Synthesis and Biological Effects of New Derivatives of Azines Incorporating Coumarin

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New synthetic routes for triazolopyridine, pyridopyrimidine, pyridotriazine, imidazopyridine and pyridazine derivatives incorporating a coumarin moiety with interesting biological activities are reported. Reactions of the 2-oxo-4-(2-dimethylaminoethenyl)-2*H*-chromene-3-carbonitrile (**4**) and 2-amino-4-(2-dimethylaminoethenyl)quinoline-3-carbonitrile (**5**) with benzotriazol-1-yl-acetic acid hydrazide (**6**) affords the substituted [1,2,4]triazolo[1,5-*a*]pyrido[3,4-*c*]coumarines **9** and quinoline **12**, respectively. Treatment of **4** with 2-amino-pyridine, glycine, urea, 3-aminocrotononitrile or cyanothioacetamide affords **14**-**18**, respectively. Treatment of 3-amino-3,4-dihydro-4-imino-chromeno[3,4-*c*]pyridin-5-one (**10**) with α-chloroacetylacetone affords pyridotriazine derivative **21**. Compound **4** was also coupled with benzenediazonium chloride to afford 2-oxo-4-[2-oxo-1-(phenyl-hydrazono)-ethyl]-2*H*-chromene-3-carbonitrile **25**. Treatment of the latter product with malononitrile afforded the 1-phenyl-3-(3'-Cyano-2'-oxo-coumarin-4'-yl)-6-oxo-pyridazine-5-carbonitrile (**27**). The structures of the newly synthesized compounds have been established on the basis of analytical and spectral data.

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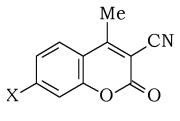
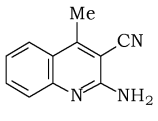
The recent literature is enriched with progressive finding about the synthesis and pharmacological results of fused heterocycles. In conjunction with previous interest in the syntheses of polyfunctionally substituted heterocycles with potential biological activites [1-5]. It was interesting to study the behaviour of system **A** towards a variety of chemical reagents, as a new synthetic route to heterocyclic nitrogen containing compounds, such as triazolopyridine, pyridopyrimidine, pyridotriazine, imidazopyridine, pyridine and pyridazine derivatives incorporating a coumarin moiety. The importance of the above compounds is due to their diverse pharmaceutical activities [6-13] and as thermal-transfer printing dye [14].

System A



1 a: X=H
b: X=OH



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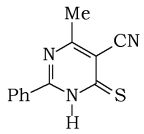

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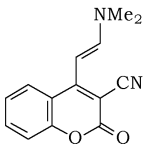

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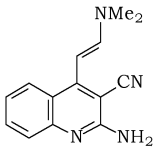

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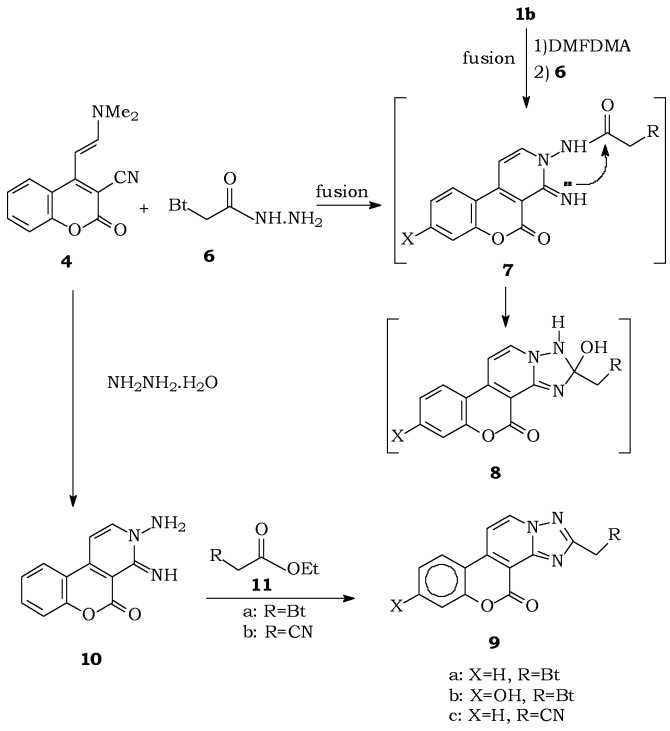
Thus, treatment of **1a** and **2** with dimethylformamide dimethylacetal (DMF DMA) in dry xylene at reflux temperature afforded the (*E*)-dimethylaminoethylene derivatives **4** and **5** in good yield [15]. Upon fusion of **4** with 1*H*-benzotriazol-1-acetic acid hydrazide [16] (**6**) afforded the corresponding [1,2,4]triazolo[1,5-*a*]pyrido-[3',4'-*c*]coumarin **9a** in 68% yield. Compound **9b** was obtained *in situ*, *via* a one step process by fusion of **1b** with DMF DMA followed by treatment of the reaction mixture with hydrazide derivative **6** (Scheme 1).

Scheme 1

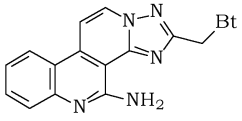


Bt = 1-*H*-Benzotriazol-1-yl

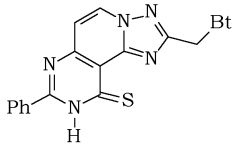
The structure of **9** was established on the basis of its elemental analysis and spectral data. Thus, the ir spectrum of compound **9a** showed an absorption band at 1740 cm^{-1} corresponding to carbonyl group. Its mass spectrum revealed molecular ion peak at *m/z* 368. The ^{13}C nmr spectrum revealed a low field signal at δ_c 163.74 ppm and a high field signal at δ_c 46.40 ppm corresponding to carbonyl and methylene carbons, respectively. Moreover, the ^1H nmr spectrum of the isolated product exhibited a singlet signal at δ_H 6.38 ppm due to methylene protons, in addition to an aromatic multiplet in the region δ_H 7.43 -9.31 ppm. Compound **9** is assumed to proceed *via* initial addition of the amino group of hydrazide derivative **6** to the activated double bond of **4** followed by cyclization and elimination of a dimethylamine molecule to generate the non-isolated iminopyridine intermediate **7**. The latter intermediate undergoes cyclization *via* nucleophilic addition of a NH-group on the carbonyl carbon, followed by aromatization *via* loss of a water molecule to afford the corresponding **9**. Further evidence for the proposed structure **9** was obtained by the independent synthesis of compound **9** *via* fusion of **4** with hydrazine hydrated to afford the *N*-aminopyridine derivative **10**. The latter compound was fused with ethyl-1*H*-benzotriazol-1-acetate **11a** to afford a product identical in all respects (mp and spectra) as *via* the fusion of **4** and **6** (Scheme 1).

In a similar manner, treatment of **10** with ethyl cyanoacetate **11b** afforded 5-cyanomethyl[1,2,4]triazolo[1,5-*a*]pyrido[3',4'-*c*]coumarin **9c** in an excellent yield. The ir spectrum of compound **9c** showed two characteristic absorption band at 2225 and 1737 cm^{-1} due to the nitrile and carbonyl functions, respectively.

Furthermore, the reactivity of compound **6** towards some of the (*E*)-4-dimethylaminoethylene heteroaromatic compounds was also investigated. Thus, fusion of the 4-dimethylaminoethylene quinoline derivative **5** with **6** afforded the triazolopyridoquinoline derivative **12**, while triazolopyridopyrimidine derivative **13** was obtained *in situ*, *via* a one step process by fusion of the 4-methyl-2-phenyl-5-thioxopyrimidine carbonitrile **3** [18,19] with DMF DMA followed by treatment of the reaction mixture with 1*H*-benzotriazol-1-acetic acid hydrazine **6**.



12



13

The structure of the isolated products **12** and **13** were confirmed on the basis of elemental analysis and spectral data. Thus, the ^1H nmr spectrum showed a resonance at approximately δ_H 6.00 ppm corresponding to methylene protons and disappearance of the characteristic signal corresponding to the *N*,*N*-dimethylamino protons. Moreover, the mass spectra for **12** and **13** revealed molecular ion peaks with *m/z* 366 and *m/z* 410, respectively.

On the other hand, the reactivity of compound **4** towards some nitrogen nucleophiles was investigated. Thus fusion of **4** with 2-aminopyridine, afforded the [1]benzopyrano[3,4-*c*]pyridine derivative **14** (Scheme 2). The structure of the isolated product was confirmed on the bases of elemental analysis and spectral data. Thus, the ir spectrum of the reaction product **14** showed imino and carbonyl absorptions at 3257 and 1687 cm^{-1}, respectively, which are compatible with the assigned structure. In a similar manner, fusion of **4** with glycine afforded a high yield of a crystalline product for which structure **15** was assigned on the basis of spectral data (ir and ^1H nmr spectra). Thus, the ir spectrum of the reaction product, showed two absorption band at 1713 and 1653 cm^{-1} due to two carbonyl groups. The ^1H nmr spectrum showed a resonance at δ_H at approximately 3.05 ppm corresponding to CH_2 protons. Moreover, the ^{13}C nmr spectrum of the reaction product revealed two low field signals at δ_C 163.97 and 161.81 ppm corresponding to two carbonyl groups and one high field signal at 36.94 ppm corresponding to the CH_2 carbon. The mass spectrum revealed a molecular ion peak with *m/z* 252 (M^+). The observation described above is consistent with structure **15**. The formation of **15** is assumed to proceed *via* addition of the amino group of glycine to the activated ethylenic double bond of **4** followed by cyclization and elimination of a dimethylamine molecule followed by a second cyclization *via* elimination of a water molecule (Scheme 2).

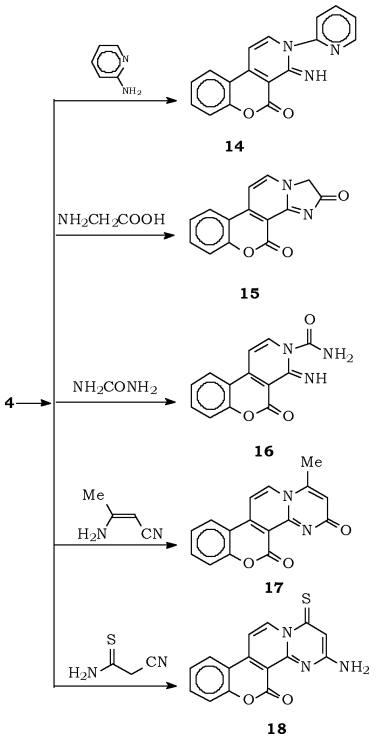
Also fusion of **4** with urea under the same experimental condition afforded a good yield of a product which was identified as [1]benzopyranopyridine derivative **16** (Scheme 2) on the basis of its spectral data. Thus, the ir spectrum of the reaction product **16** showed absorption bands at 3422 and 3284 cm^{-1} due to NH_2 group and in addition to the three absorption bands at 3160, 1668 and 1638 cm^{-1} due to the imino and two carbonyl groups, respectively. The ^1H nmr spectrum of **16** revealed two broad signals (D_2O-exchangeable) at δ 8.64 and 10.42 ppm corresponding to the NH_2 and NH protons, respectively, in addition to a multiplet corresponding to the aromatic protons in the region at δ 6.81-8.30 ppm.

Similarly, upon fusion of **4** with 3-aminocrotononitrile and cyanothioacetamide afforded **17** and **18** respectively (Scheme 2). The ^1H nmr spectra of both compounds revealed an absence of the characteristics signal corresponding the dimethylamino protons of **4**. Compound **17** showed two singlets at δ 2.73 and 8.33 ppm corresponding to the methyl protons and the pyrimidine H-5, respectively. While compound **18** showed one singlet at δ 8.30 ppm corresponding to the H-5 of pyrimidine in addition to multiplets in the

range of δ 6.88-8.63 ppm corresponding to aromatic protons. The ir spectrum of **17** showed an absorption band for the two carbonyl groups at 1720 and 1625 cm^{-1}. The ir spectrum of **18** showed absorption bands for the NH_2 group in the region 3427 and 3350 cm^{-1}, in addition to a strong absorption band at 1691 cm^{-1} for the carbonyl group.

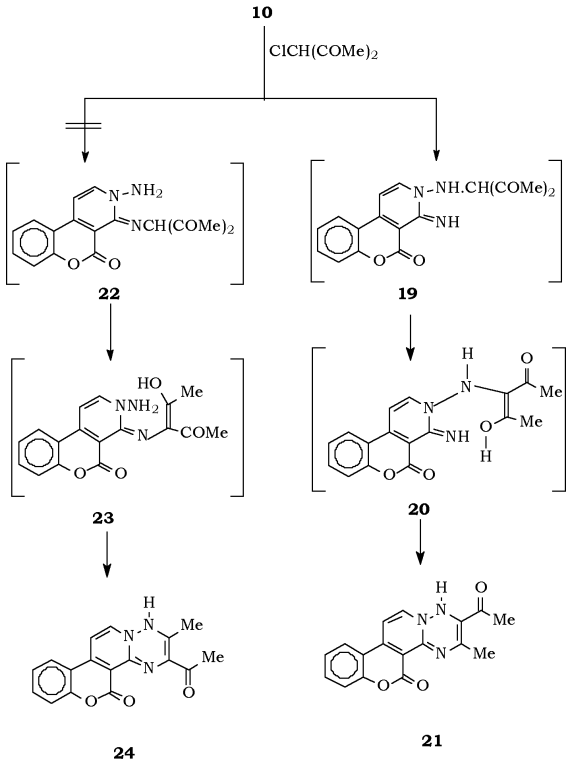
On the other hand, fusion of **10** with α-chloroacetylacetone yielded a product that could be formulated as **21** or their isomer **24**. Thus, the ir spectrum of the reaction product, showed NH and carbonyl absorptions at 3375 and 1699 cm^{-1} respectively (Scheme 3). The ^1H nmr spectrum revealed a methyl group signal at δ 2.50 ppm, an acetyl group signal at δ 2.72 ppm and a signal at δ 9.24 ppm that was assigned to the NH proton.

Scheme 2



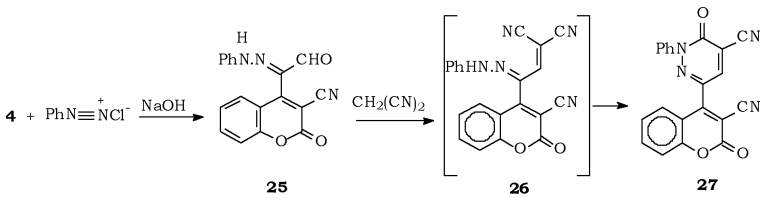
This signal underwent a facile hydrogen deuterium exchange upon addition of deuterium oxide. Structure **24** was readily ruled out on the basis of NOE difference measurements, which reveal the neighborhood of the NH proton and the *ortho* acetyl protons.

Scheme 3



On the other hand, compound **4** was coupled readily with benzene diazonium chloride in the presence of sodium hydroxide to afford the phenyl hydrazone derivative **25** in good yield. Formation of **25** is assumed to be *via* initial formed arylazo derivative which hydrolyzed by sodium hydroxide into arylhydrazono derivative **25**. The latter compound **25** was reacted with malononitrile to afford the pyridazine derivative **27** in good yield. The structure of the isolated product was confirmed on the basis of elemental analysis and spectral data. The ^1H nmr spectrum showed a resonance at δ_H 9.50 corresponding to H-4 of pyridazine in addition to an aromatic multiple at 7.25-8.52 ppm. Moreover the ir spectrum of the reaction product **27** showed strong absorption band at 2196 due to the two CN groups as well as two strong absorption bands at 1728 and 1638 cm^{-1} assignable to the ester and amide carbonyl groups, respectively. The formation of compound **27** was considered to proceed *via* the Knoevenagel condensation intermediate **26** which spontaneously

Scheme 4



cyclises in an intramolecular fashion *via* addition of the amino group of the hydrazone moiety to the CN function to form an imine, which readily hydrolyzed under the reaction condition to give the final isolated product **27** (Scheme 4). Similar phenomena have been previously reported [20].

Biological Activity.

The biological activities of some newly synthesized compounds were screened for their antifungal activity against *Aspergillus niger*, while the antibacterial activity was tested against *Escherchia coli*, *Bacillus subtilis* and *Staphylococcus aureus*. Most of the tested sample showed antibacterial and fungieidal activity (Table 1).

Table 1
In *vitro* Bactericidal and Fungicidal Activity of Newly Synthesized Compounds

Compound	*E-coli*	*B-subtilis*	*S-aureus*	*A-niger*
8a	-	-	-	-
8b	+++	++	-	-
11	-	+++	-	-
12	-	+++	+++	+++
13	+++	+++	-	++++
14	+++	+++	+++	+++
24	-	+++	-	-
26	+++	++	++	+

*No effect = - ; slight effect = + ; Moderate effect = ++ ; strong effect = +++, ++++.

EXPERIMENTAL

All melting points are uncorrected, ir spectra were recorded on a Shimadzu 2000 FT/IR spectrometer. ^{1}H and ^{13}C nmr spectra were recorded on a Brucker 400 MHz spectrometer with dimethyl-d_6 sulfoxide as solvent and tetramethylsilane (TMS) as an internal standard; chemical shifts are reported as δ units (ppm). Mass spectra were measured on GS/MS INCOL XL Finningan MAT instrument. Microanalyses were performed on a Leco-CHNS 932 Analyzer. Compounds **1b, 2-6** were prepared following literature procedure [15-19].

General Procedure for the Synthesis of **9a-c, 12** and **13**.

Method A.

A mixture of **4** or **5** (0.01 mol) and **6** (1.91 g, 0.01 mol) was fused at 120-130 °C in oil bath for one hour. The fused product was dissolved in anhydrous dimethylformamide (DMF) (10 mL) then poured into ice-cold water (100 mL). The solid product, so formed, was collected by filtration and recrystallized from a mixture of dimethylformamide (DMF) and ethanol in ratio 2:1.

Method B.

A mixture of **10** (2.27 g, 0.01 mol) and each of 1*H*-benzotriazol-1-acetate **11a** or ethyl cyanoacetate **11b** (0.01 mol) was fused at 120-130 °C in oil bath for one hour. The fused product was dissolved in anhydrous DMF (10 mL). The solid product, so formed, was collected by filtration and recrystallized from DMF.

Method C.

A mixture of **1b** or **3** and dimethylformamide dimethylacetal (DMF DMA) (1.33 g, 0.01 mol) was fused at 180 °C for 15 minutes, then allowed to cool at room temperature. The reaction mixture was dissolved in DMF and treated with 1*H*-benzotriazol-1-acetic acid hydrazide **6** (1.91 g, 0.01 mol) and then refluxed for one hour. The solvent was evaporated under reduced pressure. The solid product, so formed, was collected by filtration and recrystallized from a mixture of DMF and ethanol in ratio 2:1.

5-(N^1-Benzotriazolomethyl)[1,2,4]triazolo[1,5-*a*]pyrido-[3',4'-*c*]-coumarin (**9a**).

This compound was obtained as brown crystals (86%); mp. 264-266 °C; ir: ν_{max} 1740 cm^{-1} (CO); ^{1}H nmr: δ_H 6.38 (2H, s, CH_2); 7.43-9.31 ppm (10H, m, Ar-H); ^{13}C nmr: δ_C 163.74 (CO), 156.02 (C-8a), 153.30 (C-2), 149.83, 146.12, 140.98 (C-5, C-6a and C-3a benzotriazolyl), 135.45, 134.05, 133.99, 128.43, 126.20, 125.79, 124.98, 120.04, 118.11, 116.78, 111.81, 109.25, 108.75 (aromatic carbon atoms) and 46.40 ppm (CH_2), MS (EI): *m/z* = 368 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_6O_2$: C, 65.21; H, 3.28; N, 22.82. Found: C, 65.20, H; 3.49; N, 22.96.

5-(N'-Benzotriazolomethyl)-10-hydroxy[1,2,4]triazolo-[1,5-*a*]-pyrido[3',4'-*c*]coumarin (**9b**).

This compound was obtained as brown crystals (85%); mp. 276-278 °C; ir: ν_{max} 1757 cm^{-1} (CO); ^{1}H nmr: δ_H 6.38 (2H, s, CH_2); 6.78 (1H, s, H-9), 6.86-9.19 (8H, m, Ar-H) and 10.70 (1H, br, OH), MS (EI): *m/z* = 384 (M^+).

Anal. Calcd. for $C_{20}H_{12}N_6O_3$: C, 62.50; H, 3.15; N, 21.87. Found: C, 62.82; H, 3.51; N, 21.66.

5-Cyanomethyl-[1,2,4]triazolo[1,5-*a*]pyrido[3',4'-*c*]coumarin (**9c**).

This compound was obtained as brown crystals (76%); mp. 230-232 °C; ir: ν_{max} 2225 (CN), 1737 (CO); ^{1}H nmr: δ_H 4.50 (2H, s, CH_2), 7.31-9.38 ppm (6H, m, Ar-H).

Anal. Calcd. for $C_{15}H_8N_4O_2$: C, 65.21; H, 2.99; N, 20.28. Found: C, 64.98; H, 3.25; N, 20.02.

3-Amino-4,5-dihydro-4-imino-chromeno[3,4-*c*]pyridin-5-one (**10**).

A mixture of **4** (2.40 g, 0.01 mol) and hydrazine hydrate (1.50 mL, 0.03 mol) was fused at 120 °C for 5 minutes in oil bath. The fused product was dissolved in ethanol (20 mL). The solid product so formed, was collected by filtration and recrystallized from ethanol as pale green crystals (1.86 g, 82%); mp. 205-207 °C; ir: ν_{max} 3421 & 3306 (NH_2), 3116 (NH) and 1697 cm^{-1} (CO); ^{1}H nmr: δ_H 6.60 (2H, bs, NH_2, D_2O-exchangeable), 6.70-8.12 (6H, m, Ar-H), 9.42 (1H, bs, NH, D_2O-exchangeable).

Anal. Calcd. for $C_{12}H_9N_3O_2$: C, 63.43; H, 3.99; N, 18.49. Found: C, 63.44; H, 4.04; N, 18.59.

7-Amino-5-(N^1-benzotriazolomethyl)[1,2,4]triazolo[1,5-*a*]-pyrido-[3',4'-*c*]quinoline (**12**).

This compound was obtained as pale yellow crystals (69%); mp. 220-222 °C; ir: ν_{max} 3413 & 3329 cm^{-1} (NH_2); ^{1}H nmr: δ_H 6.43 (2H, s, CH_2); 7.45-8.33 (10H, m, Ar-H) and 9.11 ppm (2H, bs, NH_2); ^{13}C nmr: δ_c 166.34 (C-7), 160.97 (C-8a), 156.48 (C-2), 149.24, 148.06, 146.06 (C-5, C-6a, C-3a benzotriazolyl), 137.05, 134.02, 133.47, 130.73, 128.48, 126.96, 125.92, 124.76, 123.60,

121.74, 118.52, 116.94, 111.63 (aromatic carbon atoms) and 46.10 ppm (CH_2); MS (EI): *m/z*=366 (M^+).

Anal. Calcd. for $C_{20}H_{14}N_8$: C, 65.56; H, 3.85; N, 30.56. Found: C, 65.27; H, 4.01; N, 30.75.

5-(N^1-Benzotriazolomethyl)-7,8-dihydro-9-phenyl-7-thioxo[1,2,4]triazolo[1,5-*a*]pyrido[4',3'-*c*]pyrimidine (**13**).

This compound was obtained as brown crystals (68%), mp 112-115 °C; ir: ν_{max} 3439 cm^{-1} (NH); ^1H nmr: δ_H 6.19 (2H, s, CH_2); 7.45-8.31 (11H, m, Ar-H), 8.57 ppm (1H, s, NH, D_2O exchangeable); ^{13}C nmr: δ_c 179.15 (C-7), 166.05 (C-9), 164.93 (C-10a), 163.30 (C-2), 149.22, 146.72, 140.88 (C-5, C-6a, C-3a benzotriazolyl), 132.97, 132.89, 132.02, 129.78, 129.42, 128.53, 127.56, 126.44, 124.92, 124.14, 119.90 (aromatic carbon atoms) and 45.51 ppm (CH_2); MS (EI): *m/z*=410 (M^+).

Anal. Calcd. for $C_{21}H_{14}N_8S$: C, 61.46; H, 3.43; N, 27.30. Found: C, 61.38; H, 3.63; N, 27.55.

General Procedure for the Synthesis of (**14**-**18**).

A compound **4** (0.01 mol) was fused with each 2-aminopyridine (0.94, 0.01 mol) or glycine (0.75 g, 0.01 mol), or urea (0.60 g, 0.01 mol); or 2-aminocrotononitrile (0.82 g, 0.01 mol) or cyanothioacetamide (1.0 g, 0.01 mol) at 120-130 °C for one hour. The fused product was dissolved in anhydrous DMF (10 mL). The solid product, so formed, was collected by filtration and recrystallized from DMF.

4,5-Dihydro-4-imino-5-oxo-3-(pyrid-2'-yl)[1]benzopyrano[3,4-*c*]-pyridine (**14**).

This compound was obtained as brown crystals, (78%); mp. 180-182 °C; ir: ν_{max} 3257 (NH), 1687 cm^{-1} (CO); ^1H nmr: δ_H 7.05-8.60 (10H, m, Ar-H), 11.26 (1H, s, NH); ^{13}C nmr: δ_C 164.75 (C-5), 162.27 (C-6a), 155.79 (C-4), 154.57 (C-2), 154.51, 153.03 (C-2', C-6'), 149.17, 145.07, 139.22, 134.10, 125.81, 119.54, 118.17, 117.12, 114.53, 108.54 and 101.21 ppm (aromatic carbon atoms).

Anal. Calcd. for $C_{17}H_{11}N_3O_2$: C, 70.58; H, 3.80; N, 14.52%). Found: C, 70.72; H, 4.06; N, 14.60

5,7-Dihydro-4*H*-5,7-dioxo-imidazo[1,2-*a*]pyrido[3',4'-*c*]-coumarin (**15**).

This compound was obtained as brown crystals (82%), mp. 192-194 °C; ir: ν_{max} 1713 and 1653 cm^{-1} (2CO); ^1H nmr: δ_H 3.05 (2H, s, CH_2); 7.38-7.95 (6H, m, Ar-H); ^{13}C nmr: δ_C 163.97 & 161.81 (2CO), 157.92 (C-8a), 155.28 (C-2), 153.23, 152.30, 144.53, 136.23, 133.57, 127.63, 126.31, 125.72, 117.73 (aromatic carbons) and 36.94 ppm (CH_2); MS (EI): *m/z*=252 (M^+).

Anal. Calcd. for $C_{14}H_8N_2O_3$: C, 66.66; H, 3.20; N, 11.11. Found: C, 67.00; H, 3.02; N, 11.09.

3-Acetomido-4,5-dihydro-4-imino-5-oxo[1]benzopyrano[3',4'-*c*]-pyridine (**16**).

This compound was obtained as pale brown crystals (73%); mp. 210-212 °C; ir: ν_{max} 3422 & 3284 (NH_2), 3160 (NH), 1668 & 1633 cm^{-1} (2CO); ^1H nmr: δ_H 6.81-8.30 (6H, m, Ar-H), 8.64 (2H, bs, NH_2, D_2O-exchangeable) and 10.42 ppm (1H, bs, NH, D_2O-exchangeable); ^{13}C nmr: δ_C 166.04 and 162.82 (2CO), 157.43 (C-6a), 155.98 (C-4), 155.04 (C-2), 152.61, 150.79, 144.41, 139.01, 133.24, 126.39, 125.46 and 118.12 ppm (aromatic carbons), MS (EI): *m/z*=255 (M^+).

Anal. Calcd. for $C_{13}H_9N_3O_3$: C, 61.17; H, 3.55; N, 16.47. Found: C, 61.24; H, 3.62; N, 16.30.

6,8-Dihydro-4-methyl-6,8-dioxo[1]benzopyrano[3',4'-*c*]-pyrido[1,2-*a*]pyrimidine (**17**).

This compound was obtained as brown crystals (79%); mp. 160-162 °C; ir: ν_{max} 1720 and 1625 cm^{-1} (2CO); ^1H nmr: δ_H 2.73 (3H, s, Me), 7.34-8.01 (6H, m, Ar-H) and 8.33 ppm (1H, s, H-5); ^{13}C nmr: δ_C 163.47 & 160.32 (2CO), 159.19 (C-7a), 156.48 (C-9a), 154.19 (C-4), 151.74 (C-2), 150.81, 143.08, 136.11, 134.75, 132.13, 126.0, 124.82, 123.73, 119.25 (aromatic carbons) and 26.48 ppm (Me).

Anal Calcd. for $C_{16}H_{10}N_2O_3$: C, 69.06, H, 3.62, N, 10.06. Found: C, 69.33, H, 3.91, N, 10.08.

6-Amino-4,8-dihydro-4-thioxo[1]benzopyrano[3',4'-*c*]-pyrido[1,2-*a*]pyrimidine (**18**).

This compound was obtained as brown crystals (80%); mp. 212-213 °C; ir: ν_{max} 3427 & 3350 (br, NH_2) and 1691 cm^{-1} (CO); ^1H nmr: δ_H 6.88-8.63 (6H, m, Ar-H), 8.30 ppm (1H, s, H-5) and 11.74 (2H, br, NH_2, D_2O-exchangeable); ^{13}C nmr: δ_C 176.80 (C-4), 167.21 (C-8), 164.51 (C-7a), 159.61(C-6), 153.51 (C-9a), 151.59 (C-2), 136.11, 135.50 131.50, 128.91, 127.90, 126.94, 125.32, 124.55 and 118.91 (aromatic carbons); MS (EI); *m/z*=295 (M^+).

Anal. Calcd. for $C_{15}H_9N_3O_2S$: C, 61.02; H, 3.07, N, 14.23. Found: C, 60.97; H, 3.08; N, 14.26.

5-Acetyl-6-methyl-8-oxo[1]benzopyrano[3',4'-*c*]pyrido[1,6-*a*]-1,2,4-triazine (**21**).

Compound **10** (2.40 g, 0.01 mol) was fused with α-chloroacetylacetone (1.19 g, 0.01 mol) at 120-130 °C for one hour. The fused product was dissolved in anhydrous dimethylformamide (10 mL). The solid product, so formed, was collected by filtration and recrystallized from DMF as brown crystals (83%); mp. 175-177 °C; ir: ν_{max} 3375 (br, NH), 1699 & 1633 cm^{-1} (2CO); ^1H nmr: δ_H 2.50 (3H, s, Me), 2.72 (3H, s, Me), 7.16-8.57 (6H, m, Ar-H) and 9.24 (1H, bs, NH_2, D_2O-exchangeable).

Anal. Calcd. for $C_{17}H_{13}N_3O_3$: C, 66.41, H, 4.26, N, 13.66. Found: C, 66.09; H, 4.29; N, 13.97.

2-Oxo-4-[2-oxo-1-(phenylhydrazono)ethyl]-2H-chromene-3-carbonitrile (**25**).

To a cold solution **4** (2.40 g, 0.01 mol) in ethanol (50 mL) containing NaOH (0.40 g) benzenediazonium chloride was added. The mixture was stirred at room temperatuare for one hour. The solid product, so formed, was collected by filtration and recrystallized from ethanol as red crystals (71%); mp. 150-152 °C; ir: ν_{max} 3423 (NH), 2197 (CN), 1737 & 1675 cm^{-1} (2CO); ^1H nmr: δ_H 7.30-8.54 (9H, m, Ar-H); 9.90 (1H, s, CHO) and 12.20 ppm (1H, s, NH).

Anal. Calcd. for $C_{18}H_{11}N_3O_3$: C, 68.14; H, 3.49; N, 13.24. Found: C, 68.37, H, 3.78; N, 13.55.

1-Phenyl-3-(3'-Cyano-2'-oxo-coumarin-4'-yl)-6-oxo-pyridazine-5-carbo-nitrile (**27**).

A suspension of **25** (3.17 g, 0.01 mol) in a mixture of dimethylformamide and ethanol (2:1) (30 mL) was treated with malononitrile (0.66 g, 0.01 mol). The mixture was heated for 5 minutes, and then left overnight. The solid product, so formed, was col-

lected by filtration and recrystallized from ethanol as red crystals (67%), mp. 162-164 °C; ir: ν_{max} 2196 (b, 2CN), 1728 and 1638 cm^{-1} (2CO); ^1H nmr: δ_H 7.25-8.52 (9H, m, Ar-H), 9.50 (1H, s, H-4); ^{13}C nmr: δ_C 160.52 (C-2'), 159.05 (C-6), 155.95 (C-8a'), 153.93 (C-3), 152.32, 143.58, 135.43, 130.53, 129.28, 128.26, 126.49, 125.25, 123.86, 120.57, 118.41 (aromatic carbon atoms), 116.72, 115.23 (2CN), 93.52 and 89.5 ppm (C-5 and C-3').

Anal. Calcd. for $C_{21}H_{10}N_4O_3$: C, 68.85; H, 2.75; N, 15.29. Found: C, 68.90; H, 3.04; N, 15.15.

Biological Testing.

The newly synthesized compounds were tested against the specified microorganism, using 400 μg/mL (w/v) solutions in sterile dimethyl-d_6 sulfoxide (DMSO). A solution of the tested compound (0.01 mol) was poured aseptically in a well of 6 mm diameter made by a borer in seeded agar medium. After transferring *via* pipette the same volume in wells of all tested microorganisms, bacteria test plates were incubated at 37 °C for 24 hours and fungal test plates were incubated at 25 °C for 48 hours. The activities were expressed as inhibition zones (mm, diameter, as clear areas). The least concentration, which showed inhibitory effect on any specific micoorganism, was considered as the minimum inhibitory concentration (MIC) which was determined using *streptomycin* and *mycostatin* (50 μg/ml) as the references.

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