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# CYANOACETANILIDES IN HETEROCYCLIC SYNTHESIS (PART IV): A CONVENIENT ONE-STEP SYNTHESIS OF 2-IMINO CHROMENE-3-CARBOXAMIDE, CHROMENONE, BENZOCHROMENE, CHROMENOCOUMARIN AND CHROMENOPYRIDINE DERIVATIVES FOR ANTIMICROBIAL EVALUATION

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## ABSTRACT

Cyanoacetanilides (1a,b) were reacted with o-hydroxyaldehydes under different conditions. Thus, cyclocondensation of 1a,b with salicylaldehyde, 2-hydroxy-1-naphth-aldehyde and 7-hydroxy-5-methoxycoumarin-6-carboxaldehyde in ethanolic amm. acetate afforded the corresponding 2-iminochromene derivatives 3,7 and 9 respectively. On the other hand, repeating the same reaction in presence of $Ac_2O$/AcONa, the corresponding chromen-2-one derivatives 4, 8 and 10 were obtained. Compounds 4,8 and 10 were also synthesized through the hydrolysis of 2-imino derivatives using EtOH/HCl. A number of chromeno[3,4-c]-pyridine derivatives 11,13,14 and 16 were prepared from the reaction of 2-iminochromenes with malononitrile, ethyl cyanoacetate, and cyanoacetanilide. Some of these compounds were screened in vitro for their antimicrobial activities.

## KEYWORDS

Chromenone, Benzochromene, Chromenocoumarin, Chromeno-pyridine, Antimicrobial Activity

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## INTRODUCTION

It is well known that antibacterial[1], coronary dilatory[2] and hypothermal agents[3] as well as potential laser dyes[4] have been reported for many chromene derivatives. Moreover, coumarin derivatives are well known to have anticoagulant and antibacterial activities[5-9]. Furthermore, benzocoumarins are of great biological importance due to their analgesic and antihypertensive activities[10].The present study is part of our program aimed at developing easy routes for the synthesis of fused heterocyclic compounds starting with cyanoacetanilides as simple organic compounds . Also, we report here the synthesis of chromene and coumarin carboxamide derivatives and their utility as building blocks in the synthesis of novel pyridochromene derivatives to evaluate their antimicrobial activity.

## RESULTS AND DISCUSSION

Condensation of cyanoacetanilides **(1a,b)**[11] with salicylaldehyde **(2)** in ethanolic amm. acetate afforded 2-imino-3-(N-substituted-phenylcarboxamido)-2H-chromenes **(3a,b)** as colored solids in high yield**, (Scheme1)**.

The structure of compounds **(3a,b)** were established by elemental analysis and spectral data. IR spectrum of compound (3a) showed absorption bands at 3403, 3316 (NH) and 1681 $cm^{-1}$ (C=O).$^1$H-NMR spectrum of **(3a)**, (δ, ppm) (DMSO-$d_6$) 2.2 (s, 3H, $CH_3$), 6.8-7.8 (m, 8H,Ar-H), 8.5 (s, 1H, H-4). The mass spectra of **(3a,b)** display the correct molecular ions expected for the molecular formula. The fragmentation patterns are in accordance with the assigned structure. The primary cleavage of the molecular ion occurs at the amide bond giving rise to the acylium ion m/z 172.

On the other hand, interaction of **(1a,b)** with salicylaldehyde in the presence of $Ac_2O$/AcONa, gave 3-(N-substituted-phenylcarboxamido)chromen-2-ones **(4a,b)** in reasonably good yield. IR spectrum of compound **(4a)** showed absorption bands at 3271 (NH) and 1705 $cm^{-1}$ (CO-lactone). $^1$H-NMR spectrum (DMSO-$d_6$) of compound **(4b)** revealed multiplet at 7.4-8.0 ppm for aromatic protons, singlet at 8.8 ppm assigned to chromene-H and singlet at 10.6 ppm for NH. Mass spectrum of compound **(4b)** showed a molecular ion peak at 299 (25%) with a base peak at m/z = 173 (M-Cl.$C_6H_4NH$). Other significant peaks were appeared at m/z: 101 (23.9%), 89 (22%) and 51(7.9%). The structure of **4** was further confirmed through their synthesis upon hydrolysis of **3** with EtOH/HCl or acetic acid.

Similarly, compounds **1a or b** were reacted with 2-hydroxy-1-naphthaldehyde **(5)** and 7-hydroxy-5-methoxycoumarin-6-carboxaldehyde **(6)** under the same conditions of EtOH/ $AcONH_4$ to furnish 2-iminobenzo[f]chromenes **(7a,b)** and 2-iminopyrano-[2,3-g] coumarins **(9)** in high yield. While, benzocoumarins **(8a,b)** and pyrano[2,3-g]coumarin **(10)** were synthesized via interaction of **(1)** with **(5)** and **(6)** in the presence of acetic anhydride and sodium acetate. Compounds **(8)** and **(10)** were also obtained upon the treatment of compounds **(7)** and **(9)** with ethanol containing hydrochloric acid or acetic acid. **(Scheme 1)**.

The suggested structures **(7)**, **(8)**, **(9)** and **(10)** were established on the basis of both analytical and spectral data. IR spectrum of the synthesized compounds **(7a)** showed vNH vCH-aliph. vC=O at 3324, 3298 2925 1684 $cm^{-1}$ respectively. $^1$HNMR spectrum of **9** in DMSO-$d_6$ 4.0 (s, 3H, $OCH_3$), 6.42 (d, 1H, H-6), 7.05-7.52 (m, 5H, Ar-H), 8.1(d,1H, H-7), 8.5(s,1H,H-4) and 9.5, 12.8 (2s, 2H, 2NH). The mass spectrum of **9** afforded m/z: 396 (19.1%), 398 (M+2, 6.8%), 361 (M-Cl;100%), 270 (M-Cl.$C_6H_4NH$; 75.2%), 227 [M-(Cl.$C_6H_4NH$ and NHCO); 29.8%], 199 [M-(Cl.$C_6H_4NH$, NHCO and CO); 14.5%].

Moreover, the resulting chromene derivatives have latent functional substituents which have the potential for further chemical transformations giving new routes for the preparation of condensed chromene with possible biological activity.

Thus, the reaction of 2-iminochromene derivatives **(3a,b)** with malononitrile and ethyl cyanoacetate in refluxing ethanol containing catalytic amount of amm. acetate for 3 hrs afforded in each case a product with analytical and spectral data in good agreement with chromeno[3,4-c]pyridine derivatives **(12 a,b) (Scheme 2)**.

The structures **(12)** have been confirmed on the basis of elemental analysis and spectral data. IR spectrum of **(12a)** showed $NH_2$ NH at 3439, 3348, CN at 2207 and CO (amido) at 1650 $cm^{-1}$. Mass spectrum of **(12a)** showed a molecular ion peak at m/z: 342 (3.2%) with a base peak at mlz 300 [M-($CH_3$ + HCN)]. Other significant peaks were observed at m/z 272 [M-($CH_3$, HCN and CO); 34.0%], 256 [M-($CH_3$ HCN, CO and $NH_2$); 3.5%] and 230 [M-($CH_3$,HCN, CO, $NH_2$, and CN); 4.36%]. $^1$HNMR spectrum of **(12b)** in DMSO-$d_6$ revealed the following signals: = 7.3-7.6 (2m, 8H, Ar-H), 8.8 (s, 1H, NH),9.2 (s, 1H, OH). The formation of **(12a,b)** is assumed to proceed via the addition of an active methylene group to the double bond of chromene to give the Michael adduct which underwent cyclization to afford dihydrochromenopyridine as intermediate which is oxidized to yield the 5-iminochromeno-pyridine derivatives.

On the other hand, the dihydrochromenopyridine derivative **(13)** was obtained upon treatment of **(3b)** with malononitrile in boiling EtOH/$AcONH_4$. $^1$HNMR spectrum of structure **13** in DMSO-$d_6$ showed signals at: 4.71 (d, 1 H, H-4), 4.9 (d, IH, H-3),7.3-7.6 (m, 8H, Ar-H), 7.7(s,2H, $NH_2$), 8.9 (s, H, NH).

Also, benzochromenopyridine derivative **(14)** was obtained through interaction of **(7b)** with malononitrile under the same condition of EtOH/$AcONH_4$ **(Scheme 3)**.

The structure of **(14)** was established for the reaction product based on elemental analysis and spectral data.$^1$HNMR spectrum of **(14)** in DMSO-$d_6$ showed the following signals: 7.6-8.6 (m, 10H, Ar-H), 8.9-9.0 (d, 2H, $NH_2$), 9.3 (s, IH, NH).

Finally, cyanoacetanilide **(1b)** was used as active methylene compound and reacted with 2- iminochromene-3-carboxamide **(15)**[12] in 1: 1 molar ratio in the presence of amm. acetate to afford the chromenopyridine derivative **(16) (Scheme 3)**. Its $^1$H-NMR in DMSO-$d_6$ exhibited 7.4-7.8 (m, 8H, Ar-H), 9.0 (d, 2H, $NH_2$),10.3-10.5 (br, 3H, 3NH).

**Antimicrobial Activity:**

Some of synthesized compounds were tested in Vitro against Gram positive bacteria: Bacillus cereus (NCTC-14579), Gram negative bacteria: Proteus mirabilis (NCTC-289) and fungi of Penicililum chrysogenum (NCTC-289) using the agar diffusion technique[13]. A I mg/ml solution in DMSQ was used. The bacteria and fungi were maintained on nutrient agar and Czapek'sDox agar media, respectively. DMSO showed no inhibition zones. The agar media were inoculated with different microorganisms culture tested after 24 hrs. of incubation at 30°C for bacteria and 48 hrs. of incubation at 28°C for fungi, the diameter of inhibition zone (mm) were measured (Table 1). Ampicillin in a concentration (25 µg ) and Mycostatine (30 µg) were used as references for antibacterial and antifungal activities, respectively. The minimal inhibitory concentrations (MIC) of some of the tested compounds was measured by a two fold serial dilution method[14]. All the tested compounds exhibited activity towards the Gram negative bacteria. However, none of them showed activity against Penicillium chryssogenum.

Table 1: Antimicrobial activity of some synthesized compounds and inhibition zones.

| Compd. No. | Gram positive bacteria | Gram negative bacteria | Fungi |
|---|---|---|---|
| | Bacillus cereus (NCTC-14579) | Proteus mirabilis (NCTC-289) | Penicillium chrysogenum Thom (NCTC-289) |
| **3b** | - | ++ | - |
| **7b** | - | ++ | - |
| **9b** | - | +++ | - |
| **12a** | - | ++ | - |
| **12b** | - | ++ | - |
| Standard | ++++ | ++++ | ++++ |

Standard = Ampicillin 25 µg/ml$^{-1}$ mycostatine

+ : Less active (0.2-0.5 cm); ++ : Moderately active (0.6-1.4 cm);

+++ : Highly active (1.5-3.0 cm); ++++ : Very highly active (over 3.0 cm); – :Inactive

Standard: For Gram positive and Gram negative bacteria: Ampicillin 25 µg mL$^{-1}$; for fungi: Mycostatine: 30 µg mL$^{-1}$.

## EXPERIMENTAL

All melting points reported are uncorrected. IR spectra were measured ( KBr) on a Shimadzu IR 200 spectrophotometer ($\nu_{max}$ in $cm^{-1}$). $^1$H-NMR spectra were recorded on a Varian Gemini NMR spectrometer (200 MHz) using tetramethylsilane as an internal standard (Chemical shifts in $\delta$, ppm). Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out at the Microanalytical Center of Cairo University. The characteristic data of the prepared compounds are given in Table (1).

**2-Iminochromene derivatives 3, 7 and 9**:

A mixture of **1** (0.01mol), the requisite o-hydroxyaldehyde (0.01mol) and amm. acetate (0.015) was refluxed in ethanol (30ml) for 1 h. The solid product was collected by filtration and recrystallized from the proper solvent to give (**3, 7** and **9** ; Table 1).IR spectrum of compound **(3a)** showed absorption bands at 3403, 3316 (NH), 2923 (CH-aliph) and 1681 $cm^{-1}$(C=O), **(3b)** 3309 (NH), 2925(CH-aliph.) and 1683 $cm^{-1}$ (CO), **7a :** 3324, 3298 (NH), 2925 (CH-aliphatic) and 1684 (CO), **7b:** 3242 (NH), 2924 (CH-aliphatic) and 1671 (CO). **9**:3325 (NH), 2970 (CH-aliphatic) 1735 (CO- lactone).$^1$H-NMR spectra in DMSO-$d_6$ **3a**: 2.2 (s,3H, $CH_3$), 6.8-7.8 (m, 8H, Ar-H), 8.5 (s, 1H, H-4), 9.1, 10.6 (2s, 2H, 2NH).**3b**: 7.2-7.8(m, 8H, Ar-H), 8.5 (s, 1H, H-4), 9.1, 12.9 (2s,2H,2NH), **7a**: 2.3 (s, 3H, $CH_3$), 7.1-8.2 (m, 10H, Ar-H), 8.4 (S, 1H, chromene-H-4), 9.2, 12.4 (2s, 2H, 2NH), **7b**: 7.4-8.4 (m, 10H, Ar-H), 8.5 (s, 1H, chromene-H-4), 9.1, 12.9 (2s, 2H, 2NH) and **9**: 4.0 (s, 3H, $OCH_3$), 6.42 (d, 1H, H-6), 7.05-7.52 (m,5H,Ar-H), 8.1(d,1H,H-7), 8.5 (s,1H,H-4), 9.5, 12.8 (2s, 2H, 2NH). The mass spectrum of compounds **(7b)** and **(9)** afforded the following: Compd. **7b** 348 (M+; 4%), 313 (M-Cl; 100%), 222 (M-Cl.$C_6H_4NH$,; 50%), 167 [M-(Cl.$C_6H_4NH$ + HCN + CO); 10%], **9:** 396 (19.1%), M+2 (6.8%), 361 (M-Cl;100%), 270 (M Cl.$C_6H_4NH$; 75.2%), 227 [M-(Cl.$C_6H_4NH$ and HNCO); 29.8%], 199 [M-(Cl.$C_6H_4NH$, HNCO and CO); 14.5%].

**Chromene-2-one derivatives 4, 8 and 10:**

**Method a:** To a solution of **1** (0.01 mol) in acetic anhydride (20ml), the suitable o-hydroxyaldehyde (0.01mol) and sod. acetate (0.5g) were added. The mixture was refluxed for 1h, the solid product was collected by filtration and recrystallized from the proper solvent to afford (**4**[15], **7**[16] and **10**; Table 1). IR spectrum of compound **(4a)** showed absorption bands at 3271 (NH), 2916 (CH-aliph.) and 1705 $cm^{-1}$ (CO). Also, IR of **(4b)** showed bands at 3264 (NH), 2925 (CH-aliph.) and 1700, 1663 $cm^{-1}$(CO). **8b**: 3209(NH), 2923(CH-aliph.) and 1712 (CO). **10**: 3425 (NH), 2970 (CH-aliph) and 1728, 1672 (CO). $^1$H-NMR of **(4b)** revealed multiplet at 7.4-8.0 ppm for aromatic C-H, singlet at 6 8.8 ppm assigned to chromene-H and singlet at 10.6 ppm for NH.

**Method b:** A Solution of the corresponding iminochromene derivatives **3, 7** and **9** (0.01mol) in ethanol (30ml), hydrochloric acid or acetic acid (5ml) was refluxed for 1h. 2-Amino-5-imino-4-oxo-3-(4-tolyl)-3,5-dihydro-4H-chromeno[3,4-c]pyridine-1-carbonitrile (12a), 3-(4-Chlorophenyl)-2-hydroxy-5-imino-4-oxo-3,5dihydro-4H-chromeno[3,4-c]pyridine-1-carbonitrile (12b), 2-Amino-(4-chlorophenyl)-5-imino- 4-oxo-3,4a,5,10b-tetrahydro-4H-chromeno[3,4-c]pyridine-1-carbonitrile(13), 2-Amino-3-(4-chlorophenyl)-5-imino-4-oxo-3,5-dihydro-4H-benzo[f]chromeno[3,4-c]-1-carbonit-rile

(14): A mixture of 3b or 7b (0.01mol) and malononitrile or ethyl cyanoacetate (0.01mol) and amm.acetate (0.015) in ethanol (30ml) was refluxed for 3 h. The solid product was collected by filtration and recrystallized to furnish (**12a,b ,13** and **14**; Table 1). IR spectrum of **(12a)** showed NH, $NH_2$ at 3439, 3348, CN at 2207 and CO (amido) at 1650 $cm^{-1}$. IR spectrum of **(12b)** showed OH, NH broad at 3349, 3176, CN at 2196 and CO at 1715 $cm^{-1}$. **13**: $NH_2$, NH at 3444, 3348, CN at 2208 and CO at 1662 $cm^{-1}$. **14**: showed characteristic absorption bands at 3330, 3214 for $NH_2$, NH, 2216 for CN and 1715, 1682 $cm^{-1}$ for CO. $^1$H-NMR spectra in DMSO-$d_6$ revealed the following signals: **12b**: 7.3-7.6 (2m, 8H, Ar-H), 8.8 (s, 1H, NH), 9.2 (s, 1H, OH). **13**: 4.71 (d, 1H, CH-4), 4.9 (d, 1H, CH-3), 7.3-7.6 (m, 8H, Ar-H), 7.7(s, 2H, $NH_2$), 8.9 (s, H, NH). **14**: 7.6-8.6 (m, 10H, Ar-H), 8.9-9.0 (d, 2H, $NH_2$), 9.3 (s, IH, NH). Mass spectrum of **(12a)** showed a molecular ion peak at mlz 342 (3.2%) with a base peak at mlz 300 [M-($CH_3$ + HCN)], other significant peaks were observed at m/z 272 [M-($CH_3$, HCN and CO); 34.0%], 256[M-($CH_3$ HCN, CO and $NH_2$); 3.5%] and 230[M-($CH_3$, HCN, CO, $NH_2$, and CN); 4.36%].

**2-Amino-5-iminooo-4-oxo-3,5-dihydro-4H-chromeno[3,4-c]pyridine-1-N-(4-chloro-phenyl)carboxamide (16):**

A mixture of 2 iminochromene-3-carboxamide **15** (0.01 mol) and amm.acetate (0.015mol) was refluxed for 6h. The solid product was collected by filtration and crystallized to give (**16**; Table1). IR spectrum of showed characteristic absorption bands at 3268, 3133 for ($NH_2$, NH), 2960 for (CH-aliph.) and 1667 $cm^{-1}$ for (CO). $^1$H-NMR spectrum in DMSO-$d_6$ showed 7.4-7.8 (m, 8H, Ar-H), 9.0(d, 2H, $NH_2$) and 10.3-10.5(br, 3H, 3NH). Its mass spectrum of showed a molecular ion peak at mlz 380 (9.8%) with a base peak at mlz 253(M-Cl.$C_6H_4NH_2$). Other significant peaks were observed at mlz: 194 (20.9%), 153 (27%), 127 (58.5%) and 55 (73%).

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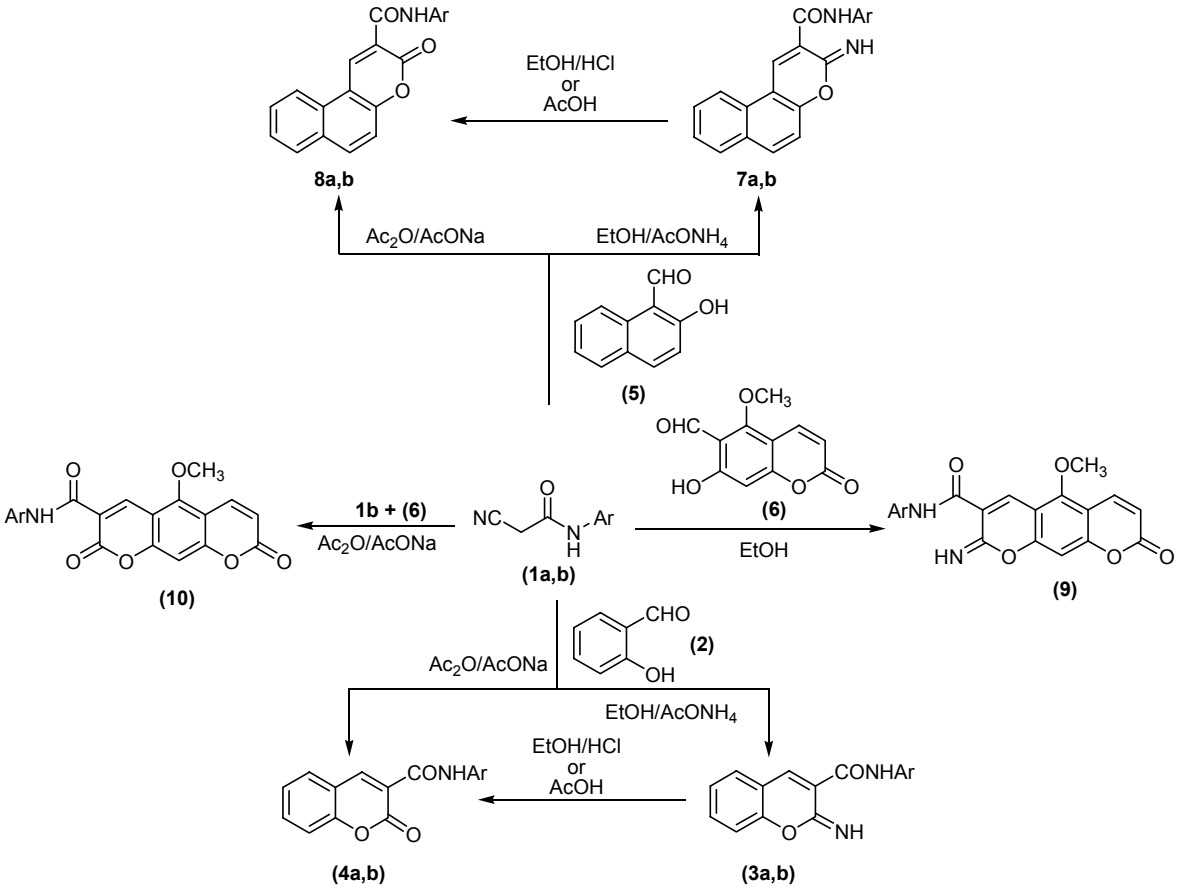
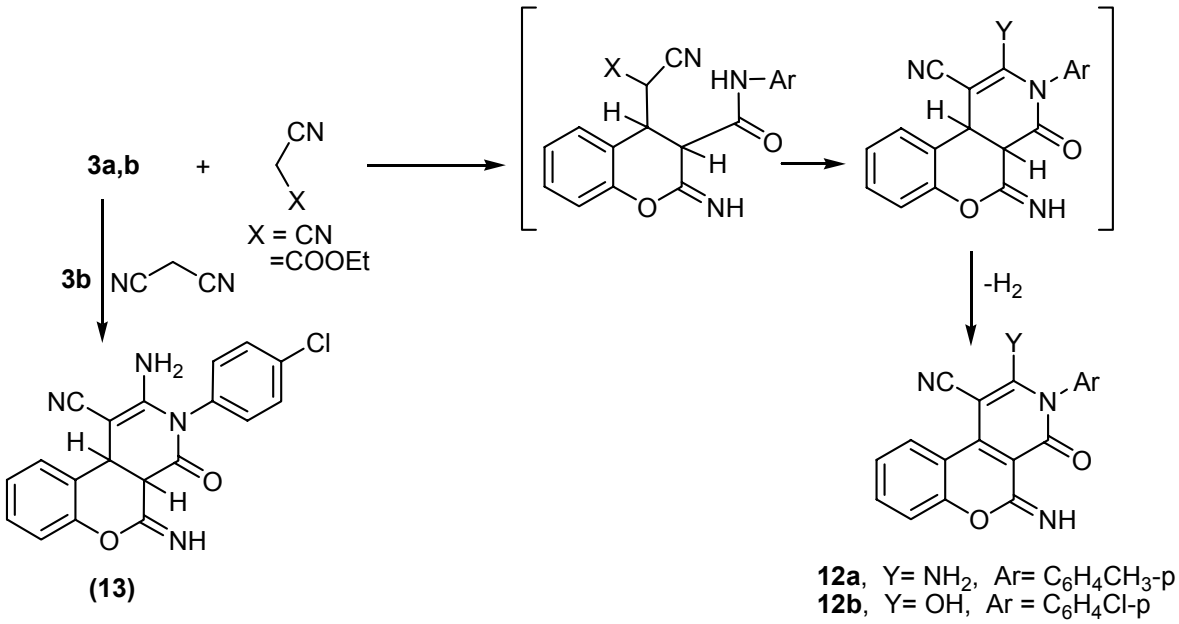
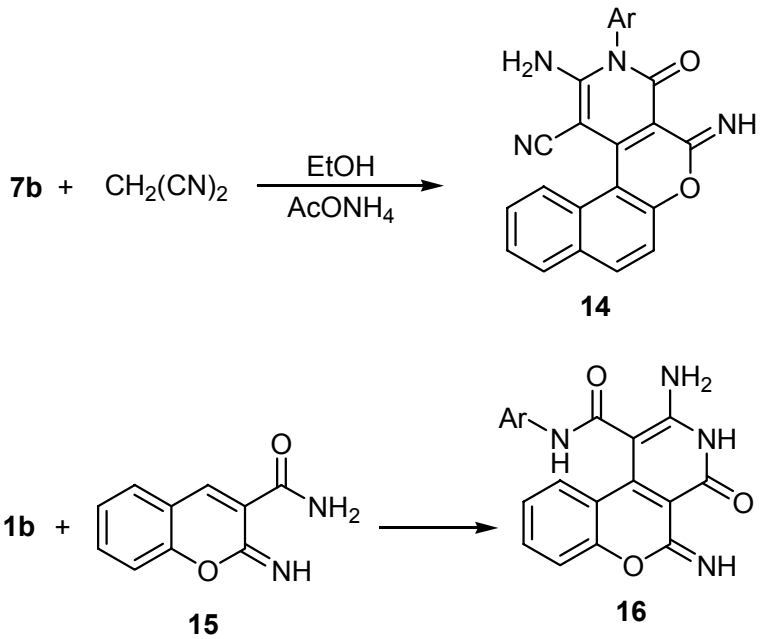



**1a**; Ar = $C_6H_4$-$CH_3$-p
**1b**; Ar = $C_6H_4Cl$-p

**Scheme 1**




**Scheme 2**




**Scheme 3**

Table 2: Physical data of the prepared compounds.

| Compd No. | M.p. (°C) | Solvent Cryst. | Yield (%) | Molecular formula (Mol. Wt.) | Elemental analyses C% | H% | N% |
|---|---|---|---|---|---|---|---|
| **3a** | 160 | DMF | 80 | $C_{17}H_{14}N_2O_3$ (278) | 73.38<br>73.40 | 5.03<br>5.10 | 10.07<br>10.00 |
| **3b** | 245 | D | 75 | $C_{16}H_{11}Cl\,N_2O_2$ (298.5) | 64.32<br>64.40 | 3.68<br>3.80 | 9.38<br>9.50 |
| **7a** | 235 | D | 75 | $C_{21}H_{16}N_2O_2$ (328) | 68.87<br>68.90 | 3.73<br>3.80 | 8.03<br>8.20 |
| **7b** | 217 | DMF | 82 | $C_{20}H_{13}ClN_2O$ (348.5) | 73.65<br>73.74 | 5.45<br>5.40 | 15.16<br>15.22 |
| **9** | 310 | DMF | 75 | $C_{20}H_{13}ClN_2O_5$ (396.5) | 60.52<br>66.60 | 3.28<br>3.40 | 7.06<br>7.20 |
| **10** | 245 | A | 60 | $C_{20}H_{12}ClNO_6$ (397.5) | 60.38<br>60.40 | 3.02<br>3.10 | 3.52<br>3.70 |
| **11a** | 315 | A | 54 | $C_{20}H_{14}N_4O_2$ (342) | 70.18<br>70.20 | 3.09<br>3.20 | 16.37<br>16.60 |
| **11b** | 315 | A | 72 | $C_{19}H_{10}ClN_3O_3$ (363.5) | 62.28<br>62.80 | 2.75<br>2.80 | 11.55<br>11.40 |
| **13** | 290 | D | 66 | $C_{19}H_{13}ClN_4O_2$ (364.5) | 62.55<br>62.60 | 3.57<br>3.60 | 15.36<br>15.40 |
| **14** | 302 | D | 58 | $C_{23}H_{13}ClN_4O_2$ (412.5) | 66.91<br>66.80 | 3.15<br>3.30 | 13.58<br>13.60 |
| **16** | 315 | DMF | 73 | $C_{19}H_{13}NClN_4O_3$ (380.5) | 59.92<br>59.60 | 3.42<br>3.70 | 14.72<br>14.90 |

**A = Acetic acid, D = Dioxane, and DMF = Dimethylformamide**