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Green synthesis of highly functionalized octahydropyrrolo[3,4-*c*]pyrrole derivatives using subcritical water, and their anti(myco)bacterial and antifungal activity

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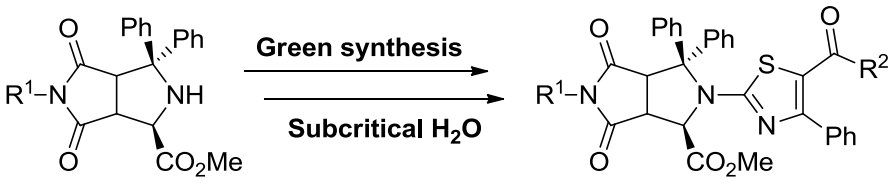
Abstract

A series of novel 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrroles was synthesized by reaction of octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives and α-haloketones in subcritical water at 130 °C in 75-91% yield. Both the thiourea intermediates and the end products were synthesized in subcritical water, which proved a suitable green alternative to acetone by delivering the desired compounds in much shorter reaction times and practically the same yields. The antimicrobial activity of the compounds was determined against five bacterial strains and three fungal strains, and MIC values of 15.62-250 μg/mL were observed. Moreover, the compounds exhibited antimycobacterial activity against *M. tuberculosis H37Rv* with MIC values of 7.81-62.5 μg/mL.



Keywords: Green chemistry, subcritical water, thiazole, pyrrolidine, pyrrolidinedione, antimicrobial

Introduction

Thiazole derivatives containing nitrogen and sulphur atoms are among the most important pharmacophore groups in drug research studies[1] and it is known that many drugs[1-3] and natural products[4] such as Abafungin, Famotidin, Meloxicam and Ritonavir contain a thiazole ring in their structures.[1-4] Thiazoles are present in a wide range of pharmacologically active compounds exhibiting antibacterial,[5-8] antimycobacterial,[9-11] antifungal,[5-8] anticancer[12-14] and antiviral[15,16] activity. Furthermore, thiazole derivatives are useful as chemosensors[17] and fluorescent sensors.[18]

The pyrrolidine moiety has been intensively studied in medicinal chemistry[19] due to its presence in the structure of many biologically active compounds such as anisomycin[20] and hygrine.[21] Furthermore, pyrrolidine derivatives show various pharmacological activities such as antimicrobial,[22-24] antiviral[25] and anticancer activity.[26,27] In addition, pyrrolidine-2,5-dione derivatives have also been reported to exhibit a wide range of pharmacological activities such as antimicrobial[28] and anticonvulsant activity.[29] Compounds containing pyrrolidine fused to pyrrolidine-2,5-dione represent an important class of bicyclic ring systems in drug research and exhibit various pharmacological activities such as antibacterial[30,31] and anticancer activity.[32]

Subcritical water is a green alternative to conventional solvents due to being an environmentally friendly, cheap, safe and non-toxic solvent.[33] Water, which is heated at a temperature range of 100 °C – 374.2 °C and pressurized enough to keep it in the liquid state in this range is defined as subcritical water.[34] Subcritical water offers the unique medium for various processes such as oxidation, extraction,[35,36] solubility[37] and organic reaction synthesis[38] through tunable solvent and other physico-chemical properties.[36] The dielectric constant that determines the polarity of a solvent can be easily reduced by increasing the temperature in subcritical water.[39] Thus, subcritical water acts as a non-polar solvent like ethanol or methanol, providing a favorable medium for organic synthesis. Many reactions such as alkylation, condensation, coupling, decomposition, Diels-Alder, decarboxylation, dehydration, elimination reactions and nano-synthesis can be carried out using subcritical water.[38,40,41]

In this study, we designed and synthesized octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthioureas and a series of novel 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives in subcritical water as green solvent, and investigated their anti(myco)bacterial and antifungal activities.

Result and Discussion

The synthesis of octahydropyrrolo[3,4-*c*]pyrrole derivatives **2a-b** was performed according to a literature method[42] *via* a 1,3-dipolar cycloaddition reaction of methyl 2-(diphenylmethyleneamino)acetate and *N*-methylmaleimide or *N*-phenylmaleimide in 85% and 82% yield, respectively.

The synthesis of the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b** and 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** in subcritical water was performed in a reaction apparatus as depicted in Figure 1. The experiments were carried out in a home-made stainless steel reactor with an internal volume of 200 mL equipped with a heater-magnetic stirrer. To synthesize the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b**, the reactor was loaded with octahydropyrrolo[3,4-*c*]pyrroles **2a-b** (1 mmol), benzoyl isothiocyanate (2 mmol) and 75 mL of ultra-pure water. After purging the reactor air with nitrogen, the internal pressure of the reactor was fixed at 30 bar supplied by nitrogen. Each experiment was performed at 130 °C for 4 hours under stirring. Finally, the reactor was depressurized and the obtained

mixture was extracted using dichloromethane. The crude product was purified by column chromatography (EtOAc:hexane / 1:3) to afford compounds **3a-b** in 80-82% yield (Scheme 1, Table 1).

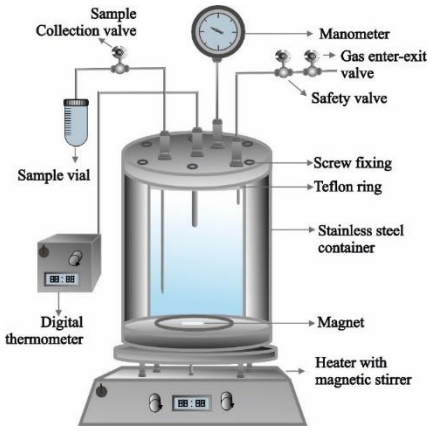
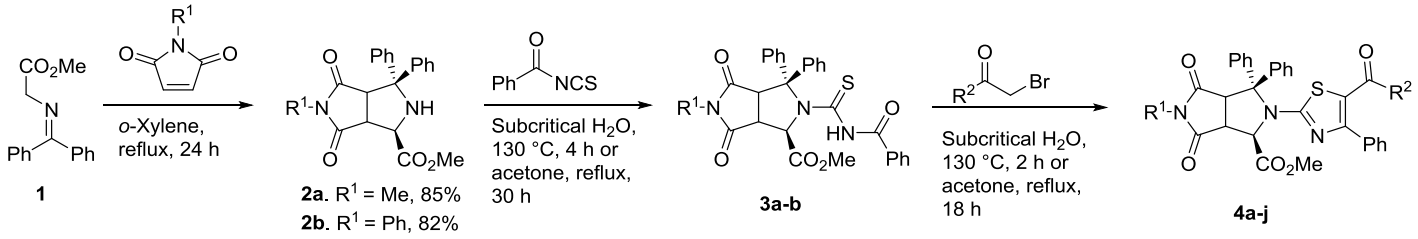


Figure 1. Schematic representation of the reactor equipped with a heater-magnetic stirrer.

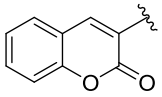
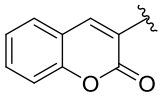
For the synthesis of 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** in subcritical water, a similar procedure described above was applied. Briefly, the reactor was loaded with octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea **3a** or **3b** (1 mmol), an appropriate α-haloketone (1.2 mmol) and 75 mL of ultra-pure water. After purging the air in the reactor with nitrogen, the internal pressure of the reactor was fixed at 30 bar supplied by nitrogen. Each experiment was performed at 130 °C for 2 hours under stirring. Finally, the reactor was depressurized and the obtained mixture was extracted using dichloromethane. The crude product was purified by column chromatography (EtOAc:hexane / 1:4) to afford compounds **4a-j** in 74-91% yield (Scheme 1, Table 1).

Furthermore, the synthesis of the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b** and the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** in subcritical water was compared with their synthesis in conventional organic solvent. The synthesis of compounds **3a-b** was performed in acetone at reflux temperature for 30 hours and the products were obtained in 80-82% yield. Similarly, the synthesis of compounds **4a-j** was also performed in acetone at reflux temperature for 18 hours and the products were obtained in 67-89% yield. Thus, the synthesis in subcritical water has practically the same yields but has the advantages of a shorter reaction time and of being a green solvent. It can be said that subcritical water is an excellent alternative to conventional organic solvent for the synthesis of both octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea and 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrroles.



Scheme 1. Synthesis of the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives.

Table 1. Structure and yield of compounds **3** and **4**

Entry	R^1	R^2	Yield (%)[a]	Yield (%)[b]
3a	Me	-	86	82
3b	Ph	-	80	80
4a	Me	Ph	78	67
4b	Me	4-CN-C_6H_4	90	84
4c	Me	4-Br-C_6H_4	83	68
4d	Me	2,4-Cl_2-C_6H_4	84	75
4e	Me		91	85
4f	Ph	Ph	74	76
4g	Ph	4-CN-C_6H_4	88	80
4h	Ph	4-Br-C_6H_4	75	71
4i	Ph	2,4-Cl_2-C_6H_4	81	76
4j	Ph		90	89

[a] Yield of the reaction in subcritical water. [b] Yield of the reaction in acetone.

The antimicrobial activity screening of the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b** and 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** was performed against five standard bacterial strains, one standard mycobacterium strain and three standard fungal strains. The compounds **3a-b** and **4a-j** exhibited antibacterial activity in the range of 15.62-250 μg/mL (Table 2). The compounds **3a-b** were less active than the reference compound Ampicillin against *S. aureus*, *B. subtilis* and *E. coli*. However, compound **3a** was more active than Ampicillin against the *A. hydrophila* and *A*. *baumannii* strains, and compound **3b** showed the same antibacterial activity as Ampicillin against these two strains. The compounds **4a-j** exhibited lower antibacterial activity than the reference compound Ampicillin against *B. subtilis*, *A. hydrophila* and *E. coli*. Compound **4b** exhibited similar antibacterial activity as Ampicillin against the *S. aureus* strain, with a MIC value of 31.25 μg/mL. Furthermore, compounds **4d** and **4j** were more active than Ampicillin against *A*. *baumannii*, an opportunistic pathogen with increasing importance in nosocomial infections. The other 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-c**, **4e-i** exhibited similar antibacterial activity with Ampicillin against the *A*. *baumannii* strain.

Table 2. The MIC values (μg/mL) of the tested compounds against the microbial strains.

Entry	*S. aureus*	*B. subtilis*	*A. hydrophila*	*E. coli*	*A. baumannii*	*C. glabrata*	*C. tropicalis*	*C. parapsilosis*	*M. tuberculosis H37Rv*
3a	125	15.62	**15.62**	250	**62.5**	31.25	125	62.5	62.5
3b	250	62.5	**31.25**	250	125	31.25	125	62.5	62.5
4a	62.5	125	125	250	125	31.25	125	62.5	7.81
4b	**31.25**	125	125	125	125	31.25	125	62.5	62.5

Entry	*S. aureus*	*B. subtilis*	*A. hydrophila*	*E. coli*	*A. baumannii*	*C. glabrata*	*C. tropicalis*	*C. parapsilosis*	*M. tuberculosis H37Rv*
4c	125	125	125	250	125	31.25	125	62.5	31.25
4d	125	125	125	250	62.5	31.25	62.5	62.5	31.25
4e	62.5	250	125	250	125	15.62	125	31.25	31.25
4f	125	125	125	250	125	62.5	250	62.5	62.5
4g	125	250	125	250	125	31.25	250	62.5	62.5
4h	125	125	125	250	125	31.25	250	62.5	62.5
4i	250	250	125	125	125	31.25	125	31.25	31.25
4j	125	125	125	250	**62.5**	31.25	125	62.5	31.25
Ampicillin	**31.25**	**0.98**	**31.25**	**15.62**	**125**	-	-	-	-
Fluconazole	-	-	-	-	-	**3.90**	**15.62**	**3.90**	-
Isoniazid	-	-	-	-	-	-	-	-	**0.98**
Ethambutol	-	-	-	-	-	-	-	-	**1.96**

MIC: The minimal inhibitory concentrations

The compounds **3a-b**, **4a-j** showed antifungal activity, in the range of 15.62-250 μg/mL, but did not exhibit higher antifungal activity than the reference compound Fluconazole, which exhibited antifungal activity against the fungi with MIC values in the range of 3.90-15.62 μg/mL (Table 2). It can be said that all of the tested compounds exhibited moderate antifungal activity against the mentioned fungi. Compounds **3a-b**, **4a-j** were also tested against the *Mycobacterium tuberculosis H37Rv* strain. Compound **4a** performed best with a MIC value of 7.81 μg/mL, but none of the compounds scored better than the reference drug Isoniazid.

Conclusions

The synthesis of octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b** and the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** was successfully performed in subcritical water as a green solvent. Despite the fact that reactive agents such as isothiocyanates and α-haloketones were used, applying subcritical water as a solvent resulted in a significant decrease of reaction times, while maintaining high yields. The synthesized compounds displayed moderate antimicrobial activity against different bacterial and fungal strains and against the *Mycobacterium tuberculosis H37Rv* strain.

Experimental Section

General. All chemicals used had high-grade commercial products purchased from Merck or Aldrich and all solvents provided by commercial suppliers had reagent grade quality and were used without further purification. A Varian Scimitar Series 1000 FT-IR spectrophotometer, using horizontal ATR, was used. Nuclear magnetic resonance spectra were determined at 400 MHz on a Bruker Ultrashield Plus Biospin GmbH. Chemical shifts are given in parts per million (δ) downfield from TMS as internal standard. Flash column chromatography was performed using silica gel 60 (230-400 mesh). Kieselgel columns were packed with silica

gel GF254. Melting points were determined on a Mettler Toledo MP90 device. Mass spectra were recorded by an Agilent 6460 Triple Quad LC/MS/MS mass spectrometer. High resolution mass spectra were recorded by an LC-MS TOF electrospray ionization technique.

General procedure for the synthesis of octahydropyrrolo[3,4-*c*]pyrrole derivatives (2a,b). The compounds **2a,b** were synthesized using a literature method.[42] To a stirred solution of methyl 2-(diphenylmethyleneamino) acetate **1** (1 mmol) in *o*-xylene (10 mL) was added a solution of N-substituted maleimide (2 mmol) in *o*-xylene (20 mL) and the reaction mixture was refluxed for 24 h. After completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate. The crude mixture was purified by column chromatography (EtOAc:hexane / 1:5) to give **2a,b** as colourless crystals.

(1*R*)-Methyl 5-methyl-4,6-dioxo-3,3-diphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (2a). Crystallized from EtOAc:hexane as colorless prisms. Yield, 0.31 g, 85%. mp 204-206 °C. IR (cm^{-1}): 3326 (m), 3053(w), 2954 (w), 1743 (s), 1694 (vs). ^{1}H NMR (400 MHz, DMSO-d_6): δ 7.51-7.49 (m, 2H, Ar-H), 7.39-7.15 (m, 8H, Ar-H), 4.27 (d, 1H, *J* 7.3 Hz, 4-H), 3.67 (s, 3H, OCH_3), 3.60 (dd, 1H, *J* 8.0 Hz, 7.4 Hz, 3-H), 3.49 (d, 1H, *J* 8.0 Hz, 2-H), 2.71 (s, 3H, NCH_3). ^{13}CNMR (100 MHz, DMSO-d_6): δ 176.0 (C=O), 175.1 (C=O), 170.4 (C=O), 144.9, 142.7, 128.3 (2 x C), 127.3 (2 x C), 127.2 (2 x C), 127.0, 126.6 (2 x C), 126.5, 71.9, 59.0, 51.8, 51.6, 47.9, 24.6. MS (ESI, M+H$^+$): *m/z* 365.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{21}H_{21}N_2O_4$ $[MH]^+$ 365.1501; found 365.1500.

(1*R*)-Methyl 4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (2b). Crystallized from EtOAc:hexane as colorless prisms. Yield, 0.35 g, 82%. mp 212-214 °C. IR (cm^{-1}): 3273 (m), 3065 (w), 2961 (w), 1716 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): δ 7.47-7.20 (m, 13H, Ar-H), 7.11-7.09 (m, 2H, Ar-H), 4.28 (d, 1H, *J* 7.5 Hz, 4-H), 3.87 (dd, 1H, *J* 7.2 Hz, 6.8 Hz, 2-H), 3.79 (s, 3H, OCH_3), 3.68 (dd, 1H, *J* 7.5 Hz, 7.2 Hz, 3-H), 2.90 (d, 1H, *J* 6.8 Hz, NH). ^{13}CNMR (100 MHz, $CDCl_3$): δ 175.0 (C=O), 174.0 (C=O), 170.7 (C=O), 144.5, 141.5, 131.7, 129.0 (2 x C), 128.9 (2 x C), 128.5, 128.0 (2 x C), 127.8, 127.7, 127.4 (2 x C), 126.5 (2 x C), 126.3 (2 x C), 73.7, 60.2, 52.9, 52.4, 49.1. MS (ESI, M+H$^+$): *m/z* 427.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{26}H_{23}N_2O_4$ $[MH]^+$ 427.1658; found 427.1662.

General procedure for the synthesis of the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives 3a,b in subcritical water. The experiments were carried out in a home-made stainless steel reactor with an internal volume of 200 mL. To synthesize the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a-b**, the reactor and magnet were firstly flushed with water and acetone, then thoroughly dried with nitrogen gas. The reactor was loaded with octahydropyrrolo[3,4-*c*]pyrroles **2a-b** (1 mmol), benzoyl isothiocyanate (2 mmol) and 75 mL of ultra-pure water, after that the reactor cover screws were tightly clamped. After purging the air in the reactor with nitrogen, the internal pressure of the reactor was fixed at 30 bar supplied by nitrogen. Each experiment was performed at 130 °C for 4 hours under stirring. Finally, the reactor was cooled, depressurized, and the obtained mixture was extracted using dichloromethane (DCM). The crude product was purified by column chromatography (EtOAc:hexane / 1:3) to afford compounds **3a-b**.

General procedure for synthesis of the octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives (3a,b) in acetone. The octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivatives **3a,b** were also synthesized by modification of a literature method.[43,44] To a stirred solution of **2a** (0.37 g, 1 mmol) or **2b** (0.43 g, 1 mmol) in acetone (20 mL) was added a solution of benzoyl isothiocyanate (0.33 g, 2 mmol) in acetone (10 mL) and the mixture was stirred at reflux temperature for 36 h. After completion of the reaction, the solvent was evaporated under reduced pressure and the crude mixture was purified by column chromatography (EtOAc:hexane / 1:3) to afford compound **3a,b**. Structures of **3a,b** were confirmed by NMR and MS techniques.

(1*R*)-Methyl 2-(benzoylcarbamothioyl)-5-methyl-4,6-dioxo-3,3-diphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (3a). Crystallized from DCM:hexane as yellow prisms. Yield, 0.45 g, 86%. mp 110-112 °C. IR (cm^{-1}): 3351 (m), 3063 (w), 2950 (w), 1741 (m), 1704 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.44 (s, 1H, N-H), 7.53-7.33 (m, 11H, Ar-H), 7.12 (t, 2H, *J* 7.6 Hz, Ar-H), 6.75 (d, 2H, *J* 7.6 Hz, Ar-H), 5.71 (d, 1H, *J* 10.4 Hz, 2-H), 4.33 (d, 1H, *J* 9.6 Hz, 4-H), 3.95 (s, 3H, OCH_3), 3.86-3.81 (m, 1H, 3-H), 2.71 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 178.4 (C=S), 173.5 (C=O), 172.9 (C=O), 168.5 (C=O), 163.6 (C=O), 140.3, 137.5, 133.0, 132.5, 129.9 (2 x C), 129.0 (2 x C), 128.8 (2 x C), 128.6 (2 x C), 128.4 (2 x C), 127.8 (2 x C), 127.0 (2 x C), 66.7, 63.2, 52.8 (2 x C), 44.1, 25.0. MS (ESI, M-H$^+$): *m/z* 526.1 (M-H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{29}H_{26}N_3O_5S$ $[MH]^+$ 528.1593; found 528.1597.

(1*R*)-Methyl 2-(benzoylcarbamothioyl)-4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (3b). Crystallized from DCM:hexane as yellow prisms. Yield, 0.47 g, 80%. mp 185-187 °C. IR (cm^{-1}): 3356 (m), 3060 (w), 2947 (w), 1716 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 8.44 (s, 1H, N-H), 7.55-7.50 (m, 6H, Ar-H), 7.39-7.32 (m, 8H, Ar-H), 7.15-7.11 (m, 2H, Ar-H), 6.81-6.77 (m, 4H, Ar-H), 5.82 (d, 1H, *J* 10.3 Hz, 2-H), 4.52 (d, 1H, *J* 9.7 Hz, 4-H), 4.08-4.03 (m, 1H, 3-H), 3.92 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 178.3 (C=S), 172.7 (C=O), 171.8 (C=O), 168.4 (C=O), 163.5 (C=O), 140.6, 137.0, 133.0, 132.5, 131.0, 129.9, 129.3, 129.1 (2 x C), 129.0 (2 x C), 128.9 (2 x C), 128.7, 128.4, 128.0, 127.8, 127.3, 127.0, 126.4, 126.3, 126.0 (3 x C), 79.7, 66.7, 63.1, 52.9, 44.3. MS (ESI, M-H$^+$): *m/z* 588.1 (M-H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{34}H_{28}N_3O_5S$ $[MH]^+$ 590.1750; found 590.1750.

General procedure for the synthesis of the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives (4a-j) in subcritical water. The experiments were carried out in steel reactor which was identified in the synthesis of **3a,b** and the same operations described above were applied. To synthesize the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j**, the required octahydropyrrolo[3,4-*c*]pyrrole *N*-benzoylthiourea derivative **3a** or **3b** (1 mmol), an appropriate α-haloketone (1.2 mmol) and 75 mL of ultra-pure water were loaded to the reactor. After purging the air in the reactor with nitrogen, the internal pressure of the reactor was fixed at 30 bar supplied by nitrogen. Each experiment was performed at 130 °C for 2 hours under stirring. Finally, the reactor was cooled, depressurized, and the obtained mixture was extracted using DCM. The crude product was purified by column chromatography (EtOAc:hexane / 1:4) to afford compounds **4a-j**.

General procedure for synthesis of the 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives (4a-j) in acetone. The 2-(thiazol-2-yl)-octahydropyrrolo[3,4-*c*]pyrrole derivatives **4a-j** were synthesized using a literature method.[45] To a stirred solution of **3a** (0.53 g, 1 mmol) or **3b** (0.59 g, 1 mmol) in acetone (20 mL) was added a solution of an appropriate α-haloketone (1.2 mmol) in acetone (10 mL) and the mixture was stirred at reflux temperature for 18 h. After completion of the reaction, the solvent was evaporated under reduced pressure, quenched with saturated aqueous sodium chloride and extracted with DCM. The crude mixture was purified by column chromatography (EtOAc:hexane/1:4) to afford compound **4a-j**. Structures of **4a-j** were confirmed by NMR and MS techniques.

(1*R*)-Methyl 2-(5-benzoyl-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3,3-diphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4a). Crystallized from DCM:hexane as yellow prisms. Yield, 0.49 g, 78%. mp 145-147 °C (decomp). IR (cm^{-1}): υ 3056 (w), 2924 (w), 1707 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.66-7.64(m, 2H, Ar-H), 7.44-7.36 (m, 10H, Ar-H), 7.24-7.21 (m, 3H, Ar-H), 7.13-7.02 (m, 5H, Ar-H), 5.29 (d, 1H, *J* 10.0 Hz, 2-H), 4.20 (d, 1H, *J* 9.2, 4-H), 3.93 (s, 3H, OCH_3), 3.84-3.79 (m, 1H, 3-H), 2.90 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 189.0 (C=O), 174.4 (C=O), 173.4 (C=O), 169.8 (C=O), 166.7, 154.8, 139.7,137.7, 135.0, 134.3, 131.9, 130.3 (2 x C), 129.9 (2 x C), 129.5, 129.4 (2 x C), 128.8 (2 x C), 128.7 (2 x C), 128.6, 128.4 (2 x C), 128.3, 127.7 (2 x C), 127.6

(2 x C), 125.6, 78.4, 65.2, 61.5, 52.6, 45.7, 25.3. MS (ESI, M+H$^+$): *m/z* 628.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{37}H_{30}N_3O_5S$ [MH]$^+$ 628.1906; found 628.1898.

(1*R*)-Methyl 2-(5-(4-cyanobenzoyl)-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3,3-diphenyl-octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (4b). Crystallized from DCM:hexane as yellow prisms. Yield, 0.59 g, 90%. mp 180-182 °C (decomp). IR (cm^{-1}): 3061 (w), 2981 (w), 2231 (w), 1745 (m), 1707 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.67-7.65 (m, 2H, Ar-H), 7.44-7.29 (m, 12H, Ar-H), 7.17-7.12 (m, 3H, Ar-H), 7.06-7.03 (m, 2H, Ar-H), 5.30 (d, 1H, *J* 10.0 Hz, 2-H), 4.21 (d, 1H, *J* 9.2 Hz, 4-H), 3.93 (s, 3H, OCH_3), 3.85-3.81 (m, 1H, 3-H), 2.90 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 187.1 (C=O), 174.2 (C=O), 173.2 (C=O), 169.7 (C=O), 167.6, 156.3, 141.5, 139.5, 134.8 133.9, 131.4 (2 x C), 130.3 (2 x C), 130.0 (2 x C), 129.7, 129.6(2 x C), 129.2, 128.9 (2 x C), 128.7 (2 x C), 128.5, 128.4 (2 x C), 127.7 (2 x C), 125.4, 118.0, 114.6, 78.5, 65.3, 61.8, 52.7, 45.7, 25.3. MS (ESI, M+H$^+$): *m/z* 653.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{38}H_{29}N_4O_5S$ [MH]$^+$ 653.1859; found 653.1864.

(1*R*)-Methyl 2-(5-(4-bromobenzoyl)-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3,3-diphenyl-octahydropyrrolo [3,4-*c*]pyrrole-1-carboxylate (4c). Crystallized from DCM:hexane as yellow prisms. Yield, 0.59 g, 83%. mp 181-183 °C (decomp). IR (cm^{-1}): 3061 (w), 2951 (w), 1744 (m), 1705 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.59-7.57 (m, 2H, Ar-H), 7.36-7.31 (m, 8H, Ar-H), 7.19-6.99 (m, 9H, Ar-H), 5.22 (d, 1H, *J* 10.0 Hz, 2-H), 4.14 (d, 1H, *J* 9.2 Hz, 4-H), 3.86 (s, 3H, OCH_3), 3.77-3.72 (m, 1H, 3-H), 2.83 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 187.7 (C=O), 174.3(C=O), 173.3 (C=O), 169.7 (C=O), 166.9, 155.1, 139.6, 136.5, 134.9, 134.1, 130.9 (4 x C), 130.3 (2 x C), 129.9 (2 x C), 129.5, 128.8 (3 x C), 128.7 (2 x C), 128.4 (3 x C), 127.7 (2 x C), 126.7, 125.3, 78.4, 65.2, 61.6, 52.6, 45.7, 25.3. MS (ESI, M+H$^+$): *m/z* 706.2 (M+H$^+$, 100), 708.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{37}H_{29}BrN_3O_5S$ [MH]$^+$ 706.1011; found 706.0995.

(1*R*)-Methyl 2-(5-(2,4-dichlorobenzoyl)-4-phenylthiazol-2-yl)-5-methyl-4,6-dioxo-3,3-diphenyl-octahydro-pyrrolo[3,4-*c*]pyrrole-1-carboxylate (4d). Crystallized from DCM:hexane as yellow prisms. Yield, 0.58 g, 84%. mp 264-266 °C (decomp). IR (cm^{-1}): 3086 (w), 2918 (w), 1744 (m), 1706 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.65-7.63 (m, 2H, Ar-H), 7.44-7.38 (m, 8H, Ar-H), 7.18-7.14 (m, 3H, Ar-H), 7.07-7.03 (m, 3H, Ar-H), 6.87 (d, 1H, *J* 8.2 Hz, Ar-H), 6.79 (dd, 1H, *J* 8.2 Hz, 1.9 Hz, Ar-H), 5.26 (d, 1H, *J* 10.0 Hz, 2-H), 4.20 (d, 1H, *J* 9.2 Hz, 4-H), 3.86 (s, 3H, OCH_3), 3.83-3.78 (m, 1H,3-H), 2.88 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 185.5 (C=O), 174.2 (C=O), 173.3 (C=O), 169.5 (C=O), 168.1, 157.4, 139.5, 136.7, 136.2, 134.7, 133.8, 132.7, 130.6, 130.3 (2 x C), 129.6, 129.5 (3 x C), 128.8 (3 x C), 128.7 (2 x C), 128.4, 129.3 (2 x C), 127.4 (3 x C), 126.2, 78.6, 65.2, 61.7, 52.6, 45.6, 25.3. MS (ESI, M+H$^+$): *m/z* 696.2 (M+H$^+$, 100), 697.2 (M+H$^+$, 45), 698.2 (M+H$^+$, 75). HRMS (ESI-TOF-MS): calcd. for $C_{37}H_{28}Cl_2N_3O_5S$ [MH]$^+$ 696.1127; found 696.1120.

(1*R*)-Methyl 5-methyl-4,6-dioxo-2-(5-(2-oxo-2H-chromene-3-carbonyl)-4-phenylthiazol-2-yl)-3,3-diphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4e). Crystallized from DCM:hexane as yellow prisms. Yield, 0.63 g, 91%. mp 200-202 °C (decomp). IR (cm^{-1}): 3063 (w), 2981 (w), 1733 (m), 1708 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.67 (m 2H, Ar-H), 7.44-7.41 (m, 9H, Ar-H), 7.30-7.26 (m, 3H, Ar-H), 7.23-7.21 (m, 1H, Ar-H), 7.18-7.11 (m, 2H, Ar-H), 7.07-6.99 (m, 3H, Ar-H), 5.28 (d, 1H, *J* 10.0 Hz, 2-H), 4.23 (d, 1H, *J* 9.2 Hz, 4-H), 3.87 (s, 3H, OCH_3), 3.84-3.79 (m, 1H, 3-H), 2.87 (s, 3H, NCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): *δ* 182.6 (C=O), 174.2 (C=O), 173.2 (C=O), 169.6 (C=O), 168.1 (C=O), 157.7 (2 x C), 154.0, 142.8, 139.4, 134.6, 134.5, 132.9, 130.3 (2 x C), 129.6 (3 x C), 128.9 (3 x C), 128.7 (2 x C), 128.5 (2 x C), 128.4 (2 x C), 127.8 (2 x C), 127.2, 127.1, 124.4, 117.8, 116.4, 78.6, 65.3, 61.8, 52.6, 45.7, 25.3. MS (ESI, M+H$^+$): *m/z* 696.2 (M+H$^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{40}H_{30}N_3O_7S$ [MH]$^+$ 696.1804; found 696.1797.

(1*R*)-Methyl 2-(5-benzoyl-4-phenylthiazol-2-yl)-4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4f). Crystallized from DCM:hexane as yellow prisms. Yield, 0.44 g, 74%. mp 251-253 °C (decomp). IR (cm^{-1}): 3063 (w), 2981 (w), 1750 (m), 1717 (vs). ^{1}H NMR (400 MHz, $CDCl_3$): *δ* 7.78 (brs, 2H, Ar-H), 7.49-7.35 (m, 16H, Ar-H), 7.25-7.22 (m, 3H, Ar-H), 7.13-7.02 (m, 4H, Ar-H), 5.39 (d, 1H, *J* 9.9 Hz, 2-H), 4.38 (d, 1H, *J* 9.4, 4-

H), 3.99-3.94 (m, 1H, 3-H), 3.93 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 189.0 (C=O), 173.5 (C=O), 172.3 (C=O), 169.8 (C=O), 166.5, 154.8, 139.8, 137.7, 134.7, 134.3, 131.9, 131.4, 130.6 (2 x C), 129.9 (2 x C), 129.5, 129.4 (2 x C), 129.2 (2 x C), 128.9, 128.8 (2 x C), 128.7, 128.6 (2 x C), 128.5, 128.0, 127.7 (2 x C), 127.6 (2 x C), 127.3, 126.4, 126.3 (2 x C), 78.7, 65.5, 61.6, 52.7, 45.7. MS (ESI, $M+H^+$): *m/z* 690.2 ($M+H^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{42}H_{32}N_3O_5S$ $[MH]^+$ 690.2063; found 690.2053.

(1*R*)-Methyl 2-(5-(4-cyanobenzoyl)-4-phenylthiazol-2-yl)-4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4g). Crystallized from DCM:hexane as yellow prisms. Yield, 0.63 g, 88%. mp 166-168 °C (decomp). IR (cm^{-1}): 3061 (w), 2923 (w), 2229 (w), 1751 (m), 1719 (vs). ^1H NMR (400 MHz, $CDCl_3$): δ 7.80 (brs, 2H, Ar-H), 7.48-7.38 (m, 13H, Ar-H), 7.31-7.26 (m, 2H, Ar-H), 7.17-7.13 (m, 3H, Ar-H), 7.07-7.03 (m, 4H, Ar-H), 5.42 (d, 1H, *J* 10.0 Hz, 2-H), 4.42 (d, 1H, *J* 9.4 Hz, 4-H), 4.04-4.00 (m, 1H, 3-H), 3.93 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.1 (C=O), 173.3 (C=O), 172.1 (C=O), 169.7 (C=O), 167.5, 156.4, 141.5, 139.6, 134.8 133.9, 131.4 (2 x C), 131.3, 130.6 (2 x C), 130.0 (2 x C), 129.7, 129.6 (2 x C), 129.2 (3 x C), 129.0, 128.9 (2 x C), 128.8 (2 x C), 128.6, 128.5 (2 x C), 127.8 (2 x C), 126.2 (2 x C), 125.5, 118.0, 114.6, 78.9, 65.6, 61.8, 52.8, 45.7. MS (ESI, $M+H^+$): *m/z* 715.2 ($M+H^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{43}H_{31}N_4O_5S$ $[MH]^+$ 715.2015; found 715.2029.

(1*R*)-Methyl 2-(5-(4-bromobenzoyl)-4-phenylthiazol-2-yl)-4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo[3,4-c]pyrrole-1-carboxylate (4h). Crystallized from DCM:hexane as yellow prisms. Yield, 0.58 g, 75%. mp 165-167 °C (decomp). IR (cm^{-1}): 3059 (w), 2956 (w), 1745 (m), 1714 (vs). ^1H NMR (400 MHz, $CDCl_3$): δ 7.79 (brs, 2H, Ar-H), 7.50-7.37 (m, 12H, Ar-H), 7.22-7.16 (m, 6H, Ar-H), 7.11-7.05 (m, 4H, Ar-H), 5.42 (d, 1H, *J* 10.0 Hz, 2-H), 4.41 (d, 1H, *J* 9.4 Hz, 4-H), 4.03-3.99 (m, 1H,3-H), 3.93 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 187.2 (C=O), 173.4 (C=O), 172.2 (C=O), 169.8 (C=O), 166.8, 155.2, 139.7, 136.5, 134.6, 134.1, 131.4, 130.9 (3 x C), 130.6 (2 x C), 129.9 (2 x C), 129.6, 129.2 (3 x C), 128.9, 128.8 (4 x C), 128.5 (3 x C), 127.7 (2 x C), 126.7, 126.2 (3 x C), 125.4, 78.8, 65.6, 61.7, 52.7, 45.7. MS (ESI, $M+H^+$): *m/z* 768.2 ($M+H^+$, 100), 770.2 ($M+H^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{42}H_{31}BrN_3O_5S$ $[MH]^+$ 768.1168; found 768.1150.

(1*R*)-Methyl 2-(5-(2,4-dichlorobenzoyl)-4-phenylthiazol-2-yl)-4,6-dioxo-3,3,5-triphenyl-octahydropyrrolo-[3,4-*c*]pyrrole-1-carboxylate (4i). Crystallized from DCM:hexane as yellow prisms. Yield, 0.61 g, 81%. mp 160-162 °C. IR (cm^{-1}): 3063 (w), 2952 (w), 1750 (m), 1717 (vs). ^1H NMR (400 MHz, $CDCl_3$): δ 7.77 (brs, 2H, Ar-H), 7.45-7.36 (m, 12H, Ar-H), 7.16-7.14 (m, 2H, Ar-H),7.07-7.01 (m, 5H, Ar-H), 6.88 (d, 1H, *J* 8.2 Hz, Ar-H), 6.79 (dd, 1H, *J* 8.2 Hz, 1.9 Hz, Ar-H), 5.36 (d, 1H, *J* 10.0 Hz, 2-H), 4.37 (d, 1H, *J* 9.4 Hz, 4-H), 3.97-3.92 (m, 1H, 3-H), 3.86 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 185.5 (C=O), 173.4 (C=O), 172.2 (C=O), 169.6 (C=O), 168.0, 157.5, 139.6, 136.7, 136.2, 134.3, 133.8, 132.7, 131.3, 130.6, 130.5, 129.7, 129.5 (3 x C), 129.2 (2 x C), 129.0, 128.9 (2 x C), 128.8 (2 x C), 128.6, 128.5 (2 x C), 128.0, 127.4 (2 x C), 127.3, 126.4, 126.3, 126.2 (2 x C), 79.0, 65.6, 61.8, 52.7, 45.7. MS (ESI, $M+H^+$): *m/z* 758.2 ($M+H^+$, 100), 759.2 ($M+H^+$, 45), 760.2 ($M+H^+$, 75). HRMS (ESI-TOF-MS): calcd. for $C_{42}H_{30}Cl_2N_3O_5S$ $[M\ H]^+$ 758.1283; found 758.1280.

(1*R*)-Methyl 4,6-dioxo-2-(5-(2-oxo-2H-chromene-3-carbonyl)-4-phenylthiazol-2-yl)-3,3,5-triphenyl-octa-hydropyrrolo[3,4-*c*]pyrrole-1-carboxylate (4j). Crystallized from DCM:hexane as yellow prisms. Yield, 0.68 g, 90%. mp 310-312 °C (decomp). IR (cm^{-1}): 3063 (w), 2981 (w), 1749 (m), 1719 (vs). ^1H NMR (400 MHz, $CDCl_3$): δ 7.81 (brs, 2H, Ar-H), 7.49-7.36 (m, 13H, Ar-H), 7.31-7.26 (m, 2H, Ar-H), 7.21-7.12 (m, 3H, Ar-H), 7.08-6.99 (m, 5H, Ar-H), 5.40 (d, 1H, *J* 10.0 Hz, 2-H), 4.45 (d, 1H, *J* 9.4 Hz, 4-H), 4.04-3.99 (m, 1H, 3-H), 3.88 (s, 3H, OCH_3). ^{13}C NMR (100 MHz, $CDCl_3$): δ 182.6 (C=O), 173.3 (C=O), 172.1 (C=O), 169.6 (C=O), 167.9 (C=O), 157.7, 157.6, 154.0, 142.8, 139.5, 134.5, 134.3, 132.9, 131.3, 130.6 (2 x C), 129.6 (3 x C), 129.2 (3 x C), 129.0, 128.9 (2 x C), 128.8, 128.6, 128.5 (3 x C), 127.8 (2 x C), 127.2 (2 x C), 126.2 (3 x C), 124.4, 117.8, 116.5, 79.0, 65.6, 61.8, 52.7, 45.7. MS (ESI, $M+H^+$): *m/z* 758.2 ($M+H^+$, 100). HRMS (ESI-TOF-MS): calcd. for $C_{45}H_{32}N_3O_7S$ $[MH]^+$ 758.1961; found 758.1951.

Antibacterial activity. The antibacterial properties of the compounds were determined in duplicate against *Bacillus subtilis* (ATCC 6633) and *Staphylococcus aureus* (ATCC 25925) as Gram-positive bacterial strains and *Acinetobacter baumannii* (ATCC 02026), *Aeromonas hydrophila* (ATCC 95080) and *Escherichia coli* (ATCC 25923) as Gram-negative bacterial strains, acquired from the Refik Saydam Hıfzıssıhha Institute, Ankara, Turkey. The compounds **4a-j** were dissolved in DMSO to prepare the stock solutions, and then diluted in Triptic soy broth and Mueller-Hinton broth to obtain an initial concentration of 1000 µg/mL. Further dilutions of **4a-j** and the control drug ampicillin were prepared at concentrations of 500-0.12 µg/mL. A negative control for the effect of DMSO on microbial growth was performed, using inoculated broth supplemented with DMSO at the same dilutions used for the test compounds, and was determined to be inactive.

Antifungal activity. The antifungal properties of **4a-j** were determined against three yeast strains (*C. parapsilosis* ATCC 22019, *C. glabrata* ATCC 90030 and *C. tropicalis* ATCC 750) using the microdilution broth procedure[46] according to the NCCLS standard document M27-A2.[47] The fungal strains were acquired from Refik Saydam Hıfzıssıhha Institute, Ankara, Turkey. Fluconazole (Sigma, F8929) was used as positive control. Antifungal activity was determined in RPMI 1640 Medium (Sigma, R6504) which was buffered to pH 7.0 with 0.165 M 3-(*N*-morpholino)-propanesulfonic acid (MOPS, Sigma, M1254) as described in the NCCLS document. A working suspension of the fungal strains was made by a 1:100 dilution followed by a 1:20 dilution of the stock suspension with RPMI 1640 medium. Stock solutions of **4a-j** and reference antifungal agent in DMSO were prepared at a concentration of 1000 µg/mL and filtered through a 0.22 µm membrane filter. Serial two fold dilutions of these solutions and reference antifungal agent were prepared in a 96-well microtitre plate using 100 µl RPMI 1640 medium. The tested concentration range was 500-0.12 µg/mL. A growth control containing no antibiotic and a sterility control without inoculum were included in each plate. The working inoculum suspension (100 µl) was added to each plate. The plates were incubated at 35 °C for 48 h in ambient air. The MIC is determined as the lowest concentration of a compound that visually inhibits growth of the organism.

Antimycobacterial activity. Antimycobacterial properties of **4a-j** were determined using the resazurin microtitre assay (REMA) plate method.[48]

Culture medium: 7H9-S medium was used for the REMA plate method, consisting of Middlebrook 7H9 broth (BBL, Becton Dickinson and Company, Sparks, MD, USA) containing 0.1% casitone, 0.5% glycerol and 10% oleic acid-albumin-dextrose-catalase (OADC, BBL, Becton Dickinson and Company, Sparks, MD, USA).

Resazurin reagent: Resazurin sodium salt powder (Sigma R7017) was dissolved in distilled water at a concentration of 0.01% (w/v) and sterilized by filtration through a 0.22 µm membrane filter (Ministar, Sartorius Stedim Biotech GmbH, Goettingen, Germany) to obtain a working solution which was stored at 4 °C for up to 1 week.

The REMA plate method was used in duplicate as described by Nateche et al.[48] with minor changes. Ethambutol (EMB) (Sigma, E4630) and isoniazid (INH) (Sigma, I3377) were used as control agents. *M. tuberculosis* H37Rv was used as the standard strain and was acquired from the Refik Saydam National Public Health Agency, National Tuberculosis Reference Laboratory, Ankara, Turkey. Compounds **4a-j** and the reference compounds were dissolved in DMSO at a concentration of 1000 µg/mL and filtered through a 0.22 µm membrane filter to obtain stock solutions. Serial twofold dilutions of these solutions were prepared in a 96-well microtitre plate using 100 µL 7H9-S. The tested concentration range was 500-0.12 µg/mL. A growth control containing no antibiotic and a sterility control without inoculum were included in each plate. The H37Rv inoculum was prepared by resuspending a loopful of the Lowenstein-Jensen culture medium in a tube containing 5 ml 7H9-S medium with several glass beads. After vortexing the tube for 2 minutes, sediment was allowed to form for 30 minutes. The supernatant was transferred to a second sterile tube and the turbidity

was adjusted to match a McFarland standard No. 1. This suspension was further diluted 1:20 in 7H9-S. The plates were inoculated with 100 µL suspension, sealed in plastic bags and incubated at 37 °C in a normal atmosphere. After 7 days of incubation, 30 µL resazurin working solution was added to each well and the plates were incubated for 24 hours at 37 °C. The results were determined visually. Bacterial growth gives reduction of resazurin and is indicated by a change in color from blue to pink. In order to conclude a positive result, the color change which indicates growth has to be comparable to that observed in the positive growth control. The MIC was defined as the lowest concentration of solution that prevented a full color change of resazurin from blue to pink.

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References

1. Arshadi, S.; Vessally, E.; Edjlali, L.; Hosseinzadeh-Khanmiri, R.; Ghorbani-Kalhor, E. *Beilstein J. Org. Chem*. **2017**, 13, 625-638. https://doi.org/10.3762/bjoc.13.61
2. Das, D.; Sikdar, P.; Bairagi, M. *Eur. J. Med. Chem*. **2016**, 109, 89-98. https://doi.org/10.1016/j.ejmech.2015.12.022
3. Arora, P.; Narang, R.; Nayak, S.K.; Singh, S.K.; Judge, V. *Med. Chem. Res*. **2016**, 25, 1717-1743. https://doi.org/10.1007/s00044-016-1610-2
4. Wang, M.; Zhang, J.; He, S.; Yan, X. *Mar. Drugs* **2017**, 15, Article Number: 126, 1-19.
5. Abhale, Y.K.; Shinde, A.; Deshmukh, K.K.; Nawale, L.; Sarkar, D.; Mhaske, P.C. *Med. Chem. Res.* **2017**, 26, 2557-2567. https://doi.org/10.1007/s00044-017-1955-1
6. Vaickelionienė, R. ; Mickevičius, V. ; Vaickelionis, G. ; Stasevych, M. ; Komarovska-Porokhnyavets, O. ; Novikov, V. *Arkivoc* **2015**, (v), 303-318. http://dx.doi.org/10.3998/ark.5550190.p009.170
7. Kaur, K.; Kumar, V.; Beniwal, V.; Kumar, V.; Kumar, N.; Sharma, V.; Jaglan, S. *Med. Chem. Res*. **2016**, 25, 2237-2249. https://doi.org/10.1007/s00044-016-1663-2
8. Argyropoulou, I.; Geronikaki, A.; Vicini, P.; Zani, F. *Arkivoc* **2009**, (vi), 89-102. http://dx.doi.org/10.3998/ark.5550190.0010.611
9. Bhalerao, M.B.; Dhumal, S.T.; Deshmukh, A.R.; Nawale, L.U.; Khedkar, V; Sarkar, D.; Mane, R.A. *Bioorg Med Chem Lett*. **2017**, 27, 288-294. https://doi.org/10.1016/j.bmcl.2016.11.056
10. Dhumal, S.T.; Deshmukh, A.R.; Bhosle, M.R.; Khedkar, V.M.; Nawale, L.U.; Sarkar, D.; Mane, R.A. *Bioorg. Med. Chem. Lett*. **2016**, 26, 3646-3651. https://doi.org/10.1016/j.bmcl.2016.05.093
11. Surineni, G.; Yogeeswari, P.; Sriram, D.; Kantevari, S. *Bioorg. Med. Chem. Lett*. **2016**, 26, 3684-3689. https://doi.org/10.1016/j.bmcl.2016.05.085

12. Titus, S.; Sreejalekshmi, K.G. *Med. Chem. Res*. **2018**, 27, 23-36. https://doi.org/10.1007/s00044-017-2039-y
13. Olawode, E.O.; Tandlich, R.; Prinsloo, E.; Isaacs, M.; Hoppe, H.; Seldon, R.; Warner, D.F.; Steenkamp, V.; Kaye, P.T. *Arkivoc* **2016**, (vi), 284-296. https://doi.org/10.24820/ark.5550190.p009.905
14. Chen, B-C.; Zhao, R.; Wang, B.; Droghini, R.; Lajeunesse, J.; Sirard, P.; Endo, M.; Balasubramanian, B.; Barrish, J.C. *Arkivoc* **2010**, (vi), 32-38. http://dx.doi.org/10.3998/ark.5550190.0011.604
15. Madni, M.; Hameed, S.; Ahmed, M.N.; Tahir, M.N.; Al-Masoudi, N.A.; Pannecouque, C. *Med. Chem. Res*. **2017**, 26, 2653-2665. https://doi.org/10.1007/s00044-017-1963-1
16. Al-Masoudi, N.A.; Al-Haidery, N.; Faili, N.T.; Pannecouque, C. *Arkivoc* **2010**,(ix), 185-195. http://dx.doi.org/10.3998/ark.5550190.0011.918
17. Sahin, O.; Ozdemir, U.O.; Seferoglu, N.; Genc, Z.K.; Kaya, K.; Aydiner, B.; Tekin, S.; Seferoglu, Z. *J. Photoch. Photobio. B*. **2018**, 178, 428-439.
18. Sun, C.; Su, R.; Bie, J.; Sun, H.; Qiao, S.; Ma, X.; Sun, R.; Zhang, T. *Dyes Pigments* **2018**, 149, 867-875. https://doi.org/10.1016/j.dyepig.2017.11.031
19. Saraswat, P.; Jeyabalan, G.; Hassan, M.Z.; Rahman, M.U.; Nyola, N.K. *Synth. Commun*. **2016**, 46, 1643-1664. https://doi.org/10.1080/00397911.2016.1211704
20. Shi, S.; Zhu, S.; Gerritz, S.W.; Esposito, K.; Padmanabha, R.; Li, W.; Herbst, J.J.; Wong, H.; Shu, Y.Z.; Lam, K.S.; Sofia, M.J. *Bioorg. Med. Chem. Lett*. **2005**, 15, 4151-4154. https://doi.org/10.1016/j.bmcl.2005.06.004
21. Milen, M.; Abranyi-Balogh, P.; Keglevich, G. *Curr. Org. Synth.* **2014**, 11, 889-901. https://doi.org/10.2174/15701794116661408182102 47
22. Nural, Y.; Gemili, M.; Seferoglu, N.; Sahin, E.; Ulger, M.; Sari, H. *J. Mol. Struct*. **2018**, 1160, 375-382. https://doi.org/10.1016/j.molstruc.2018.01.099
23. Dandia, A.; Khan, S.; Soni, P.; Indora, A.; Mahawar, D.K.; Pandya, P.; Chauhan, C.S. *Bioorg. Med. Chem. Lett*. **2017**, 27, 2873-2880. https://doi.org/10.1016/j.bmcl.2017.04.083
24. Ersen, D.; Ulger, M.; Mangelinckx, S.; Gemili, M.; Sahin, E.; Nural, Y. *Med. Chem. Res*. **2017**, 26, 2152-2160. https://doi.org/10.1007/s00044-017-1907-9
25. Kang, I-J.; Hsu, S-J.; Yang, H-Y.; Yeh, T-K.; Lee, C-C.; Lee, Y-C.; Tian, Y-W.; Song, J-S.; Hsu, T-A.; Chao, Y-S.; Yueh, A.; Chern, J-H. *J. Med. Chem.* **2017**, 60, 228-247. https://doi.org/10.1021/acs.jmedchem.6b00962
26. Liang, J.; Labadie, S.; Zhang, B.; Ortwine, D.F.; Patel, S.; Vinogradova, M.; Kiefer, J.R.; Mauer, T.; Gehling, V.S.; Harmange, J-C.; Cummings, R.; Lai, T.; Liao, J.; Zheng, X.; Liu, Y.; Gustafson, A.; Van der Porten, E.; Mao, W.; Liederer, B.M.; Deshmukh, G.; An, L.; Ran, Y.; Classon, M.; Trojer, P.; Dragovich, P.S.; Murray, L. *Bioorg. Med. Chem. Lett.*, **2017**, 27, 2974-2981. https://doi.org/10.1016/j.bmcl.2017.05.016

27. Elías-Rodríguez, P.; Moreno-Clavijo, E.; Carrion-Jimenez, S.; Carmona, A.T.; Moreno-Vargas, A.J.; Caffa, I.; Montecucco, F.; Cea, M.; Nencioni, A.; Robina, I. *Arkivoc* **2014**,(iii), 197-214. http://dx.doi.org/10.3998/ark.5550190.p008.492

28. Ghannay, S.; Bakari, S.; Ghabi, A.; Kadri, A.; Msaddek, M.; Aouadi, K. *Bioorg. Med. Chem. Lett*. **2017**, 27, 2302-2307. https://doi.org/10.1016/j.bmcl.2017.04.044
29. Kamiński, K.; Rzepka, S.; Obniska, J. *Bioorg. Med. Chem. Lett*. **2011**, 21, 5800-5803. https://doi.org/10.1016/j.bmcl.2011.07.118
30. Bharkavi, C.; Kumar, S.V.; Ali, M.A.; Osman, H.; Muthusubramanian, S.; Perumal, S. *Bioorg. Med. Chem. Lett*. **2017**, 27, 3071-3075. https://doi.org/10.1016/j.bmcl.2017.05.050
31. Gemili, M.; Sari, H.; Ulger, M.; Sahin, E.; Nural, Y. *Inorg. Chim. Acta* **2017**, 463, 88-96. https://doi.org/10.1016/j.ica.2017.04.026
32. Thaqi, A.; Scott, J.L.; Gilbert, J.; Sakoff, J.A.; McCluskey, A. *Eur. J. Med. Chem*. **2010**, 45, 1717-1723. https://doi.org/10.1016/j.ejmech.2010.01.004
33. Sirin, O.Z.; Demirkol, O.; Akbaslar, D.; Giray, E.S. *J. Supercrit. Fluid*. **2013**, 81, 217-220. https://doi.org/10.1016/j.supflu.2013.05.014
34. Bubalo, M.C.; Vidović, S.; Redovniković, I.R.; Jokić, S. *J. Chem. Technol. Biotechnol*. **2015**, 90, 1631-1639. https://doi.org/10.1002/jctb.4668
35. Yabalak, E.; Adiguzel, S.K.; Adiguzel, A.O.; Ergene, R.S.; Tuncer, M.; Gizir, A.M. *Desalin. Water. Treat*. **2017**, 81, 186-198. https://doi.org/10.5004/dwt.2017.21089
36. Yabalak, E.; Gizir, A.M. *J. Serb. Chem. Soc.* **2013**, 78, 1013-1022. https://doi.org/10.2298/JSC120321123Y
37. Yabalak, E.; Görmez, Ö.; Gözmen, B.; Gizir, A.M. *Int. J. Ind. Chem*. **2015**, 6, 23-29. https://doi.org/10.1007/s40090-014-0028-2
38. Kus, N.S. *Tetrahedron* **2012**, 68, 949-958. https://doi.org/10.1016/j.tet.2011.10.070
39. Ramos, L.; Kristenson, E.M.; Brinkman, U.A.T. *J. Chromatogr. A* **2002**, 975, 3-29. https://doi.org/10.1016/S0021-9673(02)01336-5
40. Pirmoradi, M.; Kastner, J.R. *ACS Sustain. Chem. Eng*. **2017**, 5, 1517-1527. https://doi.org/10.1021/acssuschemeng.6b02201
41. Kim, M.; Lee, B.Y.; Ham, H.C.; Han, J.; Nam, S.W.; Lee, H-S, Park, J.H.; Choi, S.; Shin, Y. *J. Supercrit. Fluid*. **2016**, 111, 8-13. https://doi.org/10.1016/j.supflu.2016.01.011
42. Khlebnikov, A.F.; Novikov, M.S.; Khlebnikov, V.A.; Kostikov, R.R. *Russ. J. Org. Chem*. **2001**, 37, 507-512. https://doi.org/10.1023/A:1012425701412
43. Gumus, I.; Solmaz, U.; Binzet, G.; Keskin, E.; Arslan, B.; Arslan, H. *J. Mol. Struct*. **2018**, 1157, 78-88. https://doi.org/10.1016/j.molstruc.2017.12.017
44. Binzet, G.; Gumus, I.; Dogen, A.; Florke, U.; Kulcu, N.; Arslan, H. *J. Mol. Struct*. **2018**, 1161, 519-529. https://doi.org/10.1016/j.molstruc.2018.02.073
45. Thomas, K.K.; Reshmy, R.; Ushadevi, K.S. *J. Indian Chem. Soc*. **2007**, 84, 1016–1019
46. Sonmez, M.; Celebi, M.; Berber, I. *Eur. J. Med. Chem*. **2010**, 45, 1935-1940. https://doi.org/10.1016/j.ejmech.2010.01.035
47. NCCLS. Reference Method for Broth Dilution Antifungal Susceptibility Testing of Yeasts; Approved Standard-Second Edition. NCCLS document M27-A2 (ISBN 1-56238-469-4). NCCLS, 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA, **2002**.

48. Nateche, F.; Martin, A.; Baraka, S.; Palomino, J.C.; Khaled, S.; Portaels, F. *J. Med. Microbiol*. **2006**, 55, 857-860.
https://doi.org/10.1099/jmm.0.46513-0

