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Synthesis of New Dihydropyrimidine-2-Thione Derivatives and Their Antibacterial Screening

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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ABSTRACT

In this work, we reported the synthesis of new dihydropyrimidine-2-thione derivatives **5a-h**. The reaction intermediates of these derivatives are chalcones or 1,3-diarylprop-2-en-1-one derivatives **3a-h**, synthesized from acetophenone and various aldehydes which have not yet been used for the synthesis of dihydropyrimidine-2-thiones. All sixteen (16) compounds synthesized were characterized by ^{1}H and ^{13}C NMR. The three (3) bacterial strains tested on the synthesized compounds were *Staphylococcus aureus*, *Klebsiella aerogenes* formerly called *Enterobacter aerogenes* and *Pseudomonas aeruginosa*. Antibacterial activity was evaluated using the agar diffusion method with a sterile disc impregnated by the compound tested at three concentrations C1 (12.5 mg/mL), C2 (6.25 mg/mL) and C3 (3.12 mg/mL). The antibiotics used as references were cefoxitin, fusidic acid, ceftazidime, imipenem and pefloxacin. Compounds **3g**, **3h**, **5b**, **5d** and **5f** revealed antibacterial activity only against the *Staphylococcus aureus* strain.

Keywords: Chalcone; dihydropyrimidine-2-thione; antibacterial; Staphylococcus aureus.

1. INTRODUCTION

Heterocycles play a major role in the chemical and pharmaceutical industry [1-3]. They have various therapeutic activities such as antifungal [4,5], antioxidant [6,7] and anticancer activities [8,9]. Among heterocyclic nitrogen compounds, dihydropyrimidines have interesting pharmacological profile [10]. Indeed, they have interesting biological activities such as anticancer [11], anti-inflammatory [12], antimicrobial [13] and antioxidant [14] activities. For example, inhibitors of protein kinase C and interleukin-8 binding are alkaloids having a pyrimidine core [15,16]. The involvement of researchers in the search for new bioactive molecules remains necessary given the appearance of pathologies resistant to existing treatment. In our previous work, we reported the synthesis and biological evaluation of 4-oxo-5-cyano thiouracil derivatives as SecA inhibitors [17] and 1,4-dihydropyrimidine derivatives as potential antibacterial agents [18]. Currently, we also described the synthesis of some methylsulfanyl-4-aryl-1,4-dihydropyrimidine-5-carbonitriles derivatives coupled with benzimidazole, benzoxazole and benzothiazole rings. Some of these compounds exhibit antibacterial activity, particularly against gram-positive bacteria such as *Enterococcus faecalis* and *Staphylococcus aureus* [19]. This work is another synthetic approach for bioactivity of new dihydropyrimidine-2-thiones derivatives.

2. EXPERIMENTAL

2.1 Materials and Analytical Details

Reactions were monitored by thin-layer chromatography (TLC) using silica gel (60 F254). Melting points were determined on the electrothermal IA 9000 melting point apparatus. Bruker spectrometer was respectively used for ^{1}H and ^{13}C NMR spectra at 400 and 101 MHz. The chemical shifts are given in parts per million (Multiplicity: s = singlet, d = doublet, dd = double doublet, dt = double triplet, t = triplet, q = quartet, m = multiplet).

2.2 General Procedure for the Synthesis of Chalcones 3a-h

An aqueous solution of 10% NaOH (3-6 mL, 2.5 eq) was added dropwise to acetophenone (1 eq) in a 50 mL flask containing absolute ethanol (5 mL). After 1-2 hours of vigorous stirring, the aromatic aldehyde (1 eq) was added. The reaction medium was brought to room temperature using ice bath. After 4-5 hours of stirring, the reaction mixture is neutralized with 0.1N hydrochloric acid [20]. The chalcones were obtained after filtration and washing with a solvent mixture (H_2O/EtOH 1:1).

(Z)-3-phenyl-1-phenylprop-2-en-1-one 3a:

Compound 3a was obtained from acetophenone 1 (0.27 mL, 2.35 mmol, 1 eq) and benzaldehyde 2a (0.24 mL, 2.35 mmol, 1 eq), as a yellow crystalline solid with a yield of 81%. MP 58°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.45-7.69 (m, 6H, H-2', H-3', H-5', H-6', H-3'', H-5''), 7.73-7.78 (d, 1H, *J* = 15.7 Hz, H-2), 7.90 (m, 2H, H-4', H-4''), 7.96 (d, 1H, *J* = 15.6 Hz, H-3), 8.16 (m, 2H, H-2'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 122.09 (C-2), 128.50 (C-4'), 128.77 (C-2', C-6'), 128.87 (C-2'', C-6''), 128.90 (C-3', C-5'), 130.61 (C-3'', C-5''), 133.12 (C-4''), 134.63 (C-1'), 137.55 (C-1''), 144.00 (C-3), 189.22 (C=O).

(Z)-3-(4-(methylthio)phenyl)-1-phenylprop-2-en-1-one 3b:

Compound 3b was obtained from acetophenone 1 (0.19 mL, 1.6 mmol, 1 eq) and 4-(methylthio)benzaldehyde 2b (0.22 mL, 1.6 mmol, 1 eq), as a yellow powder with a yield of 89%. MP 77°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 2.53 (s, 3H, SCH_3), 7.32-8.16 (m, 11H, H-2, H-3, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 14.16 (SCH_3), 120.90 (C-2), 125.55 (C-3', C-5'), 128.45 (C-2', C-6'), 128.75 (C-3'', C-5''), 129.37 (C-1'), 131.02 (C-4''), 133.03 (C-1''), 137.68 (C-4''), 142.04 (C-4'), 143.63 (C-3), 189.08 (C=O).

(Z)-1-phenyl-3-(3,4,5-trimethoxyphenyl)prop-2-en-1-one 3c:

Compound 3c was obtained from acetophenone 1 (0.15 mL, 1,27 mmol, 1 eq) and 3,4,5-trimethoxybenzaldehyde 2c (250 mg, 1.27 mmol, 1 eq), as a yellow powder with a yield of 93%. MP 131°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) : 3.72 (s, 3H, OCH_3), 3.87 (s, 6H, 2 x OCH_3), 7.58 (t, J = 7.5 Hz, 2H, H-2', H-6'), 7.24 (s, 2H, H-3'', H-5''), 7.69 (dd, J = 15.8, 11.5 Hz, 1H, H-2), 7.89 (d, J = 15.6 Hz, 1H, H-3), 8.12-8.20 (m, 2H, H-2'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 102.68 (2 x OCH3), 107.24 (OCH3), 112.81 (C-2', C-6'), 118.32 (C-2), 122.75 (C-1'), 127.26 (C-2'', C-6''), 128.58 (C-3'', C-5''), 128.77 (C-4''), 133.24 (C-1''), 137.44 (C-4'), 141.37 (C-3), 148.01 (C-3', C-5'), 150.40 (C-4'), 188.86 (C=O).

(Z)-3-(6-bromobenzo[d][1,3]dioxol-5-yl)-1-phenylprop-2-en-1-one 3d:

Compound 3d was obtained from acetophenone 1 (0.13 mL, 1.09 mmol, 1 eq) and 6-bromopiperonal 2d (250 mg, 1.09 mmol, 1 eq), as a white powder with a yield of 88%. MP 139°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 6.18 (s, 2H, OCH_2), 7.54-8.22 (m, 9H, H-2, H-3, H-2', H-5', H-2'', H-3'', H-4'', H-5'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 102.68 (OCH_2O), 107.24 (C-6'), 112.81 (C-5'), 118.32 (C-2'), 122.75 (C-2), 127.26 (C-2'', C-6''), 128.58 (C-1'), 128.77 (C-3'', C-5''), 133.24 (C-4''), 137.44 (C-1''), 141.37 (C-3), 148.01 (C-4'), 150.40 (C-3'), 188.86 (C=O).

(Z)-1-phenyl-3-(1H-pyrrol-2-yl)prop-2-en-1-one 3e:

Compound 3e was obtained from acetophenone 1 (0.31 mL, 2.63 mmol, 1 eq) and pyrrole-2-carboxaldehyde 2e (250 mg, 2.63 mmol, 1 eq), as a brown powder with a yield of 81%. MP 127°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 6.23 (m, 1H, H-3'), 6.63-6.85 (m, 1H, H-2'), 7.07-7.19 (m, 1H, H-4'), 7.46-7.74 (m, 5H, H-2, H-2'', H-3'', H-5'', H-4''), 7.88-8.19 (m, 1H, H-3), 11.73 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 110.60 (C-2'), 114.62 (C-3'), 116.38 (C-4'), 124.29 (C-2), 127.92 (C-2'', C-6''), 128.69 (C-3'', C-5''), 129.13 (C-1'), 132.50 (C-4''), 134.28 (C-1''), 138.34 (C-3), 188.43 (C=O).

(Z)-3-(3,4-dichlorophenyl)-1-phenylprop-2-en-1-one 3f:

Compound 3f was obtained from acetophenone **1** (0.17 mL, 1.43 mmol, 1 eq) and 3,4-dichlorobenzaldehyde 2f (250 mg, 1.43 mmol, 1 eq) as of a yellow powder with a yield of 85%. MP 101°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.37-8.51 (m, 10H, H-2, H-3, H-2', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 124.07 (C-2), 128.63 (C-6'), 128.78 (C-2'), 129.11 (C-2'', C-6''), 130.17 (C-3'', C-5''), 130.95 (C-5'), 131.8 (C-4'), 132.71 (C-3'), 133.34 (C-4''), 135.55 (C-1'), 137.25 (C-1''), 141.14 (C-3), 188.93 (C=O).

(Z)-3-(3,5-dichlorophenyl)-1-phenylprop-2-en-1-one 3g:

Compound 3g was obtained from acetophenone 1 (0.17 mL, 1.43 mmol, 1 eq) and 3,5-dichlorobenzaldehyde 2g (250 mg, 1.43 mmol, 1 eq) as a yellow powder with a yield of 84%. MP 121°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.57 - 7.71 (m, 5H, H-2', H-4', H-6', H-3'', H-5''), 8.03 - 8.23 (m, 5H, H-2, H-3, H-2'', H-4'', H-6''). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 124.91 (C-2), 127.27 (C-2', C-6'), 128.71 (C-4'), 128.80 (C-2'', C-6''), 129.38 (C-3'', C-5''), 133.46 (C-4''), 134.62 (C-3', C-5'), 137.16 (C-1''), 138.43 (C-1'), 140.78 (C-3), 188.91 (C=O).

(Z)-3-(4-phenoxyphenyl)-1-phenylprop-2-en-1-one 3h:

Compound 3h was obtained from acetophenone 1 (0.15 mL, 1.26 mmol, 1 eq) and 4-phenoxybenzaldehyde 2h (250 mg, 1.26 mmol, 1 eq) as a yellow powder with a yield of 98%. MP 87°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 7.04 - 8.15 (m, 16H, H-2, H-3, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6'', H-2''', H-3''', H-4''', H-5''', H-6'''). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 118.20 (C-2''', C-6'''), 119.38 (C-2), 120.95 (C-4'''), 124.21 (C-3', C-5'), 128.41 (C-1'), 128.73

(C-3''', C-5'''), 129.69 (C-2'', C-6''), 130.18 (C-2', C-6'), 130.94 (C-3'', C-5''), 132.99 (C-4''), 137.67 (C-1''), 143.34 (C-3), 155.64 (C-4'), 159.00 (C-1'''), 189.08 (C=O).

General procedure for the synthesis of dihydropyrimidine-2-thiones 5a-h:

A mixture of thiourea (1.8 eq), 10% ethanolic KOH solution (3 ml), and chalcone (1.0 eq) in absolute ethanol (3-5 mL) was heated under reflux for 30 min to 1 h. After cooling, crushed ice was added to the reaction medium which was neutralized with diluted 0.1N hydrochloric acid [18,19]. The precipitate obtained was filtered and washed with a mixture (H_2O/EtOH 1:1) and/or recrystallized from ethanol.

4,6-diphenyl-3,4-dihydropyrimidine-2(1H)-thione 5a:

Compound 5a was obtained from thiourea 4 (98.9 mg, 1.3 mmol, 1.8 eq) and compound 3a (150 mg, 0.72 mmol, 1 eq), as a yellow powder with a yield of 48%. MP 183°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.11 (dd, *J* = 2.7, 4.8 Hz, 1H), 5.40 (d, *J* = 5.0 Hz, 1H), 7.28-7.52 (m, 10H, H-2', H-3', H-4', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''), 9.11 (s, 1H, NH), 9.87 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 54.60 (C-4), 101.17 (C-5), 125.86 (C-4'), 126.35 (C-2', C-6'), 127.55 (C-4''), 128.37 (C-2'', C-6''), 128.66 (C-3', C-5'),128.82 (C-3'', C-5''), 133.30 (C-1''), 134.33 (C-1'), 144.05 (C-6), 175.14 (C=S).

4-(4-(methylthio)phenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione 5b:

Compound 5b was obtained from thiourea 4 (81 mg, 1.06 mmol, 1.8 eq) and compound 3b (150 mg, 0.59 mmol, 1 eq), as a yellow powder with a yield of 44%. MP 83°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm) : 2.46 (s, 3H, SCH_3), 5.08 (dd, J = 2.7, 4.9Hz, 1H, H-4), 5.37 (d, J = 5.0 Hz, 1H, H-5), 6.88-7.64 (m, 9H, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''), 9.10 (s, 1H, NH), 9.87 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 14.08 (SCH_3), 60.7 (C-4), 101.17 (C-5), 126.35 (C-2', C-6'), 127.55 (C-4''), 128.37 (C-2'', C-6''), 128.66 (C-3', C-5'), 128.82 (C-3'', C-5''), 133.30 (C-1''), 134.33 (C-1'), 140.5 (C-4'), 144.05 (C-6), 175.14 (C=S).

6-phenyl-4-(3,4,5-trimethoxyphenyl)-3,4-dihydropyrimidine-2(1H)-thione 5c:

Compound 5c was obtained from thiourea 4 (68.5 mg, 0.9 mmol, 1.8 eq) and compound 3c (150 mg, 0.5 mmol, 1 eq), as a yellow powder with a yield of 12%. MP 173°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 3.71 (s, 3H, OCH_3), 3.72 (s, 6H, $(OCH_3)_2$), 5.08 (dd, *J* = 2.6, 4.8 Hz, 1H, H-4), 5.41 (d, *J* = 5.0 Hz, 1H, H-5), 6.66 (s, 2H, H-2', H-6'), 7.37-7.54 (m, 5H, H-2'', H-3'', H-4'', H-5'', H-6''), 9.05 (s, 1H, NH), 9.86 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 54.51 $(OCH_3)_2$, 55.85 (OCH_3), 59.97 (C-4), 100.91 (C-5), 103.70 (C-2', C-6'), 125.86 (C-4''), 128.35 (C-2'', C-6''), 133.33 (C-3'', C-5''), 134.51 (C-1'), 136.96 (C-1''), 139.44 (C-6), 153.00 (C-3', C-5'), 175.20 (C=S).

4-(6-bromobenzo[d][1,3]dioxol-5-yl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione 5d:

Compound 5d was obtained from thiourea 4 (61.6 mg, 0.81 mmol, 1.8 eq) and compound 3d (150 mg, 0.45 mmol, 1 eq), as a yellow powder with a yield of 40%. MP 117°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.32 (s, 2H, OCH_2O), 6.06-6.11 (d, *J* = 20.1 Hz, 2H, H-4, H-5), 6.79-7.48 (m, 7H, H-2', H-5', H-2'', H-3'', H-4'', H-5'', H-6''), 9.08 (s, 1H, NH), 10.05 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 54.49 (C-4), 99.10 (C-5), 102.19 (OCH_2O), 107.46 (C-2'), 110.22 (C-6'), 112.48 (C-5'), 125.90 (C-4''), 128.37 (C-2'', C-6''), 128.95 (C-3'', C-5''), 133.08 (C-1''), 134.84 (C-1'), 136.08 (C-4'), 147.68 (C-3'), 147.85 (C-6), 175.90 (C=S).

6-phenyl-4-(1H-pyrrol-2-yl)-3,4-dihydropyrimidine-2(1H)-thione 5e:

Compound 5e was obtained from thiourea 4 (104 mg, 1.37 mmol, 1.8 eq) and compound 3e (150 mg, 0.76 mmol, 1 eq), as a brown powder with a yield of 10%. MP 222°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): m (13H, H-4, H-5, H-2'', H-3'', H-4'', H-5'', H-6'', H-3', H-4', H-5', NH, NH, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm): 106.50 (C-4), 110.51 (C-5), 113.12 (C-3'), 124.17 (C-4'), 126.80 (C-5'), 128.67 (C-4''), 128.77 (C-2'' C-6''), 131.19 (C-3'', C-5''), 135.82 (C-2'), 158.32 (C-1''), 163.12 (C-6), 168.31 (C=S).

4-(3,4-dichlorophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione 5f:

Compound 5f was obtained from thiourea 4 (73.8 mg, 0.97 mmol, 1.8 eq) and compound 3f (150 mg, 0.54 mmol, 1 eq), as a yellow-orange powder with a yield of 17%. MP 88°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.18 (m, 1H, H-4), 5.43 (d, *J* = 4.6 Hz, 1H, H-5), 7.32-7.71 (m, 8H, H-2', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6''),

9.17 (s, 1H, NH), 9.98 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 60.2 (C-4), 95.3 (C-5), 124.2 (C-6'), 127.9 (C-4''), 128.1 (C-2'), 128.3 (C-2'', C-6''), 128.6 (C-3'', C-5''), 131.4 (C-4'), 131.8 (C-3', C-5'), 138.0 (C-1''), 142.8 (C-1'), 149.6 (C-6), 174.1 (C=S).

4-(3,5-dichlorophenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione 5g:

Compound 5g was obtained from thiourea 4 (73.8 mg, 0.97 mmol, 1.8 eq) and compound 3g (150 mg, 0.54 mmol, 1 eq), as a yellow-orange powder with a yield of 24%. MP 94°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.20 (m, 1H, H-4), 5.47 (d, *J* = 4.9 Hz, 1H, H-5), 7.34-7.59 (m, 8H, H-2', H-4', H-6', H-2'', H-3'', H-4'', H-5'', H-6''), 9.19 (s, 1H, NH),10.02 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 59.7 (C-4), 95.3 (C-5), 124.8 (C-6'), 127.9 (C-4''), 128.3 (C-2'', C-6''), 128.6 (C-3'', C-5''), 135.5 (C-3', C-5'), 138.0 (C-1''), 146.1 (C-1'), 149.6 (C-6), 174.1 (C=S).

4-(4-phenoxyphenyl)-6-phenyl-3,4-dihydropyrimidine-2(1H)-thione 5h:

Compound 5g was obtained from thiourea 4 (68.5 mg, 0.9 mmol, 1.8 eq) and compound 3h (150 mg, 0.5 mmol, 1 eq), as a yellow powder with a yield of 7%. MP 102°C. ^{1}H NMR (400 MHz, DMSO) δ (ppm): 5.11 (dd, *J* = 2.1, 4.9 Hz, 1H, H-4), 5.39 (d, *J* = 4.9 Hz, 1H, H-5), 6.99 - 8.37 (m, 14H, H-2', H-3', H-5', H-6', H-2'', H-3'', H-4'', H-5'', H-6'', H-2''', H-3''', H-4''', H-5''', H-6'''), 9.10 (s, 1H, NH), 9.86 (s, 1H, NH). ^{13}C NMR (101 MHz, DMSO) δ (ppm) : 54.10 (C-4), 101.11 (C-5), 118.58 (C-2'', C-6''), 118.89 (C-3', C-5'), 123.53 (C-4''), 125.91 (C-2', C-6'), 128.28 (C-2''', C-6'''), 128.45 (C-3'', C-5''), 130.10 (C-3''', C-5'''), 133.33 (C-1'), 134.47 (C-1'''), 139.20 (C-6), 156.13 (C-4'), 156.70 (C-1''), 174.99 (C=S).

2.3 Biology

The antibacterial activity was evaluated using the disk diffusion method in agar medium using a sterile disk impregnated with the substance tested (EUCAST-CASFM 2024 Reference). The technique used is a modification of Hayes and Markovic's method [21]. It consisted of using paper discs impregnated with the different substances to be tested. The discs were placed on the surface of an agar uniformly seeded with a suspension of the bacteria to be studied. The bacteria to be tested were inoculated on Petri dishes containing selective media appropriate to the bacterial strains used and then incubated at 37°C for 24 hours, in order to obtain young and well-isolated colonies. After incubation, 1 to 2 well-isolated and perfectly identical bacterial colonies are collected using a platinum loop, then emulsified in a tube containing 2 mL of physiological water and then vortexed. The density of the inoculum was adjusted to 0.5 Mc Farland using a DENSIMAT. The inoculum was used to inoculate the surface of Mueller-Hinton agar. On the surface of the box containing the Mueller-Hinton agar, sterile blotting paper disks 6 mm in diameter (Bio Merieux) were placed. During the operation, a volume of 20 µL of the substance supplemented with 10% DMSO of varying concentrations was used to impregnate these blotting discs. Two controls were carried out, a negative control with 20 µL of sterile distilled water in the presence of 10% DMSO and an antibiotic disk as a positive control. The boxes are left for 1 hour at room temperature then turned over and incubated at 37°C for 18 to 24 hours. After incubation, the inhibition diameter was measured in millimeters disc included using a caliper.

3. RESULTS AND DISCUSSION

3.1 Chemistry

To synthesize the 1,3-diarylprop-2-en-1-ones or chalcones derivatives, we optimized the Choudhary's method [20]. Indeed, Choudhary's method indicated that a mixture of aldehyde and acetophenone were dissolved in ethanol with magnetic stirring. Subsequently, an aqueous solution of NaOH was added dropwise to the reaction medium with vigorous stirring until a cloudy solution was obtained. The temperature of the reaction medium was brought to room temperature using an ice bath. After vigorous stirring for 4-5 hours, the reaction medium was neutralized with 0.1N hydrochloric acid until a precipitate was obtained. For our work, we added the starting reagents taking into account the reaction mechanism of the chalcones to avoid the formation of several secondary reactions such as the autocondensation of acetophenone or the aldehyde and the Cannizarro reaction. Indeed, we made a dropwise addition of the 10% aqueous sodium hydroxide solution to the acetophenone in order to form the carbanion which will react with the aldehyde derivative to access to the desired chalcone. Fig. 1 indicates the percentage of presence of the desired chalcone 3a, resulting from crotonization between acetophenone and benzaldehyde, using the optimized Choudhary's method.

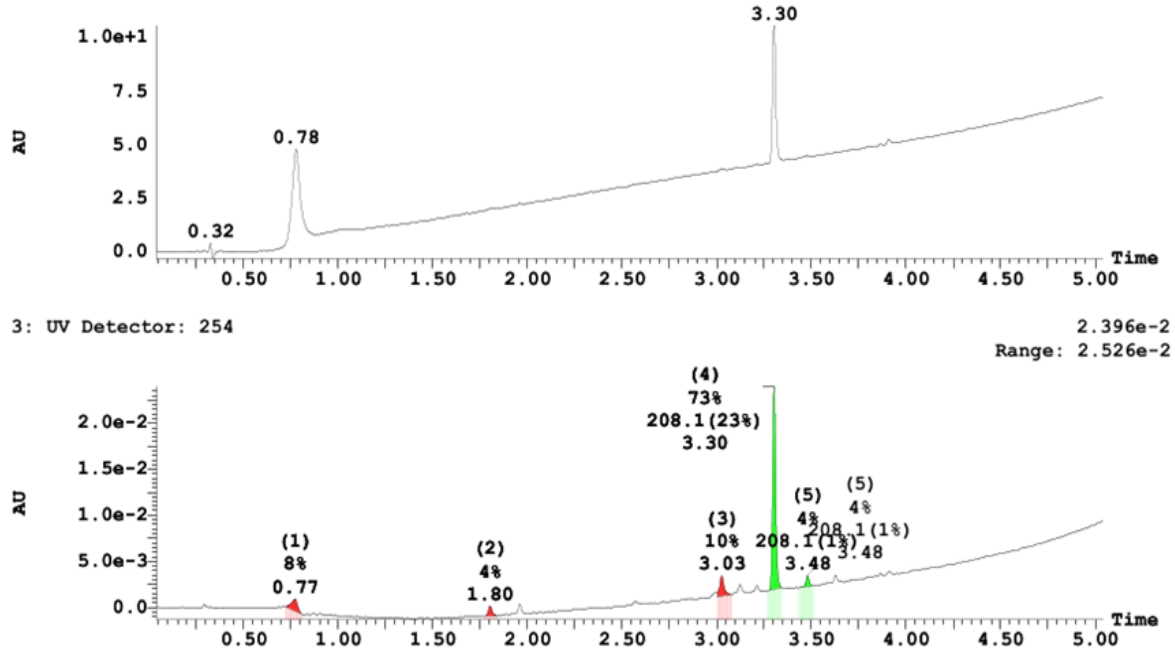
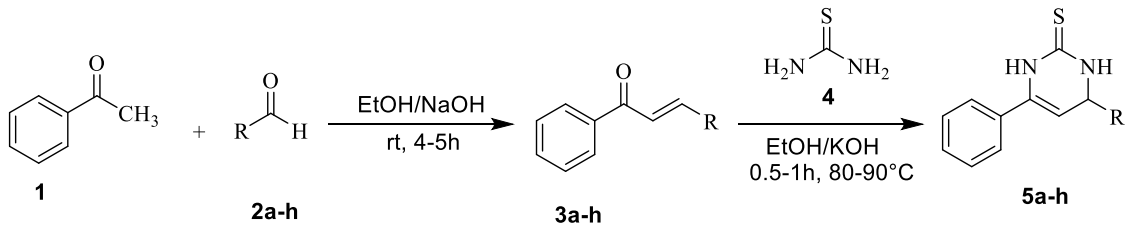


Fig. 1. UPLC-MS of chalcone 3a synthesized with the optimized Choudhary's method

Fig. 1 indicates a percentage presence of 73% (peak 4) of chalcone 3a after 4 hours of reaction using the optimized conditions while it was 36% using the Choudhary method. Thus, the percentage of presence of 3a was twice as high in the optimized conditions. Furthermore, the yield of chalcone 3a was 81% using the optimized conditions while it was 34% using the Choudhary's method [20]; the yield was also twice as high in optimized conditions. This clear improvement in yield was also observed for several synthesized chalcones. Considering these results, we therefore used optimized conditions of the Choudhary's method for the synthesis of the other 1,3-diarylprop-2-en-1-ones derivatives **3b-h** (Scheme 1), recorded in Table 1. Previous work had shown that the condensation reaction with functionalized aromatic aldehydes led to the single or majority formation of Z stereoisomer; this reaction was stereospecific in most cases. This fact was not the case with aliphatic aldehydes because this condensation produced a mixture of Z and E stereoisomers [22]. As for the dihydropyrimidine-2-thiones 5a-h compounds, they were synthesized according to the method described in the literature [23,24], Scheme 1.



2a: R = C_6H_5
2b: R = C_6H_5-4-SCH_3
2c: R = C_6H_2-3,4,5-OCH_3
2d: R = C_6H_2-OCH_2O-6-Br
2e: R = C_6H_2-3,4,5-OCH_3
2f: R = C_6H_3-3,4-Cl
2g: R = C_6H_3-3,5-Cl
2h: R = C_6H_4-O-C_6H_5

3a: R = C_6H_5
3b: R = C_6H_5-4-SCH_3
3c: R = C_6H_2-3,4,5-OCH_3
3d: R = C_6H_2-OCH_2O-6-Br
3e: R = C_6H_2-3,4,5-OCH_3
3f: R = C_6H_3-3,4-Cl
3g: R = C_6H_3-3,5-Cl
3h: R = C_6H_4-O-C_6H_5

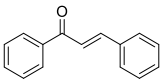
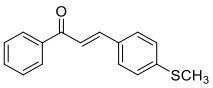
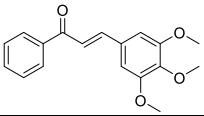
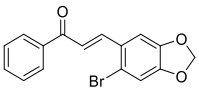
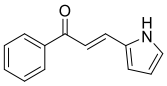
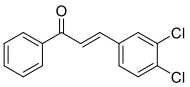
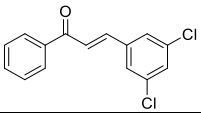
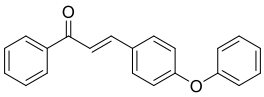
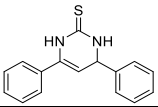
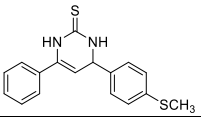
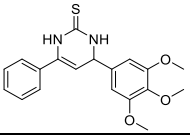
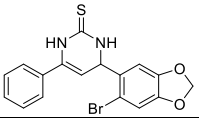
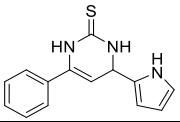
5a: R = C_6H_5
5b: R = C_6H_5-4-SCH_3
5c: R = C_6H_2-3,4,5-OCH_3
5d: R = C_6H_2-OCH_2O-6-Br
5e: R = C_6H_2-3,4,5-OCH_3
5f: R = C_6H_3-3,4-Cl
5g: R = C_6H_3-3,5-Cl
5h: R = C_6H_4-O-C_6H_5

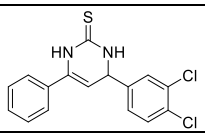
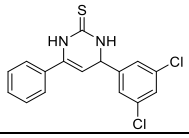
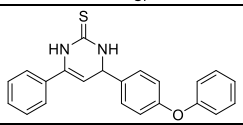
Scheme 1. Synthesis scheme of dihydropyrimidine-2-thiones 5a-h

3.2 Biology

Table 1 presents the inhibition diameters of dihydropyridine-2-thiones derivatives on the bacterial strains *Enterobacter aerogenes* (EA), *Staphylococcus aureus* (SA) and *Pseudomonas aeruginosa* (PA) and their intermediates 1,3-diarylprop-2-en-1-ones.

Table 1. Results of the antibacterial activity of the synthesized molecules

			Inhibition diameters (mm)		
Molecules	**Structures**	**Concentrations**	**EA**	**SA**	**PA**
3a		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3b		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3c		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3d		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3e		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3f		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
3g		C1	6	**9**	6
		C2	6	**9**	6
		C3	6	7	6
3h		C1	6	**9**	6
		C2	6	**8**	6
		C3	6	7	6
5a		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
5b		C1	6	**8**	6
		C2	6	**8**	6
		C3	6	7	6
5c		C1	ND	ND	ND
		C2	ND	ND	ND
		C3	ND	ND	ND
5d		C1	6	**9**	6
		C2	6	**8**	6
		C3	6	**8**	6
5e		C1	6	6	6
		C2	6	6	6
		C3	6	6	6

			Inhibition diameters (mm)		
Molecules	**Structures**	**Concentrations**	**EA**	**SA**	**PA**
5f		C1	6	**9**	6
		C2	6	**9**	6
		C3	6	**8**	6
5g		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
5h		C1	6	6	6
		C2	6	6	6
		C3	6	6	6
Antibiotics	FOX	C3	-	19	-
	FAD	C3	-	25	-
	CAZ	C3	25	-	26
	IPM	C3	-	-	22
	PEF	C3	26	-	-

C1 = 12.5 mg/mL, C2 = 6.25 mg/mL, C3 = 3.12 mg/mL, ND: Not determined
FOX: Cefoxitin, FAD: Fusidic acid, CAZ: Ceftazidime, IPM: Imipenem, PEF: Pefloxacin

According to Biyiti et al. [25], a substance is considered active when it induces an inhibition zone greater than or equal to 10 mm. When the inhibition diameter is between 6 and 10 mm, the antibacterial activity is mild or even low. Compounds **3a-3f** were inactive with an inhibition diameter of 6 mm. Compounds **3g** bearing two atoms of chlorine at positions 3,5 and **3h** with the phenoxyphenyl group showed mild inhibition with a diameter of 8 or 9 mm. Considering Table 1, we can say that dihydropyrimidine-2-thiones derivatives **5b**, **5d** and **5f** respectively with 4-methylthiophenyl, 6-bromopiperonal and 3,4-dichlorophenyl moieties revealed a mild biological activity on the *Staphylococcus aureus* strain. This mild activity could be linked to the presence of these groups, which had shown biological activity in recent studies [18,19,26]. No activity was observed on the *Enterobacter aerogenes* and *Pseudomonas aeruginosa* strains for all the compounds.

4. CONCLUSION

Among the sixteen (16) synthetic compounds, only five (5) had a mild antibacterial activity only on the strain *Staphylococcus aureus*. These are compounds **3g**, **3h**, **5b**, **5d** and **5f**. No antibacterial activity was observed on the strains *Enterobacter aerogenes* and *Pseudomonas aeruginosa*. For future work, new various substituted derivatives of thiourea could be used to provide structural diversity and enhance antibacterial activity.

DISCLAIMER (ARTIFICIAL INTELLIGENCE)

Author(s) hereby declare that NO generative AI technologies such as Large Language Models (ChatGPT, COPILOT, etc.) and text-to-image g²enerators have been used during the writing or editing of this manuscript.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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