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1st Heterocyclic Update

Cyanoacetanilides intermediates in heterocyclic synthesis. Part 6: Preparation of some hitherto unknown 2-oxopyridine, bipyridine, isoquinoline and chromeno[3,4-*c*]pyridine containing sulfonamide moiety

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Abstract Treatment of cyanoacetanilide derivative **1** with tetracyanoethylene (**2**) in dioxane/triethylamine furnished 2-pyridone derivative **6**. Aminopyridine **9** was obtained by cyclization of compound **1** with ketene dithioacetal **7**/EtONa. Cyclocondensation of **1** with malononitrile and/or acetylacetone (1:1 M ratio) gave pyridine derivatives **11** and **13**. Ternary condensation of compound **1**, aliphatic aldehydes and malononitrile (1:1:1 M ratio) yielded the 2-pyridones **20a** and **b**. Bipyridines **22a–c** were prepared by refluxing of compound **21** with active methylene reagents. Cyclization of chromene derivatives **24** and **28** with malononitrile produced the novel chromeno[3,4-*c*]pyridine **26** and pyrano[3′,2′:6,7]chromeno[3,4-*c*]pyridine **29**.

1. Introduction

Among the wide variety of heterocycles that have been explored developing pharmaceutically important molecules like pyridines, cyano-pyridines have played an important role in the heterocyclic chemistry. Pyridine derivatives have occupied a unique position in medicinal chemistry. The naturally occurring B6-vitamins (Dawane et al., 2010) pyridoxine, pyrodoxal, pyridoxamine, and codecarbaxylase contain a pyridine nucleus. In addition to this, many naturally occurring and

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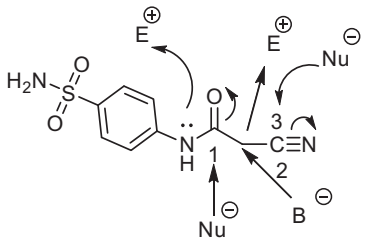
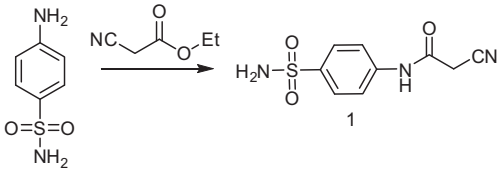


Figure 1 Reactivity of cyanoacetanilide **1**.



Scheme 1 Synthesis of cyanoacetanilide **1**.

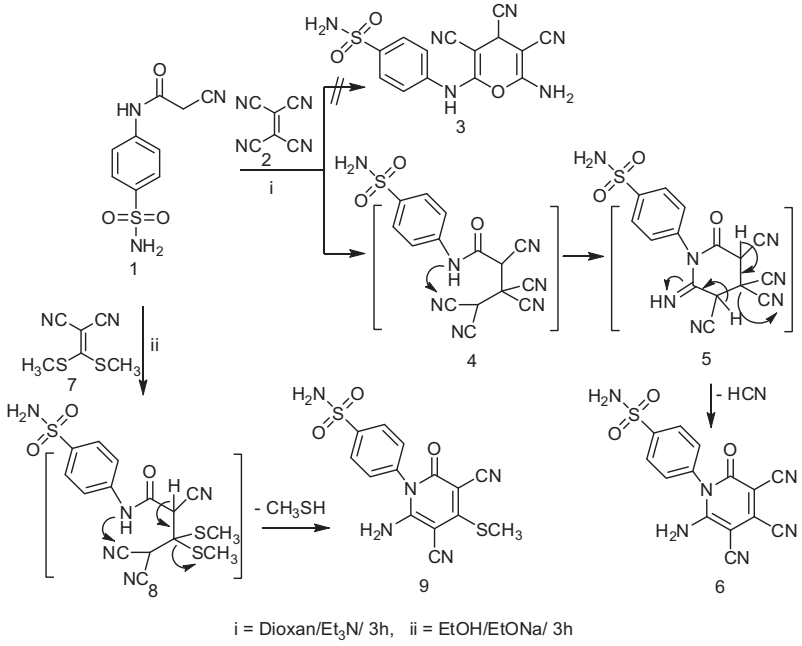
synthetic compounds containing the pyridine scaffold possess interesting pharmacological properties (Temple and Rener, 1992; Konda and Khedkar, 2010; Hossan et al., 2012). Among them, 2-amino-3-cyanopyridines have been identified as IKK-β inhibitors (Murata et al., 2003). The synthesis of 2-pyridone derivatives is of continued interest in the field of heterocyclic chemistry. Topical reviews have appeared in the literature over the last years about the synthesis of the 2-pyridone ring (Pemberton et al., 2006; Ciufolini and Chan, 2007). These heterocycles attracted attention because of their applications as bioactive compounds for example as a promising class of HIV-1 non-nucleoside reverse transcriptase inhibitors (NNRTIs) (Medina-Franco et al., 2007; Bernardino et al., 2006), as antibacterial (Suksrichavalit, 2009) antifungal (Leal and Rodrigues, 2008), anticancer agents (Romagnoli et al., 2008) and anticonvulsant agents (Farag et al., 2012). Moreover, such derivatives have recently become important due to their structural similarity to nucleosides (Yang et al., 2006; Rajeswaran and Srikrishnan, 2008). Also, sulphanilamide effectiveness extends to acute chronic Gram negative and Gram positive infections. For example, sulfapyridine (*N*1-2-pyridylsulfanilamide) is a chemotherapeutic agent for the treatment of pneumococcal and other bacterial infections. It is also used for bronchopneumonia and upper respiratory infections, even though currently it has been largely supplanted by sulfadiazine and sulfamerazine due to its high toxicity (El-Salam et al., 2005). Application of *N*-substituted cyanoacetamides as CH-acids (Dyachenko et al., 2008) allows introduction of an additional diversity point into the final 2-pyridone molecule via the amide group (Gorobets et al., 2004) or, depending on the reaction conditions, leads to *N*1-substituted 3-cyano-2-pyridones (Yermolayev et al., 2009). Cyanoacetanilide derivatives are important and versatile reagents, which have especially been used for the synthesis of polyfunctionalized three-, five- and six-membered rings and condensed heterocycles (Fadda et al., 2008; Dyachenko et al., 2008). Cyanoacetanilides are poly-functional compounds that possess both electrophilic and nucleophilic properties (Fadda et al., 2012). Two nucleophilic centers in cyanoacteanilides are localized on NH and C-2. Also, cyanoacetanilides possess two electrophilic positions (Dyachenko et al., 2008), which are associated with C-1 and C-3 (Fig. 1). In view of the above observations and in continuation of our program on the chemistry of cyanoacetanilide derivatives (Ammar et al., 2005a,b, 2008, 2011, 2006, 2009, 2013; Salem, 2009; Salem et al., 2011; Helal et al., 2013), we report herein the synthesis of the versatile hitherto unknown 2-pyridone, bipyridine, isoquinoline and chromeno-[3,4-*c*]pyridine derivatives containing sulfonamide moiety from the readily accessible cyanoaceta-nilide derivative **1**.

2. Results and discussion

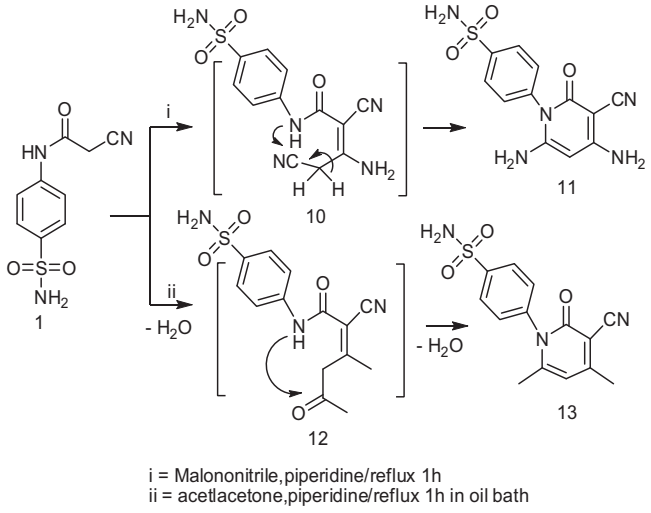
The key intermediate, 2-cyano-*N*-(4-sulfamoylphenyl)-acetamide **1** (Ammar et al., 2008) was prepared in high yield (92%) by the reaction of sulfanilamide with ethyl cyanoacetate in refluxing *m*-xylene (Scheme 1).

The active methylene in the cyanoacetanilide **1** underwent nucleophilic addition reaction to the double bond of tetracyanoethylene (TCNE) (**2**) via a Michael type addition reaction, by refluxing in dioxane containing few drops of triethylamine where a substance its structure should be either **3** or **6** was produced. The actual structure of the product was assigned as 4-(6-Amino-3,4,5-tricyano-2-oxopyridin-1(2*H*)-yl)-benzenesulfonamide **6** based on its ^{1}HNMR spectroscopic data which showed two NH_2 signals and was devoid of an imino group signal which should appear if the reaction product was **3**. Moreover **3** was excluded as reaction product since the ^{1}HNMR lacked the pyran H-4 signal which should appear at approximately δ = 4–5 ppm (Scheme 2). The structure of compound **6** was established on the basis of its elemental analysis and spectral data. Its infrared spectrum revealed absorption bands at 3320, 3306, 2222 and 1682 cm^{-1} due to amino, nitrile and carbonyl function groups, respectively. Also, its mass spectrum showed a molecular ion peak at *m*/*z* 340 (10.1%) which is characteristic for the molecular formula $C_{14}H_8N_6O_3S$ together with base peak at *m*/*z* 55. In a similar manner, cyclization of compound **1** with bis(methylsulfanyl)-methylene malononitrile (**7**) by refluxing in ethanol in the presence of sodium ethoxide furnished the 4-(6-amino-3,5-dicyano-4-(methylthio)-2-oxopyridin-1(2*H*)-yl)benzenesulfonamide **9**. The molecular structure of **9** was confirmed on the basis of its analytical and spectral data. The infrared spectrum of the isolated product showed characteristic bands at 3322, 3208, 2212 and 1652 cm^{-1} assigned for amino, nitrile and carbonyl function groups, respectively. The ^{1}HNMR spectrum (DMSO-d_6) revealed absorption at δ = 2.84 ppm attributed for methylsulfanyl protons in addition to two amino and aromatic protons. The formation of **9** is assumed to proceed via an intramolecular cyclization of the non-isolable Michael adduct **8** and loss of methyl mercaptan (Ammar et al., 2006) (Scheme 2).

The reactivity of **1** toward some active methylene reagents was investigated. Thus, compound **1** reacted with malononitrile (1:1 M ratio) in an oil bath at 160 °C to yield a single product that was identified as 4-(4,6-diamino-5-cyano-2-oxopyridin-1(2*H*)-yl)benzenesulfonamide **11** on the basis of its elemental analysis and spectral data. Its mass spectrum showed a molecular ion peak at *m*/*z* 305 (9.26%) together with base peak at *m*/*z* 65. The formation of **11** is assumed to proceed via the Michael addition of **1** to cyano function group of malononitrile to form the acyclic Michael adduct **10** followed by in situ cyclization to the pyridine skeleton, Scheme 3. Cyclocondensation of com-



Scheme 2 Synthesis of 2-pyridone derivatives **6** and **9**.

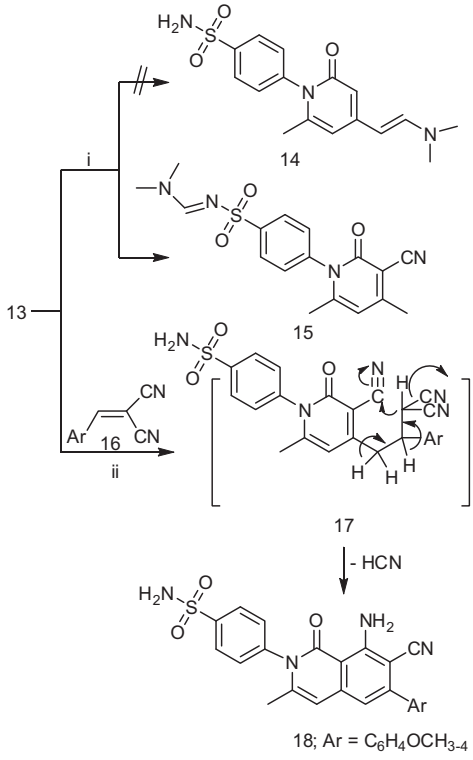


Scheme 3 Synthesis of 4,6-disubstituted-2-pyridone derivatives **11** and **13**.

pound **1** with acetylacetone furnished 4-(3-cyano-4,6-dimethyl-2-oxopyridin-1(2*H*)-yl)benzenesulfonamide **13**, via intramolecular hetero-cyclization of the non-isolable intermediate **12** by loss of water (Ammar et al., 2005a) (Scheme 3).

The reaction of compound **13** with some electrophilic reagents was examined. Condensation of compound **13** with dimethylformamide-dimethylacetal (DMF-DMA) at reflux temperature in *m*-xylene afforded *N,N*-dimethylaminomethylene derivative **15** rather than the expected product **14** based on the elemental and spectral analyses of the isolated product. The infrared spectrum showed no absorption due to the amino function group. Also, the ^{1}HNMR spectrum of compound **15** revealed a singlet at $\delta = 3.18$ ppm due to $N(CH_3)_2$ in addition to the two methyl, methine and aromatic protons. Cyclocondensation of compound **13** with 2-(4-methoxybenzylidene)malononitrile **16** in refluxing ethanol in the presence of sodium ethoxide afforded the isoquinoline derivative **18**. The structure of **18** was established on the basis of elemental and spectral data. The formation of **18** is assumed to proceed via Michael addition of the methyl function group of **13** to the activated double bond of **16** to form Michael adduct **17** followed by intramolecular cyclization and loss of hydrogen cyanide under the reaction conditions to yield **18** (Scheme 4).

Ternary condensation of compound **1**, formaldehyde and malononitrile (1:1:1 M ratio) at reflux temperature in ethanol in the presence of piperidine afforded the 2-pyridone derivative **20a** (Scheme 5). The structure of compound **20a** was elucidated on the basis of its analytical and spectral data. Its mass spectrum showed a molecular ion peak at *m*/*z* 315 (3.76%) together with base peak at *m*/*z* 92 which is characteristic for aniline moiety minus hydrogen. The plausible reaction mechanism for the formation of pyridine **20a** is illustrated in Scheme 5. In a similar manner, cyclization of compound **1** with acetaldehyde and malononitrile (1:1:1 M ratio) yielded the novel 2-pyridone derivative **20b**. Its mass spectrum revealed a molecular ion peak at *m*/*z* 329 which is base peak in the spectrum. Knoevenagel Condensation of compound **1** with terephthalaldehyde (2:1 M ratio) in ethanolic piperidine at reflux temperature furnished the bis(benzylidene) derivative **21** in high yield. Refluxing of compound **21** with active methylene reagents in ethanol in the presence of piperidine yielded the novel bis(aminopyridone) derivatives **22a–c** (Scheme 5). Assignment of structures **22** was confirmed on the basis of their elemental and spectral data. Mass spectrum of compound **22a** showed a molecular ion peak at *m*/*z* 704 (15%) and the base peak was found in the spectrum at *m*/*z* 114. the formation of **22** is assumed to proceed via the initial Michael addition of the active methylene function group of **1** to the activated double bond of **21** to form Michael adduct which cyclized and auto-oxidation



Scheme 4 Synthesis of dimethylaminomethylene and isoquinolinone derivatives **15** and **18**.

under the reaction conditions yielded **22**. Additionally, the structures of **22** were established chemically through the reaction of compound **1** with 1,4-bis-(benzylidene) derivatives **23** (2:1 M ratio) by refluxing in dioxane in the presence of piperidine (Scheme 5).

It has been reported that compounds with a chromene backbone have a wide range of biological properties (Mladenovic et al., 2010, 2009; Nawrot and Nawrot, 2006; Nandgaonkar et al., 2005). Thus, condensation of cyanoacetanilide derivative **1** with salicylaldehyde 24 using ammonium acetate as a catalyst in refluxing ethanol gave 2-imino-*N*-(4-sulfamoylphenyl)-2*H*-chromene-3-carboxamide **25** (Scheme 6). Moreover, the resulting chromene derivatives have latent functional constituents, which have the potential for further chemical transformations that give new routes for the preparation of substituted, polycondensed chromene derivatives. Reaction of chromene **25** with malononitrile in refluxing ethanol containing a catalytic amount of piperidine afforded the novel chromeno[3,4-*c*]pyridine derivative **27** in high chemical yield. The molecular structure of **27** was established through analytical and spectral data. Its infrared spectrum showed absorption bands at 3442, 3350, 3238 and 2204 cm^{-1} due to amino and cyano function groups, respectively. Also, its mass spectrum revealed a molecular ion peak at m/z = 407 (3.04%). The formation of **27** was assumed to proceed via the Michael addition of the active methylene function of malononitrile to the activated double bond center in **25** to yield the acyclic Michael adduct **26** which cyclize and aromatize through auto-oxidation under the reaction conditions (Elgemeie and El-Ghandour, 1990).In a similar manner, cyclization of compound **1** with 7-hydroxy-5-methoxy-2-methyl-4-oxo-4*H*-chromene-6-carbaldehyde (**28**) afforded the 2,8-dihydropyrano[3,2-*g*]chromene **29** which was allowed to react with malononitrile in the presence of piperidine to yield the pyrano[3′,2′:6,7]-chromeno[3,4-*c*]pyridine derivative **30**. The mass spectrum of compound **30** showed a molecular ion peak at m/z 519 (M^+; 2.74%) together with base peak at m/z 92.

3. Experimental

3.1. General methods

Melting points were determined on a digital Gallen-Kamp MFB-595 instrument and are uncorrected. IR spectra (KBr) were measured on a Shimadzu 440 spectrometer. ^{1}HNMR spectra were recorded in deuterated dimethylsulfoxide (DMSO-d_6) on a Varian Gemini 300 (300 MHz) spectrometer using TMS as an internal standard; chemical shifts are reported as δ units. Mass spectra were performed on a Shimadzu GSMS-QP 1000 Ex mass spectrometer at 70 eV. The elemental analyses were carried out at the Microanalytical Center, Cairo University, Cairo (Egypt).

3.1.1. 4-(6-Amino-3,4,5-tricyano-2-oxopyridin-1(2H)-yl)benzene-sulfonamide (6)

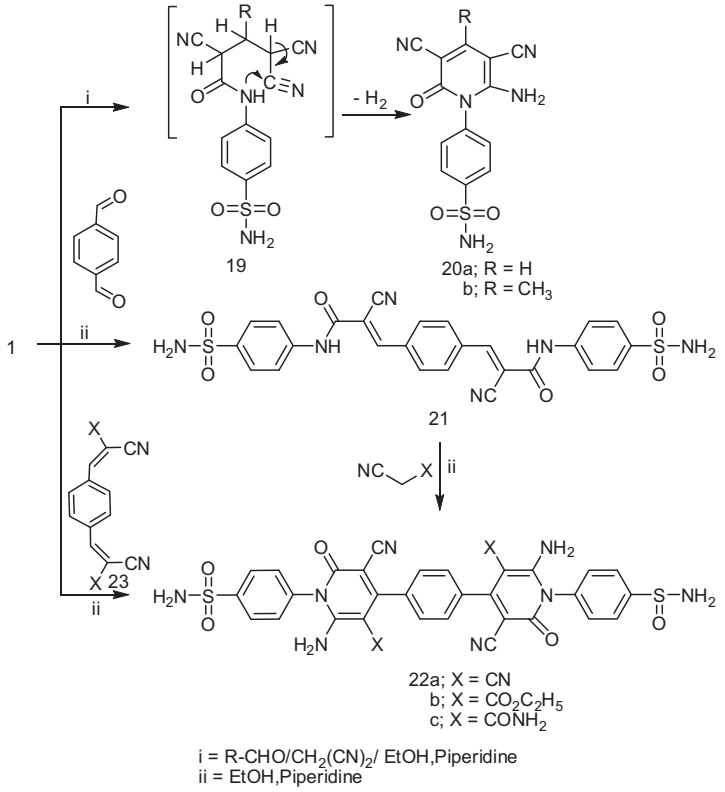
A mixture of cyanoacetanilide derivative **1** (0.01 mol), tetracyanoethylene (**2**) (0.01 mol), and triethylamine (0.5 mL) in dioxane (20 ml) was heated under reflux for 3 h, then allowed to cool. The solid product was collected and recrystallized from acetic acid. Brown crystals: Yield 50%, mp 284–286 °C; Anal. Calcd. for $C_{14}H_8N_6O_3S$: C, 49.41; H, 2.37; N, 24.69. Found: C, 49.36; H, 2.28; N, 24.61; IR (KBr, cm^{-1}): 3320, 3306 (NH_2), 2222 (C≡N), 1682 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 7.42–8.51 (m, 8H, Ar-H + 2NH_2); MS m/z (% relative intensity): 340 (M + 1; 10.1), 286 (13.13), 173 (11.1), 111 (20.2), 107 (23.2), 85 (38.3), 71 (38.3) and 55 (100).

3.1.2. 4-(6-Amino-3,5-dicyano-4-(methylthio)-2-oxopyridin-1(2H)-yl)benzenesulfon-amide (9)

A mixture of cyanoacetanilide derivative **1** (0.01 mol), bis(methylsulfanyl)-methylenemalononitrile (**7**) (0.01 mol), and sodium ethoxide (1 g sodium in 10 ml ethanol) in ethanol (30 ml) was heated under reflux for 3 h. The reaction mixture was cooled and poured into ice acidified with HCl. The solid product was filtered off and recrystallized from acetic acid. Buff crystals: Yield 70%, mp > 300 °C; Anal. Calcd. for $C_{14}H_{11}N_5O_3S_2$: C, 46.53; H, 3.07; N, 19.38. Found: C, 46.41; H, 2.95; N, 19.25; IR (KBr, cm^{-1}): 3322, 3208 (NH_2), 2212 (C≡N), 1652 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 2.84 (s, 3H, SCH_3), 7.55–8.44 (m. 8H, Ar-H + 2NH_2). ^{13}CNMR (300 MHz, DMSO-d_6, δ/ppm): 14.2 (SCH_3), 60.8 (Pyridine-C5), 88.2 (Pyridine-C3), 116.0 (2C≡N), 120.9, 128.8, 134.9, 136.5 (phenyl-C), 158.0 (Pyridine-C6), 159.90 (Pyridine-C2), 174.90 (Pyridine-C4).

3.1.3. 4-(4,6-Diamino-5-cyano-2-oxopyridin-1(2H)-yl)benzene-sulfonamide (11)

A mixture of anilide **1** (0.01 mol) and malononitrile (0.01 mol) with a few drops of piperidine in an oil bath was heated for 1 h at 160 °C, then allowed to cool. The solid product was col-



Scheme 5 Synthesis of 6-aminopyridine and bipyridine derivatives **20** and **22a–c**.

lected and recrystallized from dimethyl-formamide. Brown crystals: Yield 65%, mp > 300 °C; Anal. Calcd. for $C_{12}H_{11}N_5O_3S$: C, 47.21; H, 3.63; N, 22.94. Found: C, 47.10; H, 3.54; N, 22.83; IR (KBr, cm^{-1}): 3316, 3176 (NH_2), 2202 (C≡N), 1658 (C=O); MS *m*/*z* (% relative intensity): 305 (M^+; 9.26), 228 (10.1), 183 (11.1), 72 (38.8), 108 (58.3), 69 (64.3) and 65 (100).

*3.1.4. 4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)benzenesulfonamide (**13**)*

Equimolar amounts of **1** (0.01 mol) and acetylacetone (0.01 mol) with a few drops of piperidine in an oil bath were heated for 1 h at 160 °C, then allowed to cool. The solid product was collected and recrystallized from dioxane. White crystals: Yield 75%, mp > 300 °C; Anal. Calcd. for $C_{14}H_{13}N_3O_3S$: C, 55.43; H, 4.32; N, 13.85. Found: C, 55.31; H, 4.26; N, 13.74; IR (KBr, cm^{-1}): 3316, 3150 (NH_2), 3078 (CH-arom.), 2924 (CH-aliph.), 2226 (C≡N), 1652 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.98, 2.40 (2s, 6H, $2CH_3$), 6.52 (s, 1H, pyridine-H5), 7.54–8.01 (m, 6H, Ar-H + SO_2NH_2). ^{13}CNMR (300 MHz, DMSO-d_6, δ/ppm): 20.0, 22.0 ($2CH_3$), 106.0 (Pyridine-C5), 116.0 (Pyridine-C3), 118.0 (C≡N), 122.0, 129.3, 136.3, 140.0 (phenyl-C), 143.3 (Pyridine-C6), 155.0 (Pyridine-C4), 158.0 (Pyridine-C2).

*3.1.5. N′-((4-(3-Cyano-4,6-dimethyl-2-oxopyridin-1(2H)-yl)phenyl)-sulfonyl)-N,N-di-methylformimidamide (**15**)*

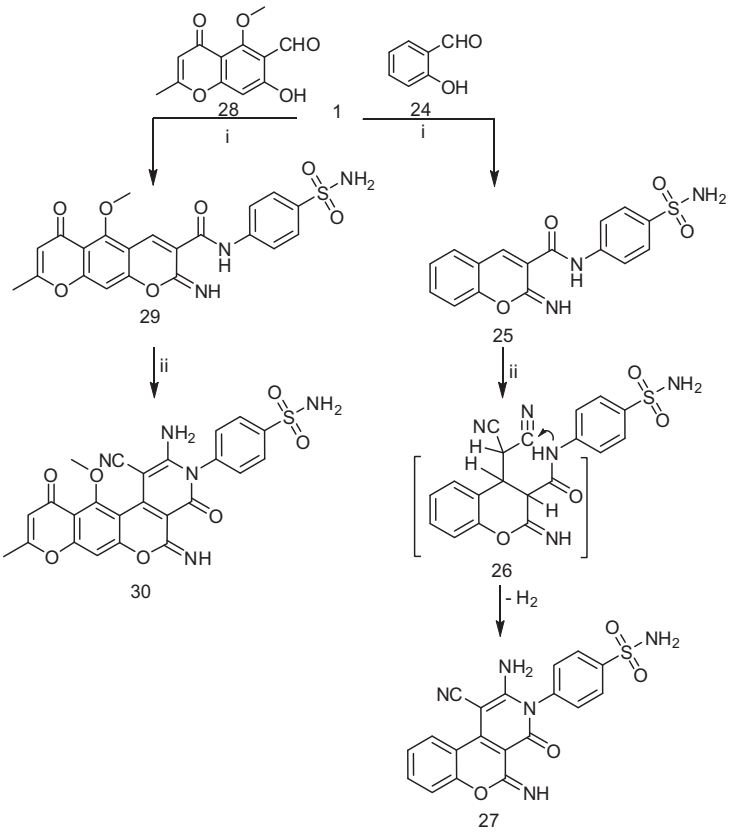
A mixture of **13** (0.01 mol) and dimethylformamide–dimethylacetal (0.01 mol) in m-xylene (30 mL) was heated under reflux for 6 h. The reaction mixture was concentrated and the obtained product was collected and recrystallized from ethanol. Reddish-brown crystals: Yield 50%, mp 240–242 °C; Anal. Calcd. for $C_{17}H_{18}N_4O_3S$: C, 56.97; H, 5.06; N, 15.63. Found: C, 56.89; H, 5.10; N, 15.67; IR (KBr, cm^{-1}): 3010 (CH-arom.), 2934 (CH-aliph.), 2214 (C≡N), 1640 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.98, 2.51 (2s, 6H, $2CH_3$), 3.18 (s, 6H, $N(CH_3)_2$), 6.50 (s, 1H, pyridine-H), 7.52–7.99 (m, 4H, Ar-H), 8.31 (s, 1H, methine-H). ^{13}CNMR (300 MHz, DMSO-d_6, δ/ppm): 20.0, 22.7 ($2CH_3$), 35.0 ($N(CH_3)$), 107.5 (Pyridine-C5), 118.0 (Pyridine-C3), 116.9 (C≡N), 123.0, 127.0, 137.0, 140.0 (phenyl-C), 141.0 (Pyridine-C6), 146.5 (Pyridine-C4), 157.0 (Pyridine-C2), 166 (N=C-$N(CH_3)$2)

*3.1.6. 4-(8-Amino-7-cyano-6-(4-methoxyphenyl)-3-methyl-1-oxo-isoquinolin-2(1H)-yl) benzenesulfonamide (**18**)*

To a solution of **13** (0.01 mol) in ethanol (30 mL), α-cyano-4-methoxyphenyl cinnamonitrile (**16**) (0.01 mol) and sodium ethoxide (1 g sodium in 10 mL EtOH) were added. The mixture was refluxed for 6 h and poured into crushed ice and acidified with HCl. The solid product was filtered off and recrystallized from acetic acid. Yellow crystals: Yield 45%, mp > 300 °C; Anal. Calcd. for $C_{24}H_{20}N_4O_4S$: C, 62.60; H, 4.38; N, 12.17. Found: C, 62.54; H, 4.29; N, 12.20; IR (KBr, cm^{-1}): 3306, 3210 (NH_2), 2222 (C≡N), 1682 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.20 (s, 3H, CH_3), 3.65 (s, 2H, NH_2), 3.80 (s, 3H, OCH_3), 6.72–8.07 (m, 12H, Ar-H + SO_2NH_2).

*3.1.7. General procedure for the preparation of pyridine derivatives **20a**,**b***

A mixture of anilide **1** (0.01 mol), appropriate aldehyde (0.01 mol), and malononitrile (0.01 mol) in ethanol (30 mL)



Scheme 6 Synthesis of chromene-3-carboxamides **25** and **29** and chromeno-[3,4-*c*]pyridine derivatives **27** and **30**.

containing piperidine (0.5 mL) was heated under reflux for 3 h. The resulting solid was filtered off and recrystallized from common solvents to afford products (**20a** and **b**).

*3.1.8. 4-(6-Amino-3,5-dicyano-2-oxopyridin-1(2H)-yl)benzenesulfonamide (**20a**)*

Compound **20a** was obtained in 73% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{13}H_9N_5O_3S$: C, 49.52; H, 2.88; N, 22.21. Found: C, 49.44; H, 2.79; N, 22.16; IR (KBr, cm^{-1}): 3324, 3264 (NH_2), 2218 (C≡N), 1684 (C=O); MS *m*/*z* (% relative intensity): 315 (M^+; 3.76), 224 (5.39), 172 (72.8), 156 (81.7), 92 (100) and 76 (25.3).

*3.1.9. 4-(6-Amino-3,5-dicyano-4-methyl-2-oxopyridin-1(2H)-yl)-benzene-sulfonamide (**20b**)*

Compound **20b** was obtained in 67% yield, mp > 300 °C (dioxane), Anal. Calcd. for $C_{14}H_{11}N_5O_3S$: C, 51.06; H, 3.37; N, 21.27. Found: C, 51.10; H, 3.26; N, 21.18; IR (KBr, cm^{-1}): 3366, 3200 (NH_2), 2224 (C≡N), 1668 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 2.43 (s, 3H, CH_3), 7.31 (s, 2H, NH_2), 7.53–7.99 (m, 6H, Ar-H + NH_2); MS *m*/*z* (% relative intensity): 329 (M^+; 100), 249 (42), 198 (9.1), 172 (2.3), 156 (12) and 92 (23.9).

*3.1.10. 3,3′-(1,4-Phenylene)bis(2-cyano-N-(4-sulfamoylphenyl)acrylamide) (**21**)*

To a solution of **1** (0.02 mol) in ethanol (30 mL), terephthaldehyde (0.01 mol) and piperidine (0.5 mL) were added. The mixture was refluxed and solid product which was produced on heating was filtered off and recrystallized from acetic acid. Brown crystals: Yield 80%, mp 284–286 °C; Anal. Calcd. for $C_{26}H_{20}N_6O_6S_2$: C, 54.16; H, 3.50; N, 14.58. Found: C, 54.10; H, 3.43; N, 14.51; IR (KBr, cm^{-1}): 3400, 3272 (NH_2), 2227 (C≡N), 1654 (C=O); ^{1}H NMR (300 MHz, DMSO-d_6, δ/ppm): 7.35–8.19 (m, 16H, Ar-H + $2SO_2NH_2$), 8.42 (s, 2H, 2 benzylidene-*H*), 10.74 (hump, 2H, 2NH); MS *m*/*z* (% relative intensity): 576 (M^+; 3.62), 537 (10.34), 350 (20.4), 264 (13.5), 185 (100), 172 (59.1) and 92 (60.2).

*3.1.11. General procedure for the preparation of Bis (2-pyridone) derivatives (**22a–c**)*

3.1.11.1. Method A. A mixture of **21** (0.01 mol), active methylene compound (0.02 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3 h, the solid product which produced on heating was collected and recrystallized from common solvents to afford products **22a–c**.

3.1.11.2. Method B. A mixture of **23** (0.01 mol), cyanoacetanilide derivative **1** (0.02 mol) and piperidine (0.5 mL) in dioxane (30 mL) was heated under reflux for 3 h. The product which produced on heating was collected and recrystallized to give **22a–c**.

*3.1.12. 4,4′-(4,4′-(1,4-Phenylene)bis(6-amino-3,5-dicyano-2-oxopyridine-4,1-(2H)-diyl)) dibenzenesulfonamide **22a***

Compound **22a** was obtained in 70% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{32}H_{20}N_{10}O_6S_2$: C,

54.54; H, 2.86; N, 19.88. Found: C, 54.42; H, 2.78; N, 19.76; IR (KBr, cm^{-1}): 3210, 3198 (NH_2), 2218 (C≡N), 1654 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 3.37 (s, 4H, 2 NH_2), 7.60–8.03 (m, 16H, Ar-H + $2SO_2NH_2$); MS *m/z* (% relative intensity): 704 (M^+; 15), 640 (24.5), 390 (28.6), 374 (20.4), 248 (34.6), 234 (20.4), 208 (71.5), 142 (22.5) and 114 (100).

3.1.13. Diethyl 4,4′-(1,4-phenylene)bis(2-amino-5-cyano-6-oxo-1-(4-sulfamoyl-phenyl)-1,6-dihydropyridine-3-carboxylate) ***22b***

Compound **22b** was obtained in 75% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{36}H_{30}N_8O_{10}S_2$: C, 54.13; H, 3.79; N, 14.03. Found: C, 54.20; H, 3.80; N, 13.94; IR (KBr, cm^{-1}): 3330, 3250 (NH_2), 2226 (C≡N), 1722, 1692 (2C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 1.31 (t, 6H, $2CH_3$), 4.34 2 (q, 4H, 2 CH_2), 7.32 (s, 4H, 2 SO_2NH_2), 7.84–8.48 (m, 16H, Ar-H + $2NH_2$).

3.1.14. 4,4′-(1,4-Phenylene)bis(2-amino-5-cyano-6-oxo-1-(4-sulfamoyl-phenyl)-1,6-di-hydropyridine-3-carboxamide) ***22c***

Compound **22c** was obtained in 60% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{32}H_{24}N_{10}O_8S_2$: C, 51.89; H,3.27; N, 18.91. Found: C, 51.81; H, 3.30; N, 18.83; IR (KBr, cm^{-1}): 3350, 3300 (NH_2), 2222 (C≡N), 1658 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 7.34 (hump, 4H, 2 SO_2NH_2), 7.86–8.18 (m, 16H, Ar-H + NH_2), 8.41 (s, 2H, NH_2), 10.75 (hump, 2H, NH_2).

3.1.15. Synthesis of 2-iminochromene-3-carboxamide derivatives ***25*** *and* ***30***

3.1.15.1. General procedure. A mixture of compound **1** (0.01 mol), requisite aldehyde [salicylaldehyde or 7-hydroxy-2-methyl-4-oxo-4*H*-chromene-6-carboxaldehyde (**29**)] (0.01 mol) and ammonium acetate (1 g) was refluxed in ethanol (30 mL) for 1 h. The solid product which produced on heating was collected and recrystallized from common solvents to afford products **25** and **30**.

*3.1.16. 2-Imino-N-(4-sulfamoylphenyl)-2H-chromene-3-carboxamide (****25****)*

Compound **25** was obtained in 80% yield, mp 260–262 °C (dioxane), Anal. Calcd. for $C_{16}H_{13}N_3O_4S$: C, 55.97; H, 3.82; N, 12.24. Found: C, 55.84; H, 3.72; N, 12.08; IR (KBr, cm^{-1}): 3322, 3232 (NH_2), 1682 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 7.14–7.85 (m, 10H, Ar-H + SO_2NH_2), 8.57 (s, 1H, chromene-H), 9.22, 13.07 (2s, 2H, 2NH).

*3.1.17. 2-Imino-5-methoxy-8-methyl-6-oxo-N-(4-sulfamoylphenyl)-2,6-dihydro-pyrano [3,2-g]chromene-3-carboxamide (****29****)*

Compound **30** was obtained in 70% yield, mp 290–291 °C (dioxane), Anal. Calcd. for $C_{21}H_{17}N_3O_7S$: C, 55.38; H, 3.76; N, 9.23. Found: C, 55.23; H, 3.70; N, 9.16; IR (KBr, cm^{-1}): 3312, 3218 (NH_2), 1654 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 2.31 (s, 3H, CH_3), 3.95 (s, 3H, OCH_3), 6.12 (s, 1H, H-7), 6.85 (s, 1H, H-10), 7.09–7.83 (m, 6H, Ar-H + SO_2NH_2), 8.56 (s, 1H, pyran-H), 9.45, 12.75 (2br, 2H, 2NH).

3.1.18. General procedure for the preparation of chromeno[3,4-c]pyridine derivatives ***27*** *and* ***30***

A mixture of **25** or **30** (0.01 mol), malononitrile (0.01 mol) and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 3 h. The solid product which produced on heating was collected by filtration and recrystallized from common solvents to afford products **27** and **30**.

*3.1.19. 4-(2-Amino-1-cyano-5-imino-4-oxo-4,5-dihydro-3H-chromeno[3,4-c]-pyridin-3-yl)benzenesulfonamide (****27****)*

Compound 27 was obtained in 84% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{19}H_{13}N_5O_4S$: C, 56.01; H, 3.22; N, 17.19. Found: C, 56.05; H, 3.16; N, 17.21; IR (KBr, cm^{-1}): 3442, 3350, 3238 (NH/NH_2), 2204 (C≡N), 1664 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 6.98–8.72 (m, 12H, Ar-H + $2NH_2$), 9.51 (s, 1H, NH); MS *m/z* (% relative intensity): 407 (M^+; 3.04), 368 (13.68), 299 (6.9), 149 (13.07), 97 (38.6), 71 (63.8) and 57 (100).

*3.1.20. 4-(2-Amino-1-cyano-5-imino-12-methoxy-9-methyl-4,11-di-oxopyrano-[3′,2′:6,7]chromeno[3,4-c]pyridin-3(4H,5H,11H)-yl)-benzenesulfonamide (****30****)*

Compound **30** was obtained in 69% yield, mp > 300 °C (dimethylformamide), Anal. Calcd. for $C_{24}H_{17}N_5O_7S$: C, 55.49; H, 3.30; N, 13.48. Found: C, 55.42; H, 3.24; N, 13.60; IR (KBr, cm^{-1}): 3336, 3200 (NH_2), 2938 (CH-aliph.), 2210 (C≡N), 1648 (C=O); ^1H NMR (300 MHz, DMSO-d_6, δ/ppm): 2.22 (s, 3H, CH_3), 3.87 (s, 3H, OCH_3), 6.29 (s, 1H, H-7), 6.81 (s, 1H, H-10), 7.14–8.49 (m, 8H, Ar-H + $2NH_2$), 9.41 (s, 1H, NH); MS *m/z* (% relative intensity): 519 (M^+; 2.74), 521 (M + 2; 3.5), 363 (6.38), 239 (7.9), 184 (8.46), 160 (8.5), 156 (60.0), 144 (7.6), 92 (100) and 65 (98.48).

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