REACTIONS WITH ACTIVATED NITRILES: NEW SYNTHETIC ROUTES TO FUNCTIONALLY SUBSTITUTED CHROMENE-3-CARBONITRILE, 2-OXO-2H-BENZO[f]CHROMENE AND BENZO[f]CHROMENOPYRIDINE DERIVATIVES.

تفاعلات علي النيتريلات النشيطة :طرق لتحضير مشتقات من الكرومين-٣-كربونيتريل, ٢-أوكسوبنزو [f]كرومين و بنزو [f]كرومينوبيريدين

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في هذا البحث تم تحضير مشتقات من الكرومين-٣-كربونيتريل , ٢-أوكسوبنزو [f]كرومين و بنزو [f] كرومينوبيريدين عديدة المجموعات الوظيفية بإستعمال اليليدينا ت ١و٢و الأريل هيدرازون (٣) كمواد أولية .

فعندما تفاعلت اليليدينا ت **1و٢** مع كل من ٢- ميثيل سيكلوهكسانون و ٣- ميثيل سيكلوهكسانون أعطي مشتقات الكرومين٧, ١٢,١٤ و ١٦ علي التوالي .

أما عند تفاعل اليليدينا ت **1** مع مشتقات بيتا- نافثول تكونت المركبات ٢٠,٢٤و٢٦ علي التوالي .

وعند تفاعل الأريل أزو ٣ مع بيتا- نافثول أدي إلي تكوين الكرومين إيمين ٢٩ .

Abstract:

Several new functionally substituted chromene-3-carbonitrile, 2-oxo-2H-benzo[f]chromene, and benzo[f]chromenopyridine were prepared from α,β-unsaturated nitriles **1,2** and arylhydrazone **3** as starting materials.

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Introduction:

Arylidenemalononitriles and ethyl arylidenecyanoacetates are versatile reagents which react with nucleophiles under mild conditions [1-6]. In the past decade, we were involved in a program aimed at developing the synthesis of polyfunctionally substituted heterocycles as potential biodegradable agrochemicals[1] and antischistosomal agents[7]. During this phase of our research, we have been investigated the base catalyzed reactions of cinnamonitriles with active hydrogen reagents. In connection to this effort, we report here new approach for synthesis of polyfunctionally substituted

chromene-3-carbonitrile, 2-oxo-2H-benzo[f]chromene and benzo[f] chromenopyridine derivatives. For this purpose, the activated nitriles **1**, 2-(2-oxoindolin-3-ylidene)malononitrile **(2)** and 2-(p-methoxyphenylazo)malononitrile **(3)**

Were selected as starting components.

Key words:

Chromene-3-carbonitrile/ benzo[f]chromene/ benzo[f]chromenopyridine

Results and discussion:

It has been found that, bezylidenemalononitrile **(1a)** reacted with 2-methylcyclohexanone **(4)** in refluxing ethanol and in presence of few drops of piperidine to give 1:1 adduct. The acyclic structure 2-(2',2'-dicyano-1'-phenyl)-2-methylcyclohexanone **(5)** and 2-amino-4,5,6,7,8-tetrahydro-8-methylchromene-3-carbonitrile **(7)** can be expected for the reaction product. Formation of **5** was assumed to proceed via addition of cyclohexanone C-2 to the activated double bond in bezylidenemalononitrile **(1a)** to give **5**. However, we believe that cyclohexanone C-2 is less acidic and

more sterically hindered than cyclohexanone C-6. Compound **7** was assumed to be fomed via Michael type addition of cyclohexanone C-6 to give Michael adduct **6** which cyclized to give the final isolable product **7**. Compound **5** was readily ruled out by ^{1}H-NMR spectrum which clearly revealed the presence of 4H-pyran proton at δ= 5.25 ppm. Thus, 2-amino-5,6,7,8-tetrahydro-8-methyl-4-phenyl-4H-chromene-3-carbonitrile **(7)** was established as a reaction product (cf.scheme 1).

Also, bezylidenemalononitrile **(1a)** reacted with 3-methylcyclohexanone **(8)** in ethanol with a piperidine catalyst to give either 2-amino-5,6,7,8-tetrahydro-5-methyl-4-phenyl-4H-chromene-3-carbonitrile **(10)** or 2-amino-5,6,7,8-tetrahydro-7-methyl-4-phenyl-4H-chromene-3-carbonitrile **(12)**. Compound **10** was suggested to be obtained by addition of the methylene group at C-2 in 3-methylcyclohexanone **(8)** to give the acyclic structure **9** which cyclized to **10**, and Compound **12** was thought to be formed by adding the methylene group at C-6 in 3-methylcyclohexanone **(8)** to give the acyclic structure **11**, which readily cyclized to **12**. Compound **12** was preferred over possible **10**, because of the steric effect caused by the methyl group at C-5 in **10**. Also, during the formation of **10**, we have found that the methylene group at C-2 in **8** less active and more sterically hindered than the methylene group at C-6, and also confirm the structure **12**.

In addition, 2-(2-oxoindolin-3-ylidene)malononitrile **(2)** reacted with 2- methylcyclohexanone **(4)** in refluxing ethanol containing catalytic amounts of piperidine to afford 2-amino-5,6,7,8-tetrahydro-8-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene-3-carbonitrile **(14)**. Compound **14** was obtained by analogous way to the formation of compound **7**. Elemental analysis and spectral data are compatible with structure **14** (cf.scheme 2).

Furthermore, 2-(2-oxoindolin-3-ylidene)malononitrile **(2)** reacted with 3- methylcyclohexanone **(8)** in ethanol containing catalytic amount of piperidine to give 2-amino-5,6,7,8-tetrahydro-7-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene -3-carbonitrile **(16)** (cf. scheme 2) .

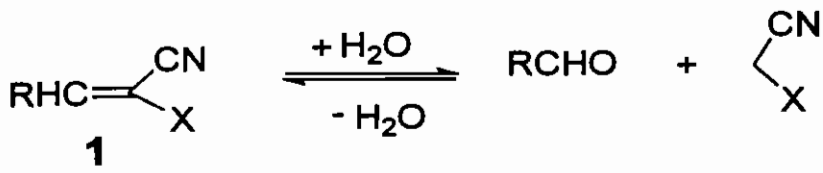
We have also studied the reactivity of 2-naphthols **17a,b** towards α,β-unsaturated nitriles **1**. Thus, 2-(4'-chloro-2',5'-dimethoxybenzamido)-2-naphthol **(17a)** reacted with bezylidenemalononitrile **(1a)** in ethanol/ piperidine in a molar ratio (1:1) or (1:2) to yield 9,11-diamino-6-(4'-chloro-2',5'-dimethoxybenzamido)-12-phenyl-12H-benzo[f]chromeno[2,3-b]pyridine-10-carbonitrile **(20)**. Elemental analysis and spectral data are in full agreement with the proposed structure **20** (cf.experimental). In ^{1}H-NMR spectrum of **20** ,we have observed that the pyran H-4 signal at δ= 5.54 ppm,which is deshielded by about δ= 0.5 ppm in comparison with that expected for 4H-pyran as a result of van der Waal,s deshielding effect of adjacent aryl protons. Compound **20** was formed via Michael type addition of the phenolic C-1 to the activated double bond in **1a** to give the acyclic adduct **18**, which cyclised into the intermediate **19**. The intermediate **19** then add one molecule of malononitrile, which exists in equilibrium with bezylidenemalononitrile **(1a)** under the reaction condition[8] to yield compound **20**.

In a previous work, we have shown that[1,9,10] a mixture of formaldehyde and malononitrile may be utilized as a synthetic equivalent of methylene malononitrile **(1b)**. By this way a variety of otherwise not readily obtainable heterocycles were synthesized[1,9]. In continuation to this work, 2-(4'-chloro-2',5' -dimethoxybenzamido)-2-naphthol **(17a)** reacted with equimolar

amounts of formaldehyde and malononitrile in ethanol and in presence of few drops of triethylamine to yield 11-amino-6-(4'chloro-2',5'-dimethoxybenzamido)-12H-benzo[f]chromeno[2,3-b]pyridine-10-carbonitrile **(24)**. Elemental analysis and spectral data are in good agreement with structure **24**. The same product was obtained by reacting formaldehyde,malononitrile and **17a** in a molar ratio 2:2:1. Compound **24** is suggested to be formed by the addition of phenolic C-1 in **17a** to **1b** giving **21** which readily cyclised to **22**. The later reacted with another molecule of methylenemalononitrile to give **24** .

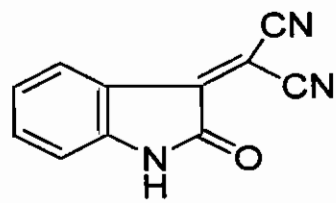
In contrast to the reported behavior of **1a** towards **17a** , ethyl α-cyanocinnamate **(1c)** reacted with **17a** to yield 6- (4'-chloro-2',5' -dimethoxybenzamido)-2-oxo-2H-benzo[f]chromene **(26)** and not the anticipated ethyl 8-amino-6- (4'-chloro-2',5' -dimethoxybenzamido)-10-phenyl-10H-benzo[f]chromene-9-carboxylate **(27)**. IR spectrum of the reaction product revealed the presence of bands corresponding to cyano and carbonyl functions .Thus , 6-(4'-chloro-2',5' -dimethoxybenzamido)-2-oxo-2H-benzo[f]chromene **(26)** structure was established for the reaction product .

Reaction of equimolecular amounts of 2-naphthol **(17b)** and 2-(p-methoxyphenylazo)malononitrile **(3)** in ethanol and few drops of piperidine afforded a product with molecular formula $C_{20}H_{16}N_4O_2$(M^+=343). 10-Amino-9-(p-ethoxyphenyl)benzo[f]chromene- 8-imine **(29)** was assigned for the reaction product.

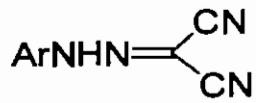


1

a, R= C_6H_5 ; X=CN
b, R = H ; X=CN
c, R= C_6H_5 ; X=$CO_2C_2H_5$

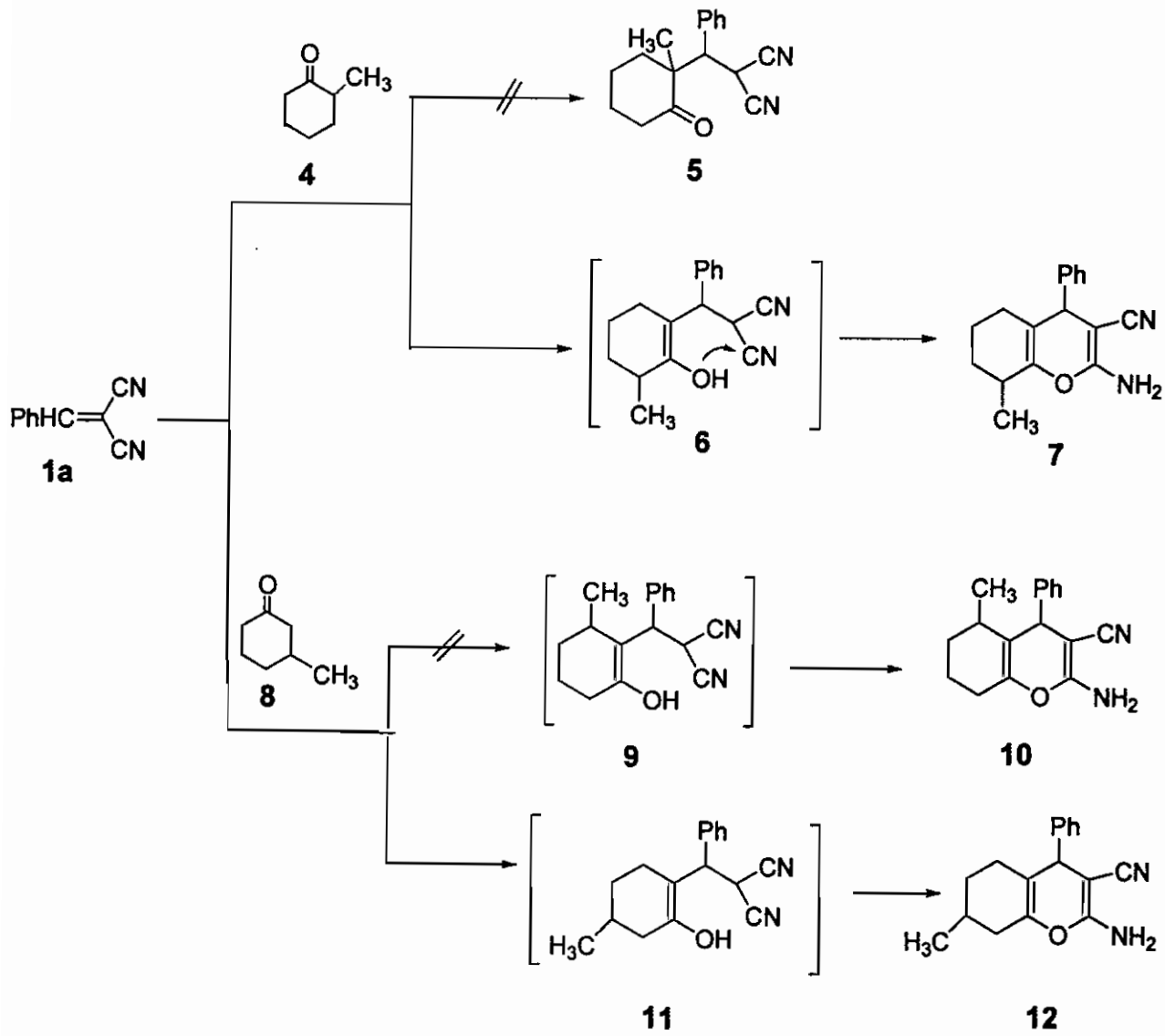


2

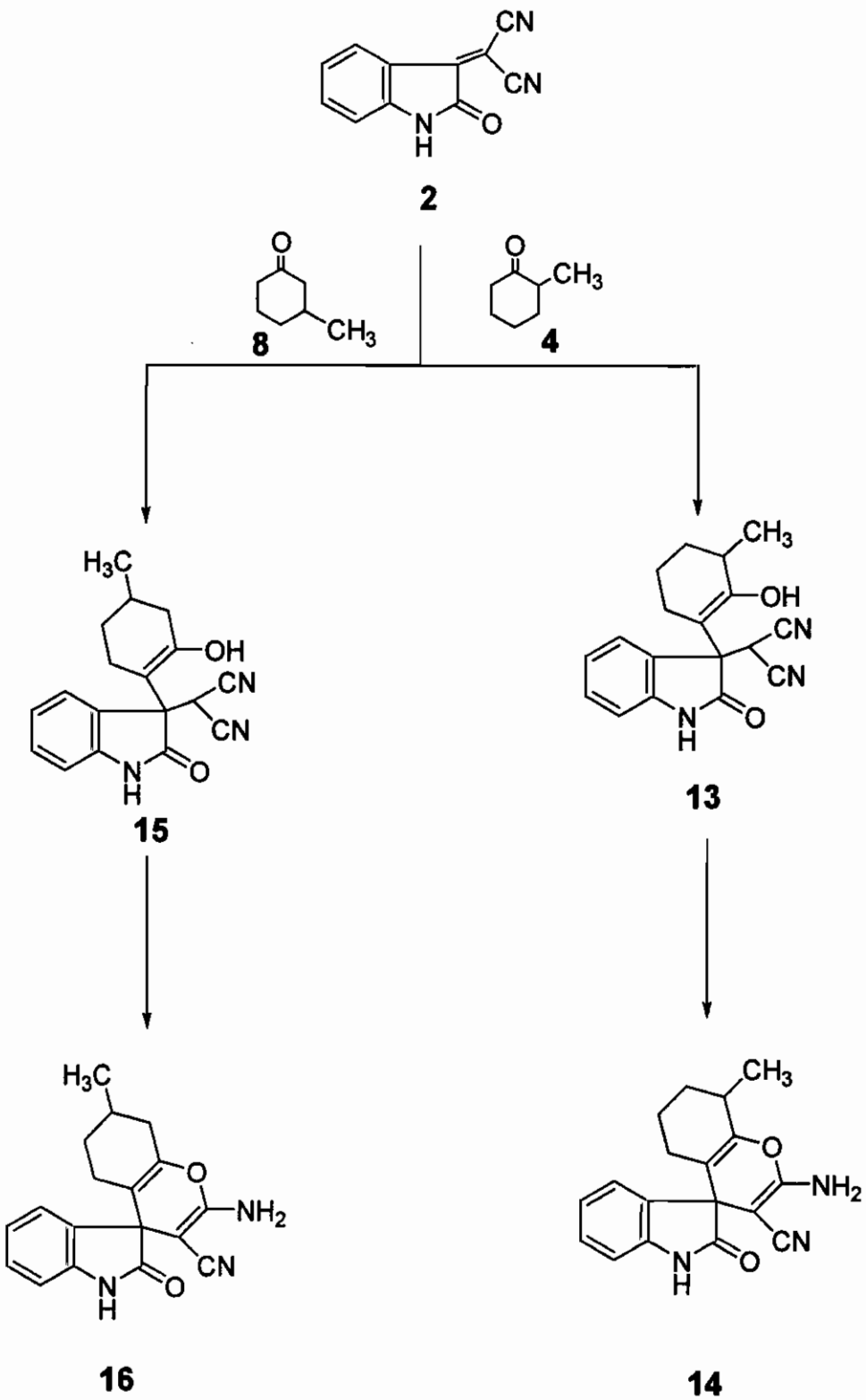


3

Ar= $C_6H_4OCH_3$(P)



Scheme 1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N
H
O
2
O
CH3
8
O
CH3
4
H3C
OH
CN
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N
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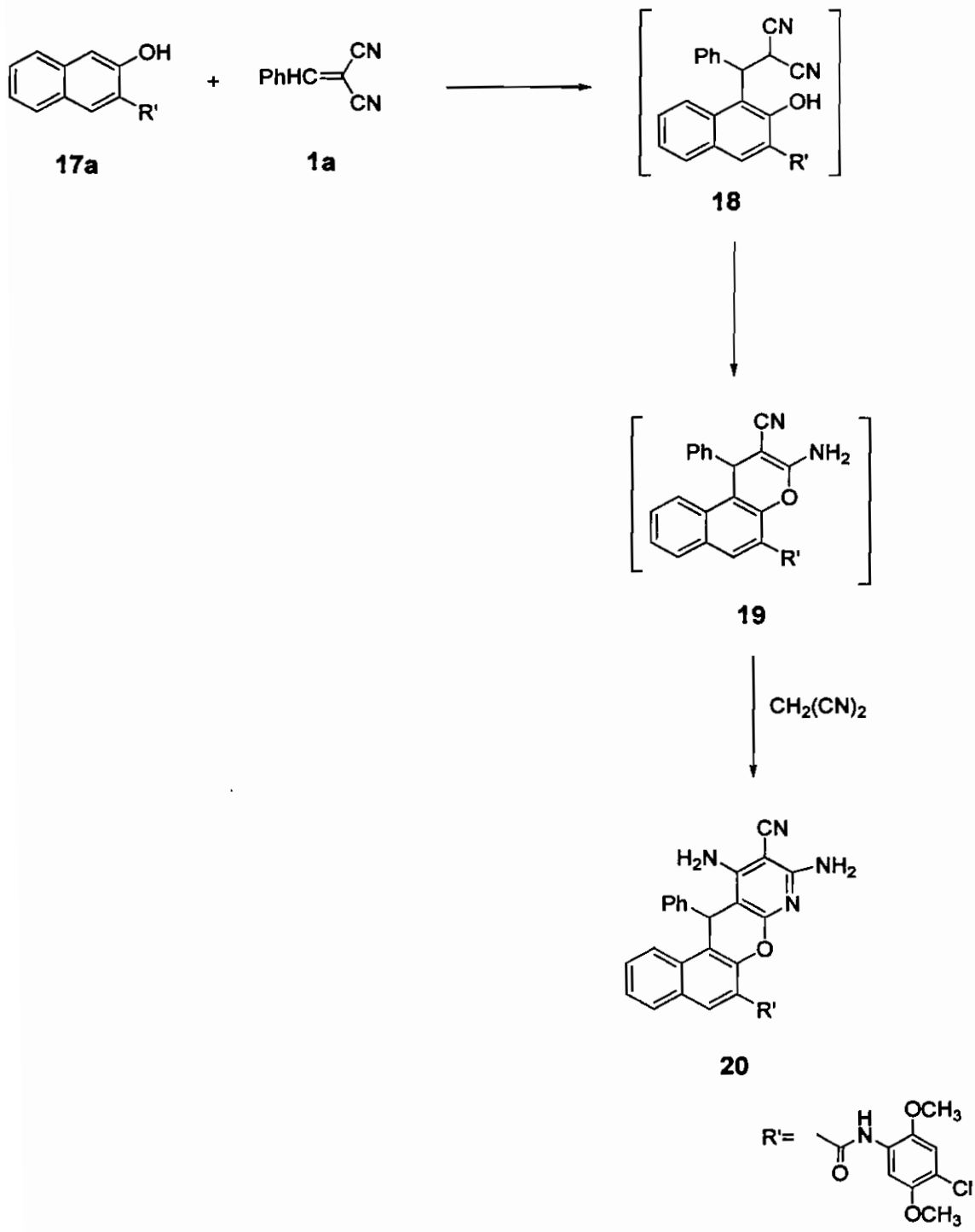
CH3
OH
CN
CN
N
H
O
13
H3C
O
NH2
CN
N
H
O
16
CH3
O
NH2
CN
N
H
O
14

Scheme 2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+
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CN
CN
17a
1a
CN
Ph
CN
OH
R'
18
CN
Ph
NH2
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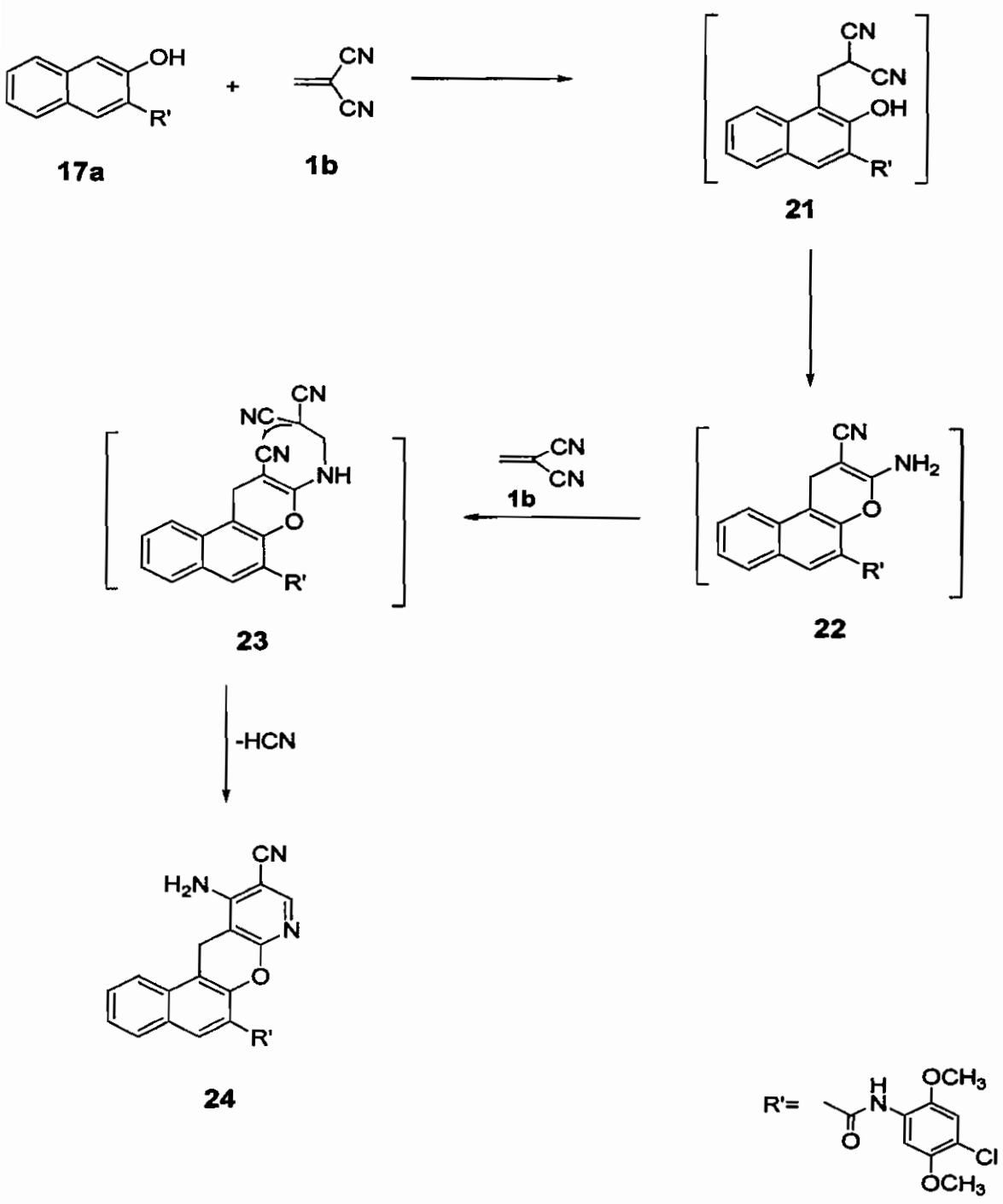
R'
19
CH2(CN)2
CN
H2N
NH2
Ph
N
O
R'
20
R'=
H
N
O
OCH3
Cl
OCH3

Scheme 3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R'
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CN
CN
1b
CN
CN
OH
R'
21
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NH2
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R'
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1b
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CN
NH
O
R'
23
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O
R'
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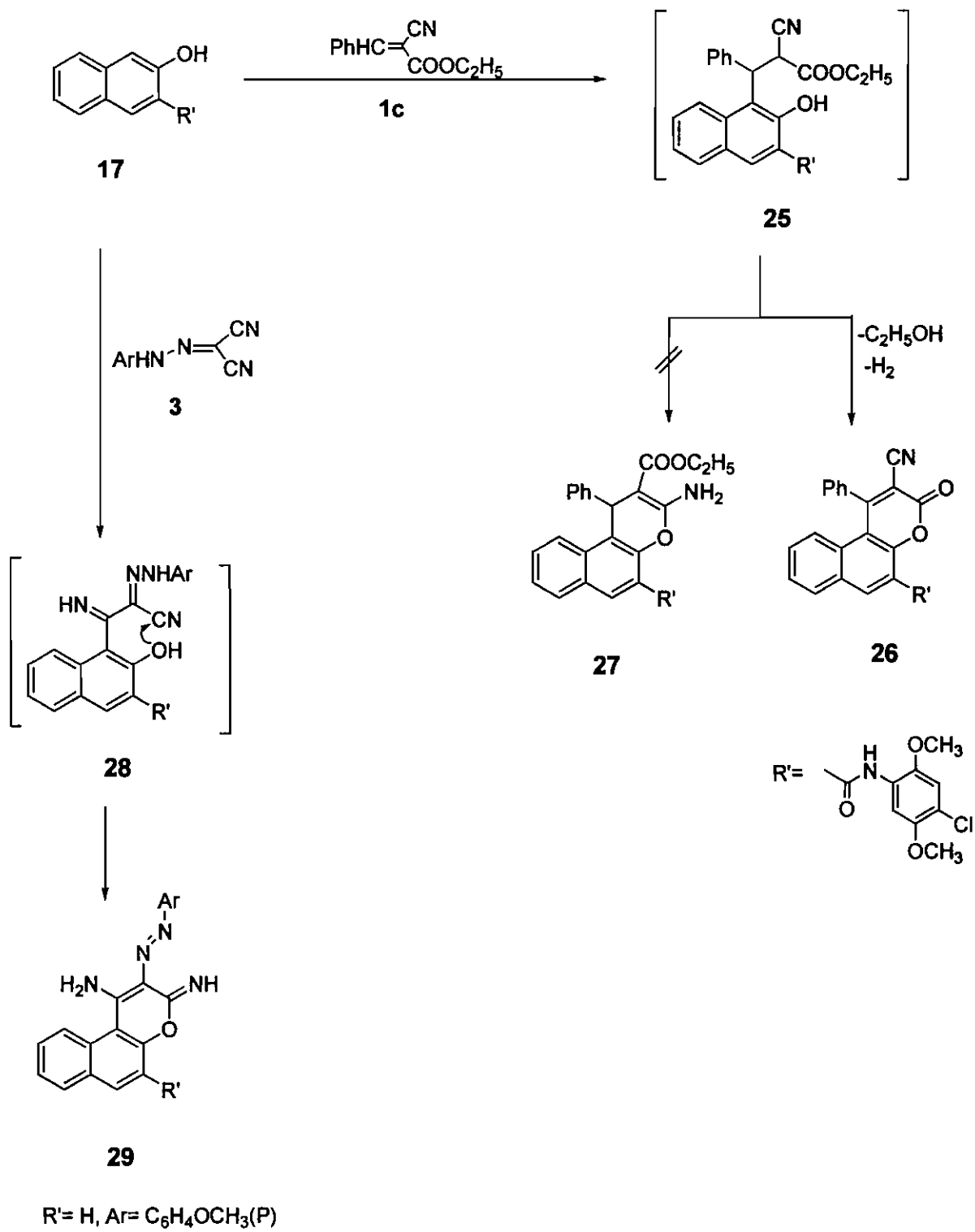
Cl
OCH3

Scheme 4



Scheme 5

Experimental:

All melting points are uncorrected. IR spectra were recorded for KBr disks a Shimadzu IR- 740 spectrometer. ^{1}H-NMR spectra were obtained on a Bruker AC-80 spectrometer with DMSO–d6 as solvent and TMS as an internal standard and chemical shifts are expressed as δ ppm. Mass spectra were measured on GC-MSINCOS XL. Flinnigan MAT. Elemental analyses were performed on LECO CHNS-932.

Synthesis of 2-amino-4,5,6,7,8-tetrahydro-8-methylchromene-3-carbonitrile ***(7)*** *and 2-amino-5,6,7,8-tetrahydro-7-methyl-4-phenyl-4H-chromene-3-carbonitrile* ***(12)*** *: General procedure:*

A solution of (0.01mol) of 2-methylcyclohexanone or 3-

methylcyclohexanone and (0.01 mol) of bezylidenemalononitrile in absolute ethanol (50 ml) containing few drops of piperidine was refluxed for three hours. The mixture was then left to cool to room temperature. The solids formed were recrystallised from ethanol and then identified as **7** and **12** respectively.

2-Amino-4,5,6,7,8-tetrahydro-8-methylchromene-3-carbonitrile ***(7)*** Yield 75 %, m.p.200°C yellow crystals. – IR : γ = 3287 cm-1(NH2), 2176 (conjugated CN); 1H-NMR : δ = 1.56-1.65 (m,4H,2CH2), 2.48 (d,3H,CH3), 3.40-3.46 (m,1H,CH), 5.26 (s,1H,4Hpyran), 7.36-7.67 (m,5H,aromatic protons), 7.74 (brs,2H,NH_2); $C_{17}H_{18}N_{2O}$ (266.34), Calcd. : C, 76.66; H, 6.81; N, 10.52 %; Found : C, 76.41; H, 6.50; N, 10.33 %.

2-Amino-5,6,7,8-tetrahydro-7-methyl-4-phenyl-4H-chromene-3-carbonitrile ***(12)***

Yield 70 %, m.p.245oC orange crystals. – IR : ν = 3414, 3337, 3235 cm-1 (NH2), 2213 (conjugated CN) ,1652 (δ, NH2); ^{1}HNMR: δ= 1.32-1.35 (m,2H,CH_2), 1.64-1.66(m,2H,CH_2) ,3.3(d,3H,CH_3), 3.45-3.50 (m,1H,CH) ,5.54 (s,1H,pyran 4H), 7.36-7.50 (m,5H,aromatic protons), 7.59 (s,2H,NH_2); $C_{17}H_{18}N_{2O}$ (266.34) , Calcd. : C,76.66; H,6.81; N,10.52 % , Found : C,76.53 ;H, 6.60; N, 10.23 % .

Synthesis of 2-amino-5,6,7,8-tetrahydro-8-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene -3-carbonitrile ***(14)*** *and 2-amino-5,6,7,8-tetrahydro-7-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene -3-carbonitrile* ***(16)*** *: General procedure :*

A suspension of (0.01mol) of 2-methylcyclohexanone or 3-methylcyclohexanone and (0.01 mol) of 2-(2-oxoindolin-3-ylidene)malononitrile **(2)** in absolute ethanol (50 ml) containing few drops of piperidine was refluxed for two hours. The mixture was then left to cool to room temperature. The solids formed were recrystallised from the proper solvents to give red crystals of **14** and **16** respectively.

2-Amino-5,6,7,8-tetrahydro-8-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene-3-carbonitrile ***(14)*** Was recrystallised from ethanol, Yield 80 % m.p.228°C. - IR : ν = 3259 cm-1 (NH_2) , 2231 (conjugated CN) , 1718 (CO), 1620 (δ, NH_2); 1H-NMR : δ = 6.91-7.87 (m,9H,aromatic protons) , 11.20 (s,2H,NH_2) ; $C_{18}H_{17}N_3O_2$ (307.36) , Calcd. : C,70.34 ; H,5.58.77; N,13.67 % , Found : C ,70.53 ; H ,5.60; N, 13.23 % .

2-Amino-5,6,7,8-tetrahydro-7-methyl-4-(1,3-dihydro-2H-indol-2-on)spirochromene-3-carbonitrile ***(16)*** Was recrystallised from1, 4-dioxan, and Yield 83 % m.p.254°C. - IR : ν = 3448, 3290 , 3169 cm-1 (NH_2) , 2194 (conjugated CN), 1713 (CO), 1630 (δ, NH_2); 1H-

NMR : δ = 6.81-7.21 (m,9H,aromatic protons) , 10.46 (s,2H,NH_2) ; $C_{18}H_{17}N_3O_2$ (307.35) , Calcd. : C, 70.34; H, 5.58; N, 13.67 %, Found : C, 70.66; H, 5.40; N ,13.33 % .

Preparation of 9,11-diamino-6-(4',chloro-2',5',-dimethoxybenzamido)-12-phenyl-12H-benzo[f]chromeno[2,3-b]pyridine-10-carbonitrile ***(20)*** To a solution of 2-(4,-chloro-2',5'-dimethoxybenzamido)-2-naphthol **(17a)** (0.01mol) in ethanol (50ml) containing piperidine (0.1ml) ,(0.01mol)of bezylidenemalononitrile **(1a)**was added .The reaction mixture was refluxed for few minutes , and the solid product formed was collected by filtration , recrystallised from ethanol / dimethylformamide to give **20** as colorless crystals , Yield 68 % m.p.227°C . - IR : γ = 3485,3440 cm-1 (NH_2 +NH) , 2210 (conjugated CN) , 1685 (CO amide) , 1630 (δ, NH2); 1-HNMR: δ = 3.75,3.80 (2s,6H,2OCH_3) , 5.45 (s,1H,pyran 4H) , 6.85 (s,2H,NH_2) , 7.15- 8.30 (m,14H, 12H aromatic protons+ 2H,NH_2) , 10.0 (s,1H,NH) ; $C_{32}H_{24}N_5O_4$ Cl (578.20), Calcd. : C, 66.47; H, 4.18; N, 12.11 %, Found : C, 66.55; H, 4.30; N, 12.43 %.

Synthesis of 11-amino-6- (4'-chloro-2',5'- -dimethoxybenzamido)-12H-benzo[f]chromeno[2,3-b]pyridine-10-carbonitrile ***(24)*** To a suspension of 2-(4'-chloro-2',5'-dimethoxybenzamido)-2-naphthol **(17a)**(0.01 mol) in ethanol (50ml) was added a mixture of formaldehyde (0.01 mol) and malononitrile (0.01 mol) , and then few drops of triehtylamine .The reaction mixture was refluxed for two hours and the solid formed on heating was collected by filtration, recrystallised from dimethylformamide to give **24** as yellow crystals, Yield m.p.260°C. - IR : γ = 3475, 3440 cm-1 (NH_2 +NH) , 2215 (conjugated CN), 1685 (CO amide), 1620 (δ, NH_2); $C_{26}H_{19}N_4O_4$ Cl (486.92), Calcd. : C, 64.14; H, 3.93; N, 11.51 %, Found : C, 66.45; H, 4.30; N, 12.43 %.

Formation of 6- (4'-chloro-2',5' -dimethoxybenzamido)- 2H-2-oxo-benzo[f]chromene ***(26)*** A

suspension of 2-(4'-chloro-2',5' -dimethoxybenzamido)-2-naphthol **(17a)** (0.01 mol) ethyl α-cyanocinnamate **(1c)** in ethanol (50ml), were refluxed for three hours in presence of pyridine (0.3ml). The reaction mixture was then left to cool over night. The solid product so formed was collected by filtration and recrystallised from dimethylformamide to give **26** as yellow crystals, Yield 75 % m.p.230oC. - IR: γ = 3425 cm-1 (NH), 2210 (conjugated CN), 1710(CO), 1685 (CO amide); $C_{29}H_{19}N_2O_5$ Cl (510. 93), Calcd. : C, 68.17; H, 3.75; N, 5.48 %, Found : C, 68.36; H, 3.30; N, 5.63 %.

*Preparation of 10-amino-9-(p-methoxyphenyl)benzo[f]chromene-8-imine **(29)*** A solution of 2-naphthol **(17b)** (0.01 mol) and 2-(p-methoxyphenylazo)malononitrile (3) (0.01 mol) in ethanol(50ml) containing few drops of piperidine were refluxed for two hours.The reaction mixture was then left to cool over night .The solid product so formed was collected by filtration and recrystallised from dimethylformamide to give **29** as brown crystals, Yield 80 % m.p.150°C. - IR : γ = 3391, 3292, 3203 cm-1 (NH_2+NH), 2189 (conjugated CN), 1621 (C=NH); 1H-NMR: δ= 3.78, (s,3H,OCH_3), 7.15-8.30 (m,13H, 10H aromatic protons+ 2H,NH_2+1H,NH); $C_{20}H_{16}N_4O_2$ I (344. 38)(M+/m/z=344), Calcd. : C, 69. 75; H, 4.68; N, 16.27 %, Found : C, 69.36; H, 4.50; N, 16.43 % .

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