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


1. Introduction

Functionalized pyridines possess 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].
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 ethanol 2a and 3-(2-bromoacetyl)-2H-chromene-2-one 2b (Scheme 1) (prepared via the boration of 4-acyethylpyridine 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 1H-NMR and 13C-NMR spectra were recorded on a Varian Mercury VX-300 spectrometer (300 MHz for 1H-NMR and 75 MHz for 13C-NMR) in DMSO-d6 using TMS as internal standard and the chemical shifts were expressed in δ ppm values. Assignments of 13C-NMR multiplicities were made by correlation of the off-resonance decoupled 1H signals and the determination of the 1H 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-LII II 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 ethanol 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; v_max cm⁻¹: 3371 (NH2), 2195 (CN); δ_H ppm= 6.25 (s, 2H, D₂O exchangeable, NH₂); 7.65 (d, 2H, Py-H, 3H); 7.33 (s, 1H, Fu 4-H), 8.72 (d, 2H, Py-H); [M⁺]= 185. Analysis Calcd. for C₁₀H₁₃N₂O (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-2H-chromen-3-ylfuran-3-carbonitrile 5b
Page crystals, Yield 2.24 g (80 %), mp 187-189 °C; v_max cm⁻¹: 3363 (NH₂), 2198 (CN), 1714 (C=O); δ_H ppm= 7.45- 8.00 (m, 7H, Ar-H+Fu 4-H+ NH₂), 8.99 (s, 1H, Chrom-4-H). [M⁺]= 252. Analysis Calcd. for C₁₉H₁₅N₂O₂ (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 ethanol 2a (2.0 g; 10 mmol) or 3-(2-bromoacetyl)-2H-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; v_max cm⁻¹: 3263 (NH₂); δ_H ppm= 7.07 (s, 1H, Thiazole 5-H), 7.44-7.67 (d, 2H, Py-3H, j=6 Hz), 8.26 (s, 2H, D₂O exchangeable, NH₂), 8.64-8.66 (d, 2H, Py-2H, j=6 Hz). [M⁺]= 177. Analysis Calcd. for C₅H₈N₂S (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; v_max cm⁻¹: 3269 (NH₂), 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, D₂O exchangeable, NH₂). Analysis Calcd. for C₁₂H₁₀N₂O₄S (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 dimethylethylvat (DMFDM) 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’-14-(pyridine-4-yl)thiazol-2-ylformimidamide 9a
Pale brown, crystals, Yield 1.81 g (78 %), mp 174-176 °C (xylene); δH ppm = 3.0, 3.12 (2s, 6H, 2CH3), 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 C13H12N4S (323.31); C, 56.87; H, 5.21; N, 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); νmax cm⁻¹: 1710 (C=O); δH ppm = 3.0, 3.14 (2s, 6H, 2CH3), 7.32-7.80 (m, 5H, Ar-H=N=CH-N), 8.34 (s, 1H, Chrom-4H), 8.67 (s, 1H, Thiazole-5H). δC = 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 (s), 152.73 (d), 157.08 (s), 159.27 (d), 173.60 (d). Analysis Calcd. for C13H12N4S (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; νmax cm⁻¹: 3175, 3168 (2NH); δH 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 C13H12N4S2 (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; νmax cm⁻¹: 3076 (br. 2NH), 1717 (C=O); δH 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 C19H11N6O2S2 (379.45); C, 60.14; H, 3.45; N, 11.07; S, 16.90; Found C, 60.06; H, 3.32; 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; νmax cm⁻¹: 3175 & 3190 (NH), 1669 (C=O); δH ppm = 2.20 (s, 3H, CH3), 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 C10H8N2O2S (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-2H-chromen-3-yl)-thiazol-2-yl]-acetamide 13b
Yellow powder, Yield 2.0 g (70 %), mp 255-256 °C; νmax cm⁻¹: 3175 (NH2), 1670 (C=O), 1705 (C=O); δH ppm = 2.18 (s, 3H, CH3), 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 C13H10N2O2S (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 7b (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]pyrimidine-7-one 16a
Hairy brown powder, Yield 1.42 g (80 %), mp 241-243 °C; νmax cm⁻¹: 3280 (NH2), 1678 (C=O); δH ppm = 4.07 (s, 1H, pyrimidinone-H), 6.32 (s, 1H, thiazole H), 6.50 (s, 2H, D2O exchangeable, NH2), 7.48 (d, 2H, pyridine-3H, j=6Hz), 8.50 (d, 2H, pyridine-2H, j=6Hz). [M]+ = 244, Analysis Calcd. for C13H12N6O2S (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-oxy-2H-chromen-3-yl)-thiazolo[3,2-a]pyrimidine-7-one 16b
Yellow powder, Yield 2.36 g (76 %), mp 283-285 °C; \( \nu_{\text{max}} \text{cm}^{-1} \): 3309 (NH2), 1678, 1637 (2C=O); \( \delta_{\text{H}} \) ppm= 4.02 (s, 1H, Pyrim.-H), 5.4 (s, 1H, Thiazole H), 6.5 (s, 2H, NH2), 7.58 (s, 1H, Chrom-4H), 7.62- 7.87 (m, 4H, Ar-H). \( \delta_{\text{C}} \): 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 C13H12N2O2S (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 aeruginosa 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), Ampthoterin 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”.

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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 \( \nu_{\max} = 3371, 2195 \text{ cm}^{-1} \) corresponding to the amino and the cyano groups respectively. The \(^1\)H NMR spectrum of 5a revealed four signals at \( \delta_{\text{H}} = 6.25 \) (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 \( \nu_{\max} = 1714 \text{ cm}^{-1} \) due to the lactone carbonyl. The \(^1\)H NMR spectrum of 5b revealed the presence of an aromatic multiplet at \( \delta_{\text{H}} = 7.45-8.00 \text{ ppm (7H)} \), and the chromene 4-H as a singlet at \( \delta_{\text{H}} = 8.99 \text{ ppm} \).

The formation of 5a,b from 2a,b and 3 presumable 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 \( \nu_{\max} = 3285 \text{ cm}^{-1} \) attributed to NH2. \(^1\)H NMR spectrum of the same compound revealed two duplets at \( \delta_{\text{H}} = 7.62 \text{ (2H)} \) and 8.63 (2H) ppm attributable to the pyridine ring and one singlet at \( \delta_{\text{H}} = 5.20 \text{ ppm} \) due to the thiazole 5-H, beside a singlet (2H) at \( \delta_{\text{H}} = 4.25 \text{ ppm (D}_2\text{O exchangeable)} \) due to the amino group. The IR spectrum of 7b revealed absorption bands at \( \nu_{\max} = 3275 \text{ and } 1706 \text{ cm}^{-1} \) due to the amino and the lactone carbonyl groups respectively. The \(^1\)H NMR spectrum of 7b showed signals at 5.02 (s, 2H, D2O 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 (DMFDMFA) 8 in refluxing dry xylene to afford the formimidamide derivatives 9a,b respectively.

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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

The \(^1\)H NMR spectrum of 9a revealed a singlet (6H) at \(\delta = 3.12\) 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 \(v_{\text{max}} = 1710\) 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 \(\delta_H = 3.10\) 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 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 \(\delta = 2.20\) and 12.44 ppm attributable for one CH3 and one NH group respectively. The \(^1\)H NMR spectrum of 13b revealed a singlet signal at \(\delta = 2.06\) ppm attributable to acetyl CH3 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

<table>
<thead>
<tr>
<th>Sample</th>
<th>Inhibition zone diameter (mm/mg sample)</th>
<th>Bacterial species</th>
<th>Fungal species</th>
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<tr>
<td></td>
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<td>G+ Bacillus cereus</td>
<td>G- Staphylococcus aureus</td>
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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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5. References


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