European Journal of Chemistry 2 (2) (2011) 158-162

European Journal of Chemistry

Journal homepage: www.eurjchem.com

# Synthesis, antifungal activity and semi-empirical AM1-MO calculations of some new 4-oxo-4*H*-chromene derivatives

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ARTICLE INFORMATION

Received: 01 January 2011
Received in revised form: 06 February 2011
Accepted: 09 February 2011
Online: 30 June 2011

KEYWORDS

Synthesis
Chromone
Chromone Derivatives
3-Formylchromones
Antifungal Activity
AM1-MO Calculation

ABSTRACT

Some new antifungal agents have been prepared through reaction of 4-oxo-4*H*-chromene-3-carbaldehydes (**1a**,**b**) with some active primary amines (**2a-e**) and amides/thioamides (**6a-d**) in different conditions. Structures of the products were established on the basis of elemental analysis, IR, $^1$H NMR, mass spectra and semi-empirical AM1-MO calculations.

## 1. Introduction

Derivatives of 4*H*-1-benzopyran-4-one, also known as 4*H*-chromen-4-ones or chromones, belong to an important class of natural oxygen-containing heterocycles that are widely distributed among many plants [1]. Many natural and synthetic chromone derivatives exhibit various types of biological activities [2] and find use as valuable synthetic intermediates in the preparation of pharmacologically relevant products and new heterocyclic systems [3-5]. In recent years, 3-formylchromones have attracted considerable attention as highly reactive compounds, which can serve as the starting materials in synthesis of a whole series of heterocycles with useful properties due to three strong electrophilic centres (carbon atoms C-2 and C-4 of the chromone system and formyl group) [6]. These compounds possess a highly polarized $C_2$-$C_3$ π-bond and their reactions with dinucleophiles start predominantly from the attack of the unsubstituted C-2 atom (1,4-addition) and are accompanied by pyrone ring opening to form the β-dicarbonyl intermediate capable of undergoing intramolecular heterocyclizations [7,8]. In continuation to our interest in the chemistry of 4-oxo-4*H*-chromene-3-carbaldehydes ring system [9-14], owing to its considerable biological activities. The present work describes the preparation of new systems derived from the reaction of 4-oxo-4*H*-chromene-3-carbaldehydes **1a**,**b** with primary amines **2a**,**e** and amide/thioamide derivatives **6a-d** in polar and non-polar solvents. The antifungal activities for some the prepared compounds were investigated. Also, the AM1 molecular orbital calculations for some new compounds were studied and compared with their experimental $^1$H NMR values.

## 2. Experimental

### *2.1. Instrumentation*

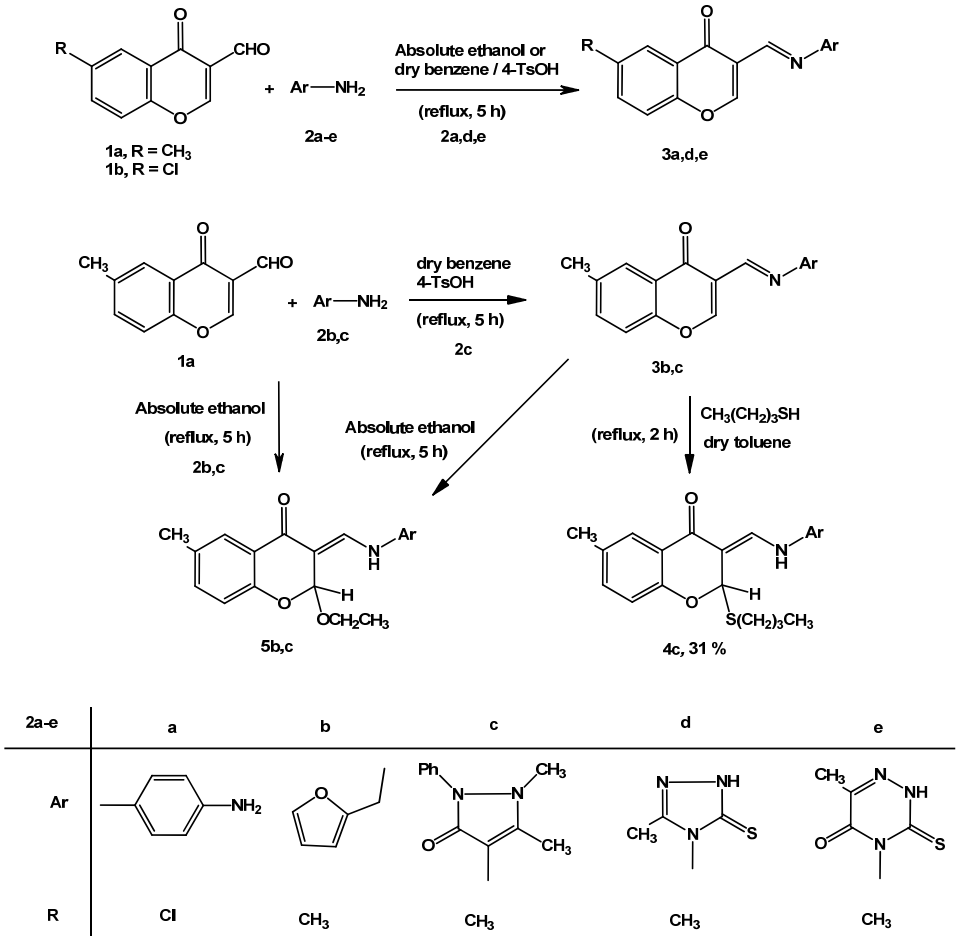
The melting point was determined in an open capillary tube on a digital Stuart SMP-3 apparatus. Infrared spectra were measured on Perkin-Elmer 293 spectrophotometer ($cm^{-1}$), using KBr disks. $^1$H NMR spectra were measured on Gemini-200 spectrometer (200 MHz), using DMSO-$d_6$ as a solvent and tetramethylsilane (TMS) (δ) as the internal standard. Mass spectra recorded on a Gas Chromatographic GCMSqp 1000 ex Shimadzu instrument at 70 eV. Elemental microanalyses were performed in microanalysis center at Cairo University. The purity of the synthesized compounds was checked by thin layer chromatography (TLC). 4-Oxo-4*H*-chromene-3-carbaldehydes **1a**,**b**, primary amines **2d-e** and amide **6b-c** were prepared by published methods: **1a**,**b** [15], **2d** [16], **2e** [17], **6b** [18], **6c** [19].

### *2.2. Synthesis*

#### *2.2.1. 3-(Aryliminomethyl)-4-oxo-4H-chromenes (3a,d,e)*

A mixture of 4-oxo-4*H*-chromene-3-carbaldehydes **1a**,**b** (10.00 mmol) and amino compounds namely 1,4-phenylenediamine (**2a**), 4-amino-5-methyl-3-thioxo-1,2,4-triazole (**2d**) and 4-amino-6-methyl-3-thioxo-1,2,4-triazin-5(2*H*)-one (**2e**) (10.00 mmol) in absolute ethanol or dry benzene (50 $cm^3$) containing of 4-toluenesulfonic acid (0.01 g) was refluxed for 5 h. The obtained solids were filtered off and crystallized to give **3a**,**d**,**e**, respectively.


ISSN 2153-2249 (Print) / ISSN 2153-2257 (Online) 
DOI:10.5155/eurjchem.2.2.158-162.381




**Scheme 1**

### *2.2.2. 3-(Aryliminomethyl)-4-oxo-4H-chromenes (3b,c)*

A mixture of **1a** (2.08 g, 10.00 mmol) and 2-furfurylamine (**2b**) or 4-aminoantipyrine (**2c**) (2.03 g, 10.00 mmol) in dry benzene (50 $cm^3$) containing 4-toluenesulfonic acid (0.01 g) was refluxed for 5 h. The obtained solids were filtered off and crystallized to give **3b**,**c**, respectively.

### *2.2.3. 4-[(2-(Butylthio)-6-methyl-4-oxo-2H-chromen-3(4H)-ylidene)methylamino]-1,2-dihydro-1,5-dimethyl-2-phenyl-pyrazol-3-one (4c)*

A mixture of **3c** (3.73 g, 10.00 mmol) and 1-butanethiol (0.9 g, 10.00 mmol) in dry toluene (50 $cm^3$), was refluxed for 2 h. The solution so obtained was concentrated to half volume. The obtained solid was filtered off and crystallized to give **4c**.

### *2.2.4. 3-[(Arylamino)methylene]-2-ethoxy-2,3-dihydro-6-methylchromen-4-ones (5b,c)*

*Method A*: A mixture of **1a** (2.08 g, 10.00 mmol) and 2-furfurylamine (**2b**) or 4-aminoantipyrine (**2c**) (10.00 mmol) in absolute ethanol (50 $cm^3$) was refluxed for 5 h. The obtained solids were filtered off and crystallized to give **5b**,**c**, respectively.

*Method B:* A compound **3b**,**c** (3.73 g, 10.00 mmol) were boiled in absolute ethanol (50 $cm^3$) for 5 h. The obtained solids were filtered off and crystallized to give **5b**,**c**, respectively.

### *2.2.5. 3-[(Arylamino)methylene]-2-ethoxy-2,3-dihydro-6-methylchromen-4-ones (7a-c)*

A mixture of **1a** (2.08 g, 10.00 mmol) and amide compounds namely 2-cyanoacetamide (**6a**), 4-chlorobenzylidene-semicarbazone (**6b**) and 2-amino-4*H*-chromen-3-carboxamide (**6c**) (10.00 mmol) in absolute ethanol (50 $cm^3$) was refluxed for 5 h. The obtained solids were filtered off and crystallized to give **7a-c**, respectively.

### *2.2.6. 3-(N-Aroylamino-1-hydroxymethyl)-6-methyl-chromen-4-ones (8a,c)*

Equimolar amounts of **1a** (2.08 g, 10.00 mmol) and amide derivatives namely 2-cyanoacetamide (**6a**), 2-amino-4*H*-chromen-3-carboxamide (**6c**) (10.00 mmol) in dry benzene (50 $cm^3$) containing 4-toulenesulfonic acid (0.01 g) were refluxed for 5 h. The obtained solids were filtered off and crystallized to give **8a**,**c**, respectively.

### *2.2.7. 1-(4-chlorobenzylidene)-4-(2-hydroxy-6-methyl-4-oxo-2H-chromen-3(4H)-ylidene)methyl)thiosemicarbazide (9d)*

Equimolar amounts of **1a** (2.08 g, 10.00 mmol) and 4-chlorobenzylidenethiosemicarbazone (**6d**) (2.13 g, 10.00 mmol) in dry benzene (50 $cm^3$) containing 4-toulenesulfonic acid (0.01 g) was refluxed for 5 h. The obtained solid was filtered off and crystallized to give **9d**.

**Table 1.** Physical properties and mass spectral data of newly prepared compounds.

| Comp. | Formula | M.p. (°C) | Yield (%) | Calc./Found% C | Calc./Found% H | M. Wt | MS, *m/z* ($I_r$/%) |
|---|---|---|---|---|---|---|---|
| **3a** | $C_{16}H_{11}N_2O_2Cl$ | 203 -205 | 61 | 64.33<br>64.38 | 3.71<br>3.54 | 298.73 | - |
| **3b** | $C_{16}H_{13}NO_3$ | 201 -203 | 25 | 71.90<br>71.64 | 4.90<br>4.64 | 267.29 | 267 ($M^+$, 28.90%), 186 (31.60), 174 (11.50), 172 (76.20), 160 (7.90), 135 (22.70), 134 (10.8), 109 (3.6), 108 (25.90), 107 (44.4), 91 (100), 82 (9.1), 81 (80.3), 78(15.1), 69 (94.50), 53 (71.8) |
| **3c** | $C_{22}H_{19}N_3O_3$ | 219 -221 | 45 | 70.76<br>70.14 | 5.13<br>4.89 | 373.41 | 373 ($M^+$, 9.20), 372 (35.60), 371 (92.90), 343 (12.20), 187 (18.60), 186 (100), 160 (57.40), 135 (20.70), 77 (26.60) |
| **3d** | $C_{14}H_{12}N_4O_2S$ | 223 -225 | 66 | 55.99<br>55.63 | 4.03<br>4.83 | 300.34 | 301 (M+1, 0.23), 300 ($M^+$, 0.44), 186 (40.20), 135 (12.00), 134 (17.91), 115 (100), 91 (13.7), 78 (23.07), 77 (30.13) |
| **3e** | $C_{15}H_{12}N_4O_3S$ | 229 -230 | 75 | 54.87<br>54.51 | 3.68<br>3.52 | 328.35 | 330 (M+2, 5.60), 329 (M+1, 20.90), 328 ($M^+$, 8.30), 186 (95.1), 160 (9.70), 143 (100), 134 (11.20), 115 (6.90), 102 (7.90), 91 (6.60), 84 (2.70), 52 (2.60) |
| **4c** | $C_{26}H_{29}N_3O_3S$ | 185 -187 | 31 | 67.36<br>67.13 | 6.30<br>6.21 | 463.60 | 389 (M-S$(CH_2)_2CH_3$, 73.5), 373 (29.50), 297 (41.70), 281 (35.10), 214 (6.90), 201 (3.20), 188 (19.40), 187 (7.20), 186 (3.10), 160 (2.40), 121(19.00), 119 (3.90), 91 (2.30), 56 (100) |
| **5b** | $C_{18}H_{19}NO_4$ | 87 -88 | 30 | 68.99<br>68.84 | 6.11<br>5.66 | 313.35 | - |
| **5c** | $C_{24}H_{25}N_3O_4$ | 197 -199 | 35 | 68.72<br>68.52 | 6.00<br>5.86 | 419.48 | 421 (M+2, 0.35), 391 (0.23), 373 (M-EtOH, 10.40), 281 (23.02), 203 (44.36), 188 (9.10), 187 (5.08), 121 (10.54), 119 (3.78), 84 (42.09), 83 (15.43), 56 (100) |
| **7a** | $C_{16}H_{16}N_2O_4$ | 204 -205 | 47 | 63.99<br>63.62 | 5.37<br>4.98 | 300.31 | - |
| **7b** | $C_{21}H_{20}N_3O_4Cl$ | 244 -246 | 31 | 60.94<br>60.74 | 4.87<br>4.69 | 413.86 | 371 (M-HCNO, 13.20), 245 (7.40), 228 (4.10), 186 (67.70), 185 (9.70), 134 (100), 95 (27.70), 91 (8.60), 77 (16.80), 51 (12.20) |
| **7c** | $C_{23}H_{20}N_2O_5$ | 261 -262 | 40 | 68.31<br>68.26 | 4.98<br>4.96 | 404.42 | 358 (M-EtOH, 31.2), 189 (100), 188 (2.70), 174 (16.80), 173 (98.90), 172 (13.10), 146 (18.20), 145 (20.30), 118 (29.20), 90 (20.30), 89 (37.00), 88 (5.80), 63 (27.00) |
| **8a** | $C_{14}H_{12}N_2O_4$ | 222 -224 | 43 | 61.76<br>61.55 | 4.44<br>4.27 | 272.26 | 272 ($M^+$, 3.40), 255 (15.20), 254 (11.80), 229 (24.10), 188 (47.30), 187 (18.90), 186 (100), 160 (13.90), 134 (25.80), 91 (10.60), 78 (11.90), 77 (22.20), 68 (11.90), 53 (6.50) |
| **8c** | $C_{21}H_{16}N_2O_5$ | 190 -192 | 28 | 67.02<br>67.70 | 4.28<br>4.56 | 376.37 | - |
| **9d** | $C_{19}H_{16}N_3O_3SCl$ | 210 -213 | 25 | 56.78<br>56.86 | 4.01<br>4.09 | 401.87 | 406 (M+4, 70.00), 368 (69.41), 338 (4.71), 305 (17.65), 274 (25.29), 260 (35.20), 238 (27.08), 220 (30.00), 203 (54.12), 178 (100), 176 (45.20), 113 (3.53) |

## 3. Results and discussion

### *3.1. Chemistry*

Condensation reactions of Equimolar quantities of 4-oxo-4*H*-chromene-3-carbaldehydes **1a**,**b** with active primary amines namely, 1,4-phenylenediamine (**2a**), 4-amino-5-methyl-3-thioxo-1,2,4-triazole (**2d**) and 4-amino-6-methyl-3-thioxo-1,2,4-triazin-5(2*H*)one (**2e**) in ethanol and/or dry benzene containing 4-toluenesulfonic acid as a catalyst yielded 3-(aryliminomethyl)-4-oxo-4*H*-chromenes **3a**,**d**,**e**, respectively (Scheme 1).

Similarly, reaction of **1a** with 2-furfurylamine (**2b**) and 4-aminoantipyrine (**2c**) in dry benzene containing 4-toluenesulfonic acid gave 3-(aryliminomethyl)-4-oxo-4*H*-chromene derivative **3b**,**c**, respectively, but when **1a** reacted with **2b**,**c** in boiling ethanol yielded 1,4-adducts **5b**,**c**, respectively (Scheme 1). Reaction of **3c** with nucleophilic reagents gave 1,4-adducts due to 1,4-addition of nucleophilic reagent. Thus, reaction of **3c** with 1-butanethiol in dry toluene gave **4c**, and when **3b**,**c** were refluxed in absolute ethanol gave **5b**,**c** (Scheme 1). Structure of products **3a**-**e**, **4c** and **5b**,**c** were confirmed by elemental analysis, IR, $^1$H NMR and mass spectra (Table 1 and 2). The 1,4-adducts **5b**,**c** were formed by condensation of aldehyde **1a** with primary amines **2b**,**c** followed by 1,4-addition of ethanol as nucleophile. In addition, $^1$H NMR spectra of **5b**,**c** support the presence of H-2 hydrogen atom on pyranone system not on pyrone system. The reason for this rather unusual ring-addition of ethanol to give 1,4-adducts **5b**,**c** was the formation of the stable hydrogen-bonded ketoamine system [20].

On the other hand, condensation of aldehyde **1a** with primary amines **2a**,**d**,**e** gave only condensation products **3a**,**d**,**e** and not gave 1,4-adducts with addition of ethanol because the primary amines **2a**,**d**,**e** are more basic amines in comparison with the amines **2b**,**c** and their basicity are sufficiently to deprotonated the 1,4-adducts and initiate the elimination of ethanol to give only the condensation products.

The behaviour of aldehyde **1a** towards amide/thioamide derivatives **6a**-**d** in polar and nonpolar medium has been studied. Thus, reaction of **1a** with cyanoacetamide (**6a**), 4-chlorobenzylidenesemicarbazone (**6b**) and 2-amino-4*H*-chromene-3-carboxamide (**6c**) in boiling ethanol afforded the 1,4-adducts **7a**-**c** with addition of ethanol [20,21] (Scheme 2) (Table 1 and 2).

On the other hand, reaction of aldehyde **1a** with **6a**,**c** in dry benzene containing 4-toluenesulfonic acid as a catalyst afforded 3-(*N*-aroylamino-1-hydroxymethyl)-6-methyl-chromen-4-ones **8a**,**c**, respectively, while its reaction with 4-chlorobenzylidene-thiosemicarbazone **6d** under the same condition afforded 1-(4-chlorobenzylidene)-4-(2-hydroxy-6-methyl-4-oxo-2*H*-chromen-3(4*H*)-ylidene)methyl) thiosemicarbazide (**9d**) (Scheme 3). Structures of **8a**,**c** and **9d** were established by $^1$H NMR spectra (Table 2). $^1$H NMR spectra of compounds **8a**,**c** support the presence of OH group on C-9 of chromone moiety, while for **9d** support the presence of OH group on C-2 of chromanone moiety.

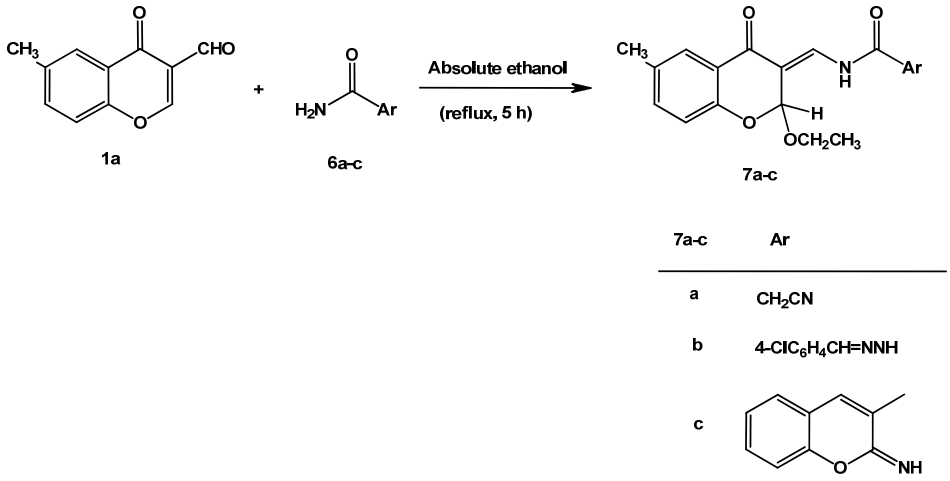
### *3.2. Molecular orbital calculations*

The experimental $^1$H-NMR spectra results were compared with theoretical data which were obtained from molecular mechanical calculations on the basis of the semi-empirical $AM_1$ methods of HyperChem 7.5 computer program. The calculated charges on H-2 and H-9 hydrogen atoms using $AM_1$-MO calculation method after geometrical optimization of the structures were compared with experimental $^1$H NMR δ values for compounds **3a**-**9d** (Table 3).

The calculated charges on H-2 and H-9 hydrogen atoms ($Q_H$) are linearly related to the measured $^1$H-NMR δ values for compounds **3a**-**9d** from the linear relations $\delta$–$NMR_{(H\text{-}2)}$ = 3.748 + 24.476 ($Q_{H\text{-}2}$), $r$ = 0.99 except (**3a**, **4c**, **5b**, **8c**) and $\delta$–$NMR_{(H\text{-}9)}$

**Table 2.** IR and $^1$H NMR spectral data of newly prepared compounds.

| Compound | IR, (υ/cm$^{-1}$) | $^1$H NMR (DMSO-$d_6$, δ) |
|---|---|---|
| **3a** | 1604 (C=N), 1641 (C=O), 3378 ($NH_2$) | 6.60 (d, 1H, $J_{7,8}$ = 6.7 Hz, H-8), 6.92 -7.28 (m, 7H, Ar-H and H-9), 7.76 (br s, H-2), 12.08-12.15 (br s, 2H, $NH_2$) |
| **3b** | 3035 ($CH_{arom}$), 2945 ($CH_{aliph}$), 1645 (C=$O_{pyrone}$), 1616 (C=N) | - |
| **3c** | 1619 (C=$O_{pyrone}$), 1652 (C=$O_{pyrazole}$) | 2.44 (s, 6H, Ar-$CH_3$), 3.14 (s, 3H, N-$CH_3$), 7.29-7.50 (m, 8H, Ar-H and Ph-H, H-9), 8.06 (s, 1H, H-5), 8.66 (s, 1H, H-2) |
| **3d** | 1601 (C=C), 1619 (C=N), 1651 (C=O), 3109 (NH) | 2.46 (s, 3H, Ar-$CH_3$), 2.50 (s, 3H, Ar-$CH_3$), 7.48-7.66 (m, 2H, H-7 and H-8), 7.93 (s, 1H, H-5), 8.20 (br s, 1H, H-9), 8.71 (br s, 1H, H-2), 11.03 (s, 1H, SH) |
| **3e** | 1641 (C=$O_{pyrone}$), 1701 (C=$O_{triazine}$), 3173 (NH) | 2.20 (s, 3H, Ar-$CH_3$), 2.47 (s, 3H, Ar-$CH_3$), 7.64-7.75 (m, 2H, H-7 and H-8), 7.93 (s, 1H, H-5), 8.76 (s, 1H, H-9), 9.14 (s, 1H, H-2), 13.66 (s, 1H, SH) |
| **4c** | 1640 (C=$O_{pyrone}$), 1673 (C=$O_{pyrazole}$), 3114 (NH) | 1.17 (t, 3H, $CH_3$), 2.09-2.73 (m, 13H, $CH_2CH_2$ and Ar-$CH_3$), 3.07-3.19 (m, 2H, $SCH_2$), 8.06 (ss, 1H, H-2), 7.00 -7.80 (m, 6H, Ar-H and Ph-H), 7.95 (s, 1H, H-5), 8.82, 8.98 (ss, 1H, H-9), 9.62 (s, 1H, NH) |
| **5b** | 1617 (C=C), 1652 (C=$O_{pyrone}$), 3254 (NH) | 1.06 (m, 3H, $CH_3$ ethoxy), 2.22 (s, 3H, Ar-$CH_3$), 3.29-3.60 (m, 2H, $CH_2$ ethoxy), 4.51-4.77 (m, 2H, N-$CH_2$-furan), 5.94, 5.96 (ss, 1H, H-2), 6.37 -6.47 (m, 3H, furan), 6.80 -8.14 (m, 4H, H-9 and Ar-H), 9.42 (d, 1H, $J_{9,10}$ = 3.4 Hz, NH) |
| **5c** | 1640 (C=$O_{pyrone}$), 1673 (C=$O_{pyrazole}$), 3389 (NH) | 1.06 (m, 3H, $CH_3$ ethoxy), 2.50 (m, 6H, Ar-$CH_3$), 3.19 (s, 3H, N-$CH_3$), 3.86 (br s, 2H, $CH_2$ ethoxy), 6.80 (br s, 1H, H-2), 7.06-7.65 (m, 7H, Ar-H and Ph-H), 7.95 (s, 1H, H-5), 8.89 (d, 1H, $J_{9,10}$ = 3.2 Hz, H-9), 9.68 (d, 1H, $J_{9,10}$ = 3.2 Hz, NH) |
| **7a** | 1616 (C=C), 1658 (C=$O_{pyrone}$), 1695 (C=$O_{amide}$), 2224 (C≡N), 3388 (NH) | 1.21 (m, 3H, $CH_3$ ethoxy), 2.42 (s, 3H, Ar-$CH_3$), 2.88, 2.95 (ss, 2H, $CH_2CN$), 3.69-3.85 (m, 2H, $CH_2$ ethoxy), 5.15 (br s, 1H, OH enolic), 6.88-8.00 (m, 5H, H-2, H-9 and Ar-H) |
| **7b** | 1618 (C=N), 1645 (C=$O_{pyrone}$), 1695 (C=$O_{amide}$), 3443, 3232 (NH, NH) | 1.07 (m, 3H, $CH_3$ ethoxy), 2.45 (s, 3H, Ar-$CH_3$), 3.32 (m, 2H, $CH_2$ ethoxy), 6.53 (br s, 1H, H-2), 7.42-8.18 (m, 9H, H-9, CH=N and Ar-H), 9.00 (br s, 1H, NH), 10.33 (br s, 1H, NH) |
| **7c** | 1604 (C=C), 1680 (C=$O_{pyrone}$), 1716 (C=$O_{amide}$), 3150 (NH=C-), 3390 (NH) | 1.10 (t, 3H, $CH_3$ ethoxy), 2.51 (s, 3H, Ar-$CH_3$), 3.55 -3.57 (br s, 2H, $CH_2$ ethoxy), 7.19-8.09 (m, 10H, H-2, H-9 and Ar-H), 8.52 (s, 1H, NH), 8.88 (s, 1H, NH) |
| **8a** | 1606 (C=C), 1667 (C=$O_{pyrone}$), 1695 (C=$O_{amide}$), 2264 (C≡N), 3333 (br s, NH, OH) | 2.42 (s, 3H, Ar-$CH_3$), 2.88, 2.95 (ss, 2H, $CH_2CN$), 5.96 (br s, 1H, OH), 7.11-7.44 (m, 4H, H-9 and Ar-H), 8.53 (s, 1H, H-2), 10.39 (s, 1H, NH) |
| **8c** | 1603 (C=N), 1648 (C=$O_{pyrone}$), 1706 (C=$O_{amide}$), 3163 (NH=C-), 3283 (OH), 3391 ($NH_{amide}$) | 2.47 (s, 3H, Ar-$CH_3$), 5.90 (br s, 1H, OH), 6.54 (d, 1H, $J_{9,10}$ = 1.22 Hz, H-9), 7.10 -8.01 (m, 7H, Ar-H), 8.16 (d, 1H, $J_{5,7}$ = 0.92 Hz, H-5), 8.46 (s, 1H, H-2), 8.93 (s, 1H, NH), 10.02 (br s, 1H, NH) |
| **9d** | 1616 (C=N), 1645 (C=$O_{pyrone}$), 3166 (br s, OH), 3388, 3227 (NH, NH) | 2.43 (s, 3H, Ar-$CH_3$), 6.87 (br s, 1H, H-2), 7.14 (d, 1H, $J_{7,8}$ = 8.5 Hz, H-8), 7.36-8.27 (m, 8H, H-9, CH=N and Ar-H), 9.12 (br s, 1H, NH), 11.54 (br s, 1H, NH) |




**Scheme 2**

**Table 3.** Calculated charges on H-2 and H-9 hydrogen atoms by AM1-MO method and their experimental $^1$H NMR δ values for compounds **3a**-**9d**.

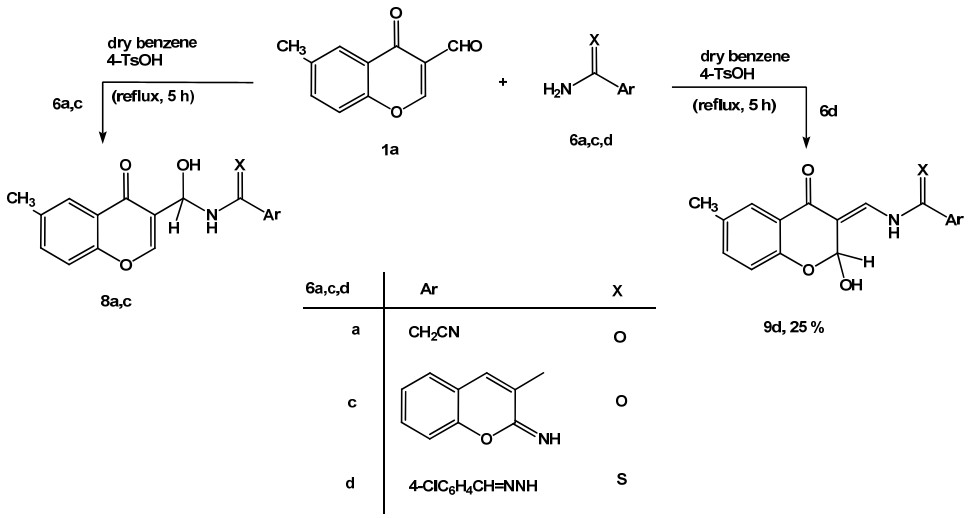
| Compound | *Q / (experimental δ values in ppm) | |
|---|---|---|
| | H -2 | H -9 |
| **3a** | 0.205 (7.76) | 0.136 (m)** |
| **3c** | 0.198 (8.66) | 0.172 (m) |
| **3d** | 0.212 (8.71) | 0.160 (8.20) |
| **3e** | 0.211 (9.14) | 0.191 (8.76) |
| **4c** | 0.126 (8.06) | 0.173 (8.90) |
| **5b** | 0.139 (5.95) | 0.168 (m) |
| **5c** | 0.130 (6.80) | 0.175 (8.89) |
| **7a** | 0.100 (m) | 0.204 (m) |
| **7b** | 0.106 (6.53) | 0.203 (m) |
| **7c** | 0.144 ((m) | 0.228 (m) |
| **8a** | 0.195 (8.53) | 0.101 (m) |
| **8c** | 0.161 (8.46) | 0.105 (6.54) |
| **9d** | 0.133 (6.87) | 0.217 (m) |

*Q = Calculated net hydrogen charges.
**m = The proton is multiplet.

= 2.975 + 33.65 ($Q_{H-9}$), $r$ = 0.995 except (**3e**), where $r$ is regression coefficient. The positive slopes reveal a direct proportionality of the calculated charges on H-2 and H-9 hydrogen atoms with measured $^1$H-NMR δ values, which support the proposed structures for these compounds. The dependence of $^1$H NMR shifts on the charge density at H-9 is more pronounced than that found at H-2, as indicated from slope values.

### *3.3. Antifungal activities*

Some of the newly synthesized compounds were screened for their antifungal activities against three species of fungi, *Alternaria alternate*, *Aspergillus niger* and *Aspergillus flavipes* using disc diffusion method [22].




**Scheme 3**

Activity of each tested compound was compared with that of Flucanazole as the standard (Table 4). Compounds **3a** and **4c** showed very high activities against the three species of fungi. Compound **9d** showed very high activities against *Aspergillus niger*, while compounds **3c**, **3e** and **5b** showed lower activities against the three species of fungi.

**Table 4.** Antifungal activities data of some the prepared compounds.

| Compound | Diameter of inhibition zone (mm)* | | |
|---|---|---|---|
| | *Alternaria alternate* | *Aspergillus niger* | *Aspergillus flavipes* |
| **3a** | ++++ | ++++ | ++++ |
| **3c** | + | + | ++ |
| **3e** | + | ++ | + |
| **4c** | ++++ | ++++ | ++++ |
| **5b** | ++ | +++ | ++ |
| **7c** | + | + | + |
| **9d** | +++ | ++++ | ++ |
| **Flucanazole** | ++++ | ++++ | ++++ |

* Very high active = ++++ (inhibition zone > 30 mm), High active = +++ (inhibition zone 21-30 mm), Moderately active = ++ (inhibition zone 11-20 mm), Lower active = + (inhibition zone 1-10 mm).

## 4. Conclusion

Condensation reactions of 4-oxo-4*H*-chromene-3-carbaldehydes **1a**,**b** with active primary amines **2a**-**e** and amides/thioamides **6a**-**d** gave condensation products or condensation with 1,4-addition of the solvent medium depends on the basicity of amine derivatives and polarity of the medium.

### *Acknowledgement*

We thank Dr. Hala Samir, Department of Biology and Geology, Faculty of Education, Ain Shams University for evaluation of antimicrobial activities for the prepared compounds.

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