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N-(4-Acetylphenyl)-2-cyanoacetamide as building block in heterocyclic synthesis: Synthesis and characterization of thiazole, pyridine, chromene and chromenopyridone

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ABSTRACT

Deferent types of thiazole derivatives were obtained via reaction of cyanoacetamide derivatve **(1)** with phenyl isothiocyanate and α-halocarbonyl compounds. Also, thiazole derivatives containing chromene moiety were synthesized through interaction of thiosemicarbazone derivative **(10)** with α-halocarbonyl compounds followed by cyclocondensation with salicyldehyde. In addition, deferent types of 3-cyanopyridine derivatives were obtained through reaction of **(1)** or **(10)** with some electrophilic reagents.

KEYWORDS

Cyanoacetamide;
Thiazoles;
Chromene;
Pyridine;
Chormeno[3,4-c]pyridine.

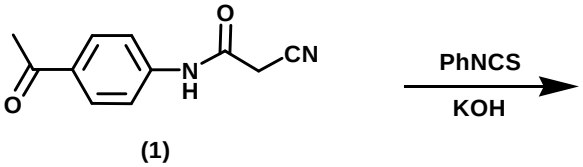
INTRODUCTION

N-aryl-2-cyanoacetamides have proven to be valuable synthon for the synthesis of a wide variety of biologically active heterocyclic systems.[1-4] As an extension of our efforts directed towards the development of convenient synthetic approaches for the construction of biologically active heterocyclic.[5-8] I want to accentuate the synthetic scope of *N*-(4-acetylphenyl)-2-cyano acetamide **(1)**[9] as a key precursor for the synthesis of some hetero unreported poly functionally substituted heterocycles and their fused systems with an expected broad spectrum of bioresposes. Since the cyanocatamide derivative **(1)** has tow nucleophilic sites, the methylene group carbon and the amide nitrogen also has three electrophilic sites the carbonyl of acetyl, the carbonyl of amide and the cyano function groups. A combination between NH-C=O & CH_2CN in addition to acetyl group in cyanoacetamide derivative **(1)** open wide synthetic opportunities for further reactions and utilizing as a ready starting materials in the synthesis of many heterocyclic compounds.

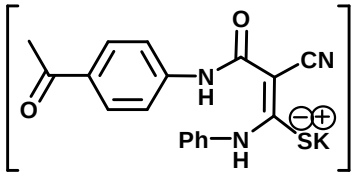
RESULT AND DISCUSSION

Many thiazole derivatives have been demonstrated to posses antibacterial[10], antifungal[11], anticonvulsant[12], anticancer[13], and antituberculosis[14] activites. In addition, thiazolidines have reported as novel inhibitors of the bacterial enzyme Mur B which aprecursos acting during the biosynthesis of peptidoglycan[15]. Thus, reaction of cyanoacetamide derivative **(1)** with phenyl isothiocyanate in *DMF* and the presence of *KOH*, at room temperature gave non-isolable potassium sulphide salte **(2)** (Scheme 1). The potassium salt **(2)** was exploited to synthesize new thiazoldine derivatives. Cyclocondensation of the intermediate **(2)** with chloroacetone **(3a)** at room temperature afforded the corresponding 4-methylthizole

derivative **(4)** and the other possible thiophene structure **(5)** was excluded according to the spectral data for the isolated product (Scheme 2). IR spectrum of **(4)** showed a nitrile absorption band at 2176 cm^{-1}. The ^{1}HNMR spectrum displayed a characteristic two singlet signals at 1.86, 2.49 ppm due to two methyl groups in addition to singlet signal at $\delta = 6.98$ ppm for thiazole H5. Also, treatment of intermediate **(2)** with ethylchloroacetate **(3b)** at room temperature gave 4-thiazoldinone derivatives **(6)**, and the other possible thiophene derivative **(7)** was excluded on the basis of elemental analysis and spectral data (MS, IR, ^{1}HNMR). The IR spectrum showed nitrile absorption bands at 2194 cm^{-1}, the mass spectrum was compatible with a molecular formula $C_{20}H_{15}N_3O_3S$ (m^+=377), and ^{1}HNMR contained a singlet at δ = 4.02 ppm assignable to an the methylene group .The reaction mechanism was assumed to proceed through initial alkylation followed by interamolecular cyclization by elimination of ethanol. Similarly, reaction of non-isolable sulphide salt **(2)** with α-bromopropionate and α-bromobutrate **(3c,d)** resulted in the formation of 1,3-thiazole derivatives **(8a)** and **(8b)** not the other possible thiophene structure **(9a)** and **(9b)** according to the spectral data of the isolated products (Scheme 2). For example, the IR spectra of the isolated products revealed, in each case, two bands due to two carbonyl groups in the region 1728-1670 cm^{-1} and showed a nitrile absorption band in the region 2198-2194 cm^{-1}. The ^{1}HNMR spectrum of **(8a)** showed a doublet at $\delta = 1.61$ and a quartet at $\delta = 4.28$ assigned to S-CH-CH_3.

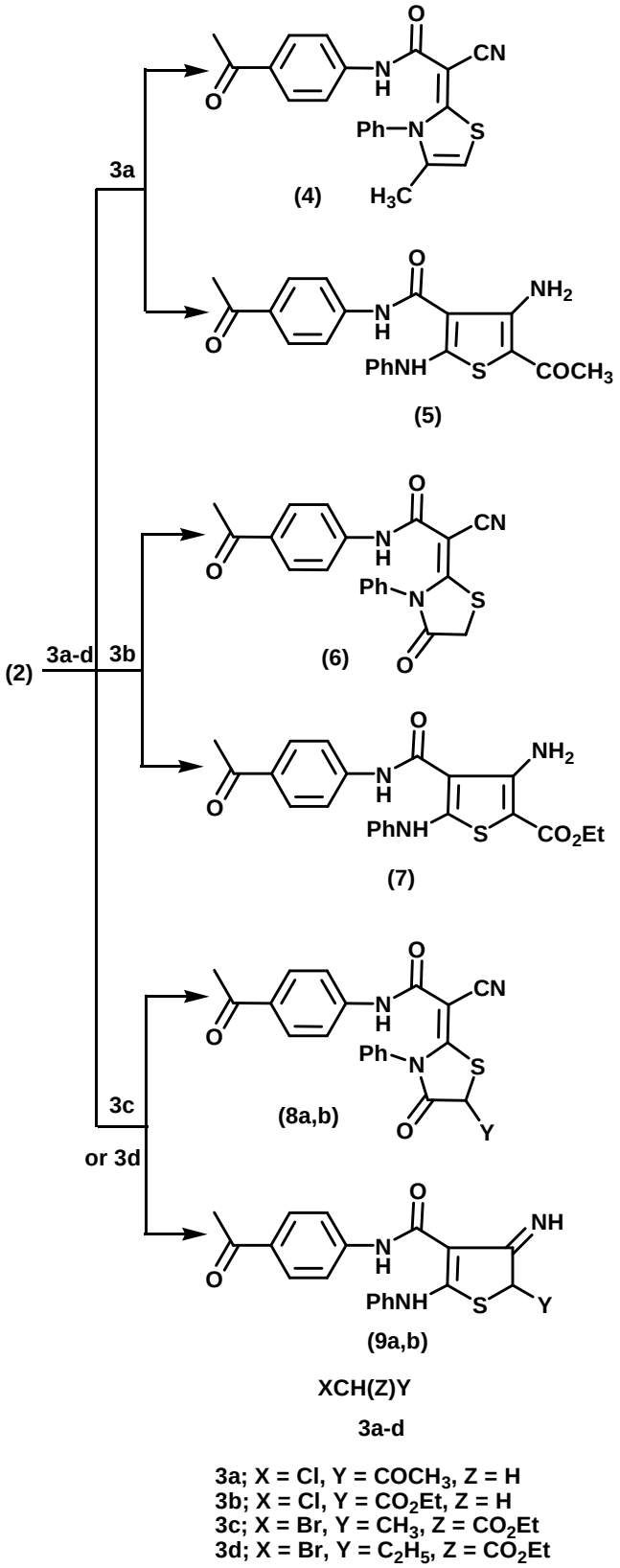


(1)



(2)

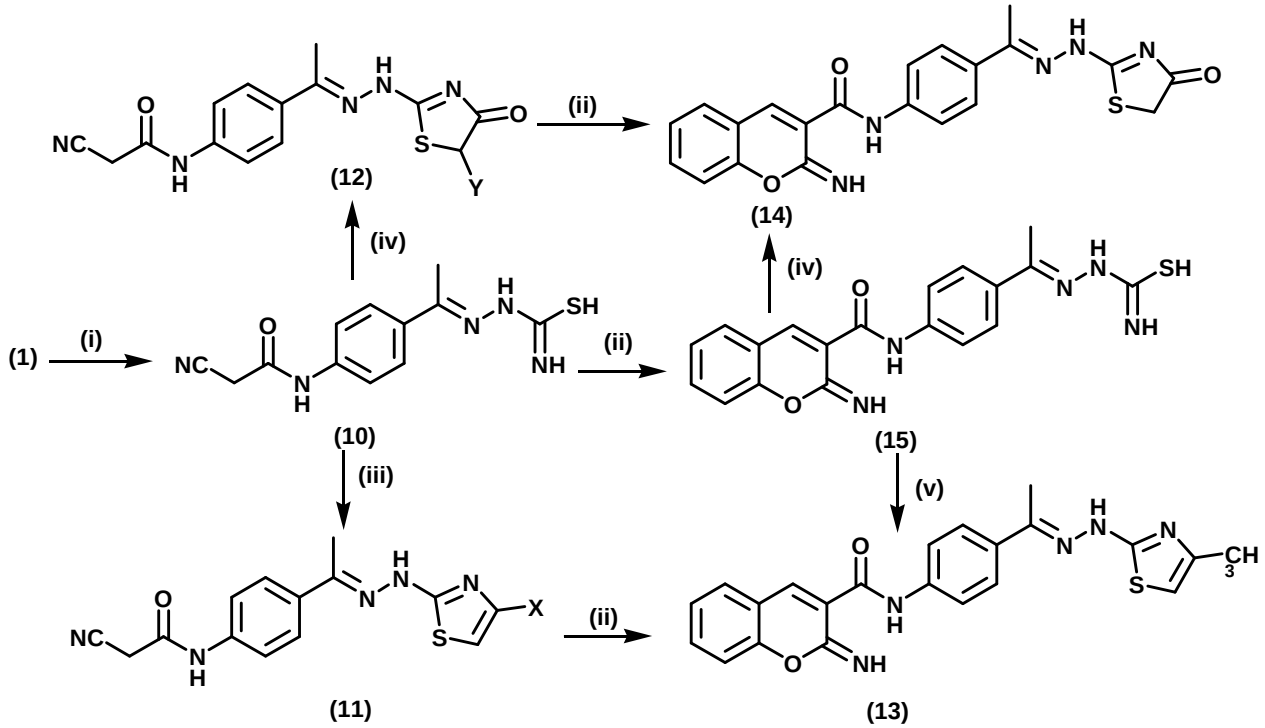
Scheme 1



Scheme 2

The reactivity of cyanoacetamide derivative **(1)** for synthesis of thiazoles not only depends on the presence

of active methylene group, but also a new types of thiazole can obtained via condensation of **(1)** with thiosemcarbazide to afford thiosemecarbazone derivatives **(10)**. The structure of compound **(10)** was confirmed on the basis of its spectral data (cf. Experimental part), (Scheme 3). Compound **(10)** reacted with chloroacetone **(3a)** and *p*-nitrophenacylbromide **(3e)** in refluxing ethanol and in the presence of catalytic amount of fused Sod.acetate resulted in the formation 1.3-thiazole derivative **(11a)** and **(11b)**, the structure of the isolated compounds **(11a)** and **(11b)** were confirmed on the basis of elemental analysis and spectral data. The ^{1}HNMR spectra of the isolated products (Scheme 3) revealed in each case singlet at 7.71 ppm assigned for CH-thiazole. The mass spectra of the same compounds showed peaks corresponding to their molecular ions, the latter reaction of the thiosemicarpazone **(10)** with α-halo compounds **(3a)** & **(3e)** proceeds in each case, through loss of hydrogen halide followed by elimination of water molecule. also, 4-thiazolidinone derivatives **(12a)** and **(12b)** were obtained via reaction of thiosemicarbazone **(10)** with ethy1-α-bromoprpionate **(3c)** and ethylchloroacetate **(3b)** under the same reaction condition afforded, in each case, only one isolable products were compatible with 4-thiazoldinone derivatives **(12a)** and **(12b)**. Protein tyrosine Kinases (PTK) play an important role in the signal transduction of normal and abnormal cell.[16-18] Increasing numbers of PTK inhibitors have been introduced as potential anticancer reagents.[19-22] For the purpose of obtaining highly specific inhibitors, bicyclic compounds as ring constrained inhibitors of PTK have recently been introduced[23]. Iminochromenes belong to this type of compound for this importance of chromenes, the previous work aimed to synthesized heterocyclic compounds containing chromene, thus cyclocondensation of thiazole derivatives **(11a)** and **(12b)** with salicyldehyde in refluxing ethanol containing a catalytic amount of amm.acetate resulted in the formation of 2-iminochromene derivatives **(13)** and **(14)**. The structures of **(13)** and **(14)** were established and confirmed for the reaction products on the basis of their elemental analysis and spectrsl data. The IR spectra of the isolated products revealed in each case a singlet for CH-chromene at 8.56 ppm, with aD_2O exchangeable signals in the region 9.25-12.89 ppm due to three NH functions (*cf*. Experimental part). Alternatively, products **(13)** and **(14)** could be obtained via an indepen-

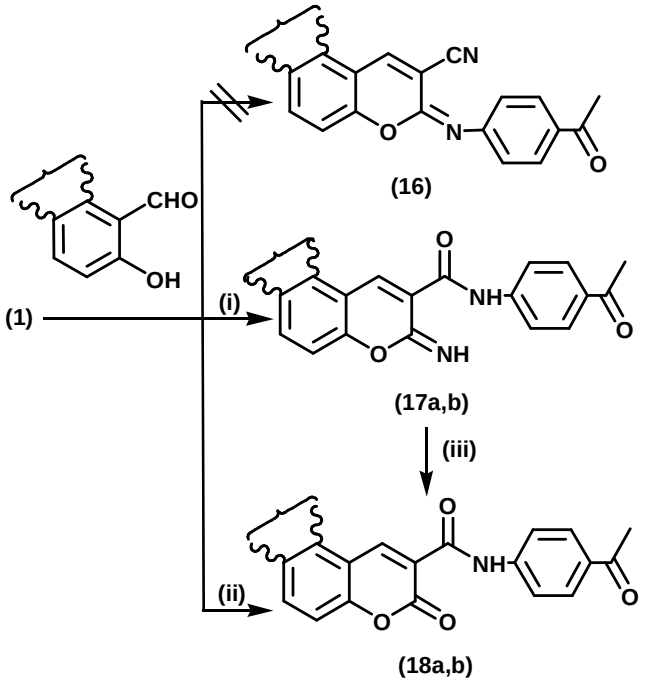


Reagents & Conditions : i) thiosemicarbazide/dioxan; ii) salicyaldehyde,EtOH/amm. acetate, iii) 3a or 3b, EtOH/sod. acetate; iv) 3c or 3e, EtOH/sod. acetate v) 3a, EtOH/Sod.acetate; vi) 3c,EtOH/Sod.acetate

Scheme 3

dent stepwise synthetic route involving the cyclocondensation of **(10)** with an equimolar amount of salicyldehyde in the presence of a catalytic amount of amm.acetate to afford the corresponding chromene derivative **(15)**. The latter, in turn, reacted with chloroacetone **(3a)** and ethylchloroacetone **(3b)** to afford a single product in each case found to be identical with **(13)** and **(14)**, (Scheme 3).

The one pot synthesis of chromene derivatives containing the carboxamide group in the 3-position is the aim strategy for this part of research. Thus, cyclocondensation of N-(4-acetylphenyl)-2-cyanoacetamide **(1)** with salicyldehde or 2-hydroxynaphthaldehyde in refluxing ethanolic ammonium acetate furnished 2-iminochromene and 2-iminobenzo[f]chromen derivative **(17a,b)** and the other possible structure **(16)** was excluded on the basis of the IR which indicated the absence of a CN absorption band and ^{1}HNMR spectrum of **(17a)** revealed a singlet at δ = 8.58 ppm assigned for CH- chromene with two singlets for 2NH cancelled with a D_2O at δ = 9.27,13.12 ppm, the mass spectrum of **(17b)** exhibited a molecular ion peak at m/z 356 (20.5%) and a base peak at m/z (120%). While, cyclocondensation of **(1)** with salicyaldehyde or 2-hydroxynaphthaldehyde in refluxing acetic anhydride containing catalytic amounts of sodium acetate, yielded chromene-2-one derivative **(18a,b)**. Structure **(18)** was readily demonstrated on the basis of spectral data. Infrared spectrum of **(18a)** afforded bands at 3150 (NH) and 1720 cm^{-1}(C=O) and ^{1}HNMR of **(18a)** showed a singlet at δ = 8.90 ppm (CH-chromene) and at 10.87 ppm (NH; cancelled with D_2O). The structure of the latter compound **(18)** further confirmed by another route of preparation via the hydrolysis of 2-iminochromene derivative **(17)** with ethanolic HCl under reflux condition (Scheme 4). (*cf.* Experimental part).



(i) Salicyldehyde or 2-hydroxynaphthaldehyde, EtOH/amm.acetate
(ii) Salicyldehyde or 2-hydroxynaphthaldehyde, acetic anhydride/sod.acetate
(iii) EtOH/HCl

Scheme 4

The synthesis of polyfunctionalized pyridines is important because of their wide spread occurrence in the nature and biological activity.[24-26] The pyridine ring is a basic unit of numerous biological active alkaloids and pharmacological products.[27,28] Also, many acetyl pyridine thiosemicabazones have been shown to exhibit antimalarial activity against plasmodium berghei in mice[29,30] thus, cyclocondensation of cyanoacetamide derivative **(1)** with acetylacetone furnished 4.6-dimethyl-2-oxo-1-(4-acetylphenyl)-1.2-dihydropyridine 3-carbonitrile **(20)**, via intramolecular heterocyclization of the non isolable intermediate **(19)** by loss of a water molecule, (Scheme 5). The structure of **(20)** was supported on the basis of elemental analysis and spectral data. The ^{1}HNMR spectrum of **(20)** revealed signals at δ = 1.97, 2.37 and 2.64 ppm for two CH_3 and $COCH_3$ with a singlet at δ = 6.46 ppm for CH- pyridine. Condensation of 4.6-dimethylpyridine derivative **(20)** with thiothemicarbazide produced pyridine-*N*-(4-acetylphenyl thiosemicarbazone) derivative **(21)**. This product was readily demonstrated on the basis of spectral data. Its infrared spectrum afforded bands at 3462, 3348, 3228 (NH_2/ NH), 2222 cm^{-1}(C≡N) and ^{1}HNMR revealed a singlet at δ = 1.98, 2.34 ($2CH_3$), 2.64 ($COCH_3$), 6.46 (CH-pyridine) and 8.02, 8.30, 10.26 (2NH & SH; cancelled with D_2O). Also, the mass spectrum of **(21)** exhibited a molecular ion peak at m / z 339 (5.5%) and a base peak at m / z 76.3. The thiosemicarbazone **(21)** could also be obtained in a good yield via the reaction of **(10)** with acetylacetone (Scheme 5).

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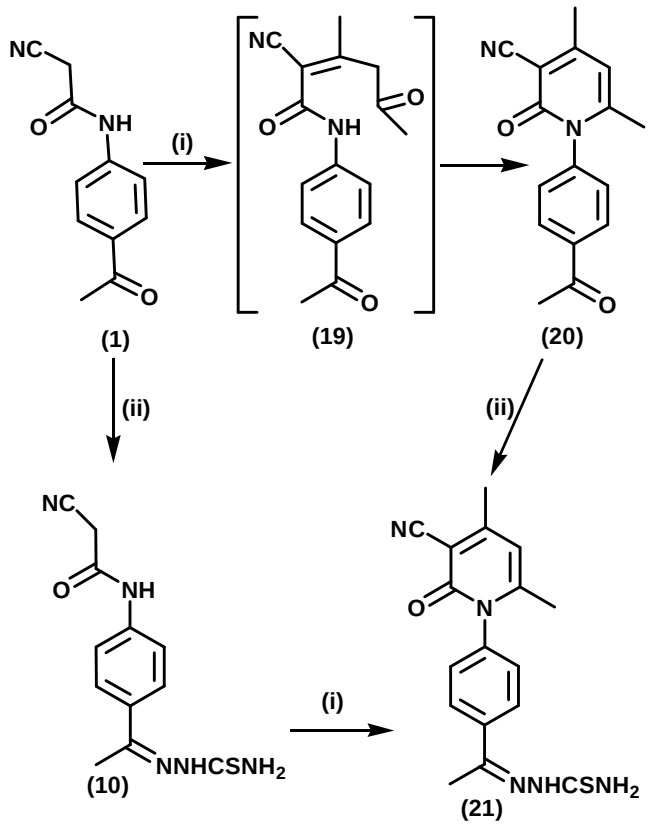
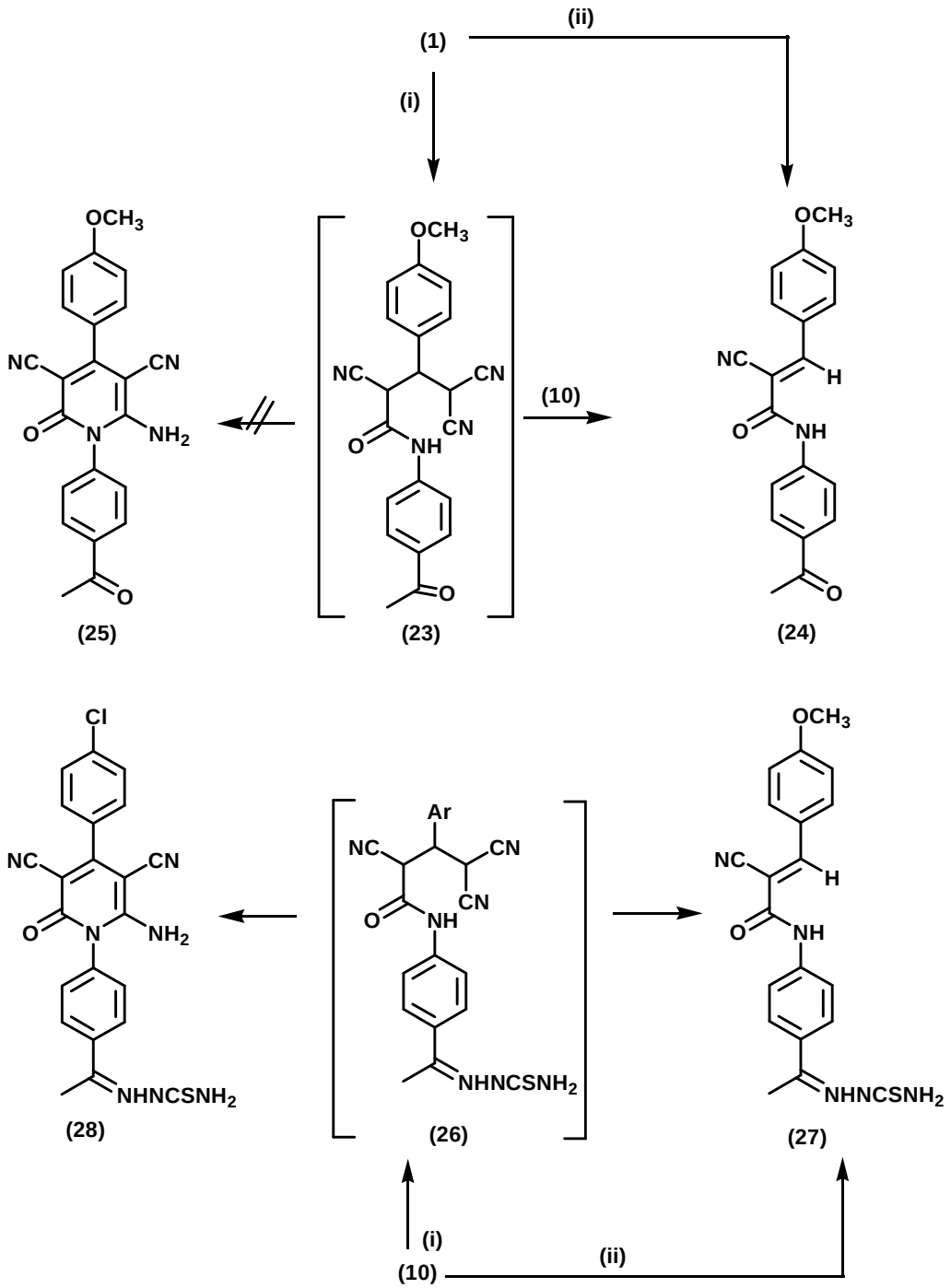


(i):Acetylacetone/fusion,(ii):Thiosemicarbazide/dioxan

Scheme 5

As a part of this research, the reaction of cyanoacetamide derivative **(1)** with unsaturated nitriles was investigated as a way for pyridine synthesis, but when compound **(1)** reacted with α-cyano-4-methoxycinnamonitryl **(22a)** in refluxing ethanol and in the presence of a catalytic amount of piperidine resulted in the formation of α-cyano-4-methoxy-*N*-(4-acetylphenyl)cinnamide **(24)** not other possible pyridine-3-carbonitrile **(25)** according to the spectral data of the isolated product (Scheme 5). The ^{1}HNMR spectrum of **(24)** displayed a characteristic singlet signal at δ = 3.87 ppm due to methoxy group, in addition to a singlet at δ = 8.24 for CH-benzylidine with a singlet at δ = 10.56 ppm for NH function group. It seems that **(24)** was formed via Michael type addition of the methylene function in 1 to the active double bond in **(22a)** to yield a cyclic Michael adduct **(23)** which then spontaneously loses the malononitrile molecule to give the final product **(24)**. Further confirmation, compound **(24)** could also be obtained in good yield via the reaction of **(1)** with anisaldehyde. Similarly thiosemicarbazone **(10)** reacted with α-cyano-4-methoxycinnamonitryl **(22a)** resulted in the formation of cinnamide derivative **(27)** not the other possible pyridine derivative **(28)** according the spectral data of the isolated product (Scheme 6). ^{1}HNMR spectrum revealed the absence of NH_2 protons in addition to the presence of signals at δ = 3.87, 8.22 ppm for methoxy and CH-benzylidene protons, respectively. The proposed structure of **(27)** was also confirmed through their synthesis from condensation of thiosemicarbazone **(10)** with anisaldehyde. On the other hand, Michael addition of the methylene function in **(10)** to the activated double bond in α-cyano-4-chlorocinnamonitryl **(22b)** yielded acyclic Michael adduct **(26)** which cyclzies followed by oxidation to form pyridine type **(28)**. Assignment of structure **(28)** was confirmed on the basis of their elemental analysis and spectral data. ^{1}HNMR of **(28)** revealed a singlet at δ = 2.36 ppm (CH3) and a D2O exchangeable signals at 8.30, 10.18, 10.29 and 10.50 ppm due to NH2 and NH, SH functions. Mass spectrum of **(28)** exhibited a molecular ion peak at m/z 387 (M-NH_2CSNH_2:3.0 %) and base peak at m/z 59.

Chromenes joined to pyridine nucleus have been reported to possess anillergic[31], anticonvulsant[32] and diabetic[33] activities. Moreover, the resulting chromene derivative **(17a)** have latent functional substituents which have the potential for further chemical transformation giving new routes for preparation of condensed chromeno[3,4-c]pyridine derivatives. Thus, treatment of compound **(17a)** with malononitrile under reflux in dioxin in the presence of piperiidne afforded the novel chromeno[3,4-c]pyridine derivative **(30)**. The molecular structure of **(30)** was established through analytical and spectral data. Its infrared spectrum showed absorption bands at 3438, 3346 and 2206 cm-1 due to amino and cyano function groups, respectively. Also, ^{1}HNMR spectrum showed the appearance of D_2O exchangeable signals at δ = 7.79 and 8.40 ppm due to the amino and imino functions. The formation of **(30)** is assumed to proceed via the Michael addition of the active methylene function of malononitrile to the activated double bond centre in **(17a)** to yield the acyclic Michael adduct **(29)** which cyclize and aromatize through auto-oxidation under condition[34].



(i):22,EtOH/pip., (ii):Anisaldehyde,EtOH/pip.

Scheme 6

Finally, chromeno[3,4-c]pyridine derivative **(32)** was achieved by reaction of 2-iminochromene derivative **(17a)** with ethyl cyanoacetate and the other possible structure **(33a)** was excluded on the basis of elemental analysis and spectral data. Its IR spectrum revealed the presence of hydroxyl, nitrile and the carbonyl function, and its ^{1}HNMR spectrum showed signals at δ = 8.68 and 11.66 ppm assigned to OH and NH groups (cancelled with D2O). It can be postulated that the reaction initially proceeds via a nucleophilic addition to the double bond of **(17a)** to form Michael type adduct **(31)** that subsequently cyclize through elimination of ethanol (Scheme 7).

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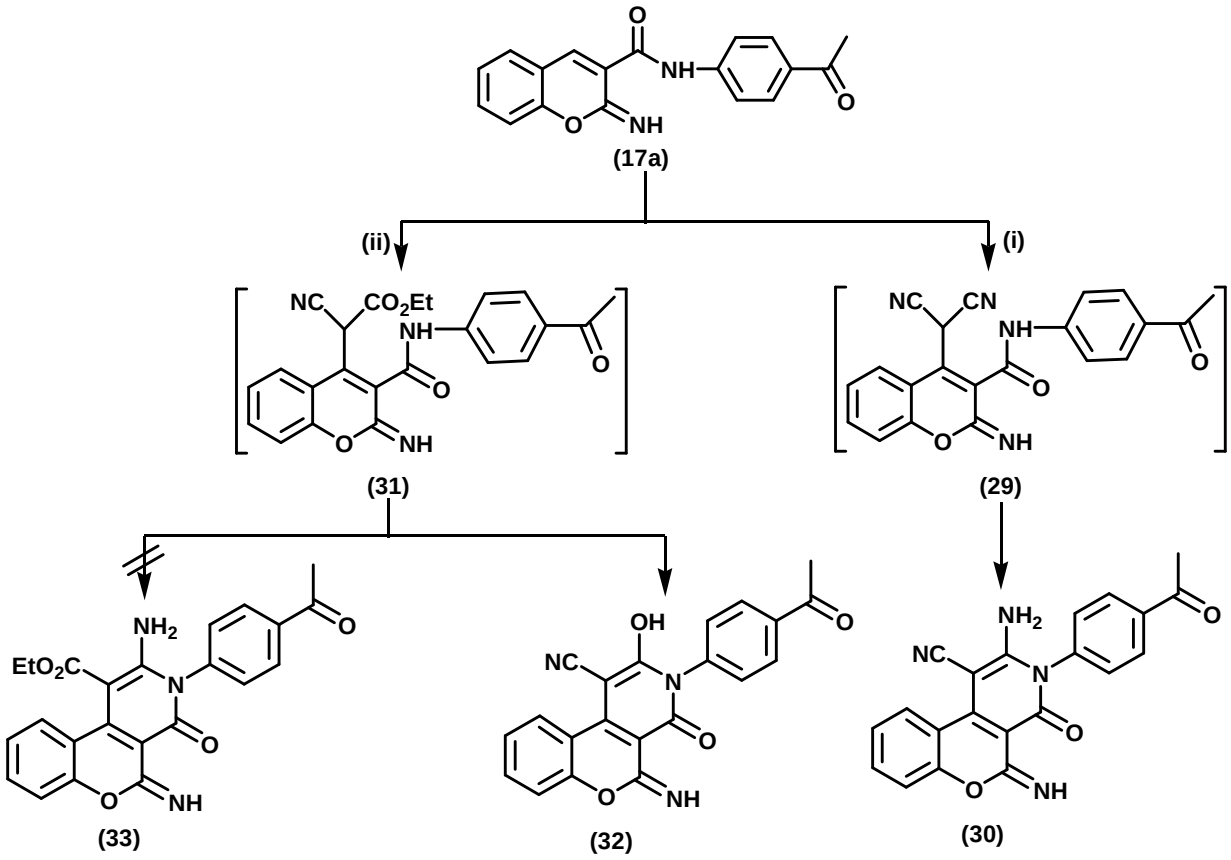

(i) Malononitrile,dioxane/pipredine, (ii) Ethylcyanoacetate,dioxane/pipredine

Scheme 7

EXPEMINTAL

All melting points are uncorrected. IR spectra (KBr) were recorded on a FTIR 5300 spectrometer (v, cm-1). The ^{1}HNMR spectra were recorded in DMSO-d_6 at 200 MHz on a Varian Gemini NMR spectrometer (δ, ppm) using TMS as an internal standard. Mass spectra were obtained on GC Ms-QP 1000 EX mass spectrometer at 70 ev. Elemental analyses were carried out by the Micro analytical Research Centre, Faculty of Science, Cairo University.

(Z)-N-(4-acetylphenyl)-2-cyano-2-(4-methyl-3-phenylthia-zol-2(3H)-ylidene)acetamide(4), (Z)-N-(4-acetylphenyl)-2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)acetamide-(6), (Z)-N-(4-acetylphenyl)-2-cyano-2-(5-methyl-4-oxo-3-phenylthia-zolidin-2-ylidene)acetamide (8a) and (Z)-N-(4-ace-tylphenyl)-2-cyano-2-(5-ethyl-4-oxo-3-phenylthia-zolidin-2-ylidene)acetamide (8b)

General procedure

A mixture of compound **(1)** (0.01 mole), appropriate α-halo compounds; 0.01 mole) and sodium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product which produced on heating was collected and recrystallized from the acetic acid.

Compound (4): white solid, m.p. = 230-232c°. IR/*v* (cm-1) 3460 (NH), 2176 (C≡N), 1672 (C=O). ^{1}HNMR (DMSO-d_6): δ = 1.86 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 6.98 (s, 1H, thiazole-H_5), 7.50-7.86 (m, 9H, Ar-H), 9.03 (s, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{21}H_{17}N_3O_2S$: C, 67.20; H, 4.55; N, 11.20. Found: C, 67.15; H, 4.50; N, 11.17.

Compound (6): White solid, m.p. = 240-243 c°. IR/*v* (cm-1) 334 (NH), 2194 (C≡N), 1748 (C=O; thiazolidinone), 1674 (C=O; amide). ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 4.02 (s, 2H, CH_2-thiazolidinone), 7.42-7.91 (m, 9H, Ar-H). 9.74 (s, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{20}H_{15}N_3O_3S$: C, 63.66; H, 3.97; N, 11.14. Found:

C, 63.60; H, 3.80; N, 11.10.
MS, m/z (%) = 377 [M+ 15.6], 243 (29.4), 215 (72.1), 132 (28.4) and 77(100, base peak).

Compound (8a): Beige solid, m.p. = 235-237c°. IR/*v* (cm-^{1}) 3360 (NH), 2926 (aliph.CH), 2194 (C≡N), 1728 (C=O; thiazolidinone), 1670 (C=O; amide). ^{1}HNMR (DMSO-d_6): δ = 1.61 (d, 3H, CH_3), 2.49 (s, 3H, COCH3), 4.25 (q, 2H, thiazoldinone-H_5), 7.45-7.91 (m, 9H, Ar-H), 9.77 (s, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{21}H_{17}N_3O_3S$: C, 64.45; H, 4.34; N, 10.74. Found: C, 64.40; H, 4.30; N, 10.70.

Compound (8b): Beige solid, m.p. = 243-245c°. IR/*v* (cm-^{1}) 3400 (NH), 2950 (aliph.CH), 2198 (C≡N), 1740 (C=O; thiazolidinone), 1666 (C=O; amide). ^{1}HNMR (DMSO-d_6): δ = 1.03 (t, 3H, CH_3), 1.96 (p, 2H, CH_2), 2.49 (s, 3h, $COCH_3$), 4.30 (t, 1H, thiazoldinone-H_5), 7.41-7.91 (m, 9H, Ar-H), 9.78(s, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{22}H_{19}N_3O_3S$: C, 65.18; H, 4.69; N, 10.37. Found: C, 65.15; H, 4.65; N, 10.30.

(E)-2-(1-(4-(2-cyanoacetamido)phenyl) ethylidene)hydrazine-carbimidothioic acid (10)

A mixture of compound **(1)** (0.01 mole), thiosemicarbazide; 0.01 mole) in dioxan(30 mL) was refluxed for 3h. The resulting solid was filtered off and recrystallized from acetic acid as yellow solid, m.p. = 215-217 c°. IR/*v* (cm-^{1}) 3390, 3260 (SH, NH), 2966 (aliph.CH), 2260 (C≡N), 1702 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 7.54-7.93 (m, Ar_H and NH; cancelled with a D_2O). 8.22, 10.14 (2s, 2H, 2NH; cancelled with a D_2O). 10.39 (s, 1H, SH; cancelled with a D_2O). Anal. Calc. for $C_{12}H_{13}N_5OS$: C, 52.36; H, 4.72; N, 25.45. Found: C, 52.30; H, 4.70; N, 25.30.

(E)-2-cyano-N-(4-(1-(2-(4-methylthiazol-2-yl)hydrazono)-ethyl)-phenyl)acetamide (11a), (E)-2-cyano-N-(4-(1-(2-(4-(4-nitro-phenyl)thiazol-2-yl)hydrazono)ethyl)phenyl)acetamide (11b), (E)-2-cyano-N-(4-(1-(2-(5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)phenyl)acetamide(12a) and (E)-2-cyano-N-(4-(1-(2-(4-oxo-4,5-di-hydrothiazol-2-yl)hydrazono)ethyl)phenyl) ace-tamide (12b)

A mixture of compound **(10)** (0.01 mole), appropriate α-halo compound namely, cloroacetone and p-nitrophenaceyl bromide, ethylchloroacetate and ethy1-α-bromoprpionate; (0.01 mole) and sodium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 3h. The solid product which produced on heating was collected and recrystallized from the proper solvents.

Compound (11a): Yellow crystals, m.p. = 210c°. IR/*v* (cm-^{1}) 3108 (NH), 2198 (C≡N), 1694 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.24, 2.37 (2s, 6H, $2CH_3$), 4.01 (s, 2H, CH_2), 6.56, 11.01 (2s, 2H, 2NH; cancelled with a D_2O), 7.65-7.87 (2d, 5H, Ar-H & thiazole-H_5). Anal. Calc. for $C_{15}H_{15}N_5OS$: C, 57.50; H, 4.79; N, 22.36. Found: C, 57.40; H, 4.70; N, 22.30.
MS, m/z (%) = 313 [M+ 64.4], 298 (16.4), 159 (11.0), 119 (39.7) and 65(100, base peak).

Compound (11b): Brown crystals, m.p. = 270-270 c°. IR/*v* (cm-^{1}) 3316 (NH), 3088 (arom. CH), 2260 (C≡N), 1678 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 3.93 (s, 2H, CH_2), 7.59 - 8.29 (m, 10H, Ar-H & thiazole-H_5). 10.45 (s, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{20}H_{16}N_6O_3S$: C, 57.14; H, 3.80; N, 20.00. Found: C, 57.10; H, 3.70; N, 19.05.
MS, m/z (%) = 420 [M+ 30.3], 354 (18.4), 249 (72.1), 132 (15.4) and 65(100, base peak).

Compound (12a): White crystals, m.p. = 250-252 c°. IR/*v* (cm-^{1}) 3260 (NH), 2948 (aliph. CH), 2262 (C≡N), 1726 (C=O; thiazolidinone), 1676 (C=O; amide).). ^{1}HNMR (DMSO-d_6): δ = 1.48 (d, 3H, CH_3), 2.38 (s, 3H, CH_3), 3.92 (s, 2H, CH_2), 4.17 (q, 1H, thiazolidinone-H_5), 7.59, 7.81 (2d, 4H, Ar-H), 10.44, 11.87 (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{15}H_{15}N_5O_2S$: C, 54.71; H, 4.55; N, 21.27. Found: C, 54.60; H, 4.40; N, 21.10.

Compound (12b): Beige crystals, m.p. = 245-247 c°. IR/*v* (cm-^{1}) 3276 (NH), 2992 (aliph. CH), 2260 (C≡N), 1712 (C=O; thiazolidinone), 1682 (C=O; amide).). ^{1}HNMR (DMSO-d_6): δ = 2.30 (s, 3H, CH_3), 3.85, 3.92 (2s, 4H, $2CH_2$). 7.59, 7.96 (2d, 4H, Ar-H), 10.46, 11.89 (2s, 2H, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{14}H_{13}N_5O_2S$: C, 53.33; H, 4.12; N, 22.22. Found: C, 53.20; H, 4.10; N, 22.00.

(E)-2-imino-N-(4-(1-(2-(4-methylthiazol-2-yl)hydrazono)ethyl)-phenyl)-2H-chromene-3-carboxamide(13) and (E)-2-imino-N-(4-(1-(2-(4-oxo-4, 5-dihydrothiazol-2-yl)hydrazono)ethyl) phenyl)-2H-chromene-3-carboxamide(14)

A mixture of compound **(13)** or **(14)** (0.01 mole),

salisaldehyde; (0.01 mole) and piperdine (0.5 ml) in DMF (30 mL) was refluxed for 3h. The resulting products which produced were collected and recrystallized from the proper solvents.

Compound (13): Yellow crystals, m.p. = 300 c°. IR/*v* (cm-^{1}) 3186 (NH), 2980 (aliph. CH), 1680 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.16, 2.27 (2s, 6H, 2CH_3), 6.31 (s, 1H, thiazole-H_5), 7.25- 7.81 (m, 8H, Ar-H), 8.57 (s, 1H, chromene-H_4), 9.25, 12.89 (2s, 2NH; cancelled with a D_2O), 11.40 (br, 1H, NH; cancelled with a D_2O). Anal. Calc. for $C_{22}H_{19}N_5O_2S$: C, 63.30; H, 4.55; N, 16.78. Found: C, 63.20; H, 4.50; N, 16.70.

Compound (14): Brown crystals, m.p. = 270 c°. IR/*v* (cm-^{1}) 3170 (NH), 2988 (aliph. CH), 1685 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.27 (s, H, CH_3), 4.10 (s, 2H, CH_2), 7.20- 7.90 (m, 8H, Ar-H), 8.60 (s, 1H, chromene-H_4), 9.30, 11.40, 12.40 (3s, 3NH; cancelled with a D_2O). Anal. Calc. for $C_{21}H_{17}N_5O_3S$: C, 60.14; H, 4.05; N, 16.07. Found: C, 60.00; H, 4.00; N, 16.00.
MS, m/z (%) = 419 [M+ 41.2], 418(13.0), 306 (5.4), 173 (100,base peak), 172 (74.4), 145(51.5) and 116(26.6).

(E)-2-(1-(4-(2-imino-2H-chromene-3-carboxamido)phenyl)ethy-lidene)hydrazine carbimidothioic acid(15)

A mixture of compound **(10)** (0.01 mole), salicyaldehyde (0.01 mole) and ammonium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 1h. The solid product which produced on heating was collected and recrystallized to furnish **(15)**

Compound (15): Yellow crystals, m.p. = 260- 262°C. IR/*v* (cm-^{1}) 3216 (NH), 2968 (aliph-CH), 1682 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 7.25-7.98 (m, 8H, Ar-H), 8.23 (s, 1H, chromene-H_4), 8.57, 9.24, 10.15, 12.91 (4s, 4H, 3NH & SH; cancelled with a D_2O). Anal. Calc. for $C_{19}H_{17}N_5O_2S$: C, 60.15; H, 4.48; N, 18.46. Found: C, 60.15; H, 4.30; N, 18.30.
MS, m/z (%) = 397 [M+ 5.5], 363 (9.4), 265 (12.3), 223 (19.0),172 (71.0) and 118 (100, base peak).

N-(4-acetylphenyl)-2-imino-2H-chromene-3-carboxamide (17a) and N-(4-acetylphenyl)-3-imino-3H-benzo[f]chromene-2-carboxam-ide (17b)

A mixture of compound **(1)** (0.01 mole), appropriate aldehyde (salicylaldehyde or 2-hydroxynaphthaldehyde; 0.01 mole) and ammonium acetate (0.01 mole) in ethanol (30 mL) was refluxed for 1h. The solid product which produced on heating was collected and recrystallized to furnish **(17a)** and **(17b)**.

Compound (17a): Yellow crystals, m.p. = 240°C. IR/*v* (cm-^{1}) 3290 (NH), 2934 (aliph-CH), 1658 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.25-8.00 (m, 8H, Ar-H), 8.58 (s, 1H, chromene-H_4), 9.27, 13.12 (2s, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.57; N, 9.15. Found: C, 70.50; H, 4.50; N, 9.00.

Compound (17b): Beige crystals, m.p. = 250°C. IR/*v* (cm-^{1}) 3288 (NH), 2918 (aliph-CH), 1656 (C=O). ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.43-8.48 (m, 10H, Ar-H), 9.17 (s, 1H, chromene-H_4), 9.26, 13.15 (2s, 2NH; cancelled with a D_2O). Anal. Calc. for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.49; N, 7.85. Found: C, 74.00; H, 4.30; N, 7.70.
MS, m/z (%) = 356 [M+ 20.5], 222 (33.5), 195 (18.1), 139 (28.4) and 120(100, base peak).

N-(4-acetylphenyl)-2-oxo-2H-chromene-3-carboxamide (18a) and N-(4-acetylphenyl)-2-oxo-2H-benzo[f]chromene-3-carboxamide (18b)

A mixture of compound **(1)** (0.01 mole), appropriate aldehyde (salicylaldehyde or 2-hydroxy-naphthaldehyde; 0.01 mole) and sodium acetate (0.01 mole) was refluxed in acetic anhydride (30 mL) for 1h. The resulting solid was filtered off and recrystallized from the suitable solvent.

Compound (18a): Beige crystals, m.p. = 260°C. IR/*v* (cm-^{1}) 3100 (NH), 1702 (C=O; lactone). 1650 (C=O; amide) ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.45- 8.02 (m, 8H, Ar-H), 8.92 (s, 1H, chromene-H_4), 10.87 (s, NH; cancelled with a D_2O). Anal. Calc. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.23; N, 4.56. Found: C, 74.30; H, 4.20; N, 4.40.

Compound (18b): Brown crystals, m.p. = 270-272°C. IR/*v* (cm-^{1}) 3186 (NH), 1718 (C=O; lactone). 1668 (C=O; amide) ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.67- 8.69 (m, 10H, Ar-H), 9.56 (s, 1H, chromene-H_4), 10.95 (s, NH; cancelled with a D_2O). Anal. Calc. for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.20; N, 3.92. Found: C, 73.90; H, 4.10; N, 3.80.

1-(4-acetylphenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (20)

Equimolar amounts of **(1)** (0.01 mole) and acetyl acetone (0.01 mole) with a few drops of piperidine in an oil bath were refluxed for 1h at 160°C, then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **(20)**.

Compound (20): White solids, m.p. = 290°C. IR/*v* (cm-^{1}) 3060(arom- CH), 2214(C≡N). 1660 (C=O) ^{1}HNMR (DMSO-d_6): δ = 1.97, 2.37, 2.49 (3s, 9H, $3CH_3$), 6.48 (s, 1H, pyridine-H_5), 7.49, 8.13 (2d, 4H, Ar-H). Anal. Calc. for $C_{16}H_{14}N_2O_2$: C, 72.18; H, 5.26; N, 10.52. Found: C, 72.10; H, 5.10; N, 10.30.

2-(1-(4-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2H)yl)phenyl) ethylidene)hydrazinecarbothioamide (21)

Equimolar amounts of **(10)** (0.01 mole) and acetyl acetone (0.01 mole) with a few drops of piperidine in an oil bath were refluxed for 1h at 160°C, then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **(21)**.

Compound (21): Yellow crystals, m.p. = 250°C. IR/*v* (cm-^{1}) 3460, 3348, 3228 (NH/NH_2), 2222 (C≡N). 1648 (C=O) ^{1}HNMR (DMSO-d_6): δ = 1.98, 2.27, 2.49 (3s, 9H, $3CH_3$), 6.46 (s, 1H, pyridine-H_5), 7.31, 8.11 (2d, 4H, Ar-H), 8.02, 8.30, 10.26 (3s, 3H, 2NH & SH; exchangeable). Anal. Calc. for $C_{17}H_{17}N_5OS$: C, 60.17; H, 5.01; N, 20.64. Found: C, 60.00; H, 5.00; N, 20.50.

MS, m/z (%) = 339 [M+ 5.5], 322 (30.2), 250 (44.9), 224 (19.6),179 (9.4) and 76(100, base peak).

(E)-N-(4-acetylphenyl)-2-cyano-3-(4-methoxyphenyl)acrylamide (24) and N-(4-(1-(2-carbamothioylhydrazono) ethyl)-phenyl)-2-cya-no-3-(4-methoxyphenyl)acrylamide (27)

General procedure

A mixture of **(1)** or **(10)** (0.01 mole) and α-cyano-4-methoxycinnamonitryle (0.01 mole) in ethanol (30 mL) was treated with piperidine (0.5 mL) and the reaction mixture was refluxed for 3h. The solid product which produced on heating was filtered and recrystallized from the proper solvent to give **(24)** and **(27)** respectively.

Anther method

A mixture of compound **(1)** or **(10)** (0.01 mole), anisaldehyde (0.01 mole) and piperidine (0.5 mL) in ethanol (30 mL) was refluxed for 1h. The solid product which produced on heating was collected and recrystallized to furnish **(24)** and **(27)**.

Compound (24): Green crystals, m.p. = 180°C. IR/*v* (cm-^{1}) 3310(NH), 3012 (arom. CH), 2220 (C≡N). 1678 (C=O) ^{1}HNMR (DMSO-d_6): δ = 2.49 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.16- 8.05 (m, 8H, Ar-H), 8.24 (s, H, benzylidine-H). 10.56 (s, 1H, NH). Anal. Calc. for $C_{19}H_{16}N_2O_3$: C, 71.25; H, 5.00; N, 8.75. Found: C, 71.25; H, 4.90; N, 8.60.

Compound (27): Yellow crystals, m.p. = 250°C. IR/*v* (cm-^{1}) 3432, 3312 (NH/SH), 2214 (C≡N). 1674 (C=O) ^{1}HNMR (DMSO-d_6): δ = 2.29 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 7.31-8.04 (m, 8H, Ar-H), 8.22 (s, 3H, benzylidine-H), 10.16, 10.37 (2s, 4H, 3NH & SH; cancelled with a D_2O). Anal. Calc. for $C_{20}H_{19}N_5O_2S$: C, 61.06; H, 4.83; N, 14.81. Found: C, 61.00; H, 4.70; N, 17.50.

2-(1-(4-(6-amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxo-pyr-idin-1(2H)-yl)phenyl)ethylidene)hydrazine carbothioamide (28)

A mixture of **(9)** (0.01 mole) and α-cyano-4-chloro-cinnamonitryle (0.01 mole) in ethanol (30 mL) was treated with piperidine (0.5 mL) and the reaction mixture was refluxed for 3h. The solid product which produced on heating was filtered and recrystallized from the proper solvent to give **(28)**.

Compound (28): Yellow crystals, m.p. = 300°C. IR/*v* (cm-^{1}) 3318, 3278 (NH/NH_2), 2218 (C≡N). 1666 (C=O) ^{1}HNMR (DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 7.37-8.30 (m, 8H, Ar-H), 8.40 (br, 2H, NH_2; cancelled with a D_2O), 10.17, 10.29, 10.45 (3s, 3H, 2NH & SH; cancelled with a D_2O). Anal. Calc. for $C_{22}H_{16}N_7OSCl$: C, 57.20; H, 3.46; N, 21.23. Found: C, 57.10; H, 3.40; N, 21.10.

MS, m/z (%) = 387 [M-76(NH_2CSNH_2)], 167 (3.5), 146 (4.0), 118(13.4), 90 (21.3) and 59(100, base peak).

3-(4-acetylphenyl)-2-amino-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]pyridine-1-carbonitrile (30) and 3-(4-acetylphenyl)-2-hydroxy-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]-

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pyridine-1-carbonitrile (32)

A mixture of **(18a)** (0.01 mole), active methylene compound (namely, malononitrile, ethyl cyanoacetate,0.01 mole) and piperidine (0.01 mole) in ethanol (30 ml) was heated under reflux for 3h. The solid product which produced on heating was collected by filtration and recrystallized from the proper solvent.

Compound (30): Brown crystals, m.p. = 290°C. IR/*v* (cm-^{1}) 3438, 3316, 3184 (NH/NH_2), 2208 (C≡N). 1650 (C=O) ^{1}HNMR (DMSO-d_6): $\delta_=$ 2.49 (s, 3H, $COCH_3$), 7.51-7.58 (m, 8H, Ar-H), 7.79, 8.40 (2s, 3H, NH_2 & NH; cancelled with a D_2O). Anal. Calc. for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.78; N, 15.13. Found: C, 68.00; H, 3.70; N, 15.00.

Compound (32): Brown crystals, m.p. > 300°C. IR/*v* (cm-^{1}) 3404 (NH), 2208 (C≡N). 1656 (C=O) ^{1}HNMR (DMSO-d_6): $\delta_=$ 2.49 (s, 3H, $COCH_3$), 7.37-9.04 (m, 8H, Ar-H), 8.68 (br, 1H, OH; cancelled with a D_2O), 11.66 (s, H, NH; cancelled with a D_2O). Anal. Calc. for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.50; N, 11.32. Found: C, 67.80; H, 3.40; N, 11.20.

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