Facile and convenient synthesis of pyrimidine, 4H-3,1-benzoxazin-4-one, pyrazolo[5,1-b]quinazoline, pyrido[1,2-a]quinazoline, and chromeno[3′,4$^{'}$:4,5]pyrido[1,2-a]quinazoline derivatives

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A convenient synthesis of a series of pyrimidine, 4H-3,1-benzoxazin-4-one, pyrazolo[5,1-b]quinazoline, pyrido[1,2-a]quinazoline, and chromeno[3′,4′:4,5]pyrido[1,2-a]quinazoline derivatives, via the reactions of versatile and readily accessible methyl 2-(2-cyanoacetamido)benzoate (**1**) with the appropriate reagents, is described here.

Key Words: Cyanoacetanilide, pyrimidine, quinazoline, pyrazolo[5,1-b]quinazoline, pyrido[1,2-a]quinazoline

Introduction

Quinazolines are considered to be important chemical synthons of various physiological significances and pharmaceutical utilities. They possess a variety of biological effects, including antihypertensive,[1,2] antimicrobial,[3,4] antihyperlipidemic,[5,6] antiinflammatory,[7,8] and anticonvulsant[9−13] activities. Moreover, many quinazolines

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contributed to the quest for an ultimate antitumor chemotherapeutic agent.[14−18] This literature survey revealed that the presence of a substituted aromatic ring at position 3 and a methyl group at position 2 are necessary requirements for central nervous system depression and anticonvulsant activities. Modification of the methyl group by some other chemical moiety yielded structural analogs with anticonvulsant activity. Recently, we have been involved in a program aiming at the synthesis of new heterocyclic compounds that may possess biologically active properties to be used as potential antimicrobial agents from a cyanoacetanilide precursor.[19−26] In the context of this program and because of increased interest in quinazoline derivatives, some new quinazoline derivatives were required for the study of biological activity. Methyl 2-(2-cyanoacetamido)benzoate (**1**) seemed to be a good precursor to fulfill this objective via its reactions with some electrophilic and nucleophilic reagents.

Experimental

General remarks

All melting points were recorded on a digital Gallen Kamp MFB-595 instrument and are uncorrected. The IR spectra (KBr) (cm^{-1}) were measured on a Shimadzu 440 spectrophotometer. ^{1}H-NMR spectra δ, ppm) were obtained in deuterated dimethyl sulfoxide on a Varian Gemini 200 (200 MHz) spectrometer, using TMS as an internal standard; chemical shifts are reported as δ_{ppm} units. Mass spectra (m/z, %) were obtained on a GC MS-QP 100 EX mass spectrometer at 70 eV. Elemental analyses were carried out by the Microanalytical Unit of Cairo University, Cairo, Egypt. Methyl 2-(2-cyanoacetamido)benzoate (**1**) was prepared according to a literature procedure reported previously.[27]

Synthesis of methyl 2-(2-cyano-3-(dimethylamino)acrylamido)benzoate (2)

A mixture of cyanoacetamide derivative **1** (2.18 g, 0.01 mol) and dimethylformamide dimethylacetal (DMF-DMA) (1.19 g, 0.01 mol) in dry xylene (30 mL) was refluxed for 4 h, then allowed to cool. The precipitated product that was obtained was filtered off, washed with petroleum ether (60-80 °C), dried, and recrystallized from ethanol, mp 170-172 °C (80%). IR (KBr): υ (cm^{-1}) = 3252 (NH), 3030 (CH-arom.), 2924 (CH-aliph.), 2188 (C≡N), 1700, 1670 (C=O), and 1618 (C=C); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.25 (s, 6H, 2CH$_3$), 3.89 (s, 3H, OCH$_3$), 7.12-7.60 (m, 4H, Ar-H), 7.89 (s, 1H, CH=), 11.00 (s, 1H, NH). Anal. Calcd. for C$_{14}$H$_{15}$N$_3$O$_3$ (273.29): C, 61.53%; H, 5.53%; N, 15.38%. Found: C, 61.50%; H, 5.48%; N, 15.40%.

Synthesis of 9-oxo-1,9-dihydropyrazolo[5,1-b]quinazoline-3-carbonitrile (6)

A mixture of compound **2** (2.73 g, 0.01 mol) and hydrazine hydrate (0.5 g, 0.01 mol) was refluxed in n-butanol (20 mL) for 12 h, and the solid product that was obtained was filtered off, washed with ethanol, dried, and recrystallized from a mixture of EtOH/DMF (2:1), mp 285-287 °C (65%). IR (KBr): υ (cm^{-1}) = 3180 (NH), 2216 (C≡N), and 1692 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 7.20-7.89 (m, 4H, Ar-H), 8.02 (s, 1H, pyrazole-H5), 11.73 (s, 1H, NH). Anal. Calcd. for C$_{11}$H$_6$N$_4$O (210.19): C, 62.86%; H, 2.88%; N, 26.66%. Found: C, 62.64%; H, 2.67%; N, 26.42%.

Synthesis of methyl 2-(2,4-diaminopyrimidine-5-carboxamido)benzoate (8)

To a mixture of compound **2** (2.73 g, 0.01 mol) and guanidine hydrochloride (0.95 g, 0.01 mol) in absolute ethanol (30 mL), triethylamine (0.5 mL) was added. The reaction mixture was refluxed for 10 h, then allowed to cool to room temperature and diluted with water (20 mL). The solid product thus formed was filtered off, washed with water, and recrystallized from DMF, mp 245-247 °C (68%). IR (KBr): υ (cm^{-1}) = 3386, 3324 (NH$_2$), and 1710, 1662 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.84 (s, 2H, NH$_2$), 3.87 (s, 3H, OCH$_3$), 5.56 (s, 2H, NH$_2$), 7.29 (s, 1H, pyrimidine-H6), 7.32-7.95 (m, 4H, Ar-H), 13.59 (s, 1H, NH). Anal. Calcd. for C$_{13}$H$_{13}$N$_5$O$_3$ (287.27): C, 54.35%; H, 4.56%; N, 24.38%. Found: C, 54.20%; H, 4.38%; N, 24.22%.

Synthesis of 3-(4-aryl)-2-cyano-N-(2-methoxycarbonylphenyl)acrylamides (9a, 9b)

To a solution of cyanoacetanilide **1** (2.18 g, 0.01 mol) and the appropriate aromatic aldehyde (0.01 mol) in ethanol (30 mL) was added a few drops of piperidine, and the reaction mixture was refluxed for 4 h and then allowed to cool. The precipitate that formed was filtered, washed with ethanol, and dried.

Methyl 2-[3-(4-chlorophenyl)-2-cyano-acryloylamino]benzoate (9a)

Recrystallized from EtOH, mp 170-172 °C (75%). IR (KBr): υ (cm^{-1}) = 3266 (NH), 2956 (CH-aliph.), 2210 (C≡N), and 1696, 1686 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.90 (s, 3H, OCH$_3$), 7.26-8.39 (m, 8H, Ar-H), 8.49 (s, 1H, olefinic CH=), 11.51 (s, 1H, NH). Anal. Calcd. for C$_{18}$H$_{13}$ClN$_2$O$_3$ (340.76): C, 63.44%; H, 3.85%; N, 8.22%. Found: C, 63.23%; H, 3.67%; N, 8.04%.

Methyl 2-[3-(4-methoxyphenyl)-2-cyano-acryloylamino]benzoate (9b)

Recrystallized from EtOH, mp 196-198 °C (79%). IR (KBr): υ (cm^{-1}) = 3250 (NH), 2962 (CH-aliph.), 2216 (C≡N), and 1696 (broad C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.85, 4.01 (2s, 6H, 2OCH$_3$), 7.26-8.19 (m, 8H, Ar-H), 8.42 (s, 1H, olefinic CH=), 12.01 (s, 1H, NH). Anal. Calcd. for C$_{19}$H$_{16}$N$_2$O$_4$ (336.34): C, 67.85%; H, 4.79%; N, 8.33%. Found: C, 67.64%; H, 4.52%; N, 8.19%.

Synthesis of 6-amino-1-(2-(methoxycarbonyl)-phenyl)-3,5-dicyano-4-(4-aryl)-2-oxo-2H-pyridines (12a, 12b)

To a solution of compounds **9a** and **9b** (0.01 mol) in ethanol (30 mL) and malononitrile (0.66 g, 0.01 mol), a few drops of piperidine were added. The reaction mixture was heated under reflux for 3 h and then left to cool. The precipitated product thus formed was collected by filtration, washed with ethanol, and dried.

6-Amino-1-(2-(methoxycarbonyl)-phenyl)-3,5-dicyano-4-(4-chlorophenyl)-2-oxo-2H-pyridines (12a)

Recrystallized from AcOH, mp 260-262 °C (67%). IR (KBr): υ (cm^{-1}) = 3174, 3130 (NH$_2$), 2216 (C≡N), and 1704, 1692 (2 C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.90 (s, 3H, OCH$_3$), 7.20-8.49 (m, 10H, Ar-H +

NH$_2$). Anal. Calcd. for C$_{21}$H$_{13}$ClN$_4$O$_3$ (404.81): C, 62.31%; H, 3.24%; N, 13.84%. Found: C, 62.14%; H, 3.07%; N, 13.68%.

6-Amino-1-(2-(methoxycarbonyl)-phenyl)-3,5-dicyano-4-(4-methoxyphenyl)-2-oxo-2H-pyridines (12b)

Recrystallized from AcOH, mp 275-277 °C (63%). IR (KBr): v (cm^{-1}) = 3244, 3202 (NH$_2$), 2956, 2850 (CH-aliph.), 2212 (C≡N), and 1702, 1684 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.87, 391 (2s, 6H, 2OCH$_3$), 7.15-8.52 (m, 8H, Ar-H), 11.47 (s, 2H, NH$_2$); MS (m/z, %): 401 (M$^+$ + 1, 19), 400 (M$^+$, 16), 324 (25), 305 (17), 266 (56), 251 (9), 222 (100), 196 (12), 177 (18), 152 (27), 75 (18). Anal. Calcd. for C$_{22}$H$_{16}$N$_4$O$_4$ (400.39): C, 66.00%; H, 4.03%; N, 13.99%. Found: C, 66.09%; H, 4.23%; N, 13.76%.

Synthesis of 3-(4-chlorophenyl)-1,6-dioxo-5,6-dihydro-1H-pyrido[1,2-a]-quinazoline-2,4-dicarbonitrile (13)

To a solution of compound **12a** (0.41 g, 0.001 mol) in DMF (30 mL), 0.5 mL of triethylamine was added and refluxed for 8 h, then allowed to cool and poured into ice cold water. The resulting precipitate was filtered off, dried, and recrystallized from a mixture of EtOH/DMF (2:1), mp > 300 °C (82%). IR (KBr): v (cm^{-1}) = 3158 (NH), 2216 (C≡N), and 1658 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 7.12-8.08 (m, 8H, Ar-H), 11.43 (s, 1H, NH). Anal. Calcd. for C$_{20}$H$_9$ClN$_4$O$_2$ (372.76): C, 64.44%; H, 2.43%; N, 15.03%. Found: C, 64.29%; H, 2.31%; N, 14.84%.

Synthesis of 2-[2-amino-4-(4-chloro-phenyl)-5,6,7,8-tetrahydro-4H-chromen-3-yl]-benzo[d][1,3] oxazin-4-one (16)

A mixture of compound **9a** (0.43 g, 0.001 mol), cyclohexanone (0.1 g, 0.001 mol), and piperidine (0.5 mL) in ethanol (30 mL) was heated under reflux for 10 h, then allowed to cool, poured into cold water (50 mL), and acidified with dilute HCl. The solid product thus formed was collected by filtration and recrystallized from a mixture of EtOH/DMF (1:1), mp > 300 °C (63%). IR (KBr): v (cm^{-1}) = 3424, 3248 (NH$_2$), 2936, 2858 (CH-aliph.), and 1706 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 1.61-1.71, 2.45 (m, 8H, cyclohexyl), 4.85 (s, 1H, pyran-H4), 6.83 (s, 2H, NH$_2$), 7.29-7.66 (m, 8H, Ar-H). Anal. Calcd. for C$_{23}$H$_{19}$ClN$_2$O$_3$ (406.86): C, 67.90%; H, 4.71%; N, 6.89%. Found: C, 67.76%; H, 4.55%; N, 6.63%.

Synthesis of 1',3,6'-trioxo-1',2',5',6'-tetrahydrospiro[cyclohexane-1,3'-pyrido[1,2-a]quinazoline]-2', 4'-dicarbonitrile (18)

To a mixture of compound **1** (2.83 g, 0.01 mol), 1,3-cyclohexanedione (1.12 g, 0.01 mol), and malononitrile (0.66 g, 0.01 mol) in ethanol (40 mL), a few drops of piperidine were added. The reaction mixture was refluxed for 6 h, and the solid product that was produced upon heating was collected by filtration and recrystallized from a mixture of EtOH/DMF (2:1), mp > 300 °C (82%). IR (KBr): v (cm^{-1}) = 3160 (NH), 3016 (CH-arom.), 2930, 2860 (CH-aliph.), 2220 (C≡N), 1695 (C=O), and 1660 (amidic C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 2.24-2.51 (m, 8H, 4CH$_2$), 5.98 (s, 1H, pyridine-H), 6.81-6.86 (m, 4H, Ar-H), 12.71 (s, 1H, NH); MS (m/z, %):

346 (M$^+$, 15), 301 (17), 278 (21), 209 (42), 195 (100), 177 (56), 164 (72), 155 (73), 140 (48), 135 (20), 64 (31). Anal. Calcd. for $C_{19}H_{14}N_4O_3$ (346.34): C, 65.89%; H, 4.07%; N, 16.18%. Found: C, 65.71%; H, 3.88%; N, 15.97%.

Synthesis of 6-imino-7-oxo-12,13-dihydro-6H,7H-chromeno[3',4':4,5]-pyrido[1,2-a]quinazolinone 14-carbonitrile (23) and 6-imino-7-oxo-12,13-dihydro-6H,7H-chromeno[3',4':4,5]pyrido[1,2-a]quinazo-linone-14-carboxylic acid amide (24)

To a mixture of **19** (3.22 g, 0.01 mol) and an active methylene compound (either malononitrile or cyanoac-etamide; 0.01 mol) in ethanol (50 mL) was added ammonium acetate (0.5 g), and the reaction mixture was refluxed for 5 h and then allowed to cool. The precipitate that formed was filtered off, washed with ethanol, and recrystallized from a mixture of EtOH/DMF (3:1).

23: Mp > 300 °C (92%). IR (KBr): υ (cm^{-1}) = 3334, 3218 (2NH), 2206 (C≡N), and 1686, 1656 (amidic C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 7.51-7.80 (m, 8H, Ar-H), 8.93, 8.97 (2s, 2H, 2NH). Anal. Calcd. for $C_{20}H_{10}N_4O_3$ (354.32): C, 67.80%; H, 2.84%; N, 15.81%. Found: C, 67.66%; H, 2.69%; N, 15.60%.

24: Mp > 300 °C. IR (KBr): υ (cm^{-1}) = 3420, 3306 (NH$_2$) and 1670, 1608 (C=O); ^{1}H-NMR in DMSO-d$_6$: δ_{ppm} = 3.56 (s, 2H, NH$_2$), 6.76-7.97 (m, 8H, Ar-H), 9.59, 9.71 (2s, 2H, 2NH). Anal. Calcd. for $C_{20}H_{12}N_4O_4$ (372.33): C, 64.52%; H, 3.25%; N, 15.05%. Found: C, 64.33%; H, 3.03%; N, 14.79%.

Results and discussion

The key intermediate, methyl 2-(2-cyanoacetamido)benzoate (**1**),[27] was readily available from the solvent-free reaction of ethyl cyanoacetate with methyl anthranilate. Compound **1** was allowed to react with DMF-DMA in refluxing xylene to afford enaminonitrile **2** in a good yield. The structure of enaminonitrile **2** was confirmed on the basis of its elemental and spectral data. The IR spectrum revealed absorption bands at 3252, 2188, 1700, and 1670 cm^{-1} assignable to NH, C≡N, carbonyl ester, and amidic carbonyl groups, respectively. The ^{1}H-NMR spectrum displayed 4 singlet signals at δ 3.25, 3.89, 7.89, and 11.0 ppm characteristic of 2 methyl groups, methoxy protons, an olefinic proton (CH=), and a NH proton, respectively.

The reactivity of enaminonitrile **2** toward some nitrogen nucleophiles was investigated. Thus, treatment of **2** with hydrazine hydrate in refluxing n-butanol afforded a colorless product for which 2 possible structures, **3** and **6**, could be formulated. The spectroscopic data of the isolated product was in complete agreement with structure **6** as its IR spectrum exhibited nitrile and carbonyl stretching frequencies at 2216 and 1692 cm^{-1}. The ^{1}H-NMR spectrum of **6** displayed a lack of methoxy and NH signals and the appearance of 2 new singlets at δ 8.0 and 11.73 ppm due to pyrazole H-5 and NH-pyrazole, respectively.

The formation of pyrazolo[5,1-*b*]quinazoline **6** is assumed to take place via a Michael-type addition of the amino group of hydrazine to the enamine double bond in **2** to form nonisolable acyclic intermediate **4**, followed by loss of methanol to afford nonisolable quinoxaline **5**, which was readily converted into the final product through water elimination.

In contrast to the behavior of enaminonitrile **2** toward hydrazine, compound **2** reacted with guanidine hydrochloride in ethanol at reflux in the presence of triethylamine to yield methyl 2-(2,4-diaminopyrimidine-5-carboxamido)benzoate (**8**). The structure of pyrimidine derivative **8** was supported on the basis of its elemental

and spectral data. The infrared spectrum of compound **8** indicated the absence of a C≡N group in addition to the presence of NH_2 bands at 3386 and 3324 cm^{-1}. Its ^{1}H-NMR spectrum exhibited 2 singlet signals at δ 3.87 and 7.29 ppm, corresponding to OCH_3 and pyrimidine-H6 protons, respectively. The formation of pyrimidine **8** is assumed to take place through the intramolecular cyclization of nonisolable intermediate **7** (Scheme 1).
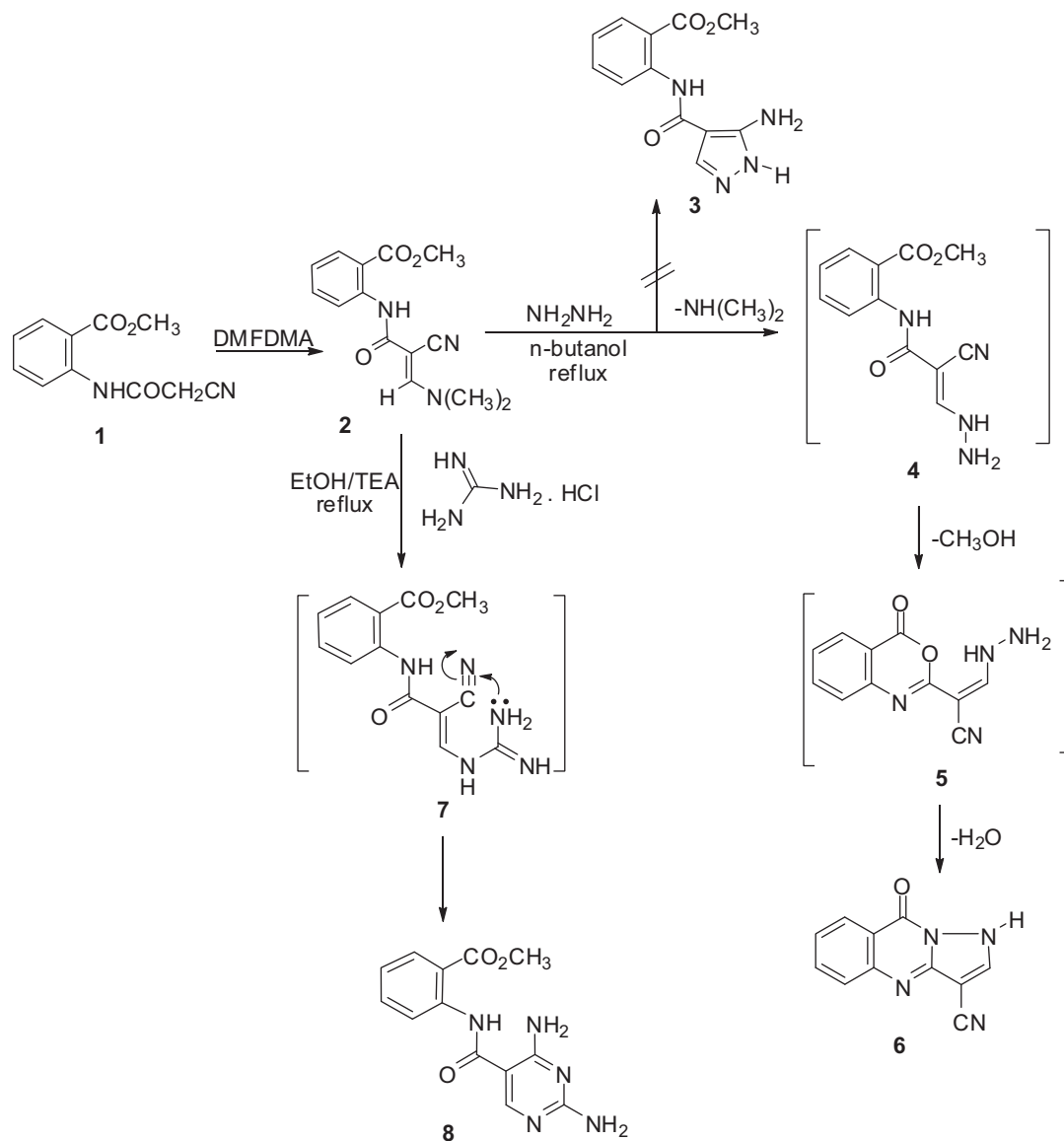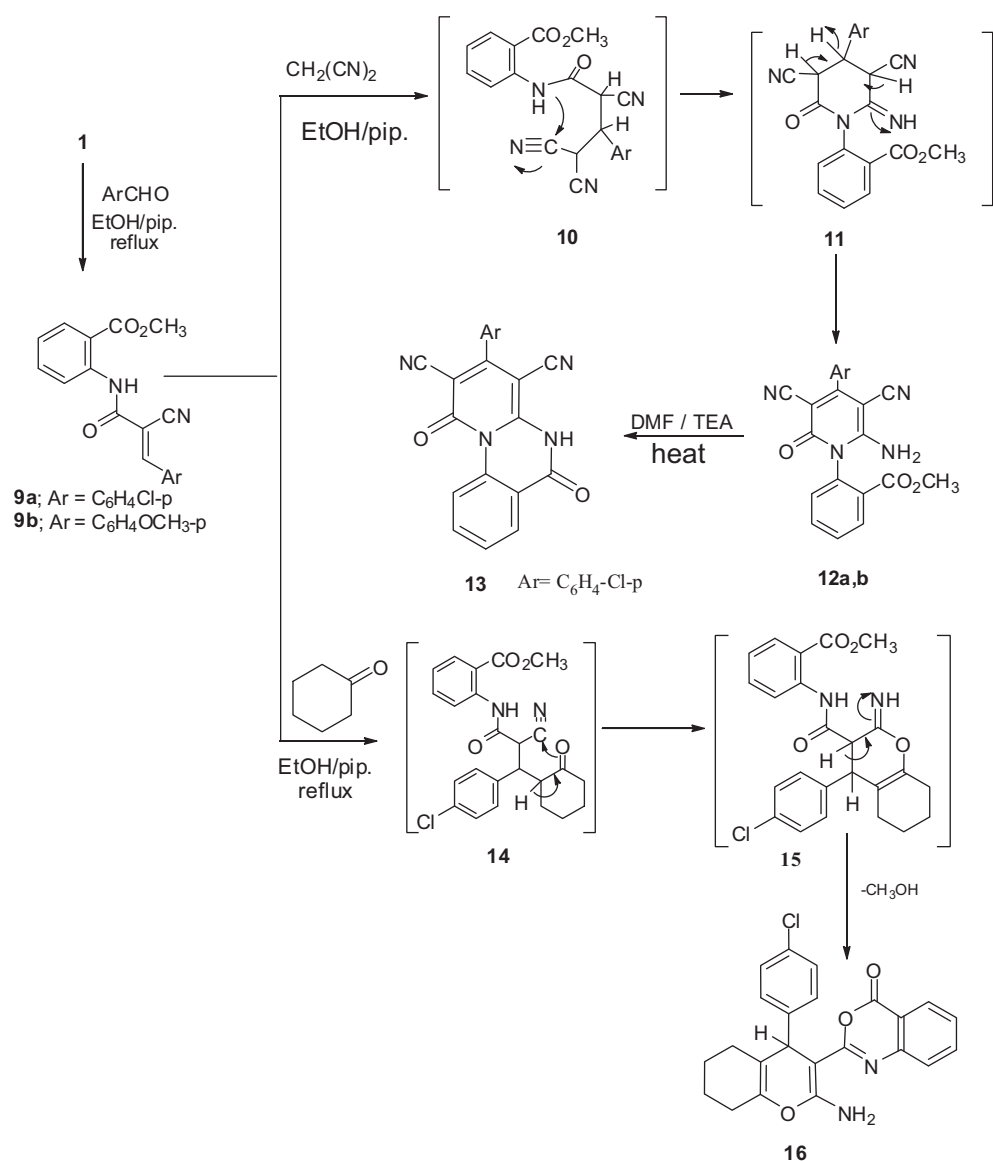

Scheme 1

To explore the synthetic potentiality of cyanoacetanilide **1** in quinazoline synthesis, we investigated the reactivity of compound **1** toward some electrophilic reagents. Thus, the Knoevenagel condensation of cyanoac-etamide **1** with aromatic aldehydes such as *p*-chlorobenzaldehyde and *p*-methoxybenzaldehyde in ethanolic piperidine solution at reflux temperature afforded the corresponding benzylidene derivatives **9a** and **9b**. The structures of compounds **9a** and **9b** were assigned on the basis of their elemental analyses and spectral data.

For example, the ^{1}H-NMR spectrum of **9a** revealed 3 singlet signals at δ 3.9, 8.49, and 11.51 ppm assignable to the methoxy, olefinic, and NH protons, respectively, besides the aromatic protons centered around 7.26-8.39 ppm.

When compounds **9a** and **9b** were reacted with malononitrile in boiling ethanol containing a catalytic amount of piperidine in an attempt to attain the quinazoline nucleus through double cyclization, aminopyridone derivatives **12a** and **12b** were obtained as the sole products via intermediates **10** and **11**. The ^{1}H-NMR spectra of **12a** and **12b** exhibited the presence of a methoxy ester singlet at 3.9 ppm. Compound **12a** could be successfully cyclized into pyrido[1,2-*a*]quinazoline derivative **13** through refluxing in DMF in the presence of triethylamine. The structure of **13** was confirmed based on its elemental analysis and spectral data. Its ^{1}H-NMR spectrum revealed a lack of the methoxy signal in addition to the appearance of a NH proton near 11.43 ppm, besides multiplet signals due to the aromatic protons.

In addition, we found that when benzylidene derivative **9a** was heated with cyclohexanone in refluxing ethanol containing a catalytic amount of piperidine, it afforded corresponding $4H$-3,1-benzoxazin-4-one derivative **16**. The structure of isolated product **16** was established on the basis of its elemental analysis and spectral data. Its IR spectrum exhibited strong stretching frequencies in the region of 3424 and 3248 cm^{-1}, attributable to the amino group, in addition to the presence of a strong absorption band at 1706 cm^{-1} due to a carbonyl group. Its ^{1}H-NMR spectrum in DMSO-d_6 showed no signals attributable to methoxy ester, but displayed a singlet signal at δ 4.85 ppm assigned to the 4-H pyran in addition to the presence of a singlet signal at δ 6.83 ppm exchangeable with D_2O assignable to the NH_2 protons. The formation of compound **16** is assumed to proceed via the Michael-type addition of the active methylene group of cyclohexanone to the activated double bond of **9** to form nonisolable acyclic intermediate **14**, which underwent in situ intramolecular cyclization to give intermediate **15** and the final product through elimination of the methanol molecule (Scheme 2).

Spiro compounds represent an important class of naturally occurring molecules characterized by highly pronounced biological properties.[28,29] In this context, we explored the synthetic versatility of cyanoacetanilide **1** for the synthesis of spiro compounds containing quinazoline moiety. Thus, the 1-pot cyclocondensation reaction of cyanoacetanilide **1**, 1,3-cyclohexanedione, and malononitrile (1:1:1 molar ratio) in a refluxing ethanolic piperidine solution afforded pyrido[1,2-*a*]quinazoline derivative **18**, as indicated by spectral data. The IR spectrum of spiro compound **18** revealed absorption bands at 3160, 2220, 1695, and 1660 cm^{-1} characteristic for NH, nitrile, ketonic carbonyl, and amidic carbonyl groups, respectively. Its ^{1}H-NMR spectrum showed multiplet signals for protons of the methylene groups centered around δ 2.24-2.51 ppm in addition to the presence of 2 singlets at 5.98 and 12.71 ppm exchangeable with D_2O attributable to pyridine-H and NH phenyl group, respectively. The mass spectrum of compound **18** revealed a molecular ion peak at $m/z = 346$ (M^+, 15%), and a base peak was observed in the spectrum at $m/z = 195$ (100%), which is compatible with its molecular formula of $C_{19}H_{14}N_4O_3$. The formation of spiropyridoquinazoline **18** is assumed to proceed through the intramolecular cyclization of nonisolable intermediate **17** via the loss of the methanol molecule (Scheme 3).

9a; Ar = C$_6$H$_4$Cl-p
9b; Ar = C$_6$H$_4$OCH$_3$-p

13   Ar= C$_6$H$_4$-Cl-p
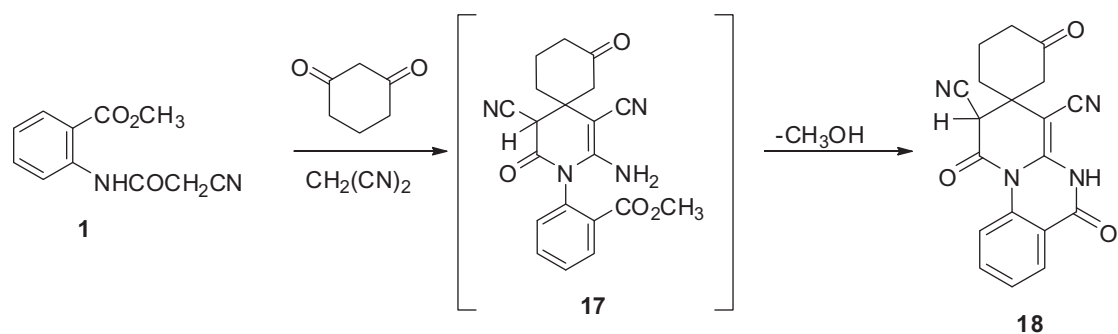
Scheme 2

Scheme 3

It has been reported that compounds with a chromene backbone have a wide range of biological properties.[30−33] Thus, methyl 2-(2-imino-2*H*-chromone-3-carboxamido) benzoate (**19**) was prepared by condensing cyanoacetanilide **1** with salicylaldehyde using piperidine as a catalyst in ethanol at room temperature, following the procedure described earlier by Bylov et al.[34]

Moreover, the resulting chromone derivatives have latent functional constituents, which have the potential for further chemical transformations that give new routes for the preparation of substituted, polycondensed quinazoline derivatives. Reaction of chromone **19** with malononitrile in refluxing ethanol containing a catalytic amount of piperidine afforded chromeno[3',4':4,5]pyrido[1,2-*a*]quinazoline derivative **23** in high chemical yield.

The structure of **23** was inferred from its spectral data. The IR spectrum showed absorption bands at 3334, 3218, 2206, 1656, and 1686 cm^{-1} corresponding to 2 NH, 1 CN, and 2 amidic C=O functions, respectively. Its ^{1}H-NMR spectrum showed a multiplet signal integrated for 8 protons centered at δ 7.51-7.80 ppm due to aromatic protons and 2 singlet signals at 8.93 and 8.97 ppm, which were exchangeable with D$_2$O assigned to 2 NH protons. Based on the foregoing data, structure **23** was assigned to this product.The formation of **23** is assumed to proceed via the Michael addition of the active methylene group of malononitrile to the activated double bond center in **19**, affording the acyclic Michael adduct that spontaneously cyclizes, aromatizes, and loses methanol to yield the final product through intermediates **20, 21**, and **22** (Scheme 4).
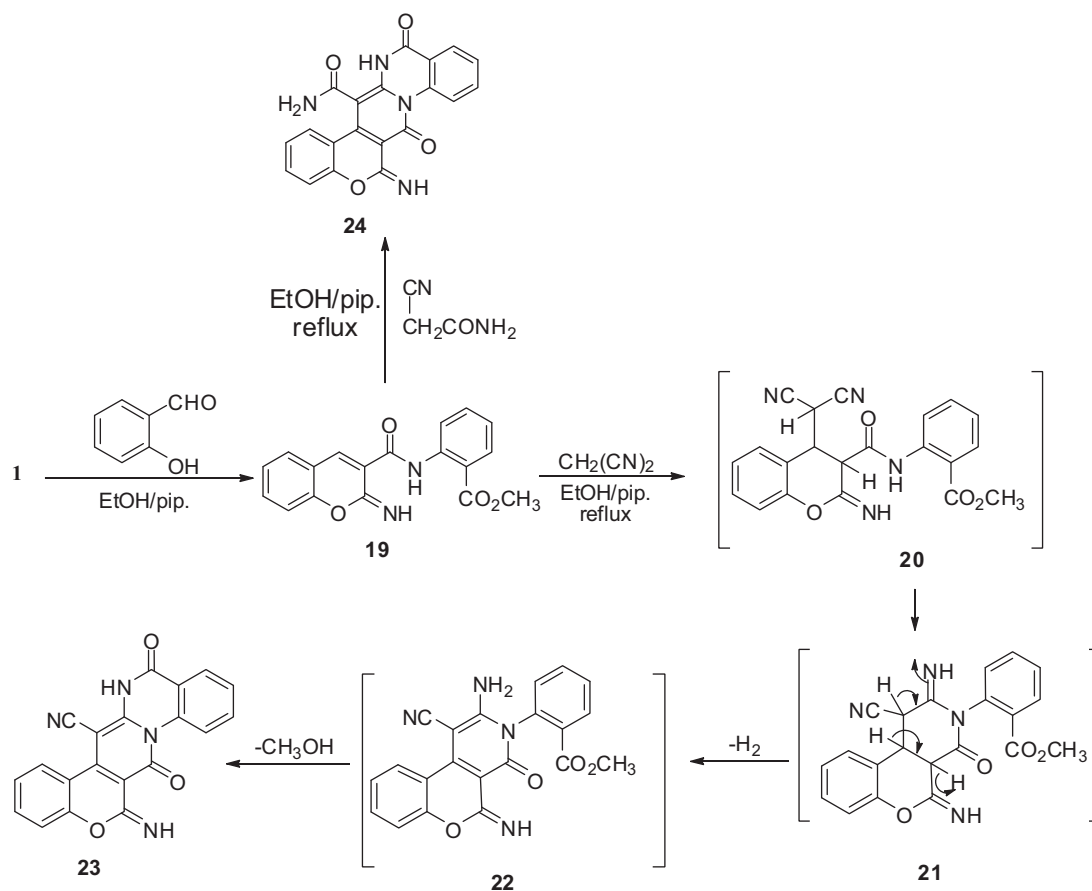
Scheme 4

In a similar manner, the cyclization of chromone **19** with cyanoacetamide in ethanol in the presence of piperidine under reflux furnished chromenopyrido- quinazoline derivative **24**. The structure of **24** was confirmed on the basis of elemental and spectral data. The IR spectrum exhibited absorption bands at 3420 and 3306 cm^{-1} characteristic of the NH$_2$ function. Its ^{1}H-NMR spectrum revealed 2 singlet signals at δ 9.59 and 9.71 ppm, exchangeable with D$_2$O due to 2 NH protons.

Conclusion

We have reported a simple and facile synthesis of new pyrimidine, 4H-3,1-benzoxazin-4-one, pyrazolo[5,1-b]quinazoline, pyrido[1,2-a]quinazoline, and chromeno[3′,4′:4,5]pyrido[1,2-a]quinazoline derivatives starting from the readily accessible methyl 2-(2-cyanoacetamido)benzoate. Plausible mechanisms to account for the formation of the products were suggested. All of the reactions are ecofriendly, and no heavy metals or hazardous solvents are involved (mostly ethanol, n-butanol, and acetic acid were used).

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