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Synthesis and biological activity evaluation of some novel heterocyclic compounds incorporating pyridine / chromene moiety

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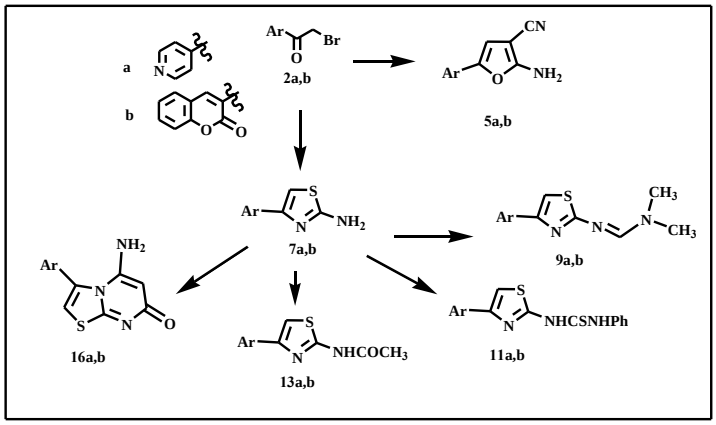
Abstract

*4-Bromoacetyl pyridine **2a** and 3-bromoacetylcoumarine **2b** react with malononitrile **3** and thiourea **6** to afford the furan and the thiazole derivatives **5a,b** and **7a,b** respectively. The thiazoles **7a,b** react with DMFDMA **8,** phenyl isothiocyanate **10,** acetic anhydride **12** and ethyl cyanoacetate **14** to afford the thiazole derivatives **9-13a,b** and the thiazolo[3,2-a]pyrimidinone derivatives **16a,b** respectively. All structures are proven by analysis and spectral methods. The biological activity of the synthesized compounds was screened as anti bacterial and anti fungal agents.*



Keywords

Acetyl pyridine, acetyl coumarine, Furans, thiazoles, thiazolo[3,2-a]pyrimidine derivatives.

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1. Introduction

Functionalized pyridines posses diverse pharmaceutical properties such as anticancer [1], anticonvulsant [2], antimicrobial [3, 4], antiviral [5], antifungal & antimycobacterial [6] and anti-HIV [7] activities. Coumarines are bioactive compounds of both natural and synthetic origin and there has been a growing interest in their synthesis due to their useful and diverse pharmaceutical and biological activities [**8**]. Several heterocyclic compounds containing coumarin ring are associated with diverse pharmacological properties as anti-inflammatory [**9**], antimicrobial [**10**], antiviral [**11**] and antitumor [**12-14**]. Moreover, coumarines bearing substitution at 4-position are known to exhibit different biological activities including antiproliferative activity against liver carcinomas [**15-18**] and breast carcinoma [**19**, **20**]. Coumarin itself also exhibited cytotoxic effects against Hep2 cells (human epithelial type 2) in a dose dependent manner and showed some typical characteristics of apoptosis with loss of membrane microvillus, cytoplasm hypervacualization and nuclear fragmentation [**21**]. Functionalized thiazole derivatives have also received much attention due to their diverse biological activities such as antimicrobial [22], antiviral [23], cytotoxic [24], and HIV-protease inhibitory agents [25].

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In the last two decades we have been involved in a program aiming to synthesize functionally substituted heterocyclic compounds with anticipated biological activities that can be used as biodegradable agrochemicals from cheap laboratory available starting materials [26-28]. In the frame of this program, it seemed to us that the combination of a pyridine or a coumarine moiety and a thiazole ring in one entity may furnish more potent and useful scaffolds due to the synergistic effect of both combined rings.

2-Bromo-1-pyridin-4-yl ethanone **2a** and 3-(2-bromoacetyl)-2*H*-chromene-2-one **2b** (Scheme 1) (prepared via the bromination of 4-acetylpyridine **1a** and 3-acetyl coumarine **1b** respectively, according to the literature method [29]) seemed suitable starting compounds to fulfill our objective.

2. Experimental

All melting points were determined on an electrothermal Gallenkamp apparatus and are uncorrected. Solvents were generally distilled and dried by standard literature procedures prior to use. The IR spectra were measured on a Pye-Unicam SP300 instrument in potassium bromide discs. The ^{1}H-NMR and ^{13}C-NMR spectra were recorded on a Varian Mercury VXR-300 spectrometer (300 MHz for ^{1}H-NMR and 75 MHz for ^{13}C-NMR) in DMSO-*d6* using TMS as internal standard and the chemical shifts were expressed in δ ppm values. Assignments of ^{13}C-NMR multiplicities were made by correlation of the off-resonance decoupled ^{13}C signals and the determination of the ^{1}H chemical shifts. Mass spectra were recorded on a GCMSQ1000-EX Shimadzu and GCMS 5988-A HP spectrometers at 70 eV ionizing potential. Elemental analyses were carried out on Elementar- Vario-LIII C-H-N-S analyzer. All elemental and spectral measurements were carried out at the Microanalytical Center at Cairo University. The biological activity studies were carried out in the Botany & Microbiology Department, Faculty of Science, Cairo University.

Synthesis of pyridin-4-yl /chromen-3-ylfuran derivatives 5a and 5b

To a mixture of 2-Bromo-1-pyridin-4-yl ethanone **2a** (10 mmol) or 3-(2-bromoacetyl)-2H-chromene-2-one **2b** (10 mmol) and malononitrile **3** (10 mmol) in absolute dioxane (30 mL) was added few drops of freshly prepared sodium ethoxide and the mixture was refluxed for 2h. The reaction mixture was left to cool to room temperature then diluted with cold water and acidified with few drops of dil. HCl. The formed precipitates were filtered off, washed with water, dried and recrystallized from ethanol to afford **5a and 5b:**

2-Amino-5-pyridin-4-ylfuran-3-carbonitrile 5a

Brown powder, Yield 1.6 g (75 %), mp 175-178 °C; ν_{max} cm^{-1}: 3371 (NH_2), 2195 (CN); δ_H ppm= 6.25 (s, 2H, D_2O exchangeable, NH_2, NH_2), 7.65 (d, 2H, Py-3H), 7.73 (s, 1H, Fu 4-H), 8.72 (d, 2H, Py-2H). [M^+]= 185. Analysis Calcd. for $C_{10}H_7N_3O$ (185.18); C, 64.86; H, 3.81; N, 22.69; Found C, 64.87, H, 3.76, N, 22.55.

2-Amino-5-(2-oxo-2*H*-chromen-3-yl)furan-3-carbonitrile 5b

Page crystals, Yield 2.24 g (80 %), mp 187-189 °C; ν_{max} cm^{-1}: 3363 (NH_2), 2198 (CN), 1714 (C=O); δ_H ppm= 7.45- 8.00 (m, 7H, Ar-H+Fu 4-H+ NH_2), 8.99 (s, 1H, Chrom-4H). [M^+]= 252. Analysis Calcd. for $C_{14}H_8N_2O_3$ (252.22); C, 66.67; H, 3.20; N, 11.11; Found C, 66.55, H, 3.16, N, 11.17.

Synthesis of the thiazole derivatives 7a,b:

To a mixture of 2-Bromo-1-pyridin-4-yl ethanone **2a** (2.0 g; 10 mmol) or 3-(2-bromoacetyl)-2*H*-chromene-2-one **2b** (2.66 g; 10 mmol) and thiourea **6** (0.67 g; 10 mmol) in absolute ethanol (30 mL) was added few drops of freshly prepared sodium ethoxide and the mixture was refluxed for 2h. The reaction mixture was left to cool to room temperature then diluted with cold water and acidified with few drops of dil. HCl. The formed precipitates were filtered off, washed with water, dried and recrystallized from ethanol to give **7a** and **7b** respectively**:**

4-Pyridine-4-yl-thiazol-2-ylamine 7a

Page powder, Yield 1.20 g (68 %), mp >300 °C; ν_{max} cm^{-1}: 3263 (NH_2)**;** δ_H ppm= 7.07 (s, 1H, Thiazole 5-H), 7.44-7.46 (d, 2H, Py-3H, j=6 Hz), 8.46 (s, 2H, D_2O exchangeable, NH_2), 8.64-8.66 (d, 2H, Py-2H, j=6 Hz). [M^+]= 177. Analysis Calcd. for $C_8H_7N_3S$ (177.23); C, 54.22; H, 3.98; N, 23.71; S, 18.09; Found C, 54.55; H, 3.75; N, 23.60; S, 17.98.

3-(2-Aminothiazol-4-yl)-chromen-2-one 7b

Yellow lustrous crystals, Yield 1.83 g (75 %), mp 287-290 °C; ν_{max} cm^{-1}: 3269 (NH_2), 1717 (C=O); δ_H ppm= 7.39- 7.83 (m, 5H, Ar-H+Thiazole 5-H), 8.26 (s, 1H, Chrom. 4-H), 8.52 (s, 2H, D_2O exchangeable, NH_2). Analysis Calcd. for $C_{12}H_8N_2O_2S$ (244.27); C, 59.00; H, 3.30; N, 11.47; S, 13.13; Found C, 59.06; H, 3.27; N, 11.25; S, 13.22.

Synthesis of the formimidamide derivatives 9a,b:

A mixture of the thiazole derivative **7a** (1.77 g; 10 mmol) or **7b** (2.44 g; 10 mmol) and dimethylformamide dimethylacetal (DMFDMA) **8** (1.19 g; 10 mmol) was refluxed in dry xylene (20 mL) for 5h, then left to cool to room temperature to

afford the formimidamide derivatives **9a,b** respectively.

***N,N*-Dimethyl-*N*`-[4-(pyridine-4-yl)thiazol-2-yl]formimidamide 9a**

Pale brown, crystals, Yield 1.81 g (78 %), mp 174-176 °C (xylene); δ_H ppm = 3.0, 3.12 (2s, 6H, $2CH_3$), 7.73 (s, 1H, N=CH-N), 7.92 (s, 1H, Thiazole 5-H), 8.02 (d, 2H, Py-3H, j=6 Hz), 8.73 (d, 2H, Py-2H, j=6 Hz). $[M^+]$= 232. Analysis Calcd. for $C_{11}H_{12}N_4S$ (232.31); C, 56.87; H, 5.21; N, 24.12; S, 13.80; Found C, 56.76; H, 5.27; N, 24.15; S, 13.72.

***N,N*-Dimethyl-*N*`-[4-(2-oxo-*2H*-chromen-3-yl)thiazol-2-yl]formimidamide 9b**

Yellow crystals, Yield 2.21 g (74 %), mp 187-190 °C (xylene); ν_{max} cm^{-1}: 1710 (C=O); δ_H ppm= 3.0, 3.14 (2s, 6H, $2CH_3$), 7.32- 7.80 (m, 5H, Ar-H+N=CH-N), 8.34 (s, 1H, Chrom-4H), 8.67 (s, 1H, Thiazole-5H). δ_C= 35.01 (q), 40.2 (q), 113.81 (s), 116.24 (s), 119,79 (d), 120.92 (d), 125.10 (s), 129.12 (s), 131.91 (s), 139.14 (S), 144.49 (d), 152.73 (d), 157.08 (s), 159.27 (d), 173.60 (d). Analysis Calcd. for $C_{15}H_{13}N_3O_2S$ (299.35); C, 60.19; H, 4.38; N, 14.04; S, 10.71; Found C, 60.15; H, 4.27; N, 14.12; S, 10.62.

Synthesis of the thiourea derivatives 11a,b:

A solution of each of **7a** or **7b** with phenyl isothiocyanate **10** in dry dioxane was refluxed for 2h, then left to cool to room temperature. The precipitated solids were filtered off and recrystallized from ethanol to afford N, N`-disubstituted thiourea derivatives **11a,b** respectively.

1-Phenyl-3-(4-pyridin-4-yl-thiazol-2-yl)-thiourea 11a

Page powder, Yield 2.56 g (82 %), mp 195-198 °C; ν_{max} cm^{-1}: 3175, 3168 (2NH); δ_H ppm= 1.66, 3.0 (2s, 2H, 2NH), 7.18-7.72 (m, 7H, Ph+ Py-3H), 7.24 (s, 1H, Thiazole 5-H), 8.52-8.54 (d, 2H, Py-2H). Analysis Calcd. for $C_{15}H_{12}N_4S_2$ (312.41); C, 57.67; H, 3.87; N, 17.93; S, 20.53; Found C, 57.60; H, 3.77; N, 17.75; S, 20.32.

1-(4-(2-Oxo-*2H*-chromen-3-yl)-thiazol-2-yl)-3-phenylthiourea 11b

Pale brown powder, Yield 2.96 g (78 %), mp 287-290 °C; ν_{max} cm^{-1}: 3076 (br. 2NH), 1717 (C=O); δ_H ppm = 7.20-7.83 (m, 9H, Arom H), 8.11 (s, 1H, chrom.-4H), 8.26 (s, 1H, Thiazole 5-H), 8.52 (s, 2H, 2NH). $[M^+]$= 379. Analysis Calcd. for $C_{19}H_{13}N_3O_2S_2$ (379.45); C, 60.14; H, 3.45; N, 11.07; S, 16.90; Found C, 60.06; H, 3.27; N, 11.65; S, 16.82.

Acetylation of the aminothiazole derivatives 7a,b: Preparation of the acetamide derivatives 13a,b:

The thiazole derivative **7a** (1.77 g; 10 mmol) or **7b** (2.44 g; 10 mmol) **were** refluxed for 2h in a mixture of glacial acetic acid / acetic anhydride **12** (15 mL; 1:1)**.** The reaction mixture was left to cool to room temperature, diluted with cold water (5mL) and neutralized with ammonia solution (5mL). The precipitated solids were collected by filtration, washed with water and recrystallized from ethanol to afford the N-acetyl derivatives **13a,b** respectively.

***N*-[4-(Pyridine-4-yl)-thiazole-2-yl]-acetamide 13a**

Brown powder, Yield 1.49 g (68 %), mp 267-269 °C; ν_{max} cm^{-1}: 3175 & 3190 (NH), 1669 (C=O); δ_H ppm= 2.20 (s, 3H, CH_3), 8.30-8.32 (d, 2H, Py-3H, j=6Hz), 8.44 (s, 1H, Thiazole 5-H), 8.90-8.92 (d, 2H, Py-2H, j=6Hz), 12.44 (s, 1H, NH). $[M^+]$= 219, Analysis Calcd. for $C_{10}H_9N_3OS$ (219.26); C, 54.78; H, 4.14; N, 19.16; S, 14.62; Found C, 54.76; H, 4.27; N, 19.25; S, 14.42.

***N*-[4-(2-Oxo-2*H*-chromen-3-yl)-thiazol-2-yl]-acetamide 13b**

Yellow powder, Yield 2.0 g (70 %), mp 255-256 °C; ν_{max} cm^{-1}: 3175 (NH_2), 1670 (C=O), 1705 (C=O); δ_H 2.18 (s, 3H, CH_3), 7.38- 7.84 (m, 4H, Ar-H), 7.97 (s, 1H, chrom. 4H), 8.56 (s, 1H, Thiazole 5-H), 12.30 (s, 1H, NH). $[M^+]$= 286. Analysis Calcd. for $C_{14}H_{10}N_2O_3S$ (286.31); C, 58.73; H, 3.52; N, 9.78; S, 11.20; Found C, 58.76; H, 3.47; N, 9.75; S, 11.22.

Reaction of the aminothiazole derivatives 7a,b with ethyl cyanoacetate 14: Preparation of the thiazolo [3,2-*a*]pyrimidine derivatives 16a,b:

A mixture of the thiazole derivatives **7a (**1.77 g, 10 mmol) or 7**b** (2.44 g, 10 mmol) and ethyl cyanoacetate **14** (1.13g, 10 mmol) in dimethylformamide (DMF; 20 mL) was refluxed for 2h (TLC control). The reaction mixture was left to cool to room temperature then diluted with cold water and acidified with few drops of dil. HCl. The formed precipitates were filtered off, washed with cold water, dried and recrystallized from ethanol to give **16a** and **16b** respectively**:**

5-Amino-(3-pyridine-4-yl)-thiazolo[3,2-*a*]pyrimidin-7-one 16a

Hairy brown powder, Yield 1.42 g (80 %), mp 241-243 °C; ν_{max} cm^{-1}: 3280 (NH_2), 1678 (C=O); δ_H ppm= 4.07 (s, 1H, pyrimidinone-H), 6.32 (s, 1H, thiazole H), 6.50 (s, 2H, D_2O exchangeable, NH_2), 7.48 (d, 2H, pyridine-3H, j=6Hz), 8.50 (d, 2H, pyridine-2H, j=6Hz). $[M^+]$= 244. Analysis Calcd. for $C_{11}H_8N_4OS$ (244.27); C, 54.09; H, 3.30; N, 22.94; S, 13.13; Found C, 54.06; H, 3.27; N, 22.75; S, 13.22.

5-Amino-3-(2-oxo-2*H*-chromen-3-yl)-thiazolo [3,2-*a*]pyrimidin-7-one 16b

Yellow powder, Yield 2.36 g (76 %), mp 283-285 °C; ν_{max} cm^{-1}: 3309 (NH_2), 1678, 1637 (2C=O); δ_H ppm= 4.02 (s, 1H, Pyrim.-H), 5.4 (s, 1H, Thiazole H), 6.5 (s, 2H, NH_2), 7.58 (s, 1H, Chrom-4H), 7.62- 7.87 (m, 4H, Ar-H). δ_C: 115.08 (d), 116.40 (d), 119.50 (s), 120.71 (s), 125.23 (d), 129.41 (d), 132.40 (d), 139.18 (d), 142.61(s), 152.94 (s), 156.47 (s), 159.23 (s), 160.45 (s). [M^+]=311. Analysis Calcd. for $C_{15}H_9N_3O_3S$ (311.32); C, 57.87; H, 2.91; N, 13.50; S, 10.30; Found C, 57.76; H, 2.87; N, 13.25; S, 10.22.

Biological activity:

Antimicrobial activity of the tested samples was determined using a modified Kirby-Bauer disc diffusion method **(Bauer, *et al.*, 1966 [31]).** Briefly, 10 µl of the test bacteria/fungi were grown in 10 ml of fresh media until they reached a count of approximately 10^8 cells/ml for bacteria or 10^5 cells/ml for fungi **(Pfaller, *et al.*, 1988 [32])**. 10 µl of microbial suspension was spread onto agar plates corresponding to the broth in which they were maintained. Isolated colonies of each organism that might be playing a pathogenic role should be selected from primary agar plates and tested for susceptibility by disc diffusion method **(NCCLS, 1997 [33]).**

Plates inoculated with filamentous fungi *as* ***Aspergillus flavus*** at 25°C for 48 hours; Gram (+) bacteria as ***Staphylococcus aureus***, ***Bacillus subtilis***; Gram (-) bacteria as ***Escherichia coli***, ***Pseudomonas aeuroginosa*** were incubated at 35-37°C for 24-48 hours and yeast as ***Candida albicans*** incubated at 30°C for 24-48 hours and, then the diameters of the inhibition zones were measured in millimeters **(Bauer *et al.*, 1966 [31]).**

Standard discs of **Ampicillin** (Antibacterial agent), **Amphotericin B** (Antifungal agent) served as positive controls for antimicrobial activity but filter discs impregnated with 10 µl of solvent (distilled water, chloroform, DMSO) were used as a negative control.

Blank paper disks (Schleicher & Schuell, Spain) with a diameter of 8.0 mm were impregnated 10µl of tested concentration of the stock solutions. When a filter paper disc impregnated with the tested chemical compound is placed on agar, the chemical compound will diffuse from the disc into the agar. This diffusion will place the chemical in the agar only around the disc. The solubility of the chemical and its molecular size will determine the size of the area of chemical infiltration around the disc. If an organism is placed on the agar it will not grow in the area around the disc if it is susceptible to the chemical. This area of no growth around the disc is known as "**Zone of inhibition**" or" **Clear zone**".

For the disc diffusion, the zone diameters were measured with slipping calipers of the National Committee for Clinical Laboratory Standards **(NCCLS, 1993 [34, 35])**.

3. Results and discussion

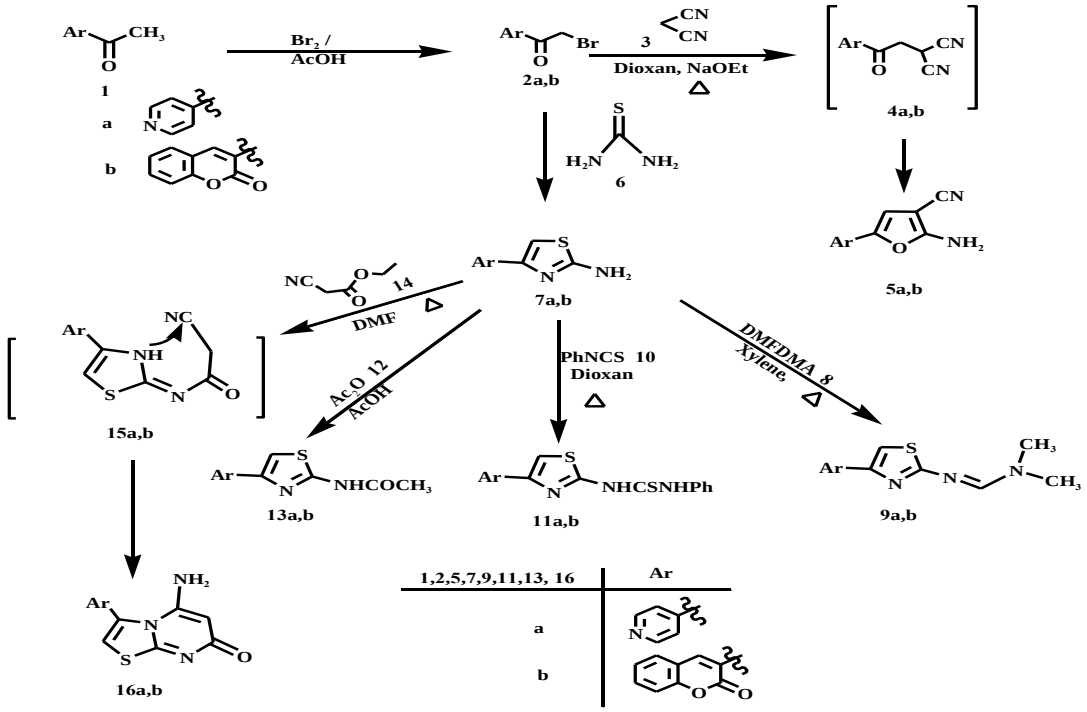
3.1. Chemistry

The bromoacetyl derivatives **2a,b** react with malononitrile **3** in Refluxing dioxane to afford two products for which the furan structures **5a,b** were assigned based on the analytical and spectral data. The IR spectrum of compound **5a** showed the disappearance of the carbonyl absorption band and revealed absorption bands at ν_{max} = 3371, 2195 cm^{-1} corresponding to the amino and the cyano groups respectively. The ^{1}H NMR spectrum of **5a** revealed four signals at δ_H = 6.25 (s), 7.65 (d, 2H), 7.73 (s, 1H), 8.72(d, 2H) which could be attributed to the amino, pyridine and the furan 4-H protons. The IR spectrum of **5b** showed a similar pattern with that of **5a** with in addition to a carbonyl absorption band at ν_{max} = 1714 cm^{-1} due to the lactone carbonyl. The ^{1}H NMR spectrum of **5b** revealed the presence of an aromatic multiplet at δ_H = 7.45- 8.00 ppm (7H), and the chromene 4-H as a singlet at δ_H = 8.99 ppm.

The formation of **5a,b** from **2a,b** and **3** presumably took place via the intermediates **4a,b** which undergo self cyclization under the reaction conditions to afford the final isolable products respectively (Scheme 1).

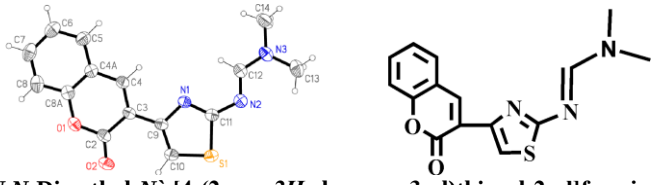
The bromoacetyl derivatives **2a,b** react with thiourea **6** in ethanol under reflux to afforded the thiazole derivatives **7a,b** in good yields. IR spectrum of compound **7a** showed absorption band at υ= 3285 cm^{-1} attributed to NH_2. ^{1}H NMR spectrum of the same compound revealed two duplets at δ= 7.62 (2H) and 8.63 (2H) ppm attributable to the pyridine ring and one singlet at δ= 7.52 ppm due to the thiazole 5-H, beside a singlet (2H) at δ= 4.25 ppm (D_2O exchangeable) due to the amino group. The IR spectrum of **7b** revealed absorption bands at ν_{max}: 3275 and 1706 cm^{-1} due to the amino and the lactone carbonyl groups respectively. The ^{1}H NMR spectrum of **7b** showed signals at δ_H = 5.20 (s, 2H, D_2O exchangeable), 7.22- 7.65 (m, 5H) and 8.16 ppm (s, 1H) assignable to the amino protons, the aromatic protons including the thiazole 5-H and the coumarine 4-H proton respectively.

The thiazole compounds **7a** or **7b** react with dimethylformamide dimethylacetal (DMFDMA) **8** in refluxing dry xylene to afford the formimidamide derivatives **9a,b** respectively.



Scheme 1

Synthesis of the furan derivatives **5a,b** and the thiazole derivatives **7a,b**; **9a,b**; **11a,b**; **13a,b** and the thiazolo[3,2-*a*]pyrimidinones **16a,b**



***N,N*-Dimethyl-*N*`-[4-(2-oxo-*2H*-chromen-3-yl)thiazol-2-yl]formimidamide 9b**

Fig 1: X- Ray crystallography of compound 9b [30]

The ^{1}H NMR spectrum of **9a** revealed a singlet (6H) at δ = 3.12 ppm due to two methyl groups and a singlet (1H) 7.20 attributable to the thiazole 5-H) beside the other signals as expected. The mass spectrum showed [M$^+$]= 232. Compound **9b** showed absorption band at ν_{max} = 1710 cm^{-1} in its IR spectrum due to the lactone (C=O). The^{1}H NMR spectrum of **9b** revealed the two methyl singlet at δ_H = 3.10 ppm beside a multiplet (5H) at 7.36- 7.86 ppm attributable to aromatic, thiazole 5-H, N=CH-N and a singlet (1H) at 8.06 ppm assignable to the chromene-4H. The ^{13}C NMR spectrum of **9b** is applicable to the suggested structure. Furthermore, the X-ray crystallographic study afforded further evidence as shown in figure 1 (*c.f.* experimental). Refluxing a solution of **7a** or **7b** with phenyl isothiocyanate **10** in dry dioxane yielded the N, N`-disubstituted thiourea derivatives **11a,b** respectively. ^{1}H NMR spectrum of **11a** and of **11b** showed two signals for 2 NH protons at 7.18 and 8.52 and aromatic multiplets at 7.04 and 7.20 ppm respectively.

Acetylation of **7a,b** by refluxing with acetic anhydride **12** afforded the N-acetyl derivatives **13a,b** respectively. ^{1}H NMR spectrum of **13a** showed signals at δ 2.20 and 12.44 ppm attributable for one CH_3 and one NH group respectively. The ^{1}H NMR spectrum of **13b** revealed a singlet signal at δ 2.06 ppm attributable to acetyl CH_3 group and 11.25 ppm attributable to the NH group.

Refluxing compound **7a and 7b** with ethyl cyanoacetate **14** in DMF afforded the thiazolo[3,2-a]pyrimidin-7-one derivatives **16a,b** respectively

(Scheme 1). The reaction presumably involves initial condensation with elimination of ethanol to afford the intermediates **15a,b** which apparently undergo cycloaddition of the thiazole NH to the CN group to afford the final isolable products **16a,b**.

3.2. Biological testing

Table 1: Anti-bacterial and anti-fungal activity of the tested compounds

Sample		Inhibition zone diameter (mm/mg sample)					
		Bacterial species				Fungal species	
		G^+		G^-			
		Bacillus cereus	*Staphylococcus aureus*	*Escherichia coli*	*Salmonella typhimrium*	*Aspergillus flavus*	*Candida albicans*
Control: DMSO		0.0	0.0	0.0	0.0	0.0	0.0
Standard	Ampicillin Antibacterial agent	26	21	25	26	--	--
Standard	Amphotericin B Antifungal agent	--	--	--	--	17	21
2a		22	23	25	24	0.0	21
5a		11	12	12	14	0.0	0.0
7a		11	12	11	13	0.0	0.0
11a		11	0.0	9	10	0.0	0.0
13a		10	11	10	15	0.0	0.0
16a		9	9	9	9	0.0	0.0
2b		17	21	22	23	0.0	16
5b		11	12	12	17	0.0	0.0
7b		10	14	9	11	0.0	0.0
11b		11	12	12	16	0.0	0.0
13b		9	12	10	13	0.0	0.0
16b		0.0	0.0	0.0	0.0	0.0	0.0

Compound **2a** reveals high activity against gram positive (G^+) bacteria and even higher than the reference (Ampicillin) in case of *staphylococcus aureus* and shows a comparative activity values to both strands of gram negative (G^-) bacteria and to *Candida albicans* fungal species. The rest of the compounds (**5a, 7a, 11a, 13a, 16a**) showed generally moderate activities against (G^+) and (G^-) bacteria and no activity against fungal species.

Compound **2b** revealed moderate activity against all species of bacteria and fungi. The rest of the tested compounds (**5b, 7b, 11b, 13b, 16b**) showed also a moderate to low activity against (G^+) and (G^-) bacteria but no activity at all against fungal species. All tested compounds are completely inert against *Aspergillus flavus* fungus. It should be deduced also that the thiazole derivatives bearing the 4-pyridyl residue are generally more potent than those bearing the 3-chromenyl residue. Table 1 reflects these results.

4. Acknowledgement

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