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Synthesis, Characterization and Reactions of 2-Deoxo-5-deazaalloxazines

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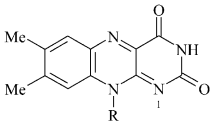
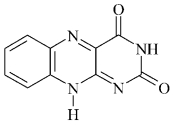
Abstract—5-Deazaflavins and their homologues have been known as potential riboflavin antagonists, bioreductives, and compounds with potent antitumor activity. 2-Amino-4-methylquinoline-3-carbonitrile (**2**) was prepared as unreported starting material for several interesting 2-deoxo-5-deazalloxazine derivatives. Cyclization of **2** using formamide afforded the 2,4-deoxo-5-deazaalloxazine derivative **7**, which was subjected to deamination with nitrous acid to give the 2-deoxo-5-deazaalloxazine (**8**). The compound **8** was also obtained via **13** by treating the latter with refluxing formic acid or formamide and used as a precursor for synthesis of several 2-deoxo-5-deazaalloxazines **18**, **19**, **20**, **21** and **22**. The pharmacological and biological properties of these compounds are still under investigation.

Introduction

From the chemical, biological and pharmaceutical point of view, a series of 5-deazaflavins and related compounds have been studied.[1–3] It is interesting that some of the 5-deazaflavin, derivatives where the nitrogen atom existing in the isoalloxazine ring at N(10) is replaced by carbon atom, revealed potential biological activity including antitumor and antiviral activities.[4]

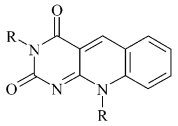


Flavin
(10-alkyl-7,8-dimethylisoalloxazine)

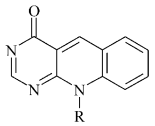


Isoalloxazine

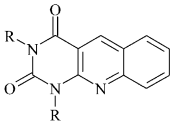
It is known that 5-deazaflavin cofactor is an essential co-enzyme, and is involved in the reduction of CO_2 to methane in the biological system.[1] 5-Deazaflavin catalyzes the splitting of thymidine dimer as photoreactivating coenzyme.[5]



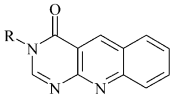
5-Deazaisoalloxazine
5-Deazaflavin
(Pyrimido[4,5-b]quinoline-2,4(3H, 10H)-dione)



2-Deoxo-5-deazaisoalloxazine
2-Deoxo-5-deazaflavin



5-Deazaalloxazine
(Pyrimido[4,5-b]quinoline-2,4(1H, 3H)-dione)



2-Deoxo-5-deazaalloxazine

5-Deazaflavins were synthesized as potential riboflavin antagonists and were also found to be multifunctional and reactive and to serve as cofactors for several flavins, naturally occurring F 420.[6] Some heterocyclic compounds containing a quinoline moiety are of importance owing to their industrial drugs and biological activities, especially antimalaria,[7] antibacterial,[8,9] analgesic agents.[10] They also show moderate activity against *Aspergillus niger*[11] and higher activity towards tumor cells.[12] A series of nitro-5-deazaflavins, possessing a nitro group at C(6)–C(9) have been designed and synthesized as a novel class of bioreductive hetero-aromatic nitro compounds, and their cytotoxicities towards L1210 and KB cells have been evaluated. The redox systems of nitro-5-deazaflavins showed much more

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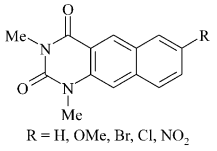
potent antitumor activities than other 5-deazaflavins bearing no nitro group.[12] 5-Deazaflavins (5-deazaisoalloxazines), have been synthesized as potential riboflavin antagonists.[13]

In 1977, Senga et al. prepared a number of isoalloxazine derivatives via treatment of uracil derivatives with aromatic amines in the presence of dimethylformamide dimethylacetal.[14] The importance of isoalloxazine in riboflavin and its coenzyme derivatives FMV and FAD was studied several years ago.[15]

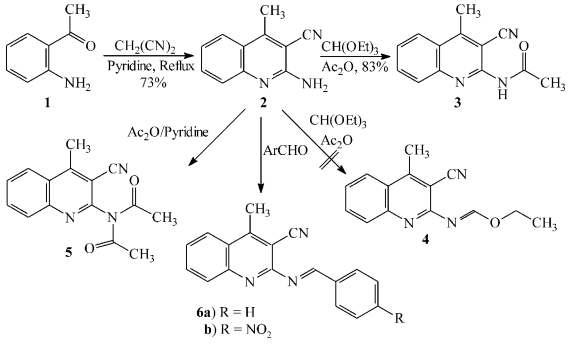


R = H, OMe, Br, Cl, NO_2

Results and Discussion

The synthetic methods of pyrimidoquinoline derivatives using pyrimidine moiety[11,16–18] or quinoline moiety[8,10,19] as starting materials have appeared in the literature. The synthetic pathway and biological properties of alloxazine derivative have been discussed recently in literature.[20] Here, we present a synthetic route to 2-amino-4-methylquinolin-3-carbonitrile (**2**), which is converted into a number of 2-deoxy-5-deazaalloxazine. 2-Amino-4-methylquinolin-3-carbonitrile (**2**) was prepared in 73% yield from 2-aminoacetophenone (**1**) by treatment with malononitrile in refluxing pyridine.

An attempt to obtain 4-methyl-2-ethoxymethylideneaminoquinoline-3-carbonitrile (**4**) via condensation of **2** with triethyl orthoformate in refluxing acetic anhydride was unsuccessful, and the *N*-acetyl derivative **3** was obtained in 83% yield. On the other hand, acetylation of **2** using a 4:1 mixture of acetic anhydride and pyridine produced the *N,N*-diacetyl derivative **5** as pale brown crystals in 69% yield. Condensation of **2** with benzaldehyde or *p*-nitrobenzaldehyde in ethanol containing a few drops of piperidine as a basic catalyst gave the corresponding arylidene derivatives **6a** and **6b** in 60 and 78% yields, respectively (Scheme 1).



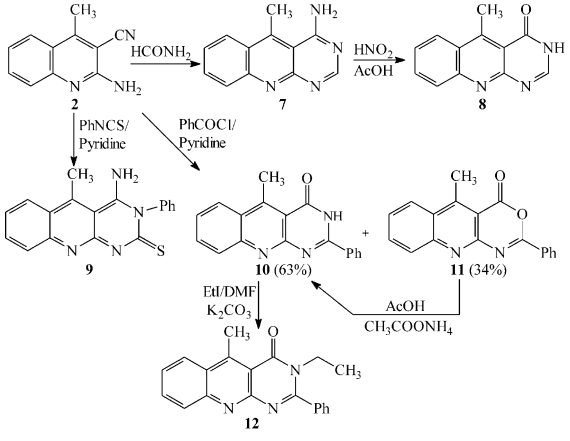
Scheme 1.

On the other hand, refluxing of **2** with formamide for 20 h afforded 4-amino-5-methyl-pyrimido[4,5-*b*]quinoline (**7**), which converted into 5-methyl-3*H*-2-deoxo-5-deazaalloxazine (**8**) in good yield by treatment with nitrous acid in acetic acid. The reaction of **2** with phenyl isothiocyanate in pyridine gave 4-amino-5-methyl-3-phenyl-2-thioxopyrimido[4,5-*b*]quinoline (**9**). The IR spectrum of compound **9** revealed the absorption bands at ν 3400, 3300 (NH_2), 1640 (C=N), 1580 (C=C), 1140 cm^{-1} (C=S). The ^1H NMR (DMSO-d_6) showed signals at δ 3.0 (s, 3H, CH_3), 4.1 (br, 2H, NH_2, exchangeable on deuteration), and 7.5–8.3 ppm (m, 9H, aromatic–H). The MS exhibited peaks at 320 (6.3) [$M^+ + 2$], 319 (23.9) [$M^+ + 1$], and 318 (100) [M^+].

The reaction of **2** with benzoyl chloride gave a separable mixture of 5-methyl-2-phenyl-2-deoxo-5-deazaalloxazine (**10**) (63% yield) and 5-methyl-2-phenyl-1,3-oxazino[4,5-b]quinoline-4-one (**11**) (34% yield). The compound **10** was independently obtained from **11** by treatment with ammonium acetate in refluxing acetic acid. Alkylation of **10** with ethyl iodide in dimethylformamide in the presence of K_2CO_3 afforded the corresponding **12** (Scheme 2).

Hydrolysis of **2** using 60% H_2SO_4 gave 2-amino-4-methylquinoline-3-carboxamide (**13**) in 90% yield. On cyclization using glacial acetic acid, **13** gave a mixture of 2,5-dimethyl-2-deoxo-5-deazaalloxazine (**14**) (63% yield) and 2-acetylamino-4-methylquinoline-3-carboxylic acid (**15**) (35% yield). The latter **15** being isolated from the derivative **14** by acidification of the filtrate of **14** with acetic acid. In addition, reaction of **13** with phenyl isothiocyanate in refluxing pyridine afforded the product **16**. Furthermore, refluxing of **13** with formamide or formic acid afforded the 5-methyl-2-deoxo-5-deazaalloxazine derivative (**8**) in good yield (61%) (Scheme 3).

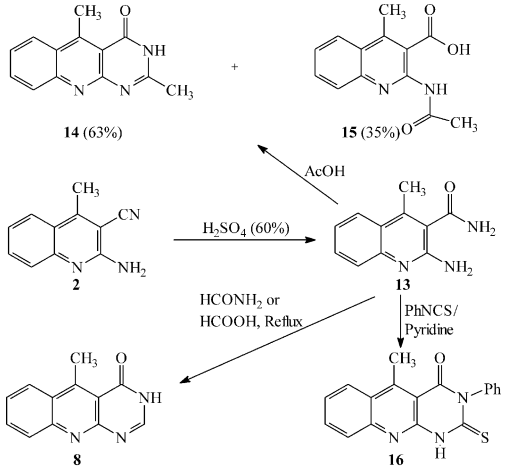
Treatment of 5-methyl-2-deoxo-5-deazaalloxazine (**8**) with hydrazine hydrate in refluxing ethanol afforded the *N*-amino derivative (**17**) in 43% yield (Scheme 4). The IR spectrum of the product (**17**) revealed absorptions at ν 3320 and 3400 cm^{-1} (NH_2) and 1660 cm^{-1} (CON). The NMR spectrum of compound **17** showed a signal at δ 7.8 ppm (NH_2, exchangeable on deuteration.



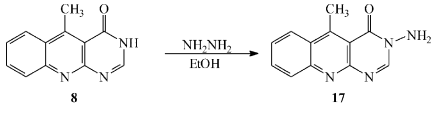
Scheme 2.

Furthermore, on refluxing **8** with a mixture of phosphorus pentachloride and phosphorus oxychloride for 4 h, the corresponding 4-chloro derivative (**18**) was obtained in 60% yield. In addition, heating **8** with phosphorus pentasulfide in pyridine gave the corresponding compound (**19**) in good yield (74%). The derivative (**19**) was also obtained in 74% yield via reaction of **18** with thiourea in refluxing ethanol. Nucleophilic substitution of the compound **18** using sodium methoxide in methanol gave the methoxy derivative **20** in 44% yield (Scheme 5).

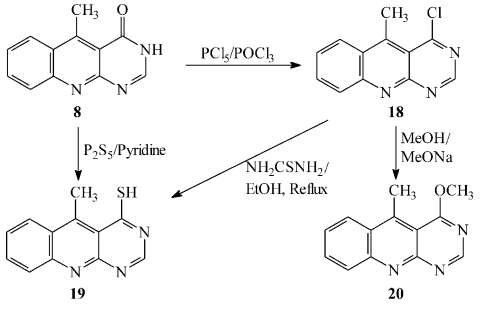
The structure of compound **17** was supported by GC–MS spectroscopy, and the spectrum showed the exact molecular ion peak at 226 [M^+]. The elemental analysis of **17** was also in agreement with the calculated value.



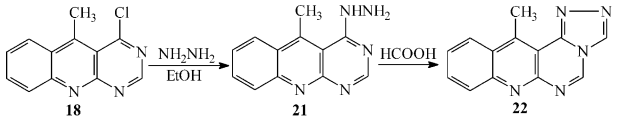
Scheme 3.



Scheme 4.



Scheme 5.



Scheme 6.

Treatment of **18** with hydrazine hydrate in ethanol gave the hydrazino derivative (**21**) in 73% yield. The hydrazino compound (**21**) was then cyclized using formic acid to afford the corresponding 12-methyl-1,2,4-triazolo[3′,4′:6,1]pyrimido[4,5-b]quinoline (**22**) in 66% yield (Scheme 6).

The structures of all new compounds were confirmed by means of spectral analysis such as IR, NMR, and MS spectra. Elemental analyses of all compounds were in satisfactory agreement with the calculated values.

Experimental

All melting points were determined in open glass capillaries and are uncorrected. The ^{1}H NMR spectra were measured in $CDCl_3$ or DMSO-d_6 using TMS as an internal standard on an EM 360 90 MHz NMR spectrometer. Elemental analyses were carried out on a Perkin-Elmer 240C microanalyser. Mass spectra were measured on GC/MS Finnigan mat SCQ 7000, Digital DEC 3000, EI eV 70.

2-Amino-4-methylquinoline-3-carbonitrile (2). A mixture of 2-aminoacetophenone (**1**) (10 mmol) and malononitrile (10 mmol) in dry pyridine (50 mL) was refluxed for 2 h. After cooling, the precipitate thus formed was collected by filtration and washed with ethanol. The crude product was recrystallized from DMF to give **1** as pale brown crystals (73% yield), mp 297–299 °C; IR (KBr): ν 3400, 3300 (NH_2), 2200 (CN), 1620 (C=N), 1600 (C=C) cm^{-1}. ^{1}H NMR (DMSO-d_6): δ = 2.90 (s, 3H, CH_3), 3.90 (br, 2H, NH_2, exchangeable with D_2O), 7.30–8.00 ppm (m, 4H, Ar-H). MS *m/e* (%) 184 [$M^+ + 1$] (9), 183 [M^+] (100). Anal. calcd for $C_{11}H_9N_3$ (183.2): C, 72.11; H, 4.95; N, 22.93. Found: C, 72.00; H, 4.68; N, 23.09.

2-Acetylamino-4-methylquinoline-3-carbonitrile (3). A mixture of **2** (10 mmol), ethyl orthoformate (10 mmol) and acetic anhydride (10 mL) was refluxed for 3 h. The reaction mixture was concentrated under reduced pressure to one third of its original volume and then poured onto ice/water mixture. The resulting precipitate was filtered and recrystallized from benzene to give the corresponding monoacetylated derivative (**3**) (83% yield), mp 138–140 °C. IR (KBr): ν 3250 (NH), 2220 (CN), 1680 ($COCH_3$), 1600 (C=N), 1580 cm^{-1} (C=C). ^{1}H NMR ($CDC1_3$): δ 2.20 (s, 3H, CH_3CO), 3.00 (s, 3H, CH_3), 7.40–8.30 ppm [m, 5H, (4H, Ar-H and 1H, NH after deuteration became integrated 4H]. Anal. calcd for $C_{13}H_{11}N_3O$ (225.2): C, 69.33; H, 4.92; N, 18.66. Found: C, 69.63; H, 4.69; N, 18.67.

2-Diacetylamino-4-methylquinoline-3-carbonitrile (5). A sample of **2** (10 mmol) was heated in a 1:4 mixture acetic anhydride (5 mL) and pyridine (20 mL) mixture at 80 °C for 1 h. After cooling, the reaction mixture was poured onto ice, and the precipitate thus formed was collected and recrystallized from dilute acetic acid to give pale

brown crystals (69% yield), mp 130–135 °C. IR (KBr): ν 2200 (C≡N), 1700 (C=O), 1600 (C=N), 1560 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 2.50 (s, 6H, 2 CH_3CO), 3.10 (s, 3H, CH_3), 6.90–7.30 ppm (m, 4H, Ar–H). Anal. calcd for $C_{15}H_{13}N_3O_2$ (267.3): C, 67.40; H, 4.90; N, 15.72. Found: C, 67.42; H, 4.87, N, 15.73.

2-Benzylideneamino/*p*-nitrobenzylideneamino-4-methylquinoline-3-carbonitrile (6a and 6b). A mixture of **2** (10 mmol) and benzaldehyde or *p*-nitrobenzaldehyde (10 mmol) was refluxed in ethanol (20 mL) containing a few drops of piperidine for 3 h. After cooling, the solid product thus formed was collected by filtration and recrystallized from ethanol to give the corresponding Shiff bases **6a** and **6b**.

2-Benzylidenamino-4-methylquinoline-3-carbonitrile (6a). The derivative **6a** was obtained in 60% yield, mp 260–261 °C. IR (KBr): ν 2200 (C≡N), 1640 (N=CH), 1600 (C = N), 1580 cm^{-1} (C=C). ^1H NMR ($CDC1_3$): δ 3.3 (s, 3H, CH_3), 7.0–8.2 (m, 9H, Ar–H), 8.6 ppm (s, 1H, N=CH). Anal. calcd for $C_{18}H_{13}N_3$ (271.3): C, 79.68; H, 4.83; N, 15.49. Found: C, 79.77; H, 5.11; N, 15.11.

2-(*p*-Nitrobenzylidenamino)-4-methylquinoline-3-carbonitrile (6b). The compound **6b** was obtained in 78% yield, mp 318–319 °C. IR (KBr): ν 2200 (C ≡ N), 1610 (N=CH), 1590 (C=N), 1570 cm^{-1} (C=C). ^1H NMR ($CDC1_3$): δ 3.0 (s, 3H, CH_3), 7.3–8.0 (m, 8H, Ar–H), 8.6 ppm (s, 1H, N=CH). Anal. calcd for $C_{18}H_{12}N_4O_2$ (316.3): C, 68.35; H, 3.83; N, 17.72. Found: C, 68.13; H, 3.78; N, 17.40.

4-Amino-5-methylpyrimido[4,5-*b*]quinoline (7). A mixture of **2** (10 mmol) and formamide (20 mL) was refluxed for 20 h. The reaction mixture was cooled, poured onto ice/water, and the solid product that appeared was collected by filtration and recrystallized from ethanol to give brown crystals of **7** in 43% yield, mp 263–266 °C. IR (KBr): ν 3400, 3300 (NH_2), 1600 (C=N), 1580 cm^{-1} (C=C). ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, CH_3), 4.75 (br, 2H, NH_2), 6.90 (m, 4H, Ar–H), 8.00 ppm (s, 1H, CH-2). MS *m/z* (%) 212 [$M^+ + 2$] (19.1), 211 [$M^+ + 1$] (1.2), 210 [M^+] (0.4), 198 (30.9), 197 (100), 180 (9), 171 (9.17), 170 (34.3), 169 (7.4), 159 (5.6), 153 (25.9), 142 (10.2), 126 (5.4), 115 (6.3), 77 (2.4). Anal. calcd for $C_{12}H_{10}N_4$ (210.2): C, 68.57; H, 4.80; N, 26.66. Found: C, 68.35; H, 4.52; N, 26.71.

5-methyl-3H-2-deoxo-5-deazaalloxazine (8).

Method A. A solution of **7** (10 mmol) in ethanol (10 mL) was added dropwise with stirring to a mixture of acetic acid (3 mL) and 5% aqueous sodium nitrite solution (7 mL) in the presence of HCl (5 mL) at 0 °C for 1 h. The precipitate that resulted was collected by filtration, washed with cold water several times, and recrystallized from ethanol to give **8** as white needles (61% yield).

Method B. A mixture of **13** (10 mmol), formamide or formic acid (20 mL) was gently heated for 2 h. After cooling, the reaction mixture was poured onto ice/water. The solid product thus formed was collected by filtration and recrystallized from ethanol to give **8** as white needle crystals in 78% yield, mp > 340 °C. IR (KBr): ν 3350 (OH), 3200 (NH), 1650 (C=O), 1580 (C=N), 1510 (C=C) cm^{-1}. ^1H NMR (DMSO-d_6): δ 3.1 (s, 3H, CH_3), 7.2–7.4 (m, 4H, Ar–H), 7.8 (s, 1H, NH), 8.0 ppm (s, 1H, CH-2). MS *m/e* (%) 213 [$M^+ + 2$] (10), 212 [$M^+ + 1$] (1.4), 211 [M^+] (1.8), 199 (13.3), 198 (100), 143 (8.8), 142 (6.2), 128 (5.3), 116 (11.7), 115 (4.9). Anal. calcd for $C_{12}H_9N_3O$ (211.2): C, 68.24; H, 4.30; N, 19.90. Found: C, 68.53; H, 4.14; N, 19.65.

4-Amino-5-methyl-3-phenyl-2-thioxo-4-deoxo-5-deazaflavin (9). A mixture of **2** (10 mmol) and phenyl isothiocyanate (12 mmol) was refluxed in pyridine (20 mL) for 7 h. The reaction mixture was cooled and diluted with ethanol, and the precipitate thus formed was collected by filtration and dried by suction. The crude product was recrystallized from a 4:1 mixture ethanol and DMF to give **9** as yellow crystals in 90% yield, mp 235–237 °C. IR (KBr): ν 3400, 3300 (NH_2), 1640 (C=N), 1580 (C=C), 1140 cm^{-1} (C=S). ^1H NMR (DMSO-d_6): δ 3.0 (s, 3H, CH_3), 4.1 (br, 2H, NH_2, exchangeable with D_2O), 7.5–8.3 ppm (m, 9H, Ar–H). MS *m/z* (%) 320 [$M^+ + 2$] (6.3), 319 [$M^+ + 1$] (23.9), 318 [M^+] (100), 317 (33.8), 285 (31.7), 260 (6.9), 259 (7.1), 258 (14.3), 242 (5.5), 241 (39.5), 231 (9.4), 183 (4), 167 (4), 155 (7.1), 141 (29.8), 140 (21.8), 129 (7.3), 128 (10), 102 (3.7), 77 (18), 51 (7.8). Anal. calcd for $C_{18}H_{14}N_4S$ (318.4): C, 67.90; H, 4.43; N, 17.60; S, 10.06; Found: C, 67.66; H, 4.30; N, 17.99; S, 10.17.

5-methyl-2-phenyl-2-deoxo-5-deazaalloxazine (10) and 5-methyl-2-phenyl-1,3-oxazino[4,5-b]quinoline-4-one (11). A mixture of **2** (10 mmol) and benzoyl chloride (80 mmol) was refluxed in pyridine (20 mL) for 6 h. The excess of the benzoyl chloride was removed by distillation under vacuum, and the residue was cooled and added to ice/water. The orange precipitate thus obtained was collected and dried. Thin layer-chromatography (TLC) of the product using ethanol/ether (1:4) as an eluent showed two spots. The mixture was found to be partially soluble in acetic acid, and the above precipitate that had been filtered off, was washed with acetic acid (×2) and recrystallized from pyridine to give **11** in 34% yield, mp 210–213 °C. IR (KBr): ν 1690 (C=O), 1590 (C=N), 1580 (C=C), 1110 cm^{-1} (C–O–C). ^1H NMR ($CDCl_3$): δ 3.00 (s, 3H, CH_3), 7.20–8.10 ppm (m, 9H, Ar–H). Anal. calcd for $C_{18}H_{12}N_2O_2$ (288.3): C, 74.98; H, 4.20; N, 9.72; Found: C, 75.00; H, 4.65; N, 10.00.

The filtrate was diluted with water, and the yellow crystals that resulted was recrystallized from dilute acetic acid to give **10** in 63% yield, mp 200 °C. IR (KBr): ν 3300 (NH), 1680 (C=O), 1620 (C=N), 1580 cm^{-1} (C=C). ^1H NMR ($CDCl_3$): δ 3.10 (s, 3H, CH_3), 7.00–8.20 ppm [m, 10H (9H, Ar–H and 1H, NH exchangeable on deuteration)]. MS *m/z* (%) 287 [M^+] (7.9), 286 (35.9), 270 (7.7), 105 (100), 77 (53.8). Elemental anal. calcd for $C_{18}H_{13}N_3O$ (287.3): C, 75.25; H, 4.56; N, 14.63. Found: C, 75.60; H, 4.84; N, 14.50.

3-Ethyl-5-methyl-2-phenyl-2-deoxo-5-deazaalloxazine (12). A mixture of **2** (10 mmol) and ethyl iodide (20 mmol) was stirred in DMF (20 mL) in the presence of anhydrous potassium carbonate (5 mmol) for 4 h. The solid product, obtained on dilution with water, was collected and recrystallized from ethanol to give the corresponding **12** as pale yellow crystals in 55% yield, mp 343–345 °C. IR (KBr): ν 1690 (C=O), 1620 (C=N), 1580 cm^{-1} (C=C). ^1H NMR (DMSO-d_6) δ 1.35 (t, 3H, CH_2CH_3), 3.10 (s, 3H, CH_3), 3.30 (q, 2H, CH_2CH_3), 7.00-8.10 ppm (m, 9H, Ar-H). Anal. calcd for $C_{20}H_{17}N_3O$ (315.4): C, 76.16; H, 5.43; N, 13.32. Found: C, 76.33; H, 5.40; N, 13.38.

2-Amino-4-methylquinoline-3-carboxamide (13). A sample of **2** (10 mmol) was warmed in 60% aqueous H_2SO_4 (10 mL) with stirring for 30 min. The reaction mixture was cooled, diluted with cold water, and then neutralized (pH 8) by addition of aqueous sodium hydroxide solution (10%). The resulting precipitate was recrystallized from ethanol to give the carboxamide derivative **13** as white crystals, in 90% yield, mp 200–203 °C. IR (KBr): ν 3400, 3300 (NH_2), 3250, 3150 (NH_2CO), 1660 (C=O), 1620 (C=qN), 1580 cm^{-1} (C=C). ^1H NMR ($CDCl_3$): δ 2.80 (s, 3H, CH_3), 3.40 (br, 2H, NH_2), 5.80 (s, 2H, $CONH_2$), 7.20–8.20 ppm (m, 4H, Ar–H). Anal. calcd for $C_{11}H_{11}N_3O$ (201.2): C, 65.66; H, 5.51; N, 20.89. Found: C, 65.65; H, 5.30; N, 21.05.

2,5-Dimethyl-2-deoxo-5-deazaalloxazine (14) and 2-Acetylamino-4-methylquinoline-3-carboxylic acid (15). A mixture of **13** (10 mmol) and glacial acetic acid (20 mL) was refluxed for 40 h. The reaction mixture was cooled and poured onto ice/water. The resulting precipitate was collected and washed several times with hot aqueous Na_2CO_3 (10%), and recrystallized from ethanol/water to give **14** as white crystals in 63% yield, mp 178–180 °C. IR (KBr): ν 3400 (OH), 3250 (NH), 1650 (C=O), 1600 (C=N), 1580 cm^{-1} (C=C). ^1H NMR (DMSO-d_6): δ 2.30 (s, 3H, CH_3), 3.00 (s, 3H, CH_3), 6.90–7.80 (m, 4H, Ar–H), 8.10 ppm (s, 1H, NH). Elemental anal. calcd for $C_{13}H_{11}N_3O$ (225.2): C, 69.33; H, 4.93; N, 18.66. Found: C, 69.29; H, 5.00; N, 18.50.

The above filtrate was acidified with acetic acid to afford a solid product, which was recystallized from acetic acid to yield **15** in 35% yield, mp 200 °C. IR (KBr): ν 3220 (*NH*CO), 1700 (COOH), 1640 (NH*CO*), 1600 (C=N), 1580 cm^{-1} (C=C). ^1H NMR ($CDCl_3$): δ 2.20 (s, 3H, $COCH_3$), 3.00 (s, 3H, CH_3), 6.90–7.90 [m, 5H, (4H, Ar–H and 1H, NH exchangeable on deuteration)], 9.80 (s, 1H, OH, exchangeable on deuteration). Anal. calcd for $C_{13}H_{12}N_2O_3$ (244.3): C, 63.91; H, 4.95; N, 11.47. Found: C, 64.02; H, 4.83; N, 11.50.

5-Methyl-3-phenyl-2-thioxo-5-deazaalloxazine (16). A mixture of **13** (10 mmol) and phenylisothiocyanate (12 mmol) was refluxed in pyridine (20 mL) for 5 h. The reaction mixture was cooled and diluted with ethanol, and the resulting precipitate was collected by filtration and recrystallized from DMF to give **16** in 86% yield, mp 263–266 °C. IR (KBr): ν 3350 (NH), 1640 (C=O), 1600 (C=N), 1550 (C=C), 1130 cm^{-1} (C=S). ^1H NMR (CF_3COOD): δ 3.10 (s, 3H, CH_3), 7.00–7.90 ppm (m, 9H, Ar–H). MS *m/z* (%) 319 [M^+] (0.1), 202 (9.2), 201 (53.7), 185 (13.2), 184 (86.1), 183 (4), 166 (7.3), 157 (43.9), 156 (12.5), 155 (29.1), 130 (12.3), 129 (19.6), 128 (17.6), 114 (6.1), 102 (9.3), 101 (11.1), 77 (4). Anal. calcd for $C_{18}H_{13}N_3OS$ (319.4): C, 67.68; H, 4.10; N, 13.16; S, 10.04. Found: C, 68.00; H, 4.13; N, 13.06; S, 10.00.

3-Amino-5-methyl-2-deoxo-5-deazaalloxazine (17). A mixture of **8** (10 mmol) and 80% hydrazine hydrate (40 mmol) was refluxed in ethanol (10 mL) for 3 h. After cooling, the solid product thus obtained was collected and recrystallized from ethanol/DMF to give **17** as pale yellow crystals in 43% yield, mp > 300 °C. IR (KBr): ν 3420, 3320 (NH_2), 1660 (C=O), 1610 (C=N), 1590 cm^{-1} (C=C). ^1H NMR (DMSO-d_6): δ 3.10 (s, 3H, CH_3), 6.8–7.7 (m, 4H, Ar–H), 7.80 (br, 2H, NH_2), 8.3 ppm (s, 1H, CH-2). MS *m/z* (%): 226 [M^+] (0.1), 184 (26), 183 (100), 182 (12.2), 168 (2.3), 167 (2.8), 166 (8), 156 (11.3), 155 (34.4), 141 (5), 140 (5.7), 139 (7), 129 (7.9), 128 (13.5), 114 (6), 102 (5.4), 101 (6.3), 77 (8.1), 76 (4.3), 51 (7.8). Anal. calcd for $C_{12}H_{10}N_4O$ (226.2): C, 63.71; H, 4.46; N, 24.77. Found: C, 63.58; H, 4.45; N, 24.80.

4-Chloro-5-methyl-2,4-deoxo-5-deazaalloxazine (18). A sample of **8** (10 mmol) was refluxed in a mixture of phosphorus pentachloride (12 mmol) and phosphorus oxychloride (7 mL) for 4 h. The reaction mixture was cooled and carefully poured onto ice/ammonia mixture. The solid product thus formed was filtered off and recrystallized from benzene to give **18** as pale yellow crystals in 60% yield, mp 173–175 °C; IR (KBr): ν 1600 (C=N), 1580 cm^{-1} (C=C). ^1H NMR ($CDC1_3$): δ 3.00 (s, 3H, CH_3), 7.00–8.10 (m, 4H, Ar–H), 8.30 ppm (s, 1H, CH-2). MS *m/z* (%) 231 [$M^+ + 2$] (28.3), 229 [M^+] (0.4), 219 (11.1), 218 (87), 217 (37.3), 216 (100), 180 (5.3), 154 (27.6), 153 (28), 142 (6.1), 140 (9.5), 128 (15.7), 127 (17.4), 126 (12), 115(8), 108 (6.4), 101 (6.6), 90 (13.9), 77 (6.1). Anal. calcd for $C_{12}H_8ClN_3$ (229.7): C, 62.75; H, 3.51; N, 18.30; Cl, 15.44. Found: C, 62.78; H, 3.60; N, 18.20; Cl, 15.90.

5-Methyl-4-thioxo-2-deoxo-5-deazaalloxazine (19)

Method A. A mixture of **18** (10 mmol) and thiourea (2.5 mmol) was refluxed in dry methanol (20 mL) for 1 h. The reaction mixture was cooled, and the yellow crystalline product that appeared was collected by filtration, washed with methanol, and then heated with 10% aqueous sodium hydroxide (20 mL). The resulting solution was acidified (pH 5.6–5.8) with dilute acetic acid. The precipitate thus formed was recrystallized from acetic acid to give **19** in 74% yield, mp 205 °C. IR (KBr): ν 2700–2550 (SH), 1620 (C=N), 1580 cm^{-1} (C=C). ^1H NMR (DMSO-d_6): δ 3.10 (s, 3H, CH_3), 7.10–7.50 [m, 5H, (4H, Ar–H and 1H, SH)], 8.35 ppm (s, 1H, CH-2). Anal. calcd for $C_{12}H_9N_3S$ (227.3): C, 63.40; H, 3.90; N, 18.50; S, 14.10. Found: C, 63.11; H, 3.68; N, 18.30; S, 14.30.

Method B. A mixture of **8** (10 mmol) and P_2S_5 (3.0 g) was refluxed in pyridine (15 mL) for 5 h. The reaction mixture was cooled, and the precipitate thus formed was

collected and triturated with acetic acid. The resulting precipitate was collected by filtration and recrystallized from acetic acid to give **19** in 70% yield.

4-Methoxy-5-methyl-2,4-deoxo-5-deazaalloxazine (20). A methanolic solution of sodium methoxide (10 mL), prepared from sodium metal (0.23 g and methanol (10 mL) was added dropwise to a solution of **18** (10 mmol) in methanol (10 mL). The reaction mixture was cooled in ice bath for 10 min, then allowed to warm to room temperature, and finally heated gently on a steam bath for 30 min. The resulting product was collected and recrystallized from methanol to give **20** in 44% yield, mp 248–249 °C. IR (KBr): ν 1600 (C=N), 1580 cm^{-1} (C=C). ^1H NMR (DMSO-d_6): δ 3.00 (s, 3H, CH_3), 3.55 (s, 3H, OCH_3), 6.80–7.40 (m, 4H, Ar–H), 8.40 ppm (s, 1H, CH-2). Anal. calcd for $C_{13}H_{11}N_3O$ (225.2): C, 69.33; H, 4.95; N, 18.66. Found: C, 69.18; H, 4.80; N, 18.21.

4-Hydrazino-5-methyl-2,4-deoxo-5-deazalloxazine (21). A sample of chloro compound **18** (10 mmol) and 80% hydrazine hydrate (40 mmol) was refluxed in ethanol (20 mL) for 1 h. The reaction mixture was cooled to 0 °C and the solid product thus obtained was collected and recrystallized from dilute acetic acid to give **21** in 73% yield, mp 205 °C. IR (KBr): ν 3470, 3220 ($NHNH_2$), 1600 (C=N), 1560 cm^{-1} (C=C). ^1H NMR (DMSO-d_6): δ 3.30 (s, 3H, CH_3), 4.20 (d, 2H, NH_2), 6.80–7.30 (m, 4H, Ar–H), 8.40 (s, 1H, CH-2), 10.60 (br, 1H, NH, exchangeable on deuteration). MS *m/z* (%) 225 [M^+] (0.1), 218 (8), 217 (25.9), 216 (100), 197 (18.1), 182 (22.1), 154 (21), 153 (24.5), 140 (8.1), 128 (13.7), 127 (14), 101 (5.7), 90 (13.4), 77 (5.9). Anal. calcd for $C_{12}H_{11}N_5$ (225.3): C, 63.97; H, 4.92; N, 31.09. Found: C, 64.00; H, 5.00; N, 31.00.

12-Methyl-1,2,4-s-triazolo[3′,4′:6,1]pyrimido[4,5-b]quinoline (22). The hydrazino derivative **21** (10 mmol) was refluxed in formic acid (5 mL) for 3 h. The reaction mixture was cooled and poured onto ice/water. The solid product thus obtained was collected and recrystallized from acetic acid to give **22** in 66% yield, mp 227–230 °C. IR (KBr): ν 1600 (C=N), 1560 cm^{-1} (C=C). ^1H NMR (CF_3COOD): δ 3.10 (s, 3H, CH_3), 6.90–7.45 (m, 4H, Ar–H), 8.40 (s, 1H, CH-5), 9.40 (s, 1H, CH-3). Anal. calcd for $C_{13}H_9N_5$ (235.2): C, 66.30; H, 3.86; N, 29.78. Found: C, 66.50; H, 3.69; N, 30.00.

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