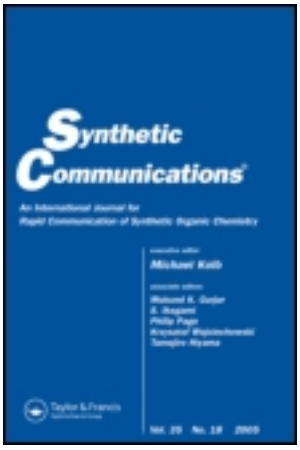

Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry
Publication details, including instructions for authors and subscription information:
http://www.tandfonline.com/loi/lsyc20

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Available online: 16 Jun 2009

To cite this article: Guang-Fan Han, Rui-Hua Wang, Wen-Tao Zhang, Yu-Yuan Zhao, Zheng Xing & Wei Dai (2009): Synthesis and Crystal Structure of 7,8-Dihydroquinolino[2,3-a]acridine Derivatives, Synthetic Communications: An International Journal for Rapid Communication of Synthetic Organic Chemistry, 39:14, 2492-2505

To link to this article: http://dx.doi.org/10.1080/00397910802656042

Synthetic Communications®, 39: 2492–2505, 2009

ISSN: 0039-7911 print/1532-2432 online
DOI: 10.1080/00397910802656042

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Synthesis and Crystal Structure of 7,8-Dihydroquinolino[2,3-a]acridine Derivatives

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Abstract: Novel 9-amino-3-substituted-1,2,3,4-acridin-1-one derivatives and 9,14-diamino-7-substituted-7,8-dihydroquinolino[2,3-a]acridine derivatives were synthesized by the condensation reaction of 5-substituted-1,3-cyclohexanedione with 2-aminobenzonitrile and substituted 2-aminobenzonitrile using *p*-toluenesulfonic acid, K_2CO_3, and Cu_2Cl_2 as catalysts. The structures of all compounds were characterized by elemental analysis, infrared, mass spectrometry, and ^1H and ^{13}C NMR spectra. The crystal and molecular structures of 6, 14-diamino-3,4,11,12-tetramethoxy-7-phenyl-7,8-dihydroquinolino[2,3-a]acridine **5a** have been determined by single-crystal x-ray diffraction analysis. The crystal of compound **5a** belongs to triclinic with space group *P-1*, $a = 1.06168(15)$ nm, $b = 1.16951(17)$ nm, $c = 1.6020(2)$ nm, $\alpha = 71.380(3)^\circ$, $\beta = 77.686(3)^\circ$, $\gamma = 66.743(3)^\circ$, $Z = 2$, $V = 1.7231(4)$ nm^3, $R_1 = 0.1060$, and $wR_2 = 0.2192$.

Keywords: Acridine derivative, anticancer activity, crystal structure, 5-substituted-1,3-cyclohexanedione, synthesis

The family of acridine derivatives is a class of the oldest bioactive compounds, which were widely used as antibacterial and antimalarial agents. The emergence of the penicillin eclipsed the acridines in antisepsis because of their greater therapeutic efficacy than the former. However, with the current rapid increase in drug-resistant bacterial infection, novel

Received September 28, 2008.
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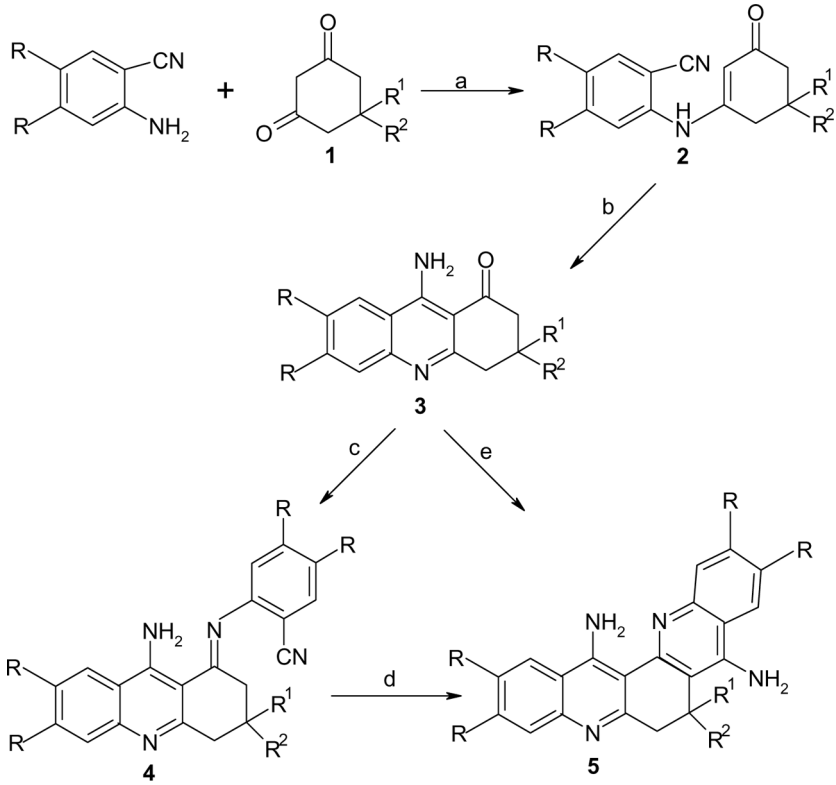
acridine derivatives may be of new use. A great amount of research and development has been carried out on acridine derivatives.[1–7] In these areas, recent study has been focused mainly on their function as anticancer drugs, because of the ability of the acridine chromophore to intercalate DNA and inhibit topoisomerase emzyme, which further blocks the pharmacological action of DNA-metabolizing proteins. These compounds have attracted the interests of biochemists and chemists for 10 years because of the possibilities of their clinical use as intercalating drugs to inhibit the synthesis of nucleic acids. Many types of drugs are known to bind to DNA through intercalation between consecutive nucleotides in the DNA strands.

This class of compounds includes several antitumor agents of clinical importance such as actinomycin-D, daunomycin, and adriamycin.[8–10]

There has been considerable synthetic attention paid to the substituted aminoacridines.[11–13] The mode of binding of acridine molecules involves intercalation of the acridine ring between adjacent base pairs in the DNA duplex, and acridine moieties are held in place by van der Waals force supplemented by stronger ionic bonds to the phosphate ions of the DNA backbone. Herein we report the synthesis of the title compounds. We hope that these novel acridine derivatives will be have anticancer activities.

SYNTHESIS AND ANALYSIS OF SPECTRA

The synthetic pathway is shown in Scheme 1. The 5-substituted-1,3-cyclohexanediones **1** were prepared as building block from aromatic aldehyde, acetone, and dimethyl molanate. The intermediate enamines **2a–d** were obtained by condensation reaction of 5-substituted-1,3-cyclohexanedione **1** with 2-amino-4,5-dimethoxybenzonitrile and 2-aminobenzonitrile using *p*-toluenesulfonic acid as a catalyst. 3-Substituted-9-amino-1,2,3,4-acridin-1-one derivatives **3a–d** were synthesized by cyclization of the intermediate enamines **2a–d** in the presence of K_2CO_3 and Cu_2Cl_2. The intermediate enamines **4a–d** were obtained by condensation reaction of 3-substituted-9-amino-1,2,3,4-acridin-1-one derivatives **3a–d** with 2-amino-4,5-dimethoxybenzonitrile and 2-aminobenzonitrile using *p*-toluenesulfonic acid as a catalyst. The quinolino[2,3-a] acridine derivatives **5a–d** of new form of pentacyclic system were obtained by condensation reaction of compounds **3a–d** with 4,5-dimethoxyanthranilonitrile and 2-aminobenzonitrile using *p*-toluenesulfonic acid, K_2CO_3, and Cu_2Cl_2 as catalysts. The quinolino [2,3-a]acridine derivatives **5a–d** of a new form of pentacyclic system were also synthesized by cyclization of the intermediate enamines **4a–d** in the presence of K_2CO_3 and Cu_2Cl_2.



Scheme 1. (a) TsOH; (b) K_2CO_3, Cu_2Cl_2; (c) TsOH; (d) K_2CO_3, Cu_2Cl_2; and (e) TsOH, K_2CO_3, Cu_2Cl_2. (**a**) R = $-OCH_3$; R^1 = phenyl, R^2 = H; (**b**) R = $-OCH_3$; $R^1 = R^2 = CH_3$; (**c**) R = H; R^1 = phenyl, R^2 = H; (**d**) R = H; $R^1 = R^2 = CH_3$.

The ^{1}H NMR, ^{13}C NMR, mass spectral (MS), and infrared (IR) data shown in the experimental section are in accordance with the chemical structures of the target compounds. In the ^{1}H NMR spectrum of compound **2**, the broad single proton peaks at δ 6.56 are the characteristic absorption proton peaks of the amino group. The single peak at δ 5.68 was the typical proton peak of the vinyl group. In the ^{1}H NMR spectrum of compound **3**, the two broad single peaks at δ 6.10 and *δ* 10.25 were observed. They disappeared after D_2O exchange and therefore were attributed to the two N–H of the amino group. Because of the existing intramolecular hydrogen bond between one proton of the amino group and the oxygen atom of the carbonyl group nearby, its proton peak drifted to δ 10.25.

^{13}C NMR signals for the individual sp, sp^2, sp^3 carbon in these compounds were observed.

The structures of these compounds were further supported by their IR spectra. Several typical absorption bands at 2240 cm^{-1} for **2, 4** (C≡N), 1730 cm^{-1} for **3** (C=O), and 3400 cm^{-1} for (N−H) were observed respectively.

CRYSTAL STRUCTURE

A summary of the crystal data and structure refinement is presented in Table 1. A perspective view of compound **5a** with atomic numbering

Table 1. Crystal parameters data collections and structure refinements for compound **5a**

Parameter	Value
Empirical formula	$C_{36}H_{46}N_4O_7$
Formula weight	646.77
Temperature	293(2) K
Wavelength	0.071073 nm
Crystal system	Triclinic
Space group	$P-1$
Unit cell dimensions	$a = 1.06168(15)$ nm, $\alpha = 71.380(3)^\circ$ $b = 1.16951(17)$ nm, $\beta = 77.686(3)^\circ$ $c = 1.6020(2)$ nm, $\gamma = 66.743(3)^\circ$
Volume	1.7231(4) nm^3
Z	2
Calculated density	1.247 mg/m^3
Absorption coefficient	0.087 mm^{-1}
F(000)	692
Crystal size	0.511 × 0.495 × 0.278 mm
Θ range for data collection	1.96° to 25.50°
Limiting indices	$-7 \le h \le 12$, $-14 \le k \le 14$, $-18 \le l \le 19$
Reflections collected/unique	9109/6313 [R(int) = 0.1508]
Completeness to $\theta = 25.50$	98.6%
Absorption correction	Empirical
Max. and min. transmission	1.00000 and 0.50505
Refinement method	Full-matrix least-squares on F^2
Data/restraints/parameters	6313/2/479
Goodness-of-fit on F^2	0.953
Final R indices [I > 2σ(I)]	$R_1 = 0.0796$, $wR_2 = 0.1989$
R indices (all data)	$R_1 = 0.1060$, $wR_2 = 0.2192$
Largest diff. peak and hole	477 and −496 $e.nm^{-3}$

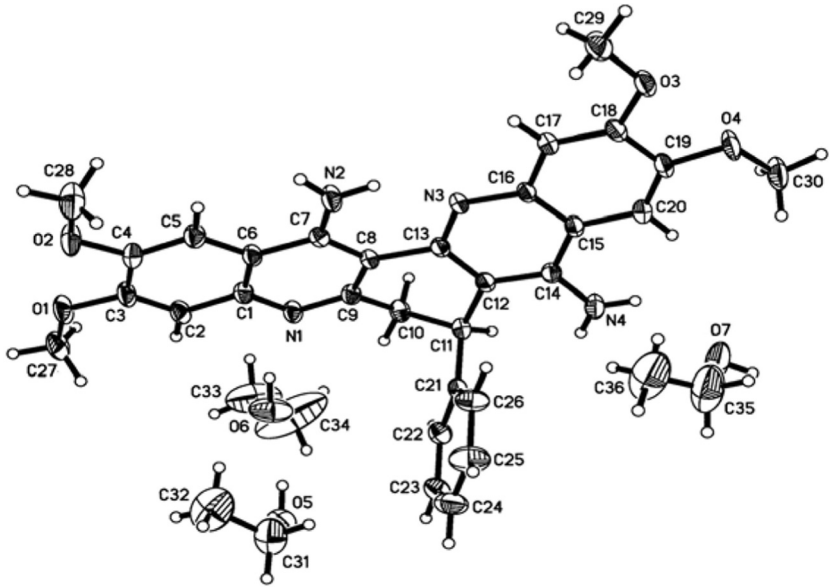


Figure 1. ORTEP plot of compound **5a**.

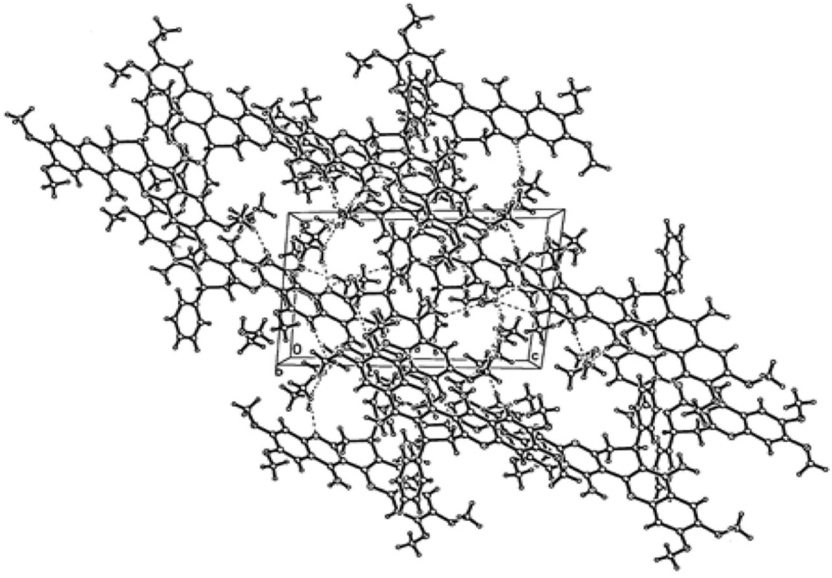


Figure 2. Packing diagram of compound **5a** in unit cell.

Table 2. Inter- and intramolecular interaction distances (Å) for the compound **5a**

D–H···A	*D–H*	*H···A*	*D···A*	*D–H···A*	Symmetry
N(4)–H(4B)···O(7)	0.8600	2.4700	3.061(4)	126.700	x, y, z
O(6)–H(6)···N(1)	0.88(4)	1.90(4)	2.761(4)	163(4)	x, y, z
N(2)–H(2B)···N(3)	0.87(4)	1.94(4)	2.674(4)	141(3)	x, y, z
O(5)–H(5A)···O(6)	0.877(19)	1.85(2)	2.716(4)	167(4)	x, y, z

scheme is shown in Fig. 1. In compound **5a**, the dihedral angle between the bond lengths and bond angles are generally normal in the phenyl and quinoline rings and the quinoline ring a [C(1), C(2), C(3), C(4), C(5), C(6), C(7), C(8), C(9), N(1)] with plane equation $-0.3657\ x + 0.8283\ y - 0.4245\ z = 1.2900$. The quinoline ring b [C(12), C(13), C(14), C(15), C(16), C(17), C(18), C(19), C(20), N(3)] with plane equation $-0.1458x + 0.9340y - 0.3263z = 4.8766$ is 15.114°. The benzene ring [C(21), C(22), C(23), C(24), C(25), C(26)] is coplanar with the conjunction C(11), whose plane equation is $-0.3087x - 0.4115y - 0.8575z = -7.0254$. The dihedral angles between the benzene ring and two quinoline ring plane are 86.588° and 82.179°, respectively.

The packing diagram of the **5a** in a unit cell is shown in Fig. 2. X-ray analysis reveals that there exist intramolecular and intermolecular hydrogen bonds in the crystal. The intermolecular hydrogen bonds N(4)−H(4B)···O(7) and O(6)−H(6)···N(1) are 3.061(4) and 2.761(4) Å, respectively, whereas the intramolecular hydrogen bond N(2)−H(2B)···N(3) is 2.674(4) Å. Moreover, the structural analysis indicates that these molecular interactions play the role of further stabilizeing the structure. The bond lengths and bond angles of primary hydrogen bonds are listed in Table 2.

CONCLUSION

In summary, the condensation reaction of 5-substituted-1,3-cyclohexanedione with 2-aminobenzonitrile and substituted 2-aminobenzonitrile using *p*-toluenesulfonic acid, K_2CO_3, and Cu_2Cl_2 as catalysts gave a series of novel 9-amino-3-substituted-1,2,3,4-acridin-1-one derivatives **3a–d**. We made the same condensation reaction again with compounds **3a–d**, 2-aminobenzonitrile, and substituted 2-aminobenzonitrile, which gave a series of quinolino[2,3-a] acridine derivatives **5a–d** of a new form of pentacyclic system. They would be expected to be useful anticancer activity compounds.

EXPERIMENTAL

Melting points were determined on an electrothermal apparatus, and the temperature was not calibrated. Microanalysis was performed by the Perkin-Elmer 2400 Microanalytical Service, and elemental analysis for C, H, and N were within ±0.3% of the calculated value. IR spectra were recorded as thin films on KBr using a Perkin-Elmer 1700 spectrophotometer. The NMR spectra were recorded by a Bruker ARX-300 spectrometer. Sample solutions were prepared in $CDCl_3$ containing tetramethysilane (TMS) as an internal reference. Mass spectra were recorded by JMS-DX300 at 70 eV.

All chemical reagents were commercially available and purified with standard methods before use. Solvents were dried in routine ways and redistilled. 5-Substituted-1,3-cyclo-hexanediones **1** were obtained from aromatic aldehyde, acetone, and dimethyl molanate according to the literature[14] method with slightly modification.

N-(5-Phenyl-3-oxo-cyclohexen-1-yl)-2-amino-4,5-dimethoxy benzonitrile 2a

2-Amino-4,5-dimethoxybenzonitrile (8.9 g, 0.050 mol) and 5-phenyl-1, 3-cyclohexanedione **1a** (9.4 g, 0.050 mol) were suspended in toluene (100 mL) containing *p*-toluenesulfonic acid monohydrate (1 g, 0.005 mol). The mixture was refluxed for 6 h, and the water was collected in a Dean–Stark water separator. At the end of the reaction, the reaction mixture was chilled to room temperature, and the product was filtered off. The yellow powder was recrystallized from ethanol to afford 13.5 g of the title compound as yellow crystals in 77.6% yield. Mp 205–206°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.50–3.54 (m, 2H, 6′-H), 2.88–2.90 (m, 2H, 4′-H), 3.39–3.41 (m, 1H, 5′-H), 3.86, 3.87 (each s, each 3H, 6H, OMe-H), 5.41 (s, 1H, vinyl-H), 6.69 (br s, 1H, exchanges with D_2O, NH), 6.88 (s, 1H, Ph-H), 6.97 (s, 1H, Ph-H), 7.21–7.23 (m, 2H, Ph-H), 7.38–7.40 (m, 3H, Ph-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 40.2, 41.6, 46.8, 56.2, 56.2 (5C, sp^3-C), 99.9, 105.9, 110.1, 117.3, 126.7 (2C), 127.8, 128.0 (2C), 143.3, 146.6, 149.3, 154.4, 155.3, 160.3 (15C, $sp + sp^2$-C), 198.6 (1C, C=O); IR (KBr) υ: 3412, 2230, 1638, 1513 cm^{-1}. Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04; found: C, 72.26; H, 5.68; N, 8.16.

The compound **2b** was obtained from 2-amino-4,5-dimethoxybenzonitrile and 5,5-dimethy-1,3-cyclohexanedione in a similar manner.

N-(5,5-Dimethy-3-oxo-cyclohexen-1-yl)-2-amino-4,5-dimethoxybenzonitrile 2b

Yield: 78.6%; mp 192–194°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.13 (s, 6H, Me-H), 2.48 (s, 2H, 6′-H), 3.12 (s, 2H, 4′-H), 3.87 (s, 3H, OMe-H), 3.97 (s, 3H, OMe-H), 5.27 (s, 1H, vinyl-H), 6.23 (br s, 1H, 1H, exchanges with D_2O, NH), 7.21 (s, 1H, ph-H), 7.51 (s, 1H, ph-H); IR (KBr) υ: 3451, 2226, 1608, 1538 cm^{-1}; MS (70 eV) m/z (%): 301.3 ($M^+ + 1$,100).

The compound **2c** was obtained from 2-aminobenzonitrile and 5-phenyl-1,3-cyclohexanedione in a similar manner.

N-(5-Phenyl-3-oxo-cyclohexen-1-yl)-2-amino-benzonitrile 2c

Yield: 75%; mp 199–200°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.59–2.61 (m, 2H, 6′-H), 2.66–2.68 (m, 1H, 4′-H), 2.88 (m, 1H, 4′-H), 3.42–3.43 (m, 1H, 5′-H), 5.68 (s, 1H, vinyl-H), 6.56 (br s, 1H, exchanges with D_2O, NH), 7.23–7.28 (m, 3H, Ph-H), 7.35–7.38 (m, 2H, Ph-H), 7.50–7.51 (m, 2H, Ph-H), 7.57 (t, $J = 7.8$ Hz, 1H, Ph-H), 7.64 (d, $J = 7.8$ Hz, 1H, Ph-H); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 37.3, 39.7, 43.4 (3C, sp^3-C), 124.7, 125.6, 125.7, 126.7 (2C), 127.2, 128.7, 128.9 (2C), 133.4 (2C), 133.9 (2C), 140.9, 142.4 (15C, $sp + sp^2$-C), 197.5 (1C, C=O); IR (KBr) υ: 3450, 2225, 1639, 1529 cm^{-1}. Anal. calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72; found: C, 79.18; H, 5.65; N, 9.59.

The compound **2d** was obtained from 2-aminobenzonitrile and 5,5-dimethy-1,3-cyclo-hexanedione in a similar manner.

N-(5,5-Dimethy-3-oxo-cyclohexen-1-yl)-2-aminobenzonitrile 2d

Yield: 86.5%; mp 210–212°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.17 (s, 6H, Me-H), 2.58 (s, 2H, 6′-H), 3.07 (s, 2H, 4′-H), 5.49 (s, 1H, vinyl-H), 6.37 (br s, 1H, exchanges with D_2O, NH), 7.52 (t, $J = 7.5$ Hz, 1H, Ph-H), 7.77 (t, $J = 7.5$ Hz, 1H, Ph-H), 7.86 (d, $J = 8.0$ Hz, 1H, Ph-H), 7.93 (s, 1H, Ph-H); IR (KBr) υ: 3415, 2223, 1621, 1524 cm^{-1}; MS (70 eV) m/z (%): 241.3 ($M^+ + 1$, 100).

9-Amino-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroacridin-1-one 3a

N-(5-Phenyl-3-oxo-cyclohexen-1-yl)-2-amino-4,5-dimethoxybenzonitrile **2a** (10.44 g, 0.030 mol) was added to tetrahydrofuran (100 mL) containing potassium carbonate (1.38 g, 0.010 mol) and cuprous chloride (0.45 g,

0.005 mol). The reaction mixture was refluxed for 12 h, and the hot mixture was filtered into hexane (200 mL). The precipitated **3a** was filtered off and washed with water. The yellow powder was recrystallized from ethanol to afford 6.2 g **3a** as yellow crystals in 59.4% yield. Mp 221–222°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.94 (dd, $J = 16.9$, 12.00 Hz, 1H, 4-H), 3.01 (dd, $J = 16.9$, 4.3 Hz, 1H, 4-H), 3.28 (dd, $J = 16.1$, 11.9 Hz, 1H, 2-H), 3.39 (dd, $J = 16.1$, 3.9 Hz, 1H, 2-H), 3.53–3.54 (m, 1H, 3-H), 4.02 (s, 6H, OMe-H), 6.04 (br s, 1H, NH), 6.99 (s, 1H, Ph-H), 7.25 (s, 1H, Ph-H), 7.27 (d, $J = 7.8$ Hz, 2H, Ph –H), 7.39 (t, $J = 7.8$ Hz, 3H, Ph-H), 10.15 (br s, 1H, exchanges with D_2O, hydrogen bonded NH); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 39.2, 41.7, 46.8, 56.2, 56.2 (5C, sp^3-C), 99.8, 105.9, 108.7, 111.1, 126.7 (2C), 126.9, 128.8 (2C), 143.1, 145.6, 148.5, 153.1, 154.1, 161.3 (total 15C, sp^2-C), 200.6 (1C, C=O); IR (KBr) υ: 3423, 1742, 1607, 1519 cm^{-1}; MS (70 eV) m/z (%): 348 (100), 319 (18.37), 244 (15.11), 229 (10.90). Anal. calcd. for $C_{21}H_{20}N_2O_3$: C, 72.40; H, 5.79; N, 8.04; found: C, 72.34; H, 5.78; N, 8.08.

The other compounds **3b–d** were obtained from enamines **2b–d** in a similar manner.

9-Amino-6,7-dimethoxy-3,3-dimethy-1,2,3,4-tetrahydroacridin-1-one 3b

Yield: 70%; mp 196–198°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.10 (s, 6H, Me-H), 2.54 (s, 2H, 4-H), 3.00 (s, 2H, 2-H), 3.97 (s, 3H, OMe-H), 4.07 (s, 3H, OMe-H), 6.36 (br s, 1H, NH_2), 7.25 (s, 1H, 8-H), 7.42 (s, 1H, 5-H), 10.24 (br s, 1H, hydrogen bonded NH_2); IR (KBr) υ: 3451, 1732, 1608, 1538 cm^{-1}; MS (70 eV) m/z (%): 301.3 ($M^+ + 1$, 100).

9-Amino-3-phenyl-1,2,3,4-tetrahydroacridin-1-one 3c

Yield: 75%; mp 212–213°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.92–2.93 (m, 2H, 4-H), 3.29–3.30 (m, 1H, 2-H), 3.43–3.44 (m, 1H, 2-H), 3.52–3.54 (m, 1H, 3-H), 6.10 (br s, 1H, NH_2), 7.24–7.36 (m, 5H, Ph-H), 7.42 (t, $J = 8.3$ Hz, 1H, Ph-H), 7.70 (t, $J = 8.3$ Hz, 1H, Ph-H), 7.82 (d, $J = 8.3$ Hz, 1H, Ph-H), 7.86 (d, $J = 8.3$ Hz, 1H, Ph-H), 10.25 (br s, 1H, exchanges with D_2O, hydrogen bonded NH_2); ^{13}C NMR ($CDCl_3$, 125 MHz) δ: 39.0, 41.8, 46.8 (3C, sp^3-C), 106.0, 117.6, 120.9, 125.0, 126.7 (2C), 126.9, 128.8 (2C), 129.3, 132.2, 143.0, 148.4, 154.3, 162.8 (total 15C, sp^2-C), 200.7 (1C, C=O); IR (KBr) υ: 3489, 1732, 1616, 1516 cm^{-1}; MS (70 eV) m/z (%): 289.3 ($M^+ + 1$, 100), 273 (85), 195 (12), 154 (98). Anal. calcd. for $C_{19}H_{16}N_2O$: C, 79.14; H, 5.59; N, 9.72; found: C, 78.98; H, 5.58; N 9.64.

9-Amino-3,3-dimethy-1,2,3,4-tetrahydroacridin-1-one 3d

Yield: 78%; mp 226–227°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.15 (s, 6H, Me-H), 2.60 (s, 2H, 4-H), 3.05 (s, 2H, 2-H), 5.23 (br s, 1H, NH_2), 7.49 (t, $J = 7.5$ Hz, 1H, Ph-H), 7.75 (t, $J = 7.5$ Hz, 1H, Ph-H), 7.85 (d, $J = 8.3$ Hz, 1H, Ph-H), 7.96 (s, 1H, Ph-H), 10.25 (br s, 1H, NH_2); IR (KBr) υ: 3415, 1721, 1584, 15411 cm^{-1}; MS (70 eV) m/z (%): 241.3 ($M^+ + 1$, 100).

N-(4,5-Dimethoxybenzo-2-nitrile)-1,9-diamino-3-phenyl-1,2,3,4-tetrahydroacridine 4a

9-Amino-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroacridin-1-one **3a** (6.96 g, 0.020 mol) and 2-amino-4,5-dimethoxybenzonitrile (3.56 g, 0.020 mol) were added to toluene (100 mL) containing *p*-toluenesulfonic acid monohydrate (1 g, 0.005 mol). The mixture was refluxed for 6 h, and the water was collected in a Dean–Stark water separator. At the end of the reaction, the reaction mixture was chilled to room temperature, and the product was filtered off. The yellow powder was recrystallized from ethanol to afford 5.54 g of the title compound as yellow crystals in 54.5% yield. Mp > 300°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 2.45 (d, $J = 15.0$ Hz, 2H, 4-H), 3.27 (d, $J = 15.0$ Hz, 2H, 2-H), 3.35 (dd, $J = 15.0$, 6.0 Hz, 1H, 3-H), 3.79, 3.81, 3.89, 3.91 (each s, each 3H, 12H, OMe-H), 6.27 (br s, 1H, NH_2), 7.01–7.12 (m, 5H, Ph-H), 7.18 (s, 1H, 8-H), 7.25 (s, 1H, 3′-H), 7.61 (s, 1H, 5-H), 7.71 (s, 1H, 6′-H), 10.09 (br s, 1H, NH_2); IR (KBr) υ: 3468, 2226, 1607, 1503 cm^{-1}; MS m/z (%): 509.4 ($M^+ + 1$, 100), 349.3 (25). Anal. calcd. for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02; found: C, 70.68; H, 5.49; N, 11.13.

The compound **4b** was obtained from **3b** and 2-amino-4,5-dimethoxybenzonitrile in a similar manner.

N-(4,5-Dimethoxybenzo-2-nitrile)-1,9-diamino-6,7-dimethoxy-3,3-dimethy-1,2,3,4-tetrahydroacridine 4b

Yield: 65.5%; mp 220–221°C; ^{1}H NMR (DMSO, 500 MHz) δ: 0.98 (s, 6H, Me-H), 2.46 (s, 2H, 4-H), 2.83 (s, 2H, 2-H), 3.84 (each s, each 3H, 12H, OMe-H), 6.67 (br s, 1H, NH_2), 7.14 (s, 1H, 5-H), 7.36 (s, 1H, 3′-H), 7.68 (s, 1H, 8-H), 8.18 (s, 1H, 6′-H), 10.52 (br s, 1H, NH_2); IR (KBr) υ: 3423, 2224, 1610, 1501 cm^{-1}; MS (70 eV) m/z (%): 461.2 ($M^+ + 1$, 100).

The other compound **4c** were obtained from **3c** and 2-aminobenzonitrile in a similar manner.

N-(2-Benzonitrile)-1,9-diamino-3-phenyl-1,2,3,4-tetrahydroacridine 4c

Yield: 71.2%; mp > 300°C; ^{1}H NMR (CD_3OD, 500 MHz) δ: 2.84 (dd, $J = 8.30$ Hz, 1H, 4-H), 2.97 (d, $J = 21.1$ Hz, 1H, 4-H), 3.47 (m, 3H, 2-H + 3-H), 6.28 (br s, 1H, NH_2), 6.98 (d, $J = 8.0$ Hz, 1H, 3-Ph-H), 7.19 (t, $J = 7.6$ Hz, 1H, 3-Ph-H), 7.27 (m, 3H, 3-Ph-H), 7.37 (t, $J = 7.5$ Hz, 2H, 4′-H + 5′-H), 7.49 (t, $J = 7.20$ Hz, 1H, 5-H), 7.57 (t, $J = 7.80$ Hz, 1H, 6-H), 7.68 (d, $J = 7.8$ Hz, 1H, 7-H), 7.74 (t, $J = 7.7$ Hz, 1H, 6′-H), 7.88 (d, $J = 8.3$ Hz, 1H, 8-H), 7.92 (d, $J = 8.8$ Hz, 1H, 3′-H), 10.86 (br s, 1H, NH_2); IR (KBr) υ: 3466, 2223, 1615, 1506 cm^{-1}; MS (70 eV) m/z (%): 389.3 ($M^+ + 1$, 100).

The compound **4d** was obtained from **3d** and 2-aminobenzonitrile in a similar manner.

N-(2-Benzonitrile)-1,9-diamino-3,3-dimethy-1,2,3,4-tetrahydroacridine 4d

Yield: 63%; mp 256–258°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 1.08 (s, 6H, Me-H), 2.46 (s, 2H, 4-H), 3.04 (s, 2H, 2-H), 6.15 (br s, 1H, NH_2), 6.96 (d, $J = 8.1$ Hz, 1H, 4′-H), 7.23 (t, $J = 18.7$ Hz, 1H, 8-H), 7.47 (d, $J = 7.6$ Hz, 1H, 6′-H), 7.62 (t, $J = 7.7$ Hz, 1H, 6-H), 7.72 (t, $J = 6.6$ Hz, 2H, 7-H + 5-H), 7.87 (d, $J = 8.3$ Hz, 1H, 5′-H), 7.95 (d, $J = 8.0$ Hz, 1H, 3′-H), 10.92 (br s, 1H, NH_2); IR (KBr) υ: 3455, 2223, 1602, 1501 cm^{-1}; MS (70 eV) m/z (%): 341.3 ($M^+ + 1$, 100).

6,14-Diamino-3,4,11,12-tetramethoxy-7-phenyl-7,8-dihydroquinolino[2,3-*a*]acridine 5a

9-Amino-6,7-dimethoxy-3-phenyl-1,2,3,4-tetrahydroacridin-1-one **3a** (6.96 g, 0.020 mol) and 2-amino-4,5-dimethoxybenzonitrile (3.6 g, 0.020 mol) were added to toluene (100 mL) containing *p*-toluenesulfonic acid monohydrate (1 g, 0.005 mol). The mixture was refluxed for 6 h, and the water was collected in a Dean–Stark water separator. K_2CO_3 (0.7 g, 0.005 mol) and Cu_2Cl_2 (0.45 g, 0.005 mol) were added to the mixture. The reaction mixture was refluxed for 12 h and was chilled to room temperature. The precipitated **5a** was filtered off and washed with water. The yellow powder was recrystallized from ethanol to afford 5.5 g of **5a** in 54.1% yield. Mp 202–203°C; ^{1}H NMR ($CDCl_3$, 500 MHz) δ: 3.35 (d, $J = 15.0$ Hz, 1H, 8-H), 3.47 (dd, $J = 15.0$, 6.0 Hz, 1H, 7-H), 3.82, 3.88, 3.90, 3.94 (each s, each 3H, 12H, OMe-H), 4.64 (s, 1H, 8-H), 6.01 (br s, 1H, NH_2), 6.57 (br s, 2H, NH_2), 7.00–7.15 (m, 5H, Ph-H), 7.00 (s, 1H, 13-H), 7.22 (s, 1H, 5-H), 7.53 (s, 1H, 10-H), 7.56 (s, 1H, 2-H),

11.08 (br s, 1H, hydrogen bonded NH_2); IR (KBr) υ: 3468, 1607, 1503 cm^{-1}; MS m/z (%): 509.4 ($M^+ + 1$, 100), 349.3 (25), Anal. calcd. for $C_{30}H_{28}N_4O_4$: C, 70.85; H, 5.55; N, 11.02; found: C, 70.68; H, 5.49; N, 11.13.

The compound **5b** were obtained from **3b** and 2-amino-4,5-dimethoxybenzonitrile in a similar manner.

6,14-Diamino-3,4,11,12-tetramethoxy-7,7-dimethy-7,8-dihydroquinolino [2,3-*a*]acridine 5b

Yield: 51.2%; mp > 300°C; ^1H NMR (DMSO, 500 MHz) δ: 1.26 (s, 6H, Me-H), 3.01 (s, 2H, 8-H), 3.96 (each s, each 3H, 12H, OMe-H), 6.27 (br s, 2H, NH_2), 6.93 (br s, 1H, NH_2), 7.29 (s, 1H ,13-H), 7.46 (s, 1H, 5-H), 7.75 (s, 1H, 10-H), 8.20 (s, 1H, 2-H), 10.91 (br s, 1H, hydrogen bonded NH_2); IR (KBr) υ: 3422, 1610, 1505 cm^{-1}; MS (70 eV) m/z (%): 461.2 ($M^+ + 1$, 100).

The compound **5c** were obtained from **3c** and 2-aminobenzonitrile in a similar manner.

6,14-Diamino-7-phenyl-7,8-dihydroquinolino[2,3-*a*]acridine 5c

Yield: 53.2%; mp 250–252°C; ^1H NMR (DMSO, 500 MHz) δ: 3.51 (d, $J = 16.5$ Hz, 1H, 8-H), 3.75 (dd, $J = 6.5$ Hz, 15.7 Hz, 1H, 7-H), 4.83 (s, 1H, 8-H), 6.23 (br s, 2H, NH_2), 6.79 (br s, 1H, NH_2), 7.09–7.17 (m, 5H, 3-Ph-H), 7.50 (t, $J = 6.7$ Hz, 1H, 4-H), 7.64 (d, $J = 6.7$ Hz, 1H, 12-H), 7.68 (d, $J = 10$ Hz, 1H, 11-H), 7.71 (d, $J = 6.7$ Hz, 1H, 10-H), 7.85 (t, $J = 6.7$ Hz, 1H, 3-H), 7.96 (d, $J = 8.0$ Hz, 1H, 2-H), 8.11 (d, $J = 8.1$ Hz, 1H, 9-H), 8.41 (d, $J = 8.4$ Hz, 1H, 5-H), 10.67 (br s, 1H, hydrogen bonded NH_2); IR (KBr) υ: 3452, 1603, 1502 cm^{-1}; MS (70 eV) m/z (%): 389.3 ($M^+ + 1$,100).

The compound **5d** was obtained from **3d** and 2-aminobenzonitrile in a similar manner.

6,14-Diamino-7,7-dimethy-7,8-dihydroquinolino[2,3-*a*]acridine 5d

Yield: 58.5%; mp > 300°C; ^1H NMR (DMSO, 500 MHz) δ: 2.50 (s, 6H, Me-H), 3.16 (s, 2H, 8-H), 6.61 (br s, 2H, NH_2), 7.02 (br s, 1H, NH_2), 7.48 (d, $J = 7.0$ Hz, 1H , 4-H), 7.69 (d, $J = 7.5$ Hz, 1H, 11-H), 7.72 (d, $J = 8.0$ Hz, 1H, 2-H), 7.85 (d, $J = 4.5$ Hz, 1H, 12-H), 7.87 (d, $J = 8.5$ Hz, 1H, 11-H), 7.95 (t, $J = 8.0$ Hz, 1H, 13-H), 8.35 (d, $J = 7.5$ Hz, 1H, 3-H),

8.64 (d, $J = 7.5$ Hz, 1H, 5-H), 12.96 (br s, 1H, hydrogen bonded NH_2); IR (KBr) υ: 3431, 1612, 1511 cm^{-1}; MS (70 eV) m/z (%): 341.3 ($M^+ + 1$, 100).

Determination of Crystal Structure

A yellowish transparent crystal 0.511 mm × 0.495 mm × 0.278 mm was selected for the crystal structure measurements. The x-ray diffraction intensities were recorded by a Bruker Smart 1000 CCD automatic diffractometer with graphite-monochromatized Mo Kα radiation ($\lambda = 0.071073$ nm) at 293(2) K. In the range of $1.96 < \theta < 25.50$, 6313 independent reflections were obtained. The structures were solved by direct methods using the SHELXL-97 program. All the nonhydrogen atoms were refined on F^2 anisotropically with the full-matrix least squares method. Hydrogen atoms were added according to the theoretical methods. The final convergence indices were $R_1 = 0.1060$, $wR_2 = 0.2192$ ($w = 1/[S^2\ (F_0^2) + (0.1186P)^2]$, and $P = (F_0^2 + 2F_0^2)/3$, $S = 0.953$. The maximum and the minimum difference peak holes were 477 and −496 e/nm^3 respectively.

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