SOME REACTIONS OF *N*-(4-ACETYLPHENYL)-2-CYANOACETAMIDE WITH VARIOUS ELECTROPHILIC REAGENTS: SYNTHESIS OF THIAZOLIDINONES,3,5-DICYANO-6-AMINO-2-OXOPYRIDINE, 2-IMINO-2H-CHROMENE-3-CARBOXAMIDE AND 5-IMINO-3H-CHROMENO[3,4-C]PYRIDINE-1-CARBONITRILE DERIVATIVES

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Abstract

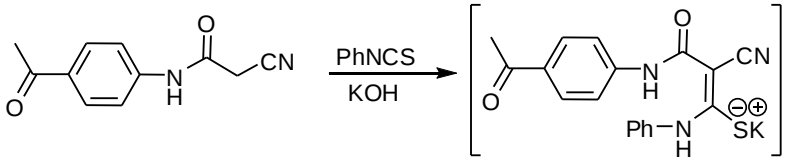
Reactions of N-(4-acetylphenyl)-2-cyanoacetamide (1) with several electrophilic reagents are reported. Thus, N-(4-acetylphenyl)-2-cyano-2-(3-phenylthiazol-2-ylidene)acetamide derivatives **4,5a-c** were obtained. 4,6-dimethyl-2-oxo-1-(4-acetylphenyl)-1,2-dihydropyridine-3-carbonitrile (**8**) and their thiosemicarbazone derivative (**9**) were synthesized. Treatment of **1** and its thiosemicarbazone derivative **6** with α-cyanocinnamonitrile **10a,b** under Michael reaction conditions afforded N-(4-acetylphenyl)-2-cyano-3-(4-methoxyphenyl)acrylamide (**12**) and 6-amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxo-pyridine derivative **15**, respectively. Condensation of **6** with α-halocarbonyl compounds gave 1,3-thiazole derivatives **16a,b & 17a,b** which on treatment of **16a, 17a** with salicyaldehyde gave 2-iminochromene derivatives **18** and **19**, respectively. Treatment of **1** with phenolic aldehydes yielded 2-iminochromenes **21a,b** which on treatment with ethanolic HCl gave chromene-2-one derivatives **22a,b**, respectively. Treatment of **21a** with malononitrile and/or ethyl cyanoacetate gave chromeno[3,4-c]pyridine derivatives **24** & **26**. IR, ^{1}HNMR and MS for the new synthesized compounds are cited.

Introduction

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[1-8]. As an extension of our efforts for the construction of biologically active heterocyclic derivatives[9-13], *N*-(4-acetylphenyl)-2-cyanoacetamide (**1**) is used in this article for the synthesis of interested biologically active thiazole derivatives[14-19]. Polyfunctionallized pyridine compounds[20-26], conjugated thiazole chromene moieties[27-35] and combined pyridine chromene nucleus[36-38]were obtained through the different chemical transformation reaction with varieties of electrophilic reagents under different reactions conditions.

Results and discussion

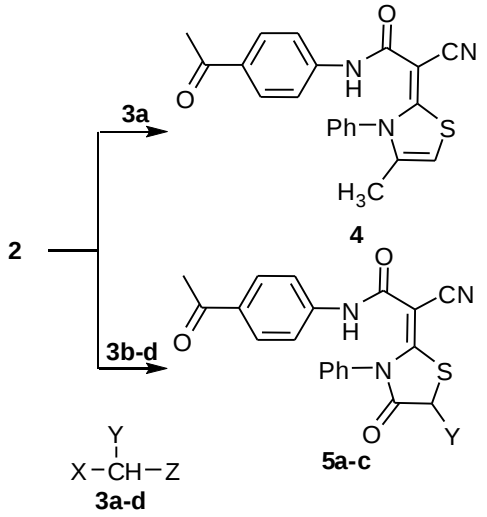
Reaction of cyanoacetamide derivative **1** with phenyl isothiocyanate in DMF in presence of potassium hydroxide, at room temperature gave non-isolable intermediate potassium sulphide salt **2**, Equation 1.



(1) **(2)**

Equation 1

Cyclocondensation of the intermediate **2** with chloroacetone (**3a)** at room temperature afforded the corresponding 4-methylthiazole derivative **4**, Scheme 1. Infrared 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 at δ = 6.98 ppm for thiazole H5. Also, treatment of intermediate **2** with respective α-halo ester **3b-d** at room temperature gave 4-thiazolidinone derivatives **5a-c**. The infrared spectrum of **5a** showed nitrile absorption bands at 2194 cm^{-1}, while its the mass spectrum was compatible with a molecular formula $C_{20}H_{15}N_3O_3S$ (M^+ = 377), ^{1}HNMR spectrum of **5a** revealed a singlet at δ 4.02 ppm corresponding to an the methylene group of thiazolidinone. The reaction may be assumed to proceed via initial alkylation followed by intramolecular cyclization with elimination of ethanol molecule.

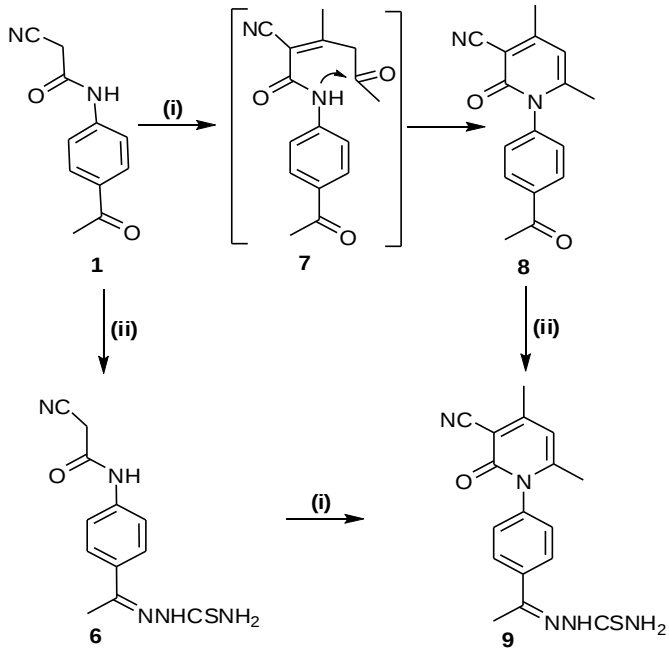


3a; X = Cl, Y = $COCH_3$, Z = H
3b; X = Cl, Y = CO_2Et, Z = H
3c; X = Br, Y = CH_3, Z = CO_2Et
3d; X = Br, Y = C_2H_5, Z = CO_2Et

5a; Y = H,
5b; Y = CH_3,
5c; Y = C_2H_5

Scheme **1**

Also, cyclocondensation of cyanoacetamide derivative **1** with acetylacetone furnished 4,6-dimethyl-2-oxo-1-(4-acetylphenyl)-1,2-dihydropyridine-3-carbonitrile (**8**) via intramolecular heterocyclization of the non isolable intermediate **7** by loss of a water molecule, Scheme 2. The ^{1}HNMR spectrum of **8** revealed signals at δ = 1.97, 2.37 and 2.49 ppm for two CH_3 and $COCH_3$ with a singlet at δ = 6.46 ppm for CH-pyridine. Simillarby, the reaction of compound 6 with ethyl chloroacetate (3b) and ethyl α-browopropionate (3c) resulted in the formation of 4-thiazolidinone derivatives 17a,b on the basis of the spectral data. Condensation of 4,6-dimethylpyridine derivative **8** with thiothemicarbazide produced pyridine-N-(4-acetylphenyl thiosemicarbazone) derivative **9**. This product was readily demonstrated on the basis of spectral data. Its infrared spectrum afforded bands at 3460, 3348, 3228 (NH_2/NH), 2222 cm^{-1} (C≡N). Mass spectrum of compound **9** exhibited a molecular ion peak at m/z = 339 (5.5%). The thiosemicarbazone derivative **9** could also be obtained in a good yield via the reaction of compound **6** with acetylacetone, Scheme 2.

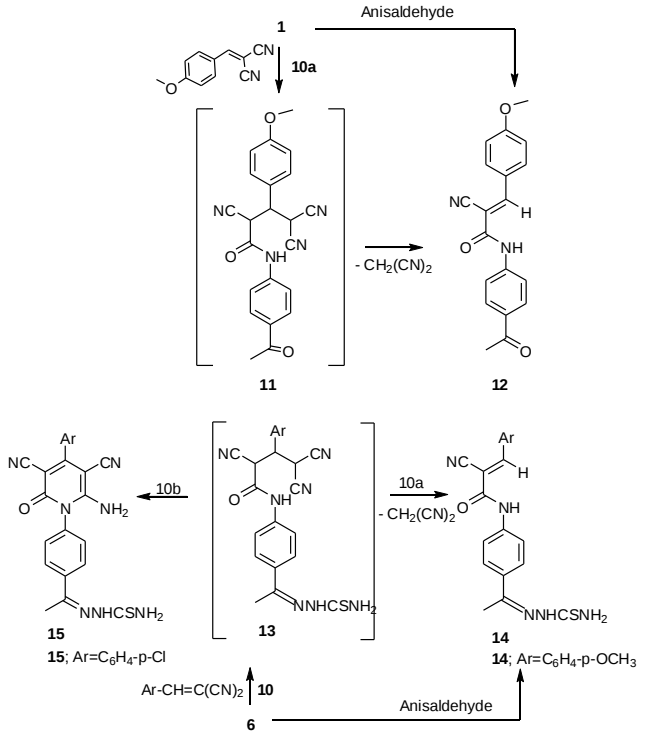


Method and reagents:(i) Acetylacetone/fusion,
(ii) Thiosemicarbazide/dioxan

Scheme **2**

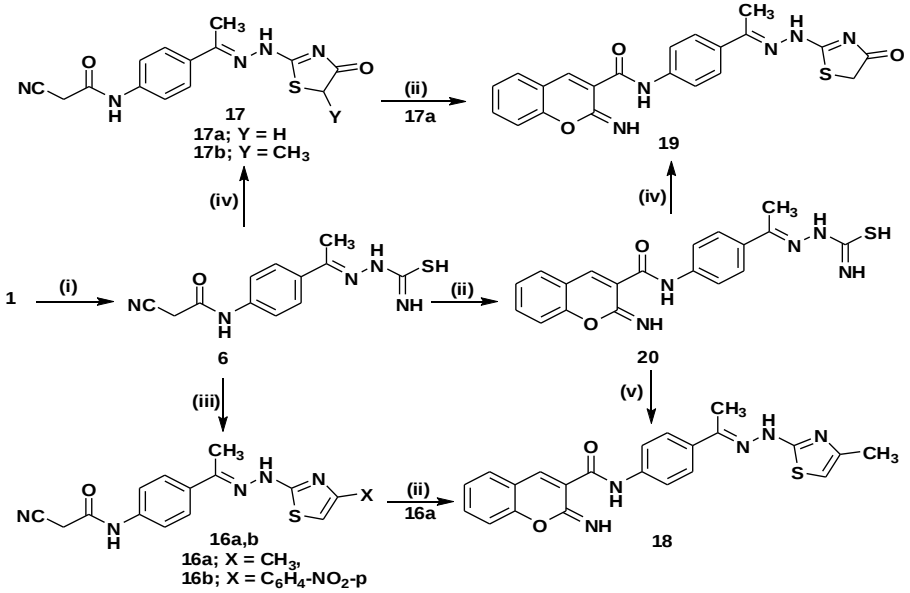
The reaction of cyanoacetamide derivative **1** with α-cyano-4-methoxycinnamonitrile (**10a**) in refluxing ethanol resulted in the formation of *N*-(4-

acetylphenyl)-2-cyano-3-(4-methoxyphenyl)acrylamide (**12**), Scheme 3. The ^{1}HNMR spectrum of **12** 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 together with a singlet at δ = 10.56 ppm for NH group. It seems that **12** was formed via Michael type addition of the methylene function in **1** to the activated double bond of **10a** to yield acyclic Michael adduct **11** which then spontaneously loses the malononitrile molecule. Further confirmation, compound **12** could also be obtained in good yield via the reaction of **1** with anisaldehyde. Similarly thiosemicarbazone derivative **6** reacted with α-cyano-4-methoxycinnamonitrile (**10a**) to give the acrylamide derivative **14** not the other possible pyridine derivative **15**. ^{1}HNMR spectrum of **14** revealed the presence of signals at δ = 3.87, 8.22 ppm for methoxy and CH-benzylidene protons, respectively. The proposed structure of **14** was also confirmed through its synthesis from condensation of thiosemicarbazone **6** with anisaldehyde. On the other hand, Michael addition of the methylene function of **6** to the activated double bond of α-cyano-4-chlorocinnnamonaitrile (**10b**) yielded acyclic Michael adduct **13** which on cyclization followed by aromatization gave pyridine type **15**. ^{1}HNMR of **15** revealed a signal at δ = 2.36 ppm (CH_3) and a D_2O exchangeable signals at 8.40, 10.17, 10.29 and 10.45 ppm due to NH_2, 2NH and SH functions. Mass spectrum of **15** exhibited peak at m/z 387 corresponding to (M-NH_2CSNH_2: 3.0%), Scheme 3.



Scheme 3

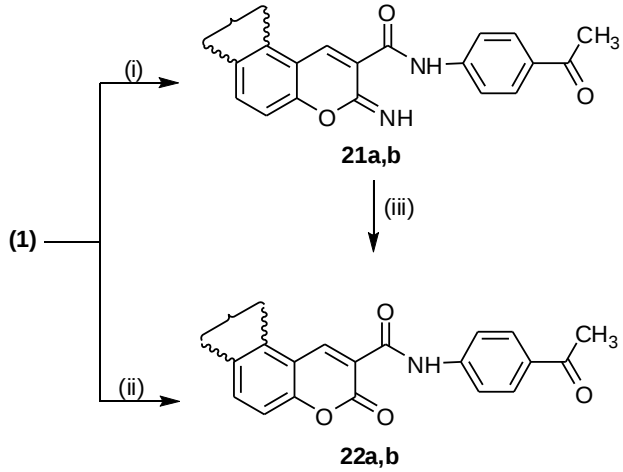
The reactivity of compound **6** toward some α-halocarbonyl compounds to afford some thiazole derivatives was investigated. Thus, condensation of **6** with chloroacetone (**3a**) and p-nitrophenacyl bromide (**3e**) in refluxing ethanol and in the presence of catalytic amount of fused sodium acetate resulted in the formation 1,3-thiazole derivative **16a,b**. The structure of the isolated compounds **16a,b** was confirmed on the basis of elemental analysis and spectral data. The ^{1}HNMR spectra of the isolated products, revealed in each case singlet at 7.71 ppm assigned for CH-thiazole. Cyclocondensation of thiazole derivatives **16a** and **17a** with salicylaldehyde in refluxing ethanol containing a catalytic amount of ammonium acetate resulted in the formation of 2-iminochromene derivatives **18** and **19**. The structures of **18** and **19** were established on the basis of their elemental analysis and spectral data. The ^{1}HNMR spectra of the isolated products revealed in each case a singlet for CH-chromene in the region 8.57-8.60 ppm, together with D_2O exchangeable signal in the region 9.25-12.89 ppm due to three NH functions (cf. Experimental part). Alternatively, products **18** and **19** could be obtained via an independent stepwise synthetic route involving the cyclocondensation of **6** with an equimolar amount of salicylaldehyde in the presence of a catalytic amount of ammium acetate to afford the corresponding chromene derivative **20**. The latter, in turn, reacted with chloroacetone (**3a**) and ethylchloroacetate (**3b**) to afford a single product in each case found to be identical with **18** and **19**, Scheme 4.



lii 3a or 3e EtOH/sod. Acetate; iv) 3b or 3c, EthO acaetate,
v) 3a, EtOH/Sod acetate; VI) 3c, EtOH/Sod acetate

Scheme **4**

Cyclocondensation of *N*-(4-acetylphenyl)-2-cyanoacetamide **(1)** with salicylaldehyde or 2-hydroxy-1-naphthaldehyde in refluxing ethanolic ammonium acetate furnished 2-iminochromene and 2-iminobenzo[f]chromene derivative **21a, b** (Scheme 5), ^{1}HNMR spectrum of **21a** revealed a singlet at δ 8.58 ppm assigned for CH-chromene with two singlets for 2NH groups at δ 9.27, 13.12 ppm (disappeared after addition of D_2O). The mass spectrum of **21b** exhibited a molecular ion peak at m/z 356 (20.5%) together with the base peak at m/z 120. On the other hand, cyclocondensation of **1** with salicylaldehyde or 2-hydroxy-1-naphthaldehyde in refluxing acetic anhydride containing catalytic amounts of sodium acetate, yielded chromene-2-one derivatives **22a, b**. Infrared spectrum of **22a** afforded absorption bands at 3100 and 1702 cm^{-1} corresponding to amide NH and carbonyl groups, respectively. The ^{1}HNMR (DMSO-d_6) of **22a** showed a singlet at δ 8.92 ppm (CH-chromene) and 10.87 ppm (NH). The structure of the latter compound **22** further confirmed by another route of preparation via the hydrolysis of 2-iminochromene derivative **21** with ethanolic HCl under reflux condition, Scheme 5. (cf. Experimental part).

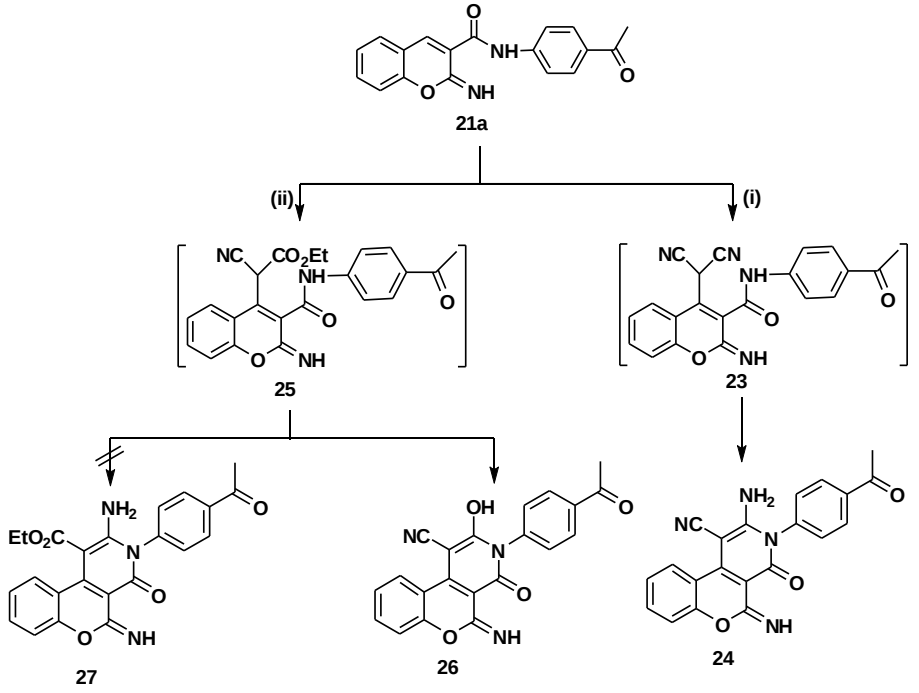


Method and reagents: (i) salicylaldehyde and/or 2-hydroxynaphthaldehyde, EtOH/amm.acetate, (ii) salicylaldehyde and/or 2-hydroxynaphthaldehyde, acetic anhydride/sod. acetate, (iii) EtOH/HCl

Scheme **5**

The resulting chromene derivative **21a** 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 **21a** with malononitrile under reflux in dioxane in the presence of piperidine afforded the novel chromeno[3,4-c]pyridine derivative **24**. The molecular structure of **24** was established through analytical and spectral data. Its infrared spectrum showed absorption bands at 3438, 3316 and 2208 and 1650 cm^{-1} due to amino, cyano and carbonyl function groups, respectively. Also, ^{1}HNMR spectrum showed the appearance of a D_2O exchangeable signals at δ = 7.79 and 8.40 ppm due to the amino and imino functions. Compound 24 may be assumed to proceed via the formation of Michael type adduct **23** which cyclize and aromatize under reaction condition. Finally, chromeno[3,4-c]pyridine derivative **26** was achieved by reaction of 2-iminochromene derivative **21a** with ethyl cyanoacetate and the other possible structure **27** was excluded on the basis of elemental analysis and spectral data. Its IR spectrum revealed the presence of hydroxyl, nitrile and the carbonyl functional, and its ^{1}HNMR spectrum showed signals at δ = 8.68 and 11.66 ppm assigned to OH and NH groups (cancelled with D_2O). It can be postulated that the reaction initially proceeds via the formation of Michael type adduct **25** that subsequently cyclize through elimination of ethanol, Scheme 6.



Method and reagents: (i)malononitrile,dioxane/pipredine, (ii)ethylcyanoacetate,dioxane/pipredine

Scheme **6**

Experimental

All melting points are uncorrected. IR spectra (KBr) were measured on Shimadzu 440 spectrometer, ^{1}H NMR spectra were obtained in DMSO on a Varian Gemini 200 MHz spectrometer using TMS as internal standard; chemical shifts are reported as (ppm). Mass spectra were obtained on GCMS\QP 1000 Ex mass spectrometer at 70 ev. Elemental analyses were carried out at the Microanalytical Center, Faculty of Science (Cairo University, Egypt).

Preparation of compounds 4, 5a-c: General procedure*:* A mixture of compound **1** (0.01 mole), appropriate α-halo compounds namely (chloroacetone **3a,** ethylchloroacetate **3b**, ethyl α-bromopropionate **3c**, ethyl α-bromobutyrate **3d**) (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.

N-(4-Acetylphenyl)-2-cyano-2-(4-methyl-3-phenylthiazol-2(3H)ylidene) acetamide (4)

Yield (70%); White solid (Acetic acid); Mp 230-232C°; IR (KBr): $\overline{\nu}$ = 3460 (NH), 2176 (C≡N), 1672 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ =1.86 (s, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 6.98 (s, 1H, thiazole-H5), 7.50-7.86 (m, 9H, Ar-H), 9.03 (s, 1H, NH; exchange). Anal. Calc. for $C_{21}H_{17}N_3O_2S$: C, 67.20; H, 4.53; N, 11.20. Found: C, 67.05; H, 4.40; N, 11.07.

N-(4-Acetylphenyl)-2-cyano-2-(4-oxo-3-phenylthiazolidin-2-ylidene)-acetamide (5a)

Yield (75%); White solid (Dioxane); Mp 240-243C°; IR (KBr): $\overline{\nu}$ = 3334 (NH), 2194 (C≡N), 1748 (C=O; thiazolidinone), 1674 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, 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; exchange). Anal. Calc. for $C_{20}H_{15}N_3O_3S$: C, 63.66; H, 3.97; N, 11.14. Found: C, 63.49; H, 3.67; N, 10.92.

MS (EI): m/z (%) = 377 (M+ 15.6), 243 (29.4), 215 (72.1), 132 (28.4) and 77(100, base peak).

N-(4-Acetylphenyl)-2-cyano-2-(5-methyl-4-oxo-3-phenylthiazolidin-2-ylidene)acetamide (5b)

Yield (65%); Beige solid (Dioxane); Mp 235-237C°; IR (KBr): $\overline{\nu}$ = 3360 (NH), 2926 (aliph.CH), 2194 (C≡N), 1728 (C=O; thiazolidinone), 1670 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 1.61 (d, 3H, CH_3), 2.49 (s, 3H, $COCH_3$), 4.28 (q, 1H, thiazoldinone-H5), 7.45-7.91 (m, 9H, Ar-H), 9.77 (s, 1H, NH; exchange). Anal. Calc. for $C_{21}H_{17}N_3O_3S$: C, 64.45; H, 4.34; N, 10.74. Found: C, 64.24; H, 4.08; N, 10.45.

***N*-(4-Acetylphenyl)-2-cyano-2-(5-ethyl-4-oxo-3-phenylthiazolidin-2-ylidene)acetamide (5c)**

Yield (65%); Beige solid (Dioxane); Mp 243-245C°; IR (KBr): $\overline{\nu}$ = 3400 (NH), 2950 (aliph.CH), 2198 (C≡N), 1740 (C=O; thiazolidinone), 1666 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, 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, thiazoli-dinone-H5), 7.41-7.91 (m, 9H, Ar-H), 9.78(s, 1H, NH; exchange). Anal. Calc. for $C_{22}H_{19}N_3O_3S$: C, 65.18; H, 4.69; N, 10.37. Found: C, 64.95; H, 4.49; N, 10.12.

***2*-(1-(4-(2-Cyanoacetamido)phenyl)ethylidene) hydrazinecarbimidothioic acid (6)**

A mixture of compound 1 (0.01 mole), thiosemicarbazide; 0.01 mole) in dioxane (30 mL) was refluxed for 3h. The resulting solid was filtered off and recrystallized from acetic acid as yellow solid; Yield (85%); Mp 215-217°C; IR (KBr): $\overline{\nu}$ = 3390, 3260 (SH, NH), 2966 (aliph.CH), 2260 (C≡N), 1702 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 3.91 (s, 2H, CH_2), 7.54-7.93 (m, 5H, Ar-H and NH; exchange). 8.22, 10.14 and 10.39 (3s, 3H, 2NH & SH; exchange). Anal. Calc. for $C_{12}H_{13}N_5OS$: C, 52.36; H, 4.72; N, 25.45. Found: C, 52.16; H, 4.49; N, 25.27.

***1*-(4-Acetylphenyl)-4,6-dimethyl-2-oxo-1,2-dihydropyridine-3-carbonitrile (8)**

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 **8**.

Yield (55%); White solids; Mp 290-292C°; IR (KBr): $\overline{\nu}$ = 3060 (arom-CH), 2214(C≡N). 1660 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 1.97, 2.37, 2.49 (3s, 9H, $3CH_3$), 6.46 (s, 1H, pyridine-H5), 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, 72.05; H, 5.10; N, 10.30.

***2*-(1-(4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)yl)phenyl)ethylidene)hydrazinecarbothioamide (9)**

Method A: Equimolar amounts of **6** (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 **9**.

Method B: Equimolar amounts of **8** (0.1 mole) and thiosemicarbazide (0.1 mole) were refluxed in dioxane (30 mL) for 3h and then allowed to cool. The solid product was collected and recrystallized from acetic acid to give **9**.

Yield (80%);Yellow crystals; Mp 250-252C°; IR (KBr): $\overline{\nu}$ = 3460, 3348, 3228 (NH/NH_2), 2222 (C≡N), 1648 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 1.98, 2.27, 2.49 (3s, 9H, $3CH_3$), 6.46 (s, 1H, pyridine-H5), 7.31, 8.11 (2d, 4H, Ar-H), 8.02, 8.30, 10.26 (3s, 3H, 2NH & SH; exchange). Anal. Calc. for $C_{17}H_{17}N_5OS$: C, 60.17; H, 5.01; N, 20.64. Found: C, 59.95; H, 4.85; N, 20.40.

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

***Preparation of compounds 12 and 14: General procedure**:*

Method A: Amixture of **1** and/or **6** (0.01 mole) and α-cyano-4-methoxycinnamonitrile (**10**a) (0.01mole) 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 off and recrystallized from the proper solvent to give **12** and **14** respectively.

Method B: A mixture of compound **1** and/or **6** (0.01 mole), anisaldehyd (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 **12** and **14**.

N-(4-acetylphenyl)-2-cyano-3-(4-methoxyphenyl)acrylamide(12)

Yield (50%); Green crystals (Dioxane); Mp 180-182°C; IR (KBr): $\overline{\nu}$ = 3310(NH), 3012 (arom.CH), 2220 (C≡N). 1678 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, 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, 71.05; H, 4.82; N, 8.55.

N-(4-(1-(2-Carbamothioylhydrazono)ethyl)phenyl)-2-cyano-3-(4-methoxyphenyl) acrylamide (14)

Yield (65%); Yellow crystals; Mp 250-252C°; IR (KBr): $\overline{\nu}$ = 3432, 3312 (NH/SH), 2214 (C≡N). 1674 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, 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; exchange). Anal. Calc. for $C_{20}H_{19}N_5O_2S$: C, 61.06; H, 4.83; N, 17.81. Found: C, 60.94; H, 4.68; N, 17.50.

2-(1-(4-(6-Amino-4-(4-chlorophenyl)-3,5-dicyano-2-oxo-pyridin-1(2H)yl)phenyl)ethylidene)hydrazinecarbothioamide (15)

A mixture of **6** (0.01 mole) and α-cyano-4-chlorocinnamonitrile **10b** (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 dioxane to give **15**.

Yield (56%); Yellow crystals; Mp 300-302C°; IR (KBr): $\overline{\nu}$ = 3318, 3278 (NH/NH_2), 2218 (C≡N). 1666 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.36 (s, 3H, CH_3), 7.37-8.30 (m, 8H, Ar-H), 8.40 (br, 2H, NH_2; exchange), 10.17, 10.29, 10.45 (3s, 3H, 2NH & SH; exchange). Anal. Calc. for $C_{22}H_{16}N_7OSCl$: C, 57.20; H, 3.46; N, 21.23. Found: C, 57.03; H, 3.22; N, 21.00.

MS (EI): 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).

Preparation of compounds 16a, b and 17a, b: General procedure*:* A mixture of compound **6** (0.01 mole), appropriate α-halo compound namely (chloroacetone **3a** and p-nitrophenacyl bromide **3e**, ethyl chloroacetate **3b** and ethy1-α-bromopropionate **3c**) (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.

2-Cyano-N-(4-(1-(2-(4-methylthiazol-2-yl) hydrazono) methyl) phenyl) acetamide (16a)

Yield (65%); Yellow crystals (Acetic acid); Mp 210-212°C; IR (KBr): $\overline{\nu}$ = 3108 (NH), 2198 (C≡N), 1694 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, 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; exchange), 7.65-7.87 (2d, 5H, Ar-H & thiazole-H5). MS (EI): m/z (%) = 313 (M^+ 64.4), 298 (16.4), 159 (11.0), 119 (39.7) and 65 (100, base peak). Anal. Calc. for $C_{15}H_{15}N_5OS$: C, 57.50; H, 4.79; N, 22.36. Found: C, 57.32; H, 4.52; N, 22.15.

2-Cyano-N-(4-(1-(2-(4-(4-nitrophenyl)thiazol-2-yl)hydrazono)ethyl)phenyl)acetamide (16b)

Yield (60%); Brown crystals (dioxane); Mp 270-270 C°; IR (KBr): $\overline{\nu}$ = 3316 (NH), 3088 (arom. CH), 2260 (C≡N), 1678 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, 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-H5). 10.45 (s, 1H, NH; exchange). MS (EI): m/z (%) = 420 (M^+ 30.3), 354 (18.4), 249 (72.1), 132 (15.4) and 65(100, base peak). Anal. Calc. for $C_{20}H_{16}N_6O_3S$: C, 57.14; H, 3.80; N, 20.00. Found: C, 56.95; H, 3.59; N, 19.85.

2-Cyano-N-(4-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)phenyl) acetamide (17a)

Yield (70%); Beige crystals (Benzene); Mp 245-247C°; IR (KBr): $\overline{\nu}$ = 3276 (NH), 2992 (aliph. CH), 2260 (C≡N), 1712 (C=O; thiazolidinone), 1682 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, 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; exchange). Anal. Calc. for $C_{14}H_{13}N_5O_2S$: C, 53.33; H, 4.12; N, 22.22. Found: C, 53.13; H, 3.98; N, 22.00.

2-Cyano-N-(4-(1-(2-(5-methyl-4-oxo-4,5-dihydrothiazol-2-yl)hydrazo-no)ethyl)phenyl)acetamide (17b)

Yield (63%); White crystals (Acetic acid); Mp 250-252 C°; IR (KBr): $\overline{\nu}$ = 3260 (NH), 2948 (aliph. CH), 2262 (C≡N), 1726 (C=O; thiazoli-dinone), 1676 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, 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-H5), 7.59, 7.81 (2d, 4H, Ar-H), 10.44, 11.87 (2s, 2H, 2NH; exchange). Anal. Calc. for $C_{15}H_{15}N_5O_2S$: C, 54.71; H, 4.55; N, 21.27. Found: C, 54.56; H, 4.38; N, 21.10.

Preparation of compounds 18 and 19: General procedure*:* A mixture of compound **16a** and/or **17a** (0.01 mole), salicylaldehyde (0.01 mole) and piperidine (0.5 mL) in dimethylformamide (30 mL) was refluxed for 3h. The resulting products which produced were collected and recrystallized from the proper solvents.

2-Imino-N-(4-(1-(2-(4-methylthiazol-2-yl)hydrazono)ethyl)phenyl)2H-chromene-3-carboxamide (18)

Yield (73%); Yellow crystals (Acetic acid); Mp 300-302C°; IR (KBr): $\overline{\nu}$ = 3186 (NH), 2980 (aliph. CH), 1680 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.16, 2.27 (2s, 6H, $2CH_3$), 6.31 (s, 1H, thiazole-H5), 7.25- 7.81 (m, 8H, Ar-H), 8.57 (s, 1H, chromene-H4), 9.25, 12.89 (2s, 2H 2NH; exchange), 11.40 (br, 1H, NH;

exchange). Anal. Calc. for $C_{22}H_{19}N_5O_2S$: C, 63.30; H, 4.55; N, 16.78. Found: C, 63.12; H, 4.38; N, 16.44.

2-Imino-N-(4-(1-(2-(4-oxo-4,5-dihydrothiazol-2-yl)hydrazono)ethyl)-phenyl)-2H-chromene-3-carboxamide(19)

Yield (67%); Brown crystals (Dioxane); Mp 270-272C°; IR (KBr): $\overline{\nu}$ = 3170 (NH), 2988 (aliph. CH), 1685 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.27 (s, H, CH3), 4.10 (s, 2H, CH_2), 7.20- 7.90 (m, 8H, Ar-H), 8.60 (s, 1H, chromene-H4), 9.30, 11.40, 12.40 (3s, 3NH; exchange). Anal. Calc. for $C_{21}H_{17}N_5O_3S$: C, 60.14; H, 4.05; N, 16.70. Found: C, 59.87; H, 3.80; N, 16.52.

MS (EI): 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).

2-(1-(4-(2-Imino-2H-chromene-3-carboxamido)phenyl)ethylidene)hydrazinecarbimidothioic acid (20)

A mixture of compound **6** (0.01 mole), salicylaldehyde (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 from dioxane to furnish **20**

Yield (70%); Yellow crystals (Acetic acid); Mp 260-262C°; IR (KBr): $\overline{\nu}$ = 3216 (NH), 2968 (aliph-CH), 1682 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.27 (s, 3H, CH_3), 7.25-7.98 (m, 8H, Ar-H), 8.23 (s, 1H, chromene-H4), 8.57, 9.24, 10.15, 12.91 (4s, 4H, 3NH & SH; exchange). Anal. Calc. for $C_{19}H_{17}N_5O_2S$: C, 60.15; H, 4.48; N, 18.46. Found: C, 59.92; H, 4.30; N, 18.27.

MS (EI): m/z (%) = 379 (M^+ 5.5), 363 (9.4), 265 (12.3), 223 (19.0), 172 (71.0) and 118 (100, base peak).

Preparation of compounds 21a,b: General procedure:

A mixture of compound **1** (0.01 mole), appropriate phenolic 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 **21a** and 22**b**.

***N*-(4-Acetylphenyl)-2-imino-2H-chromene-3-carboxamide (21a)**

Yield (80%); Yellow crystals (Dioxane); Mp 240-242C°; IR (KBr): $\overline{\nu}$ = 3290 (NH), 2934 (aliph-CH), 1658 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49

(s, 3H, $COCH_3$), 7.25- 8.00 (m, 8H, Ar-H), 8.58 (s, 1H, chromene-H4), 9.27, 13.12 (2s, 2NH; exchange). Anal. Calc. for $C_{18}H_{14}N_2O_3$: C, 70.58; H, 4.57; N, 9.15. Found: C, 70.45; H, 4.32; N, 9.00.

***N*-(4-Acetylphenyl)-3-imino-3H-benzo[f]chromene-2-carboxamide (21b)**

yield (70%); Beige crystals (Methanol); Mp 250-252C°; IR (KBr): $\overline{\nu}$ = 3288 (NH), 2918 (aliph-CH), 1656 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.43- 8.48 (m, 10H, Ar-H), 9.17 (s, 1H, chromene-H4), 9.26, 13.15 (2s, 2NH; exchange). Anal. Calc. for $C_{22}H_{16}N_2O_3$: C, 74.15; H, 4.49; N, 7.85. Found: C, 73.95; H, 4.29; N, 7.60.

MS (EI): m/z (%) = 356 (M^+ 20.5), 222 (33.5), 195 (18.1), 139 (28.4) and 120 (100, base peak).

Preparation of compounds 22a,b: General procedure: A mixture of compound 1 (0.01 mole), appropriate aldehyde (salicylaldehyde or 2-hydroxynaphthaldehyde; 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 dioxane.

***N*-(4-Acetylphenyl)-2-oxo-2H-chromene-3-carboxamide (22a)**

yield (55%); Beige crystals; Mp 260-262 C°; IR (KBr): $\overline{\nu}$ = 3100 (NH), 1702 (C=O; lactone), 1650 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.45- 8.02 (m, 8H, Ar-H), 8.92 (s, 1H, chromene-H4), 10.87 (s, NH; exchange). Anal. Calc. for $C_{18}H_{13}NO_4$: C, 70.35; H, 4.23; N, 4.56. Found: C, 70.15; H, 4.13; N, 4.40.

***N*-(4-Acetylphenyl)-2-oxo-2H-benzo[f]chromene-3-carboxamide (22b)**

yield (55%); Brown crystals; Mp 270-272C°; IR (KBr): $\overline{\nu}$ = 3186 (NH), 1718 (C=O; lactone). 1668 (C=O; amide) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.67- 8.69 (m, 10H, Ar-H), 9.56 (s, 1H, chromene-H4), 10.95 (s, 1H, NH; exchange). Anal. Calc. for $C_{22}H_{15}NO_4$: C, 73.94; H, 4.20; N, 3.92. Found: C, 73.75; H, 4.05; N, 3.70.

Preparation of compounds 24 and 26: General procedure: A mixture of **21a** (0.01 mole), active methylene compounds (namely, malononitrile, ethyl cyanoacetate) (0.01 mole) and piperidine (0.5 mL) in dioxane (30 mL) was heated under reflux for 3h. The solid product which produced on heating was collected by filtration and recrystallized from acetic acid.

3-(4-Acetylphenyl)-2-amino-5-imino-4-oxo-4,5-dihydro-3H-chromeno-[3,4-c]pyridine-1-carbonitrile (24)

Yield (55%); Brown crystals; Mp 290-292C°; IR (KBr): v = 3438, 3316, 3184 (NH/NH_2), 2208 (C≡N) 1650 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.51-7.58 (m, 8H, Ar-H), 7.79, 8.40 (2s, 3H, NH_2 & NH; exchange). Anal. Calc. for $C_{21}H_{14}N_4O_3$: C, 68.10; H, 3.78; N, 15.13. Found: C, 67.90; H, 3.64; N, 14.95.

3-(4-Acetylphenyl)-2-hydroxy-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]pyridine-1-carbonitrile (26)

Yield (60%); Brown crystals; Mp 340-342C°; IR (KBr): v = 3404 (NH/OH), 2208 (C≡N). 1656 (C=O) cm^{-1}; ^{1}HNMR (200 MHz, DMSO-d_6): δ = 2.49 (s, 3H, $COCH_3$), 7.37-9.04 (m, 8H, Ar-H), 8.68 (br, 1H, OH; exchange), 11.66 (s, H, NH; exchange). Anal. Calc. for $C_{21}H_{13}N_3O_4$: C, 67.92; H, 3.50; N, 11.32. Found: C, 67.65; H, 3.25; N, 11.12.

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