Synthesis of new dihydropyrimidine-2-thione derivatives for antibacterial purposes

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*. 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 are compounds of interest in organic and medicinal chemistry due to their interesting pharmacological profile [10]. Thus, they have interesting biological activities, namely anticancer [11], anti-inflammatory [12], antimicrobial [13] and antioxidant [14] activity. As an illustration, 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. This work is a contribution to the synthesis of new molecules for antibacterial purposes.

2. EXPERIMENTAL

2.1 Materials and analytical details

Reactions were monitored by thin-layer chromatography (TLC) using silica gel (60 F254). Capillary tubes allowed us to measure melting points (mp [°C]). 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) is 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) is added. The reaction medium is brought to room temperature using ice bath. After 4-5 hours of stirring, the reaction medium is neutralized with 0.1N hydrochloric acid [17]. The chalcones were obtained after filtration and washing with a mixture (H_2O/EtOH 1:1).

(Z)-chalcone 3a

Compound 3a is obtained according to the general procedure for the synthesis of chalcones 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 98%. 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 is obtained according to the general procedure for the synthesis of chalcones, 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 is obtained according to the general procedure for the synthesis of chalcones,from acetophenone **1**(0.15 mL, 1,27 mmol, 1 eq) and 3,4,5-trimethoxybenzaldehyde **2c** (250mg, 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 is obtained according to the general procedure for the synthesis of chalcones,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 is obtained according to the general procedure for the synthesis of chalcones, 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 is obtained according to the general procedure for the synthesis of chalcones, 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 is obtained according to the general procedure for the synthesis of chalcones, 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 is obtained according to the general procedure for the synthesis of chalcones, 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 is added to the reaction medium which is neutralized with diluted 0.1N hydrochloric acid [18, 19]. The precipitate obtained is 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, from thiourea **4** (73.8mg, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 is obtained according to the general procedure for the synthesis of dihydropyrimidine derivatives, 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 [20]. 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

3.1Chemistry

To synthesize the 1,3-diarylprop-2-en-1-ones or chalcones derivatives, we optimized the Choudhary's method [17]. 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 is 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. Figure 1 indicates the percentage of presence of the desired

chalcone 3a, resulting from crotonization between acetophenone and benzaldehyde, using the optimized Choudhary's method.

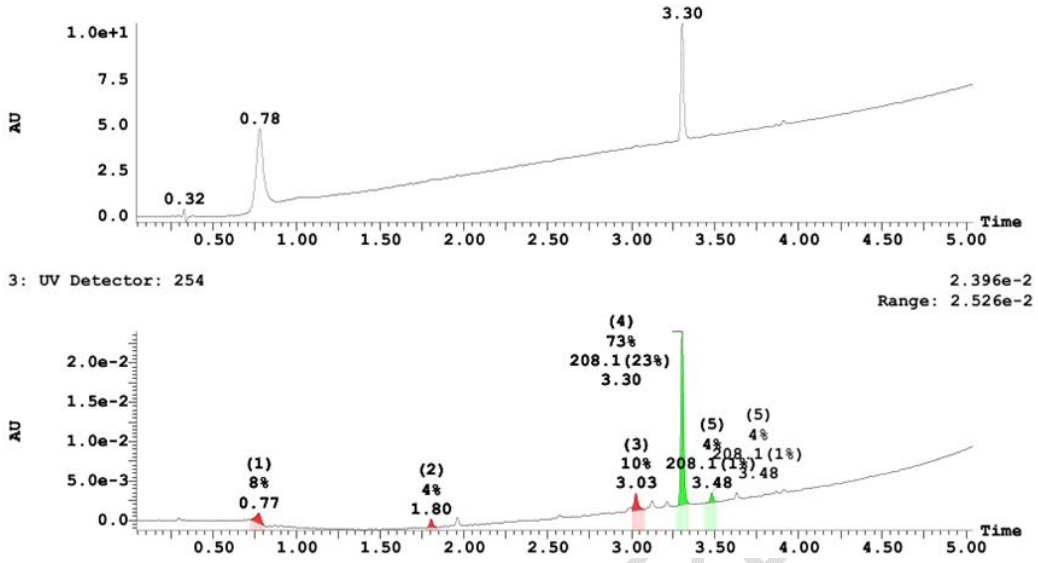
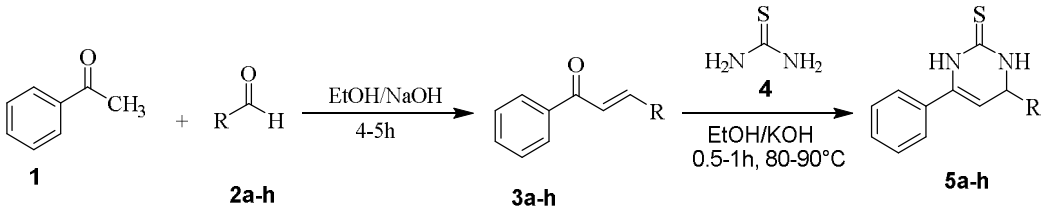


Fig. 1. UPLC-MS of chalcone 3a synthesized with the optimized Choudhary method

Figure 1 indicates a percentage presence of 73% (peak 4) of chalcone 3a after 4 hours of reaction using the optimized conditions while it is 36% using the Choudhary method. Thus, the percentage of presence of 3a is 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 [17]; the yield is also twice as high in optimized conditions. This clear improvement in yield was also observed for several synthesized chalcones. In view of these results, we therefore opted for the use of the 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 has shown that the condensation reaction with functionalized aromatic aldehydes led to the sole or majority formation of the Z stereoisomer; this reaction wasstereospecific in most cases. This fact was not the case with aliphatic aldehydes because this condensation produced a mixture of Z and E stereoisomers [21]. As for the dihydropyrimidine-2-thiones 5a-h compounds, they were synthesized according to the method described in the literature [18, 19], Schemes 1, 2.

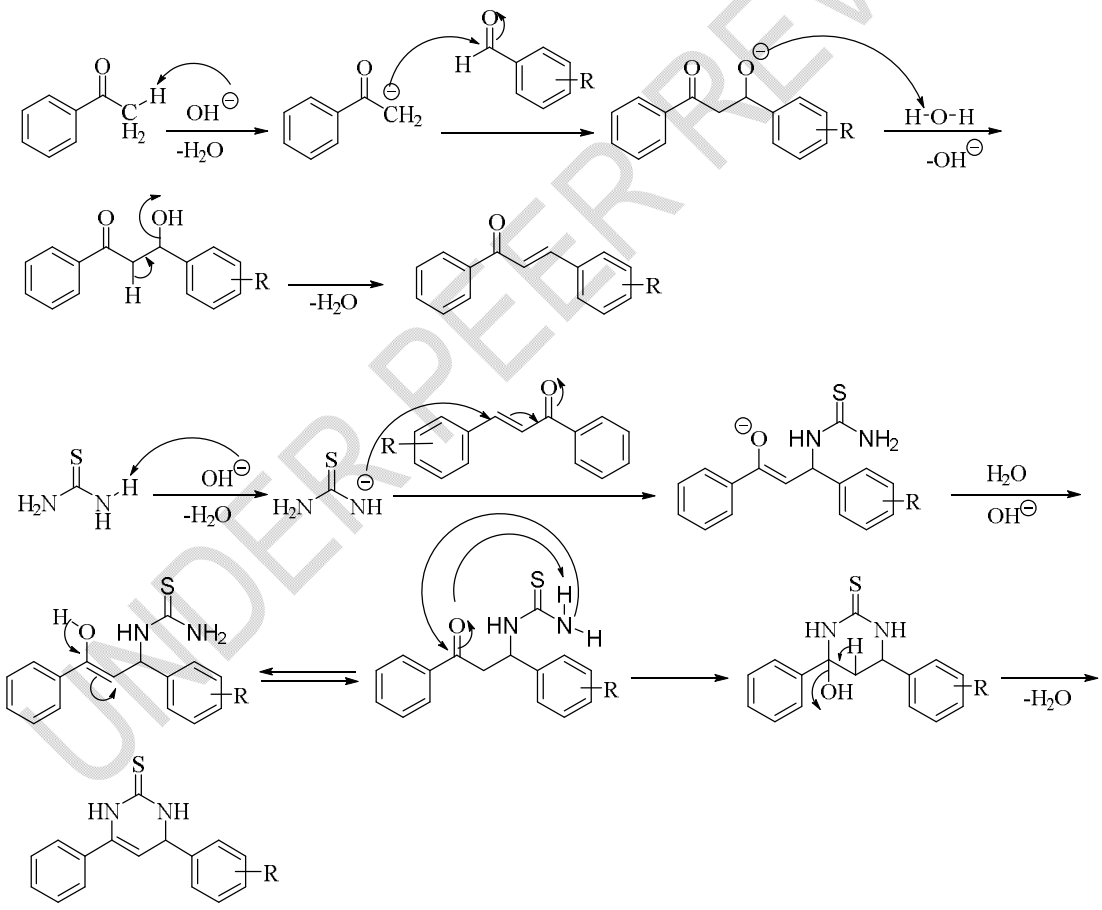


2a: R = C_6H_5
2b: R = C_6H_5-4-SCH_3
2c: R = C_6H_2-3,4,5-OCH_3
2d: R = C_6H_2-OCH_2O-6-Br
2e: R = C_6H_2-3,4,5-OCH_3
2f: R = C_6H_3-3,4-Cl
2g: R = C_6H_3-3,5-Cl
2h: R = C_6H_4-O-C_6H_5

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

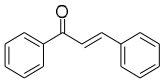
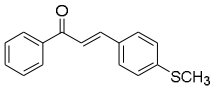
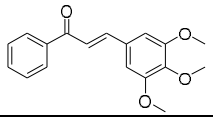
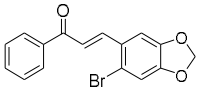
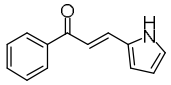
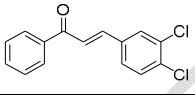
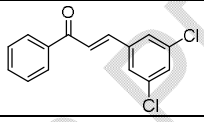
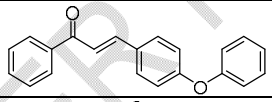
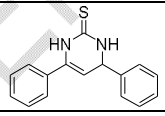
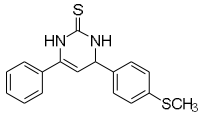
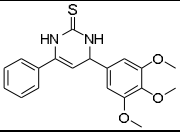
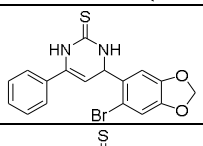
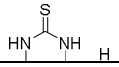


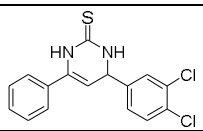
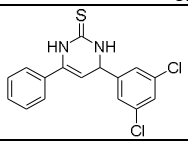
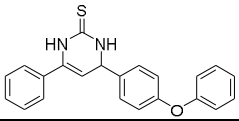
Scheme 2. Plausible reaction mechanism of DHPM-2-thiones derivatives

3.2 Biology

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

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
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
FOX: Cefoxitin, FAD: Fusidic acid, CAZ: Ceftazidime, IPM: Imipenem, PEF: Pefloxacin

According to Biyiti*and al.* [22], 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 medium or even low.Considering Table 1, we can say that compounds **3g**, **3h**, **5b**, **5d** and **5f** revealed a medium biological activity on the *Staphylococcus aureus* strain. No activity was observed on the *Enterobacter aerogenes* and *Pseudomonas aeruginosa* strains.

4. CONCLUSION

Among the sixteen (16) synthetic compounds, only five (5) had a medium antibacterial activity only on the strain *Staphylococcus aureus*. These are compounds **3g**, **3h**, **5b**, **5d** and **5f**. No antibacterial activity was observed for the eleven (11) other synthetic substances on the strains *Staphylococcus aureus*, *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.

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