria (*S. aureus* and methicillin resistant *S. aureus* (MRSA)) and four Gram negative strains (*P. aeruginosa*, *K. pneumoniae*, *E. coli* and *S. typhimurium*). In general, the *N*-phenyl thiosemicarbazones showed better activity than the *N*-methyl or unsubstituted thiosemicarbazone derivatives, with three of the compounds, **5l** (6-methyl), **5m** (6-bromo) and **5n** (6-chloro) showing activity of <1 mM against MRSA, being just one order of magnitude lower than that of levofloxacin and comparable to ciprofloxacin, currently used antibiotics.

However, all other quinolones had MBC values with 2 orders of magnitude worse than levofloxacin and 3 orders of magnitude worse than ciprofloxacin against the strains tested with the exception of *E. coli* where the activity of the compounds were 4–5 orders of magnitude worse than levofloxacin (Table 1). This indicates that in order for activity to occur, a large substituent such as chlorine, bromine or methyl is essential at C-6 and a planar aromatic ring is needed on the thiosemicarbazone portion of the molecule. This was indicated by reduced activity when a methyl group was present on the thiosemicarbazone (as in **5g**) and when a small fluorine atom was present at C-6 (as in **5o**).

Comparing the five active compounds, **5l** and **5n** showed the broadest spectrum of activity, being active at < 10 mM against 5 of the 6 strains tested against. In the literature, derivatives of 8-hydroxyquinoline thiosemicarbazones were inactive against *S. aureus*, *P. aeruginosa* and *Micrococcus luteus*, however all were active with small zones of inhibition in disc diffusion assays against *Serratia marcescens* and derivatisation of the thiosemicarbazone moiety led to moderate activity against *Bacillus cereus*, *E. coli* and *S. marcescens*.[35,36]

Table 2. Binding affinities for the quinolone-thiosemicarbazone hybrids against DNA Gyrase.

Inhibitor	Binding affinity (kcal/mol)
5g	−9.6
5k	−11.1
5l	−10.9
5n	−11.3
5o	−9.1
Levofloxacin	−13.4

Molecular docking

Quinolones such as ciprofloxacin bind to DNA gyrase, a type II topoisomerase enzyme, to inhibit negative supercoiling of DNA by preventing ligation of dsDNA breaks. The structure of the DNA gyrase complex was used as a starting point for modeling. The docking of substituted quinolone thiosemicarbazones was carried out using the potential binding sites of the receptor DNA gyrase. The main goal was to understand the ability of the synthesized molecules to interact with the target.

The docking study with the assistance of lig-plot (Figures S1–S3) indicated that compound **5g** (Figure S3) showed a similar binding mode to Ciprofloxacin, a quinolone reported to inhibit negative supercoiling of DNA by preventing ligation of dsDNA breaks. The corresponding binding affinity for each antagonist is displayed in Table 2. The test compounds showed a high –ve binding affinity and hence suggested promising antimicrobial activity. However, improvements to these structures are still needed since none of the quinolone derivatives had more binding affinity than the reference ligand. Of the five compounds, **5n** showed the highest binding affinity and this structure could be used as a starting point for modification. These results are encouraging due to a number of different hydrogen interactions observed from the different complexes. These interactions could provide a mechanism of action for the tested compounds and indicate the possibility of developing novel antibacterial agents targeting an early step in peptidoglycan biosynthesis.

Conclusions

A series of 2-chloroquinolone-3-thiosemicarbazones (**5a–o**) were easily prepared from quinolone carbaldehyde precursors. Three compounds showed good activity against MRSA, only one order of magnitude lower than levofloxacin. Better activity was seen by those compounds with a *N*-phenyl group in the thiosemicarbazide moiety and with a halogen or methyl group at C-6 on the quinolone framework. Although the thiosemicarbazones had moderate activity, the results indicate that 6-methyl and 6-chloroquinolone *N*-phenyl thiosemicarbazone moieties could be a useful scaffold to synthesize antibacterial compounds.

Experimental

General

Reagents and solvents were supplied by Sigma Aldrich, via Capital Laboratories, South Africa. Silica gel 60 (63–200 μm) was used for column chromatography. Alumina-backed silica gel 40 F_{254} plates (Merck) were used for TLC and visualized under a UV lamp at 254 nm. Melting points were determined on an Electrothermal IA 9100 Digital melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin Elmer Spectrum 100 instrument with Universal ATR sampling accessory. ^{1}H, ^{13}C and 2D NMR spectra were acquired on Bruker Avance^{III} 400 or 600 MHz spectrometers (Bruker Co., Karlsruhe, Germany) at frequencies of 400.22 MHz for ^{1}H and 100.63 MHz for ^{13}C and referenced to TMS. High-resolution mass spectral data was acquired on a Waters Micromass LCT Premier TOF-MS instrument. UV analysis was carried out on a UV-VIS-NIR Shimadzu series 3600 spectrophotometer using methanol as a solvent. The Supplemental Materials contains sample ^{1}H and ^{13}C NMR spectra for **5a–o** (Figures S3–S62).

General procedure for synthesis of 2-chloroquinoline-3-carbaldehydes (3a–e)

The different derivatives were synthesized using the method in Toth et al.[34]

General procedure for the synthesis of N-methyl, N-phenyl and thiosemicarbazone derivatives (5a–o)

The substituted 2-chloroquinoline-3-carbaldehydes (**3a–e**) (1 mmol) was heated under reflux with 70% acetic acid (10 mL) for 4–6 h and upon cooling the product preciptated out of solution to form (**4a–e**). The thiosemicarbazone derivatives were then formed according to the method in Bisceglie et al.[31] Substituted thiosemicarbazides, 4-methyl thiosemicarbazides or 4-phenylthiosemicarbazides (1.0 mmol) dissolved in methanol (80 mL) were added to an equivalent amount of **4a–e** (200 mg; 1.0 mmol) and the solution stirred at room temperature for 24 h. Upon completion, the flask was placed in an ice bath, where a solid formed, which was filtered, washed with ethanol and dried.

*2-Oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone (**5a**)* yellow solid (74% yield), mp 296–298 °C, IR υ_{max} (cm^{-1}): 3369 (Ar-N-H), 3267, 3148 (N-H), 1642 (C = O), 1519 (C = N), 824 (C = S); UV λ_{max} (MeOH) nm (log ε) 242 (4.11), 382 (4.15); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 11.99 (1H, s, H-1), 11.63 (1H, s, H-11), 8.74 (1H, s, H-4), 8.27 (2H, bs, H-9, H-13a), 8.09 (1H, bs, H-13b), 7.65 (1H, dd, J = 8.4, 1.0 Hz, H-5), 7.51 (1H, td, J = 8.4, 1.4 Hz, H-6), 7.31 (1H, d, J = 8.2 Hz, H-8), 7.31 (1H, td, J = 8.2, 1.0 Hz, H-7); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 178.0 (C-12), 160.9 (C-2), 138.8 (C-8a), 136.8 (C-9), 135.1 (C-4), 130.9 (C-6), 128.5 (C-5), 125.2 (C-3), 122.4 (C-7), 119.2 (C-4a), 115.1 (C-8); HRMS: (*m/z*) 269.0475 [M + Na] (calculated for $C_{11}H_{10}N_4ONaS$, 269.0473).

*6-Methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone (**5b**)* yellow solid (90% yield), mp 287–289 °C, IR υ_{max} (cm^{-1}): 3273 (Ar-N-H), 3155, 3015 (N-H), 1651 (C = O), 1531 (C = N), 810 (C = S); UV λ_{max} (MeOH) nm (log ε) 223 (3.90), 245 (3.82), 351 (4.10), 388 (4.22); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 11.92 (1H, s, H-1), 11.62 (1H, s, H-11), 8.69 (1H, s, H-4), 8.29 (1H, bs, H-13a), 8.26 (1H, s, H-9), 8.07 (1H, bs, H-13b), 7.42 (1H, bs, H-5), 7.35 (1H, dd, J = 8.4, 1.7 Hz, H-7), 7.22 (1H, d, J = 8.4 Hz, H-8), 2.34 (3H, s, H-6a); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 178.0 (C-12), 160.8 (C-2), 136.9 (C-8a), 136.8 (C-9), 134.8 (C-4), 132.3 (C-7), 131.3 (C-6), 128.8 (C-5), 125.2 (C-3), 119.1 (C-4a), 115.1 (C-8), 20.4 (C-6a).

*6-Bromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone (**5c**)* yellow solid (69% yield), mp 281–283 °C, IR υ_{max} (cm^{-1}): 3350 (Ar-N-H), 3214, 3146 (N-H), 1642 (C = O), 1514 (C = N), 821 (C = S); UV λ_{max} (MeOH) nm (log ε): 245 (4.37), 352 (4.05), 389 (4.17); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.13 (1H, s, H-1), 11.70 (1H, s, H-11), 8.72 (1H, s, H-4), 8.38 (1H, bs, H-13a), 8.24 (1H, s, H-9), 8.03 (1H, bs, H-13b), 7.80 (1H, d, J = 2.0 Hz, H-5), 7.66 (1H, dd, J = 8.8, 2.0 Hz, H-7), 7.26 (1H, d, J = 8.8 Hz, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 184.1 (C-12), 160.7 (C-2), 137.8 (C-8a), 136.1 (C-9), 133.7 (C-4), 133.3 (C-7), 130.1 (C-5), 126.5 (C-3), 120.9 (C-6), 117.3 (C-8), 113.8 (C-4a); HRMS: (*m/z*) 346.9578 [M + Na] (calculated for $C_{11}H_9N_4ONaSBr$, 346.9578).

*6-Chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone (**5d**)* yellow solid (94% yield), mp 283–285 °C, IR υ_{max} (cm^{-1}): 3259 (Ar-N-H), 3192, 3151 (N-H), 1645 (C = O), 1519 (C = N), 824 (C = S); UV λ_{max} (MeOH) nm (log ε): 242 (4.43), 352 (4.08), 387 (4.20); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.12 (1H, s, H-1), 11.69 (1H, s, H-11), 8.70 (1H, s, H-4), 8.35 (1H, s, H-13a), 8.25 (1H, s, H-9), 8.04 (1H, s, H-13b), 7.67 (1H, d, J = 2.3 Hz, H-5), 7.54 (1H, dd, J = 8.8, 2.3 Hz, H-7), 7.32 (1H, d, J = 8.8 Hz, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 178.1 (C-12), 160.7 (C-2), 137.5 (C-8a), 136.2 (C-9), 133.8 (C-4), 130.7 (C-7), 127.1 (C-5), 126.5 (C-6), 126.1 (C-3), 120.3 (C-4a), 117.1 (C-8); HRMS: (*m/z*) 303.0086 [M + Na] (calculated for $C_{11}H_9N_4ONaSCl$, 303.0083).

*6-Fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde thiosemicarbazone (**5e**)* yellow solid (94% yield), mp 284–286 °C, IR υ_{max} (cm^{-1}): 3273 (Ar-N-H), 3144, 3048 (N-H), 1642 (C = O), 1527 (C = N), 806 (C = S); UV λ_{max} (MeOH) nm (log ε): 223 (4.21), 351 (3.76), 387 (3.89); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.07 (1H, s, H-1), 11.69 (1H, s, H-11), 8.72 (1H, s, H-4), 8.35 (1H, bs, H-13a), 8.26 (1H, s, H-9), 8.05 (1H, bs, H-13b), 7.45-7.39 (2H, m, H-5, H-7), 7.34 (1H, dd, J = 8.6, 4.8 Hz, H-8); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 178.0 (C-12), 160.5 (C-2), 157.0 (d, J = 237.3 Hz, C-6), 136.2 (C-9), 136.2 (C-8a), 133.9 (C-4), 126.4 (C-3), 119.7 (d, J = 8.9 Hz, C-4a), 118.9 (d, J = 24.5 Hz, C-7), 116.9 (d, J = 8.5 Hz, C-8), 112.6 (d, J = 22.4 Hz, C-5); HRMS: (*m/z*) 287.0380 [M + Na] (calculated for $C_{11}H_9N_4OFNaS$, 287.0379).

*2-Oxo-1,2-dihydroquinoline-3-carbaldehyde N-methylthiosemicarbazone (**5f**)* yellow solid (78% yield), mp 285–287 °C,

IR υ_{max} (cm^{-1}) 3341 (Ar-N-H), 3156 (N-H), 1641 (C = O), 1526 (C = N), 809 (C = S), UV λ_{max} (MeOH) nm (log ε): 233 (4.30), 385 (4.06); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.02 (1H, s, H-1), 11.69 (1H, s, H-11), 8.67 (1H, s, H-4), 8.59 (1H, q, J = 4.5 Hz, H-13), 8.28 (1H, s, H-9), 7.66 (1H, d, J = 7.6 Hz, H-5), 7.52 (1H, td, J = 8.2, 0.9 Hz, H-7), 7.32 (1H, d, J = 8.2 Hz, H-8) , 7.23 (1H, t, J = 7.6, Hz, H-6), 3.05 (3H, d, J = 4.5 Hz, H-14); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 177.7 (C-12), 160.9 (C-2), 138.8 (C-8a), 136.3 (C-9), 134.6 (C-4), 130.9 (C-6), 128.4 (C-7), 125.5 (C-3), 122.4 (C-5), 119.1 (C-4a), 115.2 (C-8), 30.8 (C-14); HRMS: (*m/z*) 283.0632 [M + Na]; (calculated for $C_{12}H_{12}N_4ONaS$, 283.0630).

*6-Methyl-2-oxo-1,2-dihydroquinoline-3-carbaldeyde N-methylthiosemicarbazone (**5g**)* yellow solid (88% yield), mp 340–342 °C, IR υ_{max} (cm^{-1}): 3342 (Ar-N-H), 3245, 3161 (N-H), 1648 (C = O), 1518 (C = N), 838 (C = S); UV λ_{max} (MeOH) nm (log ε): 245 (4.36), 390 (4.22); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 11.94 (1H, s, H-1), 11.68 (1H, s, H-11), 8.61 (1H, s, H-4), 8.57 (1H, q, J = 4.6 Hz, H-13), 8.27 (1H, s, H-9), 7.43 (1H, bs, H-5), 7.35 (1H, dd, J = 8.4, 1.7 Hz, H-7), 7.23 (1H, d, J = 8.4 Hz, H-8), 3.05 (3H, d, J = 4.6 Hz, H-14), 2.35 (3H, s, H-6a); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 177.7 (C-12), 160.8 (C-2), 136.9 (C-8a), 136.4 (C-9), 134.4 (C-4), 132.3 (C-7), 131.3 (C-6), 127.7 (C-5), 125.4 (C-3), 119.1 (C-4a), 115.1 (C-8), 30.8 (C-14), 20.4 (C-6a); HRMS: (*m/z*) 297.0785 [M + Na] (calculated for $C_{13}H_{14}N_4ONaS$, 297.0786).

*6-Bromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-methylthiosemicarbazone (**5h**)* yellow solid (72% yield), mp 332–334 °C, IR υ_{max} (cm^{-1}): 3379 (Ar-N-H), 3300, 3148 (N-H), 1652 (C = O), 1519 (C = N), 816 (C = S); UV λ_{max} (MeOH) nm (log ε): 247 (4.44), 392 (4.20); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.15 (1H, s, H-1), 11.76 (1H, s, H-11), 8.63 (1H, s, H-4), 8.55 (1H, q, J = 4.6 Hz, H-13), 8.25 (1H, s, H-9), 7.83 (1H, d, J = 2.2 Hz, H-5), 7.67 (1H, dd, J = 8.8, 2.2 Hz, H-7), 7.27 (1H, d, J = 8.8 Hz, H-8), 3.05 (3H, d, J = 4.6 Hz, H-14); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 177.8 (C-12), 160.7 (C-2), 137.8 (C-8a), 135.7 (C-9), 133.3 (C-7), 133.2 (C-4), 130.1 (C-5), 126.7 (C-3), 120.8 (C-6), 117.4 (C-8), 113.8 (C-4a), 30.8 (C-14); HRMS: (*m/z*) 336.9761 [M-H] (calculated for $C_{12}H_{10}N_4OSBr$, 336.9759).

*6-Chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-methylthiosemicarbazone (**5i**)* yellow solid (78% yield), mp 324–326 °C, IR υ_{max} (cm^{-1}): 3373 (Ar-N-H), 3165 (N-H), 1647 (C = O), 1520 (C = N), 818 (C = S); UV λ_{max} (MeOH) nm (log ε): 245 (4.41), 390 (4.29); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.15 (1H, s, H-1), 11.76 (1H, s, H-11), 8.63 (1H, s, H-4), 8.56 (1H, q, J = 4.6 Hz, H-13), 8.25 (1H, s, H-9), 7.69 (1H, d, J = 2.3 Hz, H-5) , 7.56 (1H, dd, J = 8.8, 2.3 Hz, H-7), 7.33 (1H, d, J = 8.8 Hz, H-8), 3.05 (3H, d, J = 4.6 Hz, H-14); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 177.8 (C-12), 160.7 (C-2), 137.5 (C-8a), 135.8 (C-9), 133.4 (C-4), 130.6 (C-7), 127.0 (C-5), 126.8 (C-6), 126.1 (C-3), 120.3 (C-4a), 117.1 (C-8), 30.8 (C-14); HRMS: (*m/z*) 293.0273 [M-H] (calculated for $C_{12}H_{10}N_4OSCl$, 293.0264).

*6-Fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-methylthiosemicarbazone (**5j**)* yellow solid (79% yield), mp 297–299 °C, IR υ_{max} (cm^{-1}): 3399 (Ar-N-H), 3172 (N-H), 1663 (C = O), 1501 (C = N), 825 (C = S); UV λ_{max} (MeOH) nm (log ε): 229 (4.31), 280 (4.37); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.09 (1H, s, H-1), 11.74 (1H, s, H-11), 8.62 (1H, s, H-4), 8.58 (1H, q, J = 4.5 Hz, H-13), 8.27 (1H, s, H-9), 7.44 (1H, d, J = 8.6 Hz, H-5), 7.43 (1H, td, J = 8.6, 2.8 Hz, H-7), 7.34 (1H, dd, J = 8.6, 4.8 Hz, H-8), 3.05 (3H, d, J = 4.5 Hz, H-14); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 177.8 (C-12), 160.6 (C-2), 157.1 (d, J = 237.2 Hz, C-6), 135.9 (C-9), 135.6 (C-8a), 133.7 (d, J = 3.8 Hz, C-4), 126.7 (C-3), 119.7 (d, J = 8.9 Hz, C-4a), 118.9 (d, J = 24.6 Hz, C-5), 117.1 (d, J = 8.5 Hz, C-8), 112.7 (d, J = 22.4 Hz, C-7), 30.8 (C-14); HRMS: (*m/z*) 301.0529 [M + Na] (calculated for $C_{12}H_{11}N_4OFNaS$, 301.0535).

*2-Oxo-1,2-dihydroquinoline-3-carbaldehyde N-phenylthiosemicarbazone (**5k**)* yellow solid (94%), mp 331–333 °C, IR υ_{max} (cm^{-1}): 3306 (Ar-N-H), 3164 (N-H), 1650 (C = O), 1529 (C = N), 815 (C = S); UV λ_{max} (MeOH) nm (log ε): 238 (4.36), 388 (4.36); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.04 (2H, s, H-1/H-11), 10.16 (1H, s, H-13), 8.87 (1H, s, H-4), 8.40 (1H, s, H-9), 7.68 (1H, d, J = 7.7 Hz, H-8), 7.58 (2H, d, J = 7.6 Hz, H-2'/6'), 7.53 (1H, td, J = 7.7, 1.2 Hz, H-7), 7.39 (2H, t, J = 7.6 Hz, H-3'/5'), 7.33 (1H, d, J = 8.2 Hz, H-5), 7.20-7.25 (2H, m, H-4', H-6); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.0 (C-12), 160.9 (C-2), 138.98 (C-8a), 138.96 (C-1'), 137.5 (C-9), 135.5 (C-4), 131.1 (C-7), 128.5 (C-5), 128.1 (C-3'/5'), 126.1 (C-2'/6'), 125.5 (C-4'), 125.1 (C-3), 122.4 (C-6), 119.1 (C-4a), 115.2 (C-8); HRMS: (*m/z*) 345.0777 [M + Na] (calculated for $C_{17}H_{14}N_4ONaS$, 345.0786).

*6-Methyl-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-phenylthiosemicarbazone (**5l**)* yellow solid (96% yield), mp 344–346 °C; IR υ_{max} (cm^{-1}): 3312 (Ar-N-H), 3140 (N-H), 1651 (C = O), 1530 (C = N), 823 (C = S); UV λ_{max} (MeOH) nm (log ε): 246 (4.31), 357 (4.15), 393 (4.26); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.03 (1H, s, H-1), 11.97 (1H, s, H-11), 10.14 (1H, s, H-13), 8.80 (1H, s, H-4), 8.40 (1H, s, H-9), 7.58 (2H, d, J = 7.7 Hz, H-2'/6'), 7.46 (1H, bs, H-5), 7.35-7.41 (3H, m, H-3'/4'/5'); 7.21-7.25 (2H, m, H-7, H-8), 2.34 (3H, s, H-6a); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 176.0 (C-12), 160.9 (C-2), 138.9 (C-1'), 137.6 (C-9), 137.1 (C-8a), 135.3 (C-4), 132.4 (C-7), 131.3 (C-6), 128.1 (C-3'/5'), 127.9 (C-5), 125.9 (C-2'/6'), 125.5 (C-4'), 125.0 (C-3), 119.1 (C-4a), 115.1 (C-8), 20.4 (C-6a); HRMS: (*m/z*) 359.0943 [M + Na] (calculated for $C_{18}H_{16}N_4ONaS$, 359.0943).

*6-Bromo-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-phenylthiosemicarbazone (**5m**)* yellow solid (82% yield), mp 339–341 °C; IR υ_{max} (cm^{-1}): 3323 (Ar-N-H), 3141 (N-H), 1647 (C = O), 1526 (C = N), 815 (C = S); UV λ_{max} (MeOH) nm (log ε): 220 (4.37), 247 (4.36), 393 (4.21); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.17 (1H, s, H-1), 12.11 (1H, s, H-11), 10.10 (1H, s, H-13), 8.81 (1H, s, H-4), 8.37 (1H, s, H-9), 7.85 (1H, d, J = 2.2 Hz, H-5), 7.67 (1H, dd, J = 8.8, 2.2 Hz, H-7), 7.59 (2H, d, J = 7.6 Hz, H-2'/6'), 7.40 (2H, t, J = 7.6 Hz, H-3'/5'), 7.35 (1H, d, J = 8.8 Hz, H-8), 7.24 (1H, t, J = 7.6 Hz, H-4'); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 176.1 (C-12), 160.7 (C-2), 138.8 (C-1'), 137.6 (C-8a), 136.8 (C-9), 134.1 (C-4), 133.4 (C-7), 130.2 (C-5), 128.2 (C-3'/5'), 126.3 (C-3), 125.9 (C-2'/6'), 125.5 (C-4'), 120.8 (C-6), 117.4

(C-8), 113.8 (C-4a); HRMS: (*m/z*) 422.9888 [M + Na] (calculated for $C_{17}H_{13}N_4ONaSBr$, 422.9891).

6-Chloro-2-oxo-1,2-dihydroquinoline-3-carbaldehyde N-phenylthiosemicarbazone (***5n***) yellow solid (86% yield), mp 325–327 °C; IR υ_{max} (cm^{-1}): 3315 (Ar-N-H), 3146 (N-H), 1650 (C = O), 1527 (C = N), 819 (C = S); UV λ_{max} (MeOH) nm (log ε): 230 (4.17), 245 (4.25), 393 (4.12); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.17 (1H, s, H-1), 12.10 (1H, s, H-11), 10.11 (1H, s, H-13), 8.81 (1H, s, H-4), 8.37 (1H, s, H-9), 7.71 (1H, d, J = 2.4 Hz, H-5), 7.60 (2H, d, J = 7.6 Hz, H-2'/6'), 7.56 (1H, dd, J = 8.8, 2.4 Hz, H-7), 7.40 (2H, t, J = 7.6 Hz, H-3'/5'), 7.34 (1H, d, J = 8.8 Hz, H-8), 7.24 (1H, t, J = 7.6 Hz, H-4'); ^{13}C NMR (DMSO-d_6, 100 MHz) δ_C 176.1 (C-12), 160.7 (C-2), 138.9 (C-1'), 137.6 (C-8a), 136.9 (C-9), 134.2 (C-4), 130.8 (C-7), 128.2 (C-3'/5'), 127.2 (C-5), 126.4 (C-3), 126.1 (C-4a), 125.9 (C-2'/6'), 125.5 (C-4'), 120.3 (C-6), 117.1 (C-8); HRMS: (*m/z*) 379.0394 [M + Na] (calculated for $C_{17}H_{13}N_4ONaSCl$, 379.0396).

6-Fluoro-2-oxo-1,2-dihydroquinoline-3-carbaldehdye N-phenylthiosemicarbazone (***5o***) yellow solid (90% yield), mp 296–298 °C, IR υ_{max} (cm^{-1}): 3312 (Ar-N-H), 3156 (N-H), 1650 (C = O), 1531 (C = N), 826 (C = S); UV λ_{max} (MeOH) nm (log ε): 223 (4.42), 351 (4.45), 387 (4.46); ^{1}H NMR (DMSO-d_6, 400 MHz) δ_H 12.12 (1H, s, H-1), 12.09 (1H, s, H-11), 10.14 (1H, s, H-13), 8.81 (1H, s, H-4), 8.39 (1H, s, H-9), 7.58 (2H, d, J = 7.6 Hz, H-2'/6'), 7.34-7.46 (5H, m, H-5, H-7, H-8, H-3'/5'), 7.23 (1H, t, J = 7.6, Hz, H-4'); ^{13}C NMR (DMSO-d_6, 100 MHz) δ 176.1 (C-12), 160.6 (C-2), 157.1 (d, J = 237.4 Hz, C-6), 138.9 (C-1'), 137.0 (C-9), 135.7 (C-8a), 134.5 (d, J = 3.4 Hz, C-4), 128.1 (C-3'/5'), 126.4 (C-3), 125.9 (C-2'/6'), 125.5 (C-4'), 119.7 (d, J = 8.9 Hz, C-4a), 119.2 (d, J = 24.7 Hz, C-7), 117.1 (d, J = 8.1 Hz, C-8), 112.8 (d, J = 22.4 Hz, C-5); HRMS: (*m/z*) 363.0686 [M + Na] (calculated for $C_{17}H_{13}N_4OFNaS$, 363.0692).

Antibacterial activity

The thiosemicarbazone derivatives were tested for antibacterial activity against two Gram positive strains, *S. aureus* ATCC 25923 *(S.a)*, and *S. aureus* Rosenbach ATCC BAA-1683 (methicillin resistant *S. aureus,* MRSA) and four Gram negative bacterial strains (*P. aeruginosa* ATCC 27853 *(P.a)*, *K. pneumoniae* ATCC 31488 *(K.p), E. coli* ATCC 25922 *(E.c)* and *S. typhimurium ATCC 14026 (S.t)).* The compounds were first subject to a preliminary screen using the disc diffusion assay[37] and based on their activity, selected compounds were chosen to determine their minimum bactericidal concentration (MBC).

The different bacterial strains were grown in Nutrient Broth (Biolab, South Africa) at 37 °C in a shaking incubator at 115 rpm for 18 h. The bacteria were diluted with sterile distilled water to achieve a final concentration equivalent to a 0.5 McFarland's standard using a McFarland's densitometer. Mueller-Hinton agar plates (Biolab, South Africa) were lawn inoculated with the bacteria using a throat swab. A 5 µL sample of each compound (10 mg mL^{-1} in DMSO) was placed onto the Mueller-Hinton plates in triplicate and incubated at 37 °C for 18 h. After the incubation period, the plates were examined for activity, which was indicated by zones of inhibition around the area where the sample was placed. Those compounds that showed broad spectrum activity were selected for the MBC assay.

The MBCs were determined in triplicate using a modification of the Broth Dilution Method.[38] A 10 mg sample of the test compounds was dissolved in 1 mL DMSO and serially diluted in triplicate. Mueller-Hinton agar plates were lawn inoculated with the different bacterial strains, which were prepared as described above. A 5 µL sample of each dilution of the selected compounds was spotted onto the Mueller-Hinton agar plates and incubated for 24 h at 37 °C. The experiment was conducted in triplicate and averaged. The MBC was the lowest concentration that showed a zone of inhibition around the area where the sample was placed.

Molecular docking

The crystal structure (PDB ID: 2XCT) of the DNA gyrase complex was taken from the Protein from the RSCB Protein Data Bank.[39] The missing residues were added using a graphical user interface tool of molecular modeling, Chimera[40] and a ligand interaction map was generated using the web version of Pose View. The docking calculations were performed using Autodock Vina.[41] During docking, Geister partial chargers were assigned and the Autodock atom types were defined using the Autodock Graphical user interface supplied by MGL tools.[42] The docked conformations were generated using the Lamarckian Genetic Algorithm, considered to be one of the best docking methods available.[43,44] The files were converted into the pdbqt format required for docking using Raccoon software. The gridbox was defined using Autodock Vina with the grid parameters being X = 40, Y = 36 and Z = 24 for the dimensions and X = 54.750, Y = 39.250 and Z = −19.389 for the center grid box and the reports for each calculation were in (kcal/mol). This technique has been validated in previous studies.[45]

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