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Synthesis of new tetracyclic 7-oxo-pyrido[3,2,1-*de*]acridine derivatives

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ABSTRACT

A series of (±)3-hydroxyl- and 2,3-dihydroxy-2,3-dihydro-7-oxopyrido[3,2,1-*de*]acridines were synthesized for antitumor evaluation. These agents can be considered as analogues of glyfoline or (±)1,2-dihydroxyacronycine derivatives. The key intermediates, 3,7-dioxopyrido[3,2,1-*de*]acridines (**15a**,**b** or **24a**,**b**), for constructing the target compounds were synthesized either from 3-(*N*,*N*-diphenylamino) propionic acid (**14a**,**b**) by treating with Eaton's reagent (P_2O_5/MsOH) (Method 1) or from (9-oxo-9*H*-acridin-10-yl)propionic acid (**23a**–**c**) via ring cyclization under the same reaction conditions (Method 2). Compounds **15a**,**b** and **24a**,**b** were converted into (±)3-hydroxy derivatives (**25a**–**d**), which were then further transformed into pyrido[3,2,1-*de*]acridin-7-one (**28a**–**d**) by treating with methanesulfonic anhydride in pyridine via dehydration. 1,2-Dihydroxylation of **28a**–**d** afforded (±)*cis*-2,3-dihydroxy-7-oxopyrido[3,2,1-*de*]acridine (**29a**–**d**). Derivatives of (±)3-hydroxy (**25a**,**b**) and (±)*cis*-2,3-dihydroxy (**29a**–**d**) were further converted into their *O*-acetyl congeners **26a**,**b** and **30a**–**d**, respectively. We also synthesized 2,3-cyclic carbonate (**31**, **32**, and **33**) from **29a**–**c**. The anti-proliferative study revealed that these agents exhibited low cytotoxicity in inhibiting human lymphoblastic leukemia CCRF-CEM cell growth in culture.

1. Introduction

One of our ongoing research programs is searching for the antitumor agents that have a novel mechanism of action. We have previously studied the antitumor effect of naturally occurring acridone alkaloids, glyfoline (**1**, Fig. 1) and acronycine (**2**) derivatives. Acridone alkaloids were also known as potential antitumor agents since acronycine (**2**) was found to have potent antitumor activity in the middle of the 1960s.[1–4] Previously, we have evaluated the anti-proliferative activity of a series of acridone alkaloids and found that glyfoline (**1**) was the most cytotoxic against human leukemia HL-60 cell growth in vitro.[5] The alkaloid was first isolated from *Glyfoline citrifolia* (Willd.) Lindl. (Rutaceae), an indigenous plant from Taiwan. Glyfoline was about 10-fold more potent than acronycine and exhibited moderate in vivo antitumor activity in mice bearing murine and human tumors xenograft.[6] Remarkably, we have recently found that the alkaloid exhibits a novel mechanism of action by targeting the mitochondria and releasing cytochrome c to induce tumor cell death.[7] More recently, we studied on the detailed mechanism of action of glyfoline, and found that this agent induced the appearance of spindle abnormalities, chromosome mis-segregation, multipolar cell division, and multiple nuclei, traits indicative of mitotic catastrophe.[8]

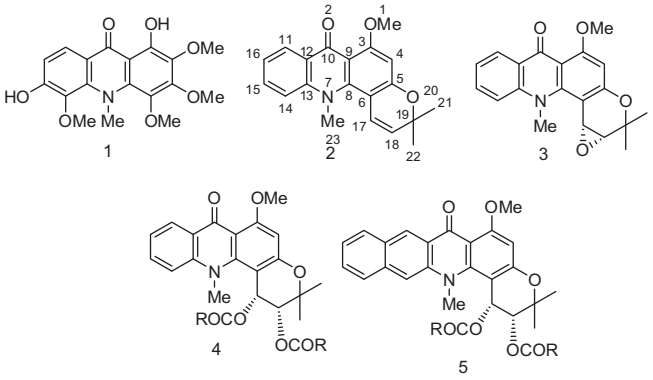

Fig. 1. Structures of glyfoline (**1**) and acronycine derivatives (**2**–**5**).

Acronycine (**2**, Fig. 1), isolated from the Australian scribe ash *Acronychia baueri Schott* (Rutaceae), possessed moderate in vitro potency and a broad spectrum of antitumor activity.[2,3,9,10] This alkaloid was in clinical trials.[1] However, limited efficacy was

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observed, probably due to its poor physiochemical properties. Dorr and Liddil have demonstrated that this alkaloid may interact with DNA, either by intercalation or by some other noncovalent process.[11] Recently, several acronycine derivatives, such as unstable natural epoxides (**3**, Fig. 1) and synthetic diesters of (±)-*cis*-1,2-dihydroxy-1,2-dihydroacronycine (**4**)[12] and its benzo[*b*]acronycine derivatives (**5**)[13] or their acetates,[14–16] were reported to have markedly improved antitumor activity. Particular interest is that the latter compound was able to covalently bind with DNA.[17,18] It was reported that (±)1,2-dihydroxy-1,2-dihydroacronycine diesters (**6**, Fig. 2) exhibited potent in vivo antitumor activity against murine P388 leukemia and colon 38 adenocarcinoma when compared with acronycine. Costes et al. synthesized a series of (±)-*cis*-1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine derivatives.[13] The diacetates (**7**, S23906-1) and the cyclic carbonate **8** displayed potent antitumor effects in mice bearing P388 leukemia and colon 38 adenocarcinoma. More than 80% of tumors were suppressed in mice at doses 16-fold lower than the effective dose of acronycine itself. Compound **7** was the most active, with all the treated mice being tumor-free on day 23 at the dose of 12.5 mg/kg (drug was administrated by intraperitoneous injection on day 2 and 9).[14] Compound **7** is currently undergoing phase I clinical trials.[17] It was found to be as efficient as a variety of clinically used drugs in human orthotopic models of carcinomas.[19,20]

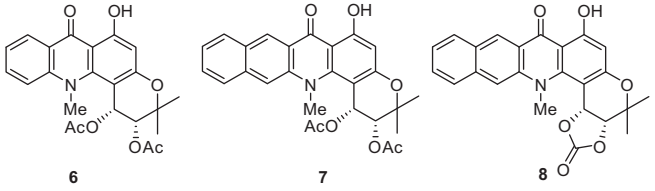


Fig. 2. Structures of acronycine derivatives (**6**–**8**).

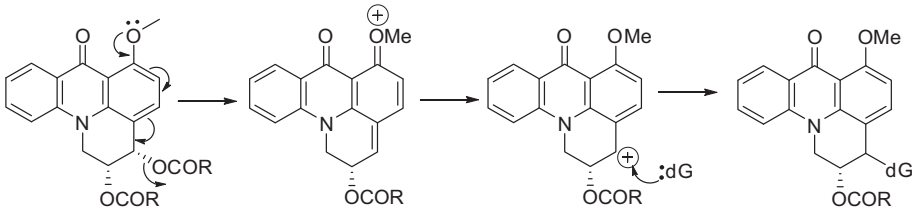
At the cellular level, compound **7** induced an irreversible *S*-phase blockade of the cell cycle and efficiently triggered apoptosis in several cancer cell types.[13,21,22] At the molecular level, diacetates **7** were found to bind covalently both with purified DNA fragments and with genomic DNA extracted from treated tumor cells.[17,23] The studies have demonstrated that compound **7** readily alkylated G·C base pairs and specifically bonded to the exocyclic NH_2 group of the guanine residue.[22] The study showed that there was a strong correlation between DNA alkylation by the various 1,2-dihydroxy-1,2-dihydrobenzo[*b*]acronycine diesters and their respective cytotoxic potential.[23] Studies on the mechanism of action of 1,2-dihydroxy-1,2-dihydro-benzo[*b*]acronycine diesters revealed that the ester at C-1 acts as a leaving group, which generates a cation at C-1 and allows the nucleophilic attack by DNA (Scheme 1). Since (±)*cis*-1,2-diesters and (±)2-monoester were equally potent, it suggests that the monoester at C-2 could spontaneously lead to the corresponding more reactive monoester at C-1 by a transesterification process.[23]

On the basis of the super antitumor activity and mechanism of action of (±)-*cis*-1,2-dihydroxy-1,2-dihydroacronycine derivatives (**6** and **7**), we have design and synthesize new glyfoline analogues, namely (±)6-methoxy-7-oxo-3-hydroxy- (or *cis*-2,3-dihydroxy)-2,3-dihydro-1*H*,7*H*-pyrido[3,2,1-*de*]-acridin-3-yl derivatives (**A**, Scheme 2) for antitumor evaluation. These compounds can be considered as analogues of glyfoline with an additional fused cyclohexanyl ring on the C4-N10 position of the acridin-9-one chromophore. One can anticipate that the *O*-acetyl function at C2 of these derivatives might be more acceptable for nucleophilic attack by DNA than the corresponding *O*-acetyl function in 1,2-dihydroxyacronycine derivatives (**6** or **7**), since they lack the sterical hindrance of the *N*-Me function. We herein describe the chemical synthesis and antitumor activity of 2,3-dihydroxy-7-oxo-pyridoacridines.

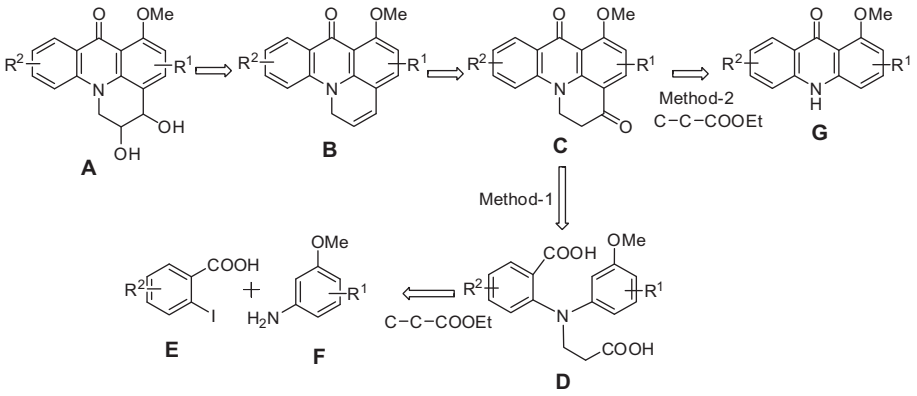
2. Results and discussion

Scheme 2 shows the retro-synthesis of the newly synthesized compounds. The target compound **A** could be easily prepared by 1,2-dihydroxylation of the olefin function of **B**. To prepare the intermediate **B**, it is necessary to construct the key intermediate 3,7-dioxopyrido[3,2,1-*de*]acridines **C**, which can be reduced to alcohols, followed with dehydration to yield **B**. The 3,7-di-oxo compound **C** can be synthesized from 3-(*N*,*N*-diphenylamino)propionic acid **D** by ring cyclization via Friedel–Craft acylation (Method 1). The intermediate can be prepared by Ullmann condensation of 2-iodobenzoic acid **E** and *m*-anisidines **F**, followed with N-alkylation with ethyl acrylate. Alternatively, one can prepare the intermediate **C** from 9-acridones by reacting with propionate, followed by intramolecular cyclization (Method 2). The synthesis of the desired compound **A** was then carried out and is described as follows.

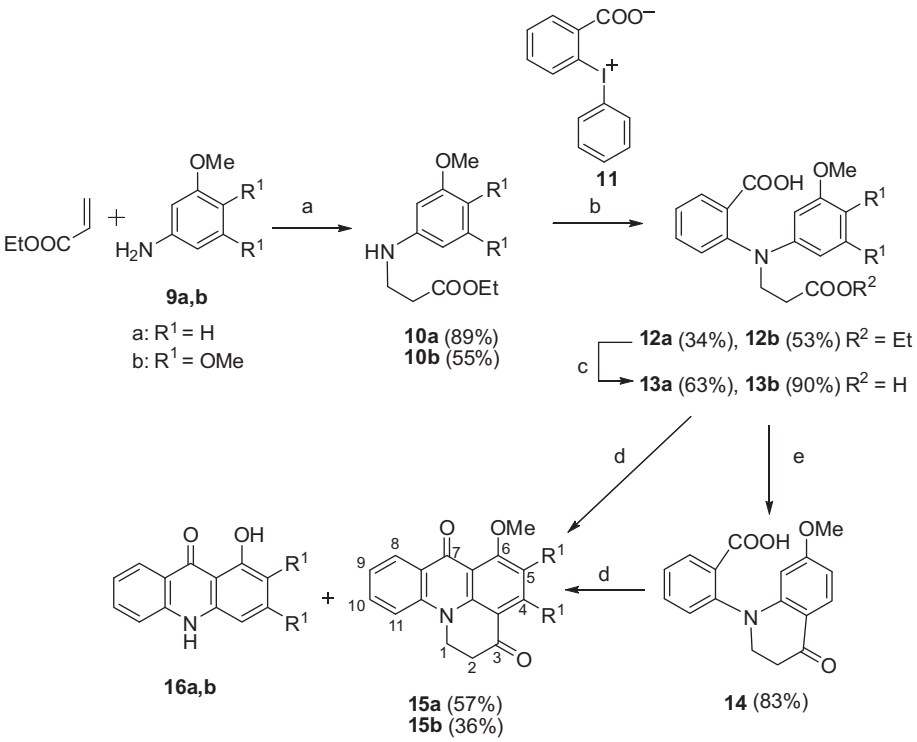
In Method 1, attempts to prepare ethyl 3-(*N*,*N*-diphenylamino) propionate (**12a**,**b**) either by Ullmann condensation of 2-iodobenzoic acid with *m*-anisidine derivatives, followed by N-alkylation with ethyl acrylate or reaction of 2-iodobenzoic acid with 3-(*m*-anisidinyl)propionate failed. We finally found that diphenyliodonium-2-carboxylate (DPIC, **11**) is an appropriate reactant for the Ullmann condensation with *m*-anisidine. Thus, the known ethyl 3-anisidinypropionates (**10a**,**b**)[24,25] was synthesized in good yield (85%) by reacting *m*-anisidine (**9a**) with a large excess of ethyl acrylate in the presence of acetic acid under refluxing for one day (Scheme 3). However, under the same reaction conditions, the reaction of 3,4,5-trimethoxyaniline with ethyl acrylate required a longer reaction time (about 2 weeks) to yield **10b** in moderate yield (55%). Condensation of **10a**,**b** with diphenyliodonium-2-carboxylat (DPIC, **11**) afforded ethyl 3-(*N*,*N*-diphenylamino)propionates (**12a**,**b**), which were then saponified (NaOH/MeOH) to give propionic acid derivatives **13a**,**b**. We attempted to prepare pyridoacridines **15a**,**b** by treating **13a**,**b** with various Lewis acids. Among these agents, we found the reaction of **13a** with trifluoroacetic anhydride gave tetrahydroquinolin-4-one **14** in good yield at low temperature (−5 to −10 °C). It indicated that the cyclization preferably occurred on the *para*-position to the MeO function of the



Scheme 1. The proposed mechanism of DNA alkylation by new acridine derivatives.



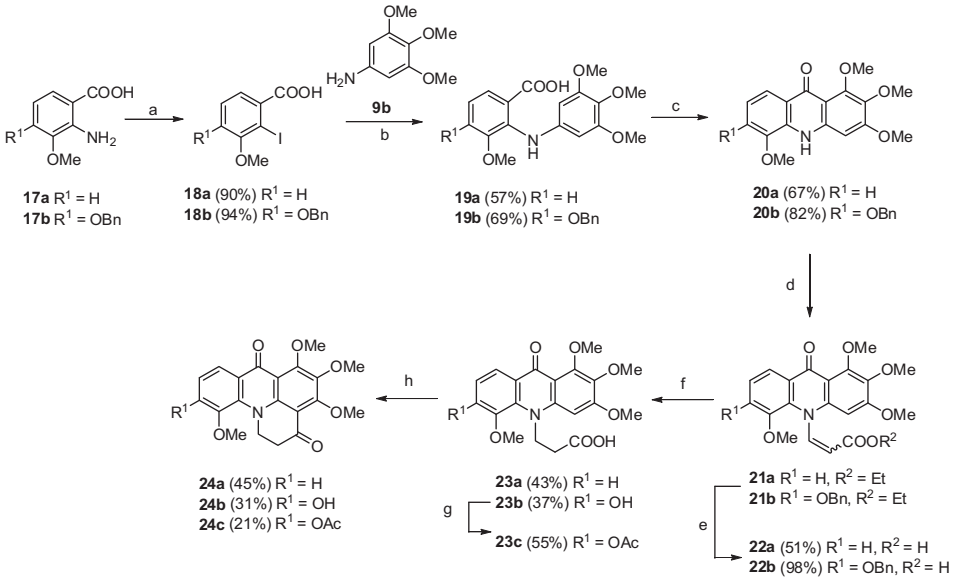
Scheme 2. Retrosynthetic analysis.



Scheme 3. Reagents and conditions: (a) AcOH/EtOH, reflux; (b) $Cu(OAc)_2$/DMF, 90 °C; (c) NaOH/MeOH, rt; (d) 10% P_2O_5/MsOH (Eton's reagent), rt; (e) trifluoroacetic anhydride, rt.

Interestingly, we were able to convert **13a** directly to the desired tetra-cyclic **15a** by reacting with Eaton's reagent. It should be noted that when the reaction was carried out in concentrated sulfuric acid, polyphosphoric acid, or phosphoryl chloride,[27] a mixture of acridin-9-ones **15a**,**b** together with 1-hydroxyacridin-9-ones (**16a**,**b**) was obtained. It suggested that the propionic acid side-chain is unstable under acidic conditions and may undergo β-elimination to form acrdin-9-one. Method 1, however, can not be applied for synthesizing **24a**–**c** derivatives, which bear substituent(s) on the A-ring of the acridin-2-one, since we could not prepare the substituted DPIC derivative.

Method 2 was then developed to construct the key intermediate **C**, 3,7-dioxopyrido[3,2,1-*de*]acridines having substituent(s) on the A-ring (i.e., compounds **24a**–**c** Scheme 4). We first synthesized substituted 2-iodobenzoic acids **18a**,**b** in high yield from anthranilic acid **17a**,**b** by treating with $NaNO_2$/HCl/KI following the known procedure.[6,28] Ullmann condensation of anthranilic acid **18a**,**b** with 3,4,5-trimethoxyaniline (**9b**) gave *N*-phenylanthranilic acids **19a**,**b**, which were then ring cyclized by treating with phosphoryl chloride to give acridin-9-ones **20a**,**b**. It is noted that one should work up the reaction with caution, since the methoxy function at the C1 position is labile and can be hydrolyzed into C1–OH (nor acridin-9-one) under acidic conditions. Reaction of **20a**,**b** with ethyl propiolate afforded mainly the *trans*-isomer. The pure *trans*-**21a**,**b** (major products) can be obtained by recrystallization or chromatography, while the *cis*-**21a**,**b** isomer (>2%) was rather difficult to be separated from the mixture. The ^{1}H NMR spectrum analyses for **21b** reveal the protons on the double bond: for *trans*-isomer, appeared at δ 5.45 and 8.11 with a coupling constant of J=14.0 Hz; for *cis*-isomer, located at δ 6.18 and 7.94 having coupling constant of J=8.4 Hz. Since compounds **21a**,**b** were not suitable for ring cyclizing to give the tetra-cyclic derivatives, these derivatives were directly converted into *N*-propionic acid derivatives **22a**,**b** via saponification (NaOH/MeOH), followed by hydrogenation (10% Pd/C, H_2, EtOH). Under the reaction conditions, the *O*-benzyl protecting function of **22b** (R=OBn) was removed during the hydrogenation to form **23b**, which was reprotected by treating with acetic anhydride/pyridine to afford *O*-acetyl **23c**. Similarly, compound **23a** was then



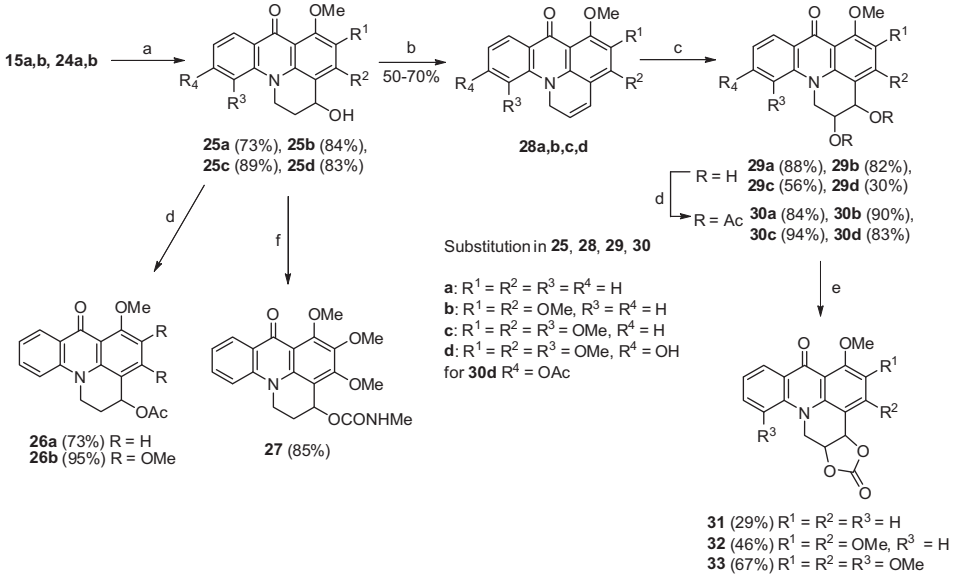
Scheme 4. Reagents and conditions: (a) $NaNO_2$/HCl, KI, 5 °C; (b) CuI, Cu, K_2CO_3/DMF, 40–80 °C; (c) $POCl_3$, 40 °C, and then 5% HCl 40 °C; (d) ethyl propionate/K_2CO_3/DMF, rt; (e) NaOH/Ac_2O; (f) 10% Pd/C, H_2/EtOH, 40 psi; (g) Ac_2O/pyridine; (h) 10% P_2O_5/MsOH (Eton's reagent), rt.

treated with Eaton's reagent (P_2O_5/MsOH) to give the tetra-cyclic **24a**. In the case of **23c**, the *O*-acetyl function was partially hydrolyzed to form **24b** and **24c** upon treatment of Eaton's reagent.

Using 3,7-dioxopyrido[3,2,1-*de*]acridines (**15a**,**b** and **24a**,**b**) as the starting materials, we successfully converted them into the corresponding 2,3-dihydroxy derivatives (Scheme 5). Thus, compounds **15a**,**b** and **24a**,**b** were reduced with $NaBH_4$ in THF to 3-hydroxy derivatives (±)**25a**–**d**, which were then treated with methanesulfonyl chloride in the presence of triethylamine in chloroform to give the desired 7-oxo-1*H*,7*H*-pyrido-[3,2,1-*de*]acridin-3-yl derivatives **28a**–**d** in high yield (Scheme 5). The reaction proceeded smoothly without observing the formation of *O*-methanesulfonyl intermediate. Dihydroxylation of the 2,3-olefin in **28a**–**d** using OsO_4 in the presence of 4-methylmorpholin *N*-oxide in THF gave (±) 2,3-dihydroxy derivatives (**29a**–**d**).

To design and synthesize pyrido[3,2,1-*de*]acridines with DNA alkylating potential, we prepare (±)3-*O*-acetyl (**26a**,**b**), (±)3-*O*-methylcarbamoyl (**27**), and (±)2,3-di-*O*-acetate (**30a**–**d**) derivatives to realize whether the C3-*O*-acetyl or 3-*O*-methylcarbamoyl can act as a leaving group to generate a cation for nucleophilic attack by DNA as that of (±)1,2-di-*O*-acetylacronycine analogues. Thus, compounds (±)**25a**,**b** or (±)**29a**–**d** were reacted with acetic anhydride in pyridine, affording *O*-acetate derivatives (±)**26a**,**b** and (±)**30a**–**d**, respectively (Scheme 5). Compound (±)**27** was prepared in good yield from **25a** by treating with methylisocyanate in $CHCl_3$ solution in the presence of triethylamine. Similarly, we also prepared cyclic carbonate derivatives, (±)**31**, (±)**32**, (±)**33**, from (±)**29a**, (±)**29b**, and (±)**29c**, respectively, by reacting with *N*,*N*-carbonyldiimidazole in 2-butanone.

Our earlier studies revealed that glyfoline and related acridin-9-ones exhibited cytotoxic effects in inhibiting human leukemia HL-60 cell growth in culture.[5] In the present study, we have synthesized a series of (±)3-hydroxy-7-oxo-1*H*,7*H*-pyrido[3,2,1-*de*]acridin-3-yl (**25a**–**d**) and (±)2,3-dihydroxy derivatives (**29a**–**d**) and their *O*-acetyl derivatives (**26a**,**b** and **30a**–**d**). These agents can be also considered as analogues of glyfoline or (±)1,2-dihydroxy-1,2-



Scheme 5. Reagents and conditions: (a) $NaBH_4$/THF/H_2O; (b) $(MeSO_2)_2O$/Et_3N, pyridine or DMAP/$CHCl_3$, rt; (c) OsO_4/4-methylmorpholine-*N*-oxide/THF, rt; (d) Ac_2O/pyridine, rt; (e) *N*,*N*-carbonyldiimidazole/butanone; (f) MeN=C=O/Et_3N.

dihydroacronycine. The newly synthesized compounds were subjected to antitumor evaluation against human lymphoblastic leukemia cell (CCRF/CEM) growth in vitro. However, it was shown that these agents exhibited low cytotoxicity against the tested tumor cell line. Comparing the chemical structure of 2,3-dihydroxy-2,3-dihydro-1*H*,7*H*-pyrido-[3,2,1-*de*]acridin-3-yl and 1,2-dihydroxyacronycines, the later derivatives bearing a 1,2-dihydroxy-3,3-dimethylpyrano ring angularly fused in the position of [2,3-*d*] on the acridin-9-one basic skeleton, which may be essential for anti-proliferative activity. While our newly synthesized derivatives were inactive probably due to have a 2,3-dihydroxy-2,3-dihydropyrido ring fused in position [3,2,1-*de*] on the acridin-9-one chromophore.

3. Conclusion

We have designed and synthesized a new series of (±)3-hydroxyl- and 2,3-dihydroxy-2,3-dihydro-7-oxopyrido[3,2,1-*de*] acridines for antitumor evaluation. These agents can be considered as analogues of glyfoline and (±)1,2-dihydroxyacronycine derivatives and anticipate to have antitumor activity. However, these congeners were found to have low biological activity due to their compact structure and lacking of1,2-dihydroxy-3,3-dimethylpyrano ring.

4. Experimental section

4.1. General methods and materials

All commercial chemicals and solvents were reagent grade and were used without further purification unless otherwise specified. Melting points were determined on a Fargo melting point apparatus and are uncorrected. Column chromatography was carried out on silica gel G60 (70–230 mesh, ASTM; Merck and 230–400 mesh, Silicycle Inc.). Thin-layer chromatography was performed on silica gel G60 F_{254} (Merck) with short-wavelength UV light for visualization. All reported yields are isolated yields after chromatography or crystallization. Elemental analyses were done on a Heraeus CHN-O Rapid instrument. ^{1}H NMR spectra were recorded on a 500 MHz, Brucker AVANCE 500 DRX and 400 MHz, Brucker Top-Spin spectrometers in the indicated solvent. The chemical shifts were reported in parts per million (δ) relative to TMS.

4.2. Ethyl 3-(3-methoxyphenylamino)propionate (10a)[24]

A mixture of *m*-anisidine (**9a**, 172 mL, 1.5 mol) and ethyl acrylate (184 mL, 1.7 mol) containing acetic acid (6 mL) was heated under reflux for 24 h. The mixture was evaporated to remove excess ethyl acrylate and acetic acid and the residue was chromatographed on a silica gel column (10×33 cm) using hexane/EtOAc (20:1 v/v) as the eluant. Compound **9a** was eluated by hexane/EtOAc (5:1 v/v) as orange syrup (298 g, 89%); ^{1}H NMR (500 MHz, DMSO-d_6): 7.08 (1H, t, J=8.80 Hz, ArH), 6.28 (1H, m, ArH), 6.24 (1H, m, ArH), 6.17 (1H, m, ArH), 4.15 (2H, q, J=7.3 Hz, OCH_2), 4.05 (1H, br s, NH), 3.77 (3H, s, OMe), 3.43 (2H, t, J=6.6 Hz, CH_2), 2.60 (2H, t, J=6.6 Hz, CH_2), 1.27 (3H, t, J=7.3 Hz, Me).

*4.2.1. Ethyl 3-(3,4,5-trimethoxyphenylamino)propionate (**10b**)[25].* By following the same procedure as that for the synthesis of **10a**, compound **10b** was prepared from 3,4,5-trimethoxyaniline (**9b**, 55 g, 300 mmol), ethyl acrylate (33 g, 330 mmol), and acetic acid (2 mL) in EtOH (1 L) by refluxing for 2 weeks. The product was crystallized from ethyl acetate/hexane, 47 g (55%); mp 51–52 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 5.87 (2H, s, 2× ArH); 4.16 (2H, q, J=7.1 Hz, CH_2), 3.81 (6H, s, 2× OMe), 3.76 (3H, s, OMe), 3.41 (2H, t, J=6.4 Hz, CH_2), 2.61 (2H, t, J=6.4 Hz, CH_2), 1.26 (3H, t, J=7.1 Hz, Me). Anal. Calcd for $C_{14}H_{21}NO_5$: C, 59.35; H, 7.47; N, 4.94, found: C, 59.15; H, 7.44; N, 4.77.

4.3. 2-((3-Ethoxy-3-oxopropyl)(3-methoxyphenyl)amino) benzoic acid (12a)

A mixture of DPIC (78 g, 240 mmol), **10a** (44.66 g, 200 mmol), $CuOAc_2$ (3.63 g, 20 mmol) in dry DMF (400 mL) was stirred at room temperature for 1h, and then heated at 80–90 °C for 4 h. The mixture was evaporated in vacuo to remove DMF. The residue was dissolved in $CHCl_3$ (250 mL) and extracted with 0.2 N aqueous solution of K_2CO_3 (200 mL×6) until no more product in the organic layer. The water layer was acidified with acetic acid, extracted with $CHCl_3$ (100 mL×2), dried over Na_2SO_4, and evaporated to dryness. The product was purified by silica gel column chromatography (4×29 cm, hexane/EtOAc, 3:2 v/v) to give **12a** as yellow syrup (23.54 g, 34%); ^{1}H NMR (500 MHz, DMSO-d_6): 12.74 (1H, br s, COOH), 7.81 (1H, m, ArH), 7.61 (1H, m, ArH), 7.39 (1H, m, ArH), 7.27 (1H, m, ArH), 6.99 (1H, m, ArH), 6.24 (1H, m, ArH), 6.03(1H, m, ArH), 5.98 (1H, br s, ArH), 3.99 (2H, q, J=7.2 Hz, CH_2), 3.86 (2H, t, J=7.1 Hz, CH_2), 3.62 (3H, s, OCH_3), 2.64 (2H, t, J=7.1 Hz, CH_2), 1.12 (3H, t, J=7.2 Hz, CH_3); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 172.3, 169.7, 159.4, 151.3, 148.3, 136.9, 134.8, 131.2, 122.5, 120.4, 119.4, 117.4, 115.5, 92.5, 56.5, 55.9, 55.6, 32.5, 14.0. Anal. Calcd for $C_{19}H_{21}NO_5$: C, 66.46; H, 6.18; N, 4.08, found: C, 66.37; H, 6.05; N, 4.11.

*4.3.1. 2-((3-Ethoxy-3-oxopropyl)(3,4,5-trimethoxyphenyl)amino) benzoic acid (**12b**).* By following the same procedure as that for the preparation of **12a**, compound **12b** was prepared from **10b** (17.0 g, 60 mmol) and DPIC (19.5 g, 60 mmol). Yield, 13 g (53%) as syrup; ^{1}H NMR (500 MHz, $CDCl_3$): 8.34 (1H, d, J=7.8 Hz, ArH), 7.62 (1H, t, J=7.6 Hz, ArH), 7.46 (2H, t, J=7.5 Hz, ArH), 7.28 (1H, d, J=7.9 Hz, ArH), 6.21 (2H, s, 2× ArH), 4.12 (2H, q, J=7.1 Hz, CH_2), 3.91 (2H, t, J=7.2 Hz, CH_2), 3.79 (3H, s, OMe), 3.76 (6H, s, 2× OMe), 2.61 (2H, t, J=7.2 Hz, CH_2), 1.24 (3H, t, J=7.1 Hz, Me); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 171.6, 167.8, 153.2, 145.2, 144.6, 132.8, 131.2, 130.9, 130.1, 129.7, 125.9, 92.5, 60.1, 55.9, 55.6, 48.2, 32.5, 14.0. Anal. Calcd for $C_{21}H_{25}NO_7 \cdot 0.5H_2O$: C, 61.15; H, 6.35; N, 3.39, found: C, 61.33; H, 6.17; N, 3.07.

4.4. 2-((2-Carboxyethyl)(3-methoxyphenyl)amino)benzoic acid (13a)

To a stirred solution of **12a** (10.3 g, 30 mmol) in methanol (50 mL) was slowly added 1 N NaOH aqueous solution (60 mL) at room temperature until TLC indicated absence of the ester. After stirring an additional 1 h, the methanol was removed and aqueous layer was neutralized with saturated NH_4Cl solution to pH 7 and then extracted with $CHCl_3$ (100 mL×5). The combined organic extract was washed with water (100 mL×2), dried over Na_2SO_4, and evaporated under reduced pressure. The residue was crystallized from $CHCl_3$. Addition product was obtained from mother liquid by column chromatography (SiO_2, $CHCl_3$/MeOH, 30:1) to give **13a**, total 5.1 g (63%); mp 85–87 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 12.54 (2H, br s, 2× COOH), 7.81 (1H, m, ArH), 7.62 (1H, m, ArH), 7.40 (1H, m, ArH), 7.30 (1H, m, ArH), 6.99 (1H, m, ArH), 6.24 (1H, m, ArH), 6.02 (1H, m, ArH), 5.98 (1H, m, ArH), 3.83 (2H, t, J=7.4 Hz, CH_2), 3.62 (3H, s, OMe), 2.58 (2H, t, J=7.4 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 173.0, 167.5, 160.2, 149.3, 145.2, 133.1, 131.4, 131.2, 130.7, 129.6, 126.5, 106.4, 102.1, 99.6, 54.7, 48.1, 32.3. Anal. Calcd for $C_{17}H_{17}NO_5$: C, 64.75; H, 5.43; N, 4.44, found: C, 64.45; H, 5.65; N, 4.18.

*4.4.1. 2-((2-Carboxyethyl)(3,4,5-trimethoxyphenyl)amino)benzoic acid (**13b**).* By following the same procedure as that for the synthesis of **13a**, compound **13b** was prepared from **12b** (12 g,

30 mmol). Yield, 10 g (90%) as syrup. The crude product was used directly for the next reaction without further purification. A small amount of sample was purified by column chromatography for ^{1}H NMR spectrophotometric analysis; ^{1}H NMR (500 MHz, $CDCl_3$): 8.26 (1H, m, ArH), 7.61 (1H, m, ArH), 7.43 (1H, m, ArH), 7.28 (1H, m, ArH), 7.25 (2H, s, ArH), 3.92 (2H, t, J=6.8 Hz, CH_2), 3.78 (3H, s, OMe), 3.74 (6H, s, 2× OMe), 2.65 (2H, t, J=6.8 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.5, 171.1, 149.2, 144.2, 134.1, 131.3, 131.2, 130.8, 123.9, 118.1, 115.2, 106.2, 102.9, 99.6, 58.9, 56.2, 55.6, 49.8, 33.4.

4.5. 2-(7-Methoxy-4-oxo-3,4-dihydroquinolin-1(2*H*)-yl) benzoic acid (14)

A solution of freshly distillated trifluoroacetic anhydride (2.8 mL, 20 mmol) in dry CH_2Cl_2 (650 mL) was added dropwise to a solution of **13a** (3.15 g, 10 mmol) in dry CH_2Cl_2 (150 mL) at −5 to −10 °C during 2.5 h under argon. After stirring for additional 4 h, the precipitate appeared in the reaction mixture was separated by filtration. Additional product was obtained after the concentration of the filtrate. The combined solid was recrystallized from $CHCl_3$ to give **14** (2.46 g, 83%); mp 227–229 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 8.32 (1H, m, ArH), 8.27 (1H, m, ArH), 7.80 (2H, m, 2× ArH), 7.33 (1H, m, ArH), 7.16 (1H, s, ArH), 6.92 (1H, m, ArH), 4.72 (2H, t, J=7.5 Hz, CH_2), 3.97 (3H, s, OMe), 2.83 (2H, t, J=7.5 Hz, CH_2). Anal. Calcd for $C_{17}H_{15}NO_4\cdot H_2O$: C, 64.75; H, 5.43; N, 4.44; found: C, 64.51; H, 5.32; N, 4.41.

4.6. 2-Iodo-3-methoxybenzoic acid (18a)[29]

To a suspension of 3-methoxy-2-amino-benzoic acid (**17a**, 20.06 g, 120 mmol) in a mixture of ice-water (300 mL), acetone (100 mL), and HCl (57.6 mL, 720 mmol) was added dropwise a solution of $NaNO_2$ (16.6 g, 240 mmol) in water (120 mL) over 1 h at 7–10 °C (interior temperature). After being stirred for 2 h, the solid KI (39.84 g, 240 mmol) was added directly during 5 min and kept the temperature at 7–10 °C for additional 30 min. The reaction mixture was heated at 80–90 °C until purple gas disappear and then cooled to room temperature. The inorganic solid was removed by filtration and the filtrate was concentrated under reduced pressure to remove acetone. The aqueous solution was extracted with $CHCl_3$ (200 mL×5), and the organic layer was combined and washed with water (100 mL×2), dried over Na_2SO_4, and evaporated to dryness. The residue was crystallized from MeOH to give **18a**, 29.9 g (90%), mp 148–149 °C (MeOH) (lit.[30] 146.5–149.5 °C); ^{1}H NMR (500 MHz, DMSO-d_6): 13.26 (1H, br s, COOH), 7.48 (1H, m, ArH), 7.11 (2H, t, J=8.5 Hz, 2× ArH), 3.86 (3H, s, OMe).

*4.6.1. 4-Benzyloxy-2-iodo-3-methoxybenzoic acid (**18b**).* By following the same procedure as that for the synthesis of **18a**, compound **18b** was prepared from 4-benzyloxy-3-methoxyanthranilic acid **18b** (41 g, 150 mmol),[6] sodium nitrite (300 mL, 300 mmol), and KI (49.7 g, 300 mmol). Yield, 49 g (94%), mp 191–192 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.48–7.51 (3H, m, 3× ArH), 7.41–7.44 (2H, m, 2× ArH), 7.34–7.36 (1H, m, ArH), 7.21 (1H, m, ArH), 5.23 (2H, s, CH_2), 3.72 (3H, s, OMe). Anal. Calcd for $C_{15}H_{13}O_4I$: C, 46.90; H, 3.41, found: C, 46.76; H, 3.49.

4.7. 3-Methoxy-2-(3,4,5-trimethoxyphenylamino)benzoic acid (19a)

A mixture of **18a** (22.25 g, 80 mmol), 3,4,5-trimethoxyaniline (**9b**, 21.98 g, 120 mmol), Cu (0.51 g, 8 mmol), CuI (1.52 g, 8 mmol), and potassium carbonate (33.17 g, 240 mmol) in DMF (500 mL) was stirred and heated at 40–50 °C for overnight. The solvent was removed in vacuo and the residue was dissolved in MeOH (300 mL), filtered with a pad of Celite, and washed with MeOH. The combined filtrate and washings was diluted with water (1 L) and then acidified with CH_3COOH to pH 4–5. The precipitate was collected by filtration. It was dissolved in NaOH aqueous solution and then acidified with acetic acid to pH 4–5 and then extracted with $CHCl_3$ (200 mL×5). The organic layer was washed with water, dried over Ns_2SO_4, and evaporated to dryness. The residue was crystallized from EtOH to give **19a** (15.05 g, 57%); mp: 185–189 °C (EtOH); ^{1}H NMR (500 MHz, DMSO-d_6): 7.80 (1H, m, ArH), 7.21 (1H, m, ArH), 7.14 (1H, m, ArH), 6.04 (2H, s, 2× ArH), 3.79 (6H, s, 2× OMe), 3.76 (6H, s, 2× OMe). Anal. Calcd for $C_{17}H_{19}NO_6$: C, 61.25; H, 5.74; N, 4.20; found: C, 61.06; H, 5.59; N, 4.11.

*4.7.1. 4-Benzyloxy-3-methoxy-2-(3,4,5-trimethoxy-phenyl-amino) benzoic acid (**19b**).* By following the same procedure as that for the synthesis of **19a**, compound **19b** was prepared from **18b** (20.45 g, 60 mmol) and 3,4,5-trimethoxyaniline **9b** (12 g, 66 mmol). Yield, 18.2 g (69%), mp 159–160 °C; ^{1}H NMR (DMSO-d_6): 12.85 (1H, br, COOH), 8.85 (1H, br, NH), 7.64 (1H, m, ArH), 7.47–7.48 (2H, m, ArH), 7.39–7.42 (2H, m, ArH), 7.34–7.36 (1H, m, ArH), 6.84 (1H, d, J=9.0 Hz, ArH), 6.15 (1H, s, ArH), 5.22 (2H, s, CH_2), 3.67 (6H, s, 2× OMe), 3.59 (3H, s, OMe), 3.47 (3H, s, OMe). Anal. Calcd for $C_{24}H_{25}NO_7\cdot 0.5H_2O$: C, 64.27; H, 5.84; N, 3.12; found: C, 64.90; H, 5.90; N, 3.12.

4.8. 1,2,3,5-Tetramethoxy-10*H*-acridin-9-one (20a)

A mixture of **19a** (10 g, 30 mmol) and $POCl_3$ (30 mL) containing 4 drop of DMF was heated at 40 °C for 1 h. The reaction mixture was evaporated in vacuo to dryness and the residue was dissolved in $CHCl_3$ (50 mL). 5% aqueous solution of HCl (40 mL) was added slowly in the $CHCl_3$ solution with stirring and then diluted with EtOH (400 mL). After being stirred at room temperature for overnight, the mixture was concentrated and the solid was collected by filtration. The solid product was purified by column chromatography (SiO_2, $CHCl_3$/MeOH 10:1) to give **20a**, 6.35 g (67%); mp 93–94 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 10.08 (1H, br s, NH), 7.73 (1H, m, ArH), 7.35 (1H, s, ArH), 7.24 (1H, m, ArH), 7.12 (1H, m, ArH), 4.02, 3.82, 3.90, and 3.75 (each 3H, s, 4× OCH_3). Anal. Calcd for $C_{17}H_{17}NO_5\cdot HCl\cdot 1.5H_2O$: C, 53.90; H, 5.59; N, 3.70; found: C, 53.45; H, 5.61; N, 3.73.

*4.8.1. 6-Benzyloxy-1,2,3,5-tetramethoxy-10H-acridin-9-one (**20b**).* A mixture of **19b** (13.18 g, 30 mmol) in $POCl_3$ (30 mL) containing 3-drops of DMF was heated at 60 °C for 1 h. After cooling, the mixture was evaporated in vacuo to dryness and the residue was dissolved in MeOH (500 mL) containing 5% HCl (40 mL) and then stirred at 40 °C for overnight. The reaction mixture was concentrated to 100 mL and the solid appeared was collected by filtration. The solid was recrystallized from EtOH to give **20b** (10.4 g, 82%); mp 227–228 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 10.71 (1H, s, NH), 7.86 (1H, d, J=9.0 Hz, ArH), 7.51–7.52 (2H, m, ArH), 7.41–7.44 (2H, m, ArH), 7.36–7.37 (1H, m, ArH), 7.28 (1H, s, ArH), 7.10 (1H, d, J=9.0 Hz, ArH), 5.29 (2H, s, CH_2), 3.89, 3.72, 3.79, and 3.70 (each 3H, s, OMe). Anal. Calcd for $C_{24}H_{23}NO_6$: C, 68.40; H, 5.50; N, 3.32; found: C, 68.43; H, 5.48; N, 3.31.

4.9.. 3-(1,2,3,5-Tetramethoxy-9-oxo-9*H*-acridin-10-yl)acrylic acid (22a)

To a mixture of **20a** (3.15 g, 10 mmol) and K_2CO_3 (2.76 g, 20 mmol) in DMF (30 mL) was added dropwise ethyl propiolate (2.04 mL, 20 mmol) in an ice bath under argon atmosphere over 30 min. A reaction mixture was stirred at room temperature for overnight. The reaction was not complete. Additional K_2CO_3 (2.76 g, 20 mmol) and ethyl propiolate (2.04 mL, 20 mmol) were added into

the reaction mixture per day (total 6 days). The solvent was removed under reduced pressure and the residue was dissolved in EtOH (250 mL), followed with addition of 2 N NaOH aqueous solution (10 mL) and stirred at room temperature for 1.5 h. The reaction mixture was acidified with acetic acid to pH 5–6. The solvent was removed under reduced pressure and the residue was crystallized from EtOH to give *trans*-**22a** (1.82 g). The mother liquid was concentrated and the residue [containing two product with R_f values of 0.41 and 0.21 by monitoring with thin-layer chromatography, TLC: SiO_2, $CHCl_3$/MeOH (5:1 v/v)] was chromatographed on a silica gel column (2×30 cm) using $CHCl_3$/MeOH (5:1 v/v) as the eluant. Additional *trans*-**22a**, 0.18 g (total 2.0 g, 51%) was eluted first, followed with a mixture of *trans*- and *cis*-**22a**, 95 mg (2.4%).

Compound *trans*-**22a**: mp 194–196 °C (EtOH); ^{1}H NMR (500 MHz DMSO-d_6): 11.90 (1H, br s, COOH), 8.12 (1H, d, J=14.0 Hz, =CH), 7.62 (1H, s, ArH), 7.47 (1H, s, ArH), 7.46 (1H, m, ArH), 7.34 (1H, s, ArH), 5.23 (1H, d, J=14.0 Hz, =CH), 3.98 (6H, s, 2× OMe), 3.87 (3H, s, OMe), 3.78 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.4, 164.6, 157.0, 152.8, 148.6, 142.0, 141.8, 137.5, 133.0, 125.6, 121.9, 118.0, 116.0, 110.9, 95.0, 61.4, 60.9, 56.7, 56.0; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{19}NO_7$: 386.1234; found: 386.1224. Anal. Calcd for $C_{20}H_{19}NO_7\cdot 0.5H_2O$: C, 60.91; H, 5.11; N, 3.55; found: C, 60.52; H, 5.00; N, 3.21.

Compound *cis*-**22a**: ^{1}H NMR (500 MHz, DMSO-d_6): 11.90 (1H, br s, COOH), 8.12 (1H, d, J=8.4 Hz, =CH), 7.62 (1H, s, ArH), 7.47 (1H, s, ArH), 7.46 (1H, m, ArH), 7.34 (1H, s, ArH), 6.03 (1H, d, J=8.4 Hz, =CH), 3.97 and 3.98 (each 3H, 2× OMe), 3.78 (3H, s, OMe), 3.87 (3H, s, OMe). Anal. Calcd for $C_{20}H_{19}NO_7\cdot 0.5H_2O$: C, 60.91; H, 5.11; N, 3.55; found: C, 60.52; H, 5.00; N, 3.21.

*4.9.1. 3-(6-Benzyloxy-1,2,3,5-tetramethoxy-9-oxo-9H-acridin-10-yl) acrylic acid (**22b**).* By following the same procedure as that for the synthesis of **22a**, compound **22b** was prepared from **20b** (16.85 g, 40 mmol) and ethyl propiolate (7.8 g, 80 mmol). The reaction was complete in 3 days. The solid residue contained a mixture of trans- and cis-isomer (total yield, 19.2 g, 98%), which were difficult to be separated by column chromatography. However, a small amount of trans- and cis-isomer were isolated for structural determination.

Compound *trans*-**22b**: mp 175–176; ^{1}H NMR (500 MHz, $CDCl_3$): 12.32 (1H, br s, COOH), 8.11 (1H, d, J=14.0 Hz, CH), 7.78 (1H, d, J=9.0 Hz, ArH), 7.52–7.56 (2H, m, ArH), 7.42–7.45 (2H, m, ArH), 7.34–7.38 (1H, m, ArH), 7.33 (1H, d, J=9.0 Hz, ArH), 7.31 (1H, s, ArH), 5.45 (1H, d, J=14.0 Hz, =CH), 5.31 (2H, s, CH_2), 3.97 (3H, s, OMe), 3.85 (3H, s, OMe), 3.80 (3H, s, OMe), 3.77 (3H, s, OMe). Anal. Calcd for $C_{27}H_{25}NO_8$: C, 65.98; H, 5.13; N, 2.85; found: C, 65.79; H, 5.15; N, 2.75.

Compound *cis*-**22b**: ^{1}H NMR (500 MHz, $CDCl_3$): 12.32 (1H, br s, COOH), 7.94 (1H, d, J=8.0 Hz, CH), 7.69 (1H, d, J=9.0 Hz, ArH), 7.51–7.53 (2H, m, ArH), 7.41–7.44 (2H, m, ArH), 7.36–7.37 (1H, m, ArH), 7.18 (1H, d, J=9.0 Hz, ArH), 6.82 (1H, s, ArH), 6.18 (1H, d, J=8.0 Hz, =CH), 5.27 (2H, s, CH_2), 3.88 (3H, s, OMe), 3.82 (3H, s, OMe), 3.74 (3H, s, OMe), 3.69 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.8, 164.5, 156.8, 155.1, 153.1, 142.4, 141.8, 137.4, 136.7, 136.6, 135.8, 128.6, 128.1, 127.8, 122.2, 119.9, 119.2, 110.4, 108.9, 94.8, 70.3, 61.5, 60.9, 59.8, 56.0; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{27}H_{25}NO_8$: 492.1653; found: 492.1614.

4.10. 3-(1,2,3,5-Tetramethoxy-9-oxo-9*H*-acridin-10-yl) propionic acid (23a)

A suspension of **22a** (1.93 g, 5 mmol) and Pd/C 10% (0.58 g) in MeOH (300 mL) containing acetic acid (3 drops) was hydrogenated at 30–35 psi for 2 days. The reaction mixture was filtered through a pad of Celite, and washed with MeOH. The combined filtrate and washings were concentrated and the product was purified by column chromatography (SiO_2, $CHCl_3$/MeOH 100:1 v/v) to give **23a** (840 mg, 43%); mp 210–211 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 7.75–7.77 (1H, m, ArH), 7.32–7.33 (1H, m, ArH), 7.20–7.23 (1H, m, ArH), 7.09 (1H, s, ArH), 4.56 (2H, t; J=8.3 Hz, CH_2), 3.96 (3H, s, OMe), 3.93 (3H, s, OMe), 3.80 (3H, s, OMe), 3.74 (3H, s, OMe), 2.64 (2H, t, J=8.3 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.4, 172.8, 157.6, 152.8, 149.5, 143.5, 137.5, 133.4, 127.0, 122.3, 117.8, 115.1, 112.1, 95.1, 61.4, 60.9, 56.5, 56.1, 48.5, 34.3; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{21}NO_7$: 388.1391; found: 388.1378. Anal. Calcd for $C_{20}H_{21}NO_7\cdot H_2O$: C, 59.40; H, 5.48; N, 3.46; found: C, 59.62; H, 5.55; N, 3.56.

*4.10.1. 3-(6-Hydroxy-1,2,3,5-tetramethoxy-9-oxo-9H-acridin-10-yl) propionic acid (**23b**).* By following the same procedure as that for the synthesis of **23a**, compound **23b** was prepared from **22b** (4.90 g, 10 mmol) and Pd/C (0.49 g). Yield, 1.5 g (37%), mp 234–235 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.75 (1H, d, J=8.0 Hz, ArH), 7.23 (1H, s, ArH), 6.85 (1H, d, J=8.0 Hz, ArH), 4.56 (1H, br s, CH_2), 3.95 (3H, s, OMe), 3.79 (3H, s, OMe), 3.76 (3H, s, OMe), 3.73 (3H, s, OMe), 2.41 (3H, br s, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.0, 172.6, 157.2, 154.7, 153.0, 143.2, 137.6, 137.4, 135.7, 122.3, 120.2, 112.5, 112.2, 95.6, 61.4, 60.9, 60.2, 56.1, 47.2 33.3; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{21}NO_8$: 404.1340; found: 404.1320. Anal. Calcd for $C_{20}H_{21}NO_8\cdot 0.5H_2O$: C, 58.25; H, 5.38; N, 3.40; found: C, 58.32; H, 5.35; N, 3.46.

*4.10.2. 3-(6-Acetoxy-1,2,3,5-tetramethoxy-9-oxo-9H-acridin-10-yl)-propionic acid (**23c**).* To a solution of **23b** (6.05 g, 15 mmol) in 1 N NaOH (45 mL) was added dropwise Ac_2O (2.3 g, 22.5 mmol) at room temperature. The reaction mixture was stirred at room temperature for overnight. The reaction mixture was acidified with acetic acid to pH 5–6 and extracted with $CHCl_3$ (30 mL×3). The combined extract was concentrated under reduced pressure and the residue was chromatographed on a silica gel column (6×40 cm) using $CHCl_3$/MeOH (20:1 v/v) as the eluant. The fractions containing main product were combined and concentrated in vacuo. The product was crystallized from EtOH to give **23c** (3.47 g, 55%); mp 210–211 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 12.29 (1H, br s, COOH), 7.91 (1H, d, J=9.0 Hz, ArH), 7.11 (1H, d, J=9.0 Hz, ArH), 7.03 (1H, s, ArH), 4.71 (1H, t, J=6.5 Hz, CH_2), 3.99 (3H, s, OMe), 3.80 (3H, s, OMe), 3.77 (3H, s, OMe), 3.75 (3H, s, OMe), 2.59 (2H, t, J=6.5 Hz, CH_2), 2.38 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.0, 172.4, 168.6, 157.7, 152.9, 147.2, 143.3, 141.4, 137.8, 137.1, 125.4, 121.7, 117.6, 112.5, 95.9, 61.4, 61.0, 60.9, 56.2, 46.8, 33.0, 20.6; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{22}H_{23}NO_9$: 446.1446; found: 446.1416. Anal. Calcd for $C_{22}H_{23}NO_9\cdot 0.5H_2O$: C, 58.15; H, 5.32; N, 3.08; found: C, 58.36; H, 5.43; N, 2.98.

4.11. 6-Methoxy-1,2-dihydropyrido[3,2,1-*de*]acridine-3,7-dione (15a)

To a solution of Eaton's reagent [freshly prepared from P_2O_5 (5.5 g, 39 mmol) and methanesulfonic acid (55 g)] was added dropwise a solution of **13a** (3.89 g, 13 mmol) in dry CH_2Cl_2 (100 mL). The reaction mixture was stirred for overnight at room temperature. The mixture was poured onto ice and then basified with saturated $NaHCO_3$ aqueous solution followed with NH_4OH. The organic layer was separated and the aqueous layer was extracted with $CHCl_3$ (100 mL×5). The combined organic extract was washed with water (100 mL×2), dried over Na_2SO_4, and evaporated to dryness. The product was purified by column chromatography (SiO_2, $CHCl_3$/MeOH, 80:1 v/v) and was crystallized from EtOH to give **15a**, 2.07 g (57%); mp 235–236 °C; ^{1}H NMR (500 MHz, DMSO-d_6): 8.49 (1H, d, J=9.1 Hz, ArH), 8.31 (1H, m, ArH), 7.80–7.82 (2H, m, ArH), 7.39 (1H, m, ArH), 7.16 (1H, d, J=9.1 Hz, ArH), 4.59 (2H, t, J=7.1 Hz, CH_2), 3.97 (3H, s, OMe), 2.94 (2H, t, J=7.1 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 190.2, 175.3, 163.7, 144.5, 141.7, 134.2, 134.0, 126.3, 122.1, 121.6, 115.7, 115.2, 109.2, 107.1, 56.5, 43.4, 37.6; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{17}H_{13}NO_3$: 280.0968; found:

280.0962. Anal. Calcd for $C_{17}H_{13}NO_3$: C, 70.82; H, 4.89; N, 4.86; found: C, 71.03; H, 4.86; N, 4.82.

By following the same procedure as that for the synthesis of **15a**, the following compounds were prepared:

*4.11.1. 4,5,6-Trimethoxy-1,2-dihydropyrido[3,2,1-de]acridin-3,7-dione (**15b**).* Compound **15b** was prepared from **13b** (15 g, 40 mmol) and Eaton's reagent [freshly prepared from P_2O_5 (34 g, 240 mmol) in 340 mL of TsOH]. Yield, 4.86 g (36%); mp 156–157 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): 8.46 (1H, m, ArH), 7.71 (1H, m, ArH), 7.48 (1H, m, ArH), 7.33 (1H, m, ArH), 4.46 (2H, t, J=6.9 Hz, CH_2), 4.13 (3H, s, OMe), 4.10 (3H, s, OMe), 3.89 (3H, s, OMe), 2.98 (2H, t, J=6.9 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 190.1, 175.0, 159.4, 159.0, 142.4, 140.7, 140.6, 133.6, 126.3, 122.8, 122.0, 115.3, 112.5, 111.5, 62.3, 61.7, 61.4, 43.4, 37.4; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{19}H_{17}NO_5$: 340.1179; found: 340.1176. Anal. Calcd for $C_{19}H_{17}NO_5$: C, 67.25; H, 5.05; N, 4.13; found: C, 67.10; H, 5.11; N, 4.09.

*4.11.2. 4,5,6,11-Tetramethoxy-1,2-dihydropyrido[3,2,1-de]acridine-3,7-dione (**24a**).* Compound **24a** was prepared from **23a** (1.94 g, 5 mmol) and Eaton's reagent (P_2O_5, 2.1 g and TsOH 20 mL). Yield, 0.83 g (45%), mp 144–145 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.97 (1H, m, ArH), 7.28 (1H, m, ArH), 7.19 (1H, m, ArH), 4.47 (2H, t, J=6.0 Hz, CH_2), 4.13 (3H, s, OMe), 4.10 (3H, s, OMe), 4.01(3H, s, OMe), 3.90 (3H, s, OMe), 3.04 (2H, t, J=6.0 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 191.1, 175.6, 160.4, 158.4, 149.5, 145.7, 141.0, 132.4, 126.6, 123.2, 117.4, 115.5, 112.8, 112.2, 62.0, 61.6, 61.4, 56.8, 56.6, 48.5, 40.1; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{19}NO_6$: 370.1285; found: 370.1276. Anal. Calcd for $C_{20}H_{19}NO_6$: C, 65.03; H, 5.18; N, 3.79; found: C, 64.82; H, 5.16; N, 3.70.

*4.11.3. 10-O-Acetyl-4,5,6,11-tetramethoxy-1,2-dihydropyrido[3,2,1-de]acridine-3,7-dione (**24b**) and 10-hydroxy-4,5,6,11-tetramethoxy-1,2-dihydropyrido[3,2,1-de]acridine-3,7-dione (**24c**).* Compound **24b** was prepared from **23c** (0.64 g, 1.5 mmol) and Eaton's reagent [freshly prepared from P_2O_5 (638 mg, 4.5 mmol) in TsOH (6.3 mL)]. Two products, **24b** and **24c**, were separated by column chromatography (SiO_2, $CHCl_3$/MeOH, 100:2 v/v):

Compound **24b**: yield, 181 mg (31%), mp 208–209 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (1H, d, J=9.0 Hz, ArH), 7.01 (1H, d, J=9.0 Hz, ArH), 6.37 (1H, br s, OH), 4.62 (2H, t, J=6.5 Hz, CH_2), 4.12 (3H, s, OMe), 4.10 (3H, s, OMe), 3.90 (3H, s, OMe), 3.89 (3H, s, OMe), 3.08 (2H, t, J=6.5 Hz, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 191.1, 174.8, 160.0, 158.6, 155.5, 145.6, 141.1, 136.9, 135.6, 122.5, 119.4, 113.3, 112.7, 112.3, 62.0, 61.7, 61.4, 60.6, 48.2; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{19}NO_7$: 386.1234; found: 386.1223. Anal. Calcd for $C_{20}H_{19}NO_7$: C, 62.33; H, 4.97; N, 3.63; found: C, 62.10; H, 5.03; N, 3.67.

Compound **24c**: yield, 132 mg (21%), mp 190–191 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): 8.18 (1H, d, J=9.0 Hz, ArH), 7.07 (1H, d, J=9.0 Hz, ArH), 4.60 (2H, t, J=6.5 Hz, CH_2), 4.13 (3H, s, OMe), 4.11 (3H, s, OMe), 3.90 (3H, s, OMe), 3.87 (3H, s, OMe), 3.04 (2H, t, J=6.5 Hz, CH_2), 2.41 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 190.8, 175.0, 168.5, 160.5, 158.5, 148.0, 145.6, 141.4, 141.3, 136.5, 124.6, 122.0, 118.4, 112.8, 112.4, 63.0, 61.8, 61.7, 61.4, 48.1, 20.5; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{22}H_{21}NO_8$: 428.1340; found: 428.1326. Anal. Calcd for $C_{22}H_{21}NO_8$: C, 61.82; H, 4.95; N, 3.28; found: C, 61.63; H, 4.89; N, 3.30.

4.12. (±)3-Hydroxy-6-methoxy-2,3-dihydro-1*H*-pyrido[3,2,1-*de*]acridin-7-one (25a)

To a solution of **15a** (1.68 g, 6 mmol) in THF (100 mL) containing H_2O (5 mL) was added portionwise $NaBH_4$ (0.23 g, 6 mmol) at 10 °C over 30 min. After being stirred at 10 °C for 5 h, the solvent was removed in vacuo and the residue was dissolved in EtOAc (200 mL), washed with water (200 mL×2), dried with Na_2SO_4, and evaporated to dryness. The residue was crystallized from ethanol/hexane to give **25a** (1.24 g, 73%) as a mixture of enantiomeric isomers (1:1); mp 224–225 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.29–8.33 (2H, m, 2× ArH), 7.84 (1H, m, ArH), 7.78–7.80 (1H, m, ArH), 7.30–7.33 (1H, m, ArH), 7.11 (1H, d, J=8.9 Hz, ArH), 5.19 (1H, d, J=3.8 Hz, CH), 5.11 (1H, d, J=3.8 Hz, OH, exchangeable), 4.46–4.48 (1H, m, 1/2× CH_2), 4.04–4.09 (1H, m, 1/2× CH_2), 3.96 (3H, s, OMe), 2.24–2.26 (1H, m, 1/2× CH_2), 1.92–1.96 (1H, m, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 176.1, 156.9, 151.3, 141.1, 139.8, 137.5, 131.2, 122.2, 121.9, 120.1, 116.7, 112.8, 107.9, 65.1, 57.6, 42.7, 29.5; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{22}H_{21}NO_8$: 282.1125; found: 282.1118. Anal. Calcd for $C_{17}H_{15}NO_3\cdot 0.5H_2O$: C, 70.33; H, 5.55; N, 4.82; found: C, 70.51; H, 5.47; N, 4.68.

By following the same procedure as that for the synthesis of **25a**, the following compounds were prepared:

*4.12.1. (±)3-Hydroxy-4,5,6-trimethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**25b**).* Compound **25b** was prepared from **15b** (2.04 g, 6 mmol) and $NaBH_4$ (227 mg, 6 mmol). Yield, 1.74 g (84%); mp 160–161 °C (EtOH/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 8.48 (1H, m, ArH), 7.66 (1H, m, ArH), 7.50 (1H, m, ArH), 7.25–7.28 (1H, m, ArH), 5.30 (1H, s, CH), 4.37–4.39 (1H, m, 1/2× CH_2), 4.09–4.14 (1H, m, 1/2× CH_2), 4.15 (3H, s, OMe), 4.04 (3H, s, OMe), 3.93 (3H, s, OMe), 2.47 (1H, s, OH, exchangeable), 2.43 (1H, J=2.7 and 14.0 Hz, 1/2× CH_2), 2.00–2.06 (1H, m, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.3, 155.5, 153.7, 141.1, 140.3, 136.6, 133.3, 126.2, 122.4, 121.2, 116.2, 114.8, 113.2, 61.7, 61.5, 61.2, 56.7, 40.1, 28.2; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{19}H_{19}NO_5$: 342.1336; found: 342.1328. Anal. Calcd for $C_{19}H_{19}NO_5$: C, 66.85; H, 5.61; N, 4.10; found: C, 66.68; H, 5.68; N, 4.06.

*4.12.2. (±)3-Hydroxy-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**25c**).* Compound **25c** was prepared from **24a** (554 mg, 1.5 mmol) and $NaBH_4$ (55 mg, 1.5 mmol). Yield, 0.5 g (89%), mp 159–160 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.03–8.05 (1H, m, ArH), 7.19–7.21 (1H, m, ArH), 7.15–7.16 (1H, m, ArH), 5.17 (1H, s, CH), 4.83–4.86 (1H, m, 1/2× CH_2), 4.15 (3H, s, OMe), 4.04 (3H, s, OMe), 3.99–4.04 (1H, m, 1/2× CH_2), 3.95 (3H, s, OMe), 3.93 (3H, s, OMe), 2.80 (1H, s, OH), 2.31–2.37 (1H, m, 1/2× CH_2), 2.15–2.20 (1H, m, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.5, 155.8, 153.1, 149.7, 140.3, 137.9, 133.3, 126.1, 122.2, 117.8, 116.7, 116.1, 113.0, 61.7, 61.4, 61.1, 57.5, 56.9, 44.0, 30.2; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{21}NO_6$: 372.1442; found: 372.1425. Anal. Calcd for $C_{20}H_{21}NO_6\cdot 0.5H_2O$: C, 63.15; H, 5.82; N, 3.68; found: C, 63.68; H, 5.74; N, 3.67.

*4.12.3. (±)3,10-Dihydroxy-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**25d**).* Compound (±)**25d** was prepared from **24b** (0.19 g, 0.5 mmol) and $NaBH_4$ (18.9 mg, 0.5 mmol). Yield, 0.16 g (83%), mp 220–221 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.19 (1H, d, J=9.0 Hz, ArH), 6.95 (1H, d, J=9.0 Hz, ArH), 6.31 (1H, s, OH), 5.20 (1H, s, CH), 4.90–4.93 (1H, m, 1/2× CH_2), 4.17 (3H, s, OMe), 4.09–4.16 (1H, m, 1/2× CH_2), 4.04 (3H, s, OMe), 3.93 (3H, s, OMe), 3.77 (3H, s, OMe), 2.74 (1H, s, OH), 2.37–2.40 (1H, m, 1/2× CH_2), 2.16–2.19 (1H, m, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.8, 155.4, 155.3, 153.3, 140.2, 137.6, 137.2, 135.4, 122.5, 119.1, 116.7, 113.0, 112.4, 61.6, 61.4, 61.0, 60.8, 57.3, 43.0, 30.0; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{21}NO_7$: 388.1391; found: 388.1373. Anal. Calcd for $C_{20}H_{21}NO_7\cdot 0.5H_2O$: C, 60.60; H, 5.59; N, 3.53, found: C, 60.93; H, 5.50; N, 3.46.

*4.12.4. (±)3-Acetyl-6-methoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**26a**).* A solution of (±)**25a** (100 mg, 0.35 mmol) in a mixture of pyridine (2 mL) and acetic anhydride (2 mL) was stirred at room temperature for overnight. MeOH (10 mL) was

added into the reaction mixture in an ice bath, and then evaporated in vacuo to dryness. The residue was crystallized from ethanol to give (±)**26a**, 84 mg (73%); mp 178–179 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.59 (1H, d, *J*=9.0 Hz, ArH), 8.56–8.58 (1H, m, ArH), 7.71–7.74 (1H, m, ArH), 7.55–7.57 (1H, m, ArH), 7.30–7.33 (1H, m, ArH), 6.94 (1H, d, *J*=8.9 Hz, ArH), 6.50 (1H, s, CH), 4.46–4.48 (1H, m, 1/2× CH_2), 4.02–4.08 (1H, m, 1/2× CH_2), 4.00 (3H, s, OMe), 2.57–2.60 (1H, m, 1/2× CH_2), 2.16–2.19 (1H, m, 1× CH_2), 2.12 (3H, s, COOMe); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 175.6, 169.7, 161.0, 141.9, 139.8, 133.9, 129.7, 126.4, 121.5, 121.3, 115.7, 115.0, 108.3, 106.4, 60.8, 56.5, 25.3, 21.0; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{19}H_{17}NO_4$: 324.1230; found: 324.1223. Anal. Calcd for $C_{19}H_{17}NO_4 \cdot 0.5H_2O$: C, 68.66; H, 5.46; N, 4.21, found: C, 68.70; H, 5.46; N, 4.15.

*4.12.5. (±)3-Acetyl-4,5,6-trimethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**26b**).* By following the same procedure, compound **26b** was prepared from (±)**25b** (1.37 g, 4 mmol) and Ac_2O/pyridine (each 6 mL). Yield, 1.4 g (95%); mp 157–158 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): 8.53–8.55 (1H, m, ArH), 7.70–7.73 (1H, m, ArH), 7.52–7.54 (1H, m, ArH), 7.31–7.34 (1H, m, ArH), 6.48 (1H, s, CH), 4.43–4.45 (1H, m, 1/2× CH_2), 4.09 (6H, s, 2× OMe), 4.00–4.04 (1H, m, 1/2× CH_2), 3.97 (3H, s, OMe), 2.57–2.60 (1H, m, 1/2× CH_2), 2.17–2.20 (1H, m, 1/2× CH_2), 2.14 (3H, s, COOMe); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 175.1, 169.5, 155.9, 155.2, 140.9, 140.1, 137.2, 133.4, 126.3, 122.5, 121.4, 114.6, 113.0, 110.6, 61.5, 61.4, 61.3, 61.2, 39.9, 25.3, 21.0; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{21}H_{21}NO_6$: 384.1442; found: 384.1431. Anal. Calcd for $C_{21}H_{21}NO_6 \cdot 1.5H_2O$: C, 65.79; H, 5.52; N, 3.65, found: C, 65.88; H, 5.50; N, 3.58.

*4.12.6. 4,5,6-Trimethoxy-7-oxo-1,2,3,7-tetrahydropyrido[3,2,1-de]acridin-3-yl methylcarbamate (**27**).* To a solution of (±)**25b** (683 mg, 2 mmol) and triethylamine (1.4 mL, 10 mmol) in $CHCl_3$ (10 mL) was slowly added methylisocyanate (570 mg, 10 mmol). The mixture was stirred for overnight at room temperature and then evaporated in vacuo to dryness. The solid residue was recrystallized from EtOAc/hexane to give **27**, 672 mg (85%); mp 184–185 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.49–8.50 (1H, m, ArH), 7.65–7.68 (1H, m, ArH), 7.47–7.48 (1H, m, ArH), 7.26–7.29 (1H, m, ArH), 6.32 (1H, s, CH), 4.72 and 4.73 (each 1H, s, NH, exchangeable), 4.36–4.38 (1H, m, 1/2× CH_2), 4.05 (6H, s, 2× OMe), 3.94–3.99 (1H, m, 1/2× CH_2), 3.93 (3H, s, OMe), 2.86–2.87 (3H, m, NMe), 2.63–2.66 (1H, m, 1/2× CH_2), 2.06–2.10 (1H, m, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 175.2, 155.9, 155.8, 154.9, 141.0, 140.2, 137.1, 133.5, 126.3, 122.5, 121.5, 114.7, 113.1, 111.5, 61.6, 61.5, 61.2, 61.1, 40.2, 26.9, 25.7; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{21}H_{22}N_2O_6$: 399.1551; found: 399.1541. Anal. Calcd for $C_{21}H_{22}N_2O_6$: C, 63.31; H, 5.57; N, 7.03, found: C, 63.10; H, 5.56; N, 6.99.

4.13. 6-Methoxy-1*H*-pyrido[3,2,1-*de*]acridin-7-one (28a)

A mixture of (±)**25a** (1.1 g, 4 mmol) and methanesulfonic anhydride (418 mg, 2.4 mmol) in pyridine (0.97 mL, 12 mL) containing a catalytic amount of dimethylaminopyridine (DMAP) was heated at 110 °C under argon. After being stirred for 5 h, the reaction mixture was cooled down to room temperature and then poured into ice water (150 mL). The crude solid product was collected by filtration, washed with water, and dried. The crude product was purified by column chromatography (SiO_2, hexane/$CHCl_3$ 1:9 v/v) and recrystallized from EtOH to give **28a** (525 mg, 50%); mp 199–200 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.59–8.60 (1H, m, ArH), 8.33 (1H, d, *J*=9.1 Hz, ArH), 7.72–7.75 (1H, m, ArH), 7.33–7.35 (2H, m, 2× ArH), 6.96 (1H, dt, *J*=10.0 and 2.6 Hz, =CH), 6.83 (1H, d, *J*=9.1 Hz, ArH), 5.92 (1H, dd, *J*=10.0 and 3.6 Hz, =CH), 5.06 (2H, t, *J*=2.6 Hz, CH_2), 3.96 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 175.3, 157.4, 141.2, 138.6, 133.8, 127.6, 126.4, 121.8, 115.0, 108.5, 107.3, 56.2, 47.6; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{17}H_{13}NO_2$: 264.1019; found: 264.1013. Anal. Calcd for: C, 77.55; H, 4.98; N, 5.32; found: C, 77.40; H, 4.81; N, 5.12.

By following the same procedure as that for the synthesis of **28a**, the following compounds were prepared:

*4.13.1. 4,5,6-Trimethoxy-1H-pyrido[3,2,1-de]acridin-7-one (**28b**).* Compound **28b** was prepared from **25b** (1.7 g, 5 mmol), methanesulfonic anhydride (1.74 g, 10 mmol), and triethylamine (1.65 ml, 12 mmol). Yield, 1.1 g (70%); mp 184–185 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 8.57 (1H, m, ArH), 7.71 (1H, m, ArH), 7.33 (2H, m, 2× ArH), 6.89 (1H, m, =CH), 5.59 (1H, m, =CH), 5.04 (2H, m, CH_2), 4.02 (3H, s, OMe), 4.00 (3H, s, OMe), 3.93 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 174.6, 153.0, 152.5, 140.6, 140.2, 136.2, 133.4, 126.4, 122.9, 121.7, 121.6, 117.1, 114.7, 112.8, 111.0, 61.5, 61.4, 61.1, 47.9; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{19}H_{17}NO_4$: 324.1230; found: 324.1223. Anal. Calcd for $C_{19}H_{17}NO_4$: C, 70.58; H, 5.30; N, 4.33; found: C, 70.33; H, 5.31; N, 4.25.

*4.13.2. 4,5,6,11-Tetramethoxy-1H-pyrido[3,2,1-de]acridin-7-one (**28c**).* Compound **28c** was prepared from **25c** (0.45 g, 1.2 mmol), pyridine (20 mL), methanesulfonic anhydride (0.42 g, 2.4 mmol), and DMAP (catalytic amount). The crude product was not stable during purification by column chromatography and was used directly for the next reaction. However, a small amount of pure **28c** was isolated for NMR analysis; ^{1}H NMR (500 MHz, $CDCl_3$): 8.04–8.05 (1H, m, ArH), 7.23–7.27 (1H, m, ArH), 7.17–7.18 (1H, m, ArH), 6.97 (1H, d, *J*=9.5 Hz, m, =CH), 6.19 (1H, t, *J*=4.5 and 9.5 Hz, =CH), 4.87 (2H, dd, *J*=1.0 and 4.5 Hz, CH_2), 4.04 (3H, s, OMe), 4.02 (3H, s, OMe), 4.01 (3H, s, OMe), 3.94 (3H, s, OMe).

*4.13.3. 10-Hydroxy-4,5,6,11-tetramethoxy-1H-pyrido[3,2,1-de]acridin-7-one (**28d**).* Compound **28d** was prepared from **25d** (129 mg, 0.33 mmol), pyridine (0.97 mL, 12 mL), methanesulfonic anhydride (418 mg, 2.4 mmol), and DMAP (catalytic amount). The crude product **28d** was not stable during the purification and was used directly for the next reaction. A small amount of pure compound was used for NMR analysis; ^{1}H NMR (500 MHz, $CDCl_3$): 8.14 (1H, d, *J*=9.0 Hz, ArH), 6.98 (1H, dd, *J*=1.5 and 9.5 Hz, =CH), 6.95 (1H, d, *J*=9.0 Hz, ArH), 6.36 (1H, br, OH), 6.20 (1H, dd, *J*=4.5 and 9.5 Hz, =CH), 4.84 (2H, dd, *J*=1.5 and 4.5 Hz, CH_2), 4.03 (6H, s, 2× OMe), 3.93 (3H, s, OMe), 3.88 (3H, s, OMe).

4.14. 2,3-Dihydroxy-6-methoxy-2,3-dihydro-1*H*-pyrido[3,2,1-*de*]acridin-7-one (29a)

A mixture of **28a** (395 mg, 1.5 mmol), OsO_4 (catalytic amount), and 4-methylmorpholine-*N*-oxide (4.8 N, 0.33 mL, 1.6 mmol) in a mixture of THF (40 mL) and H_2O (8 mL) was stirred at room temperature for overnight. HCl (2% aqueous solution) was added dropwise into the reaction mixture and then quenched with 15% $NaHSO_3$. The solvent was evaporated under reduced pressure to dryness and the solid residue was recrystallized from EtOH to give **29a**, 0.39 g (88%); mp 235–236 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.30–8.31 (1H, m, ArH), 8.30 (1H, *J*=8.9 Hz, ArH), 7.77–7.82 (2H, m, 2× ArH), 7.23–7.34 (1H, m, ArH), 7.13 (1H, *J*=8.9 Hz, ArH), 5.38 (1H, d, *J*=5.6 Hz, OH, exchangeable), 5.19 (1H, d, *J*=4.6 Hz, OH, exchangeable), 5.08 (1H, s, CH), 4.21 (1H, dd, *J*=5.2 and 10.5 Hz, CH), 3.97 (3H, s, OMe), 3.93–4.15 (2H, m, CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (*δ*, ppm): 175.7, 160.7, 142.0, 139.0, 133.8, 128.4, 126.3, 121.3, 121.2, 115.8, 115.0, 113.2, 106.6, 65.8, 60.6, 56.2, 44.5; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{17}H_{15}NO_4$: 298.1074; found: 298.1067. Anal. Calcd for $C_{17}H_{15}NO_4 \cdot H_2O$: C, 64.75; H, 5.43; N, 4.44; found: C, 64.56; H, 5.40; N, 4.28.

By following the same procedure as that for the synthesis of **29a**, the following compounds were prepared:

*4.14.1. (±)2,3-Dihydroxy-3,4,5-trimethoxy-2,3-dihydro-1H-pyrido [3,2,1-de]acridin-7-one (**29b**).* Compound (±)**29b** was prepared from **28b** (607 mg, 2 mmol), 4-methylmorpholine-*N*-oxide (4.8 N, 0.46 mL, 2.2 mmol), and OsO_4 (catalytic amount). Yield, 0.59 g (82%); mp 183–184 °C (EtOAc/hexane); ^{1}H NMR (500 MHz, $CDCl_3$): 8.39–8.42 (1H, m, ArH), 7.60–7.63 (1H, m, ArH), 7.41–7.42 (1H, m, ArH), 7.23–7.26 (1H, m, ArH), 5.27 (1H, m, CH), 4.30 (1H, dd, *J*=11.1 and 5.3 Hz, 1/2× CH_2), 4.14–4.19 (1H, m, 1/2× CH_2), 4.15 (3H, s, OMe), 4.00 (3H, s, OMe), 3.95 (1H, t, *J*=11.1 Hz, 1/2× CH_2), 3.91 (3H, s, OMe), 3.31 (1H, d, *J*=3.5 Hz, OH, exchangeable), 3.21 (1H, d, *J*=8.6 Hz, OH, exchangeable); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.9, 155.7, 153.9, 141.0, 140.5, 136.4, 133.4, 126.3, 122.4, 121.2, 115.8, 114.7, 113.0, 65.4, 61.8, 61.5, 61.3, 61.1, 45.1; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{19}H_{19}NO_6$: 358.1285; found: 358.1274. Anal. Calcd for $C_{19}H_{19}NO_6$: C, 63.86; H, 5.36; N, 3.92; found: C, 63.61; H, 5.48; N, 3.85.

*4.14.2. (±)2,3,-Dihydroxy-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**29c**).* Compound (±)**29c** was prepared from crude **28c** (424 mg, 1.2 mmol), 4-methylmorpholine-*N*-oxide (4.8 N, 0.5 mL, 2.4 mmol), and OsO_4 (catalytic amount). Yield, 0.26 g (56%, calculated from **25c**), mp 118–119 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.01 (1H, dd, *J*=1.6 and 8.0 Hz, ArH), 7.21 (1H, t, *J*=8.0 Hz, ArH), 7.15 (1H, dd, *J*=1.6 and 8.0 Hz, ArH), 5.15 (1H, d, *J*=3.8 Hz, CH), 4.82 (1H, dd, *J*=3.8 and 12.0 Hz, CH), 4.21 (1H, br, 1/2× CH_2), 4.15 (3H, s, OMe), 4.02 (3H, s, OMe), 3.95–4.00 (1H, m, 1/2× CH_2), 3.97 (3H, s, OMe), 3.91 (3H, s, OMe), 3.12 (2H, br s, OH, exchangeable); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.3, 155.8, 153.3, 149.7, 140.4, 137.5, 133.3, 126.0, 122.3, 118.0, 116.4, 115.8, 112.8, 66.3, 61.9, 61.7, 61.4, 61.1, 56.9, 48.8; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{20}H_{21}NO_7$: 388.1391; found: 388.1379. Anal. Calcd for $C_{20}H_{21}NO_7$: C, 62.00; H, 5.46; N, 3.62; found: C, 62.18; H, 5.35; N, 3.51.

*4.14.3. (±)2,3,10-Trihydroxy-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**29d**).* Compound (±)**29d** was prepared from crude **28d** (122 mg, 0.33 mmol), 4-methylmorpholine-*N*-oxide (4.8 N, 0.14 mL, 0.66 mmol), and OsO_4 (catalytic amount). Yield, 40.7 mg (30%, calculated from **25d**), mp 217–218 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.17 (1H, d, *J*=8.8 Hz, ArH), 6.95 (1H, d, *J*=8.8 Hz, ArH), 6.27 (1H, s, OH), 5.18 (1H, t, *J*=4.0 Hz, CH–OH), 4.78 (1H, dd, *J*=3.0 and 11.5 Hz, CH), 4.13–4.26 (1H, m, CH_2), 4.16 (3H, s, OMe), 4.03 (3H, s, OMe), 3.92 (3H, s, OMe), 3.81 (3H, s, OMe), 3.13 (1H, d, *J*=2.5 Hz, OH, exchangeable), 3.02 (1H, d, *J*=8.0 Hz, OH, exchangeable); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.6, 156.4, 155.3, 153.4, 140.4, 137.4, 137.3, 135.3, 122.5, 115.8, 112.8, 112.6, 66.2, 61.8, 61.6, 61.4, 61.1, 60.8, 48.0; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{20}H_{21}NO_8$: 404.1340; found: 404.1326. Anal. Calcd for $C_{20}H_{21}NO_8$: C, 59.55; H, 5.25; N, 3.47; found: C, 59.47; H, 5.20; N, 3.42.

4.15. (±)2,3-Diacetyl-6-methoxy-2,3-dihydro-1*H*-pyrido[3,2,1-*de*]acridin-7-one (30a)

A solution of (±)**29a** (99 mg, 0.33 mmol) in a mixture of pyridine (1 mL) and Ac_2O (1 mL) was stirred at room temperature overnight. MeOH (2 mL) was added dropwise to the reaction mixture and then evaporated under reduced pressure the residue was co-evaporated several times with EtOH and the solid residue was recrystallized from EtOH to give (±)**30a**, 0.11 g (84%); mp 231–232 °C. ^{1}H NMR (500 MHz, $CDCl_3$): 8.56 (1H, d, *J*=9.0 Hz, ArH), 8.52–8.54 (1H, m, ArH), 7.69–7.72 (1H, m, ArH), 7.46–7.48 (1H, m, ArH), 7.29–7.32 (1H, m, ArH), 6.91 (1H, d, *J*=9.0 Hz, ArH), 6.80 (1H, m, CH), 5.36–5.39 (1H, m, CH), 4.38 (1H, dd, *J*=5.9 and 11.0 Hz, 1/2× CH_2), 4.05 (1H, t, *J*=11.0 Hz, 1/2× CH_2), 3.94 (3H, s, OMe), 2.11 (3H, s, OAc), 2.07 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.5, 169.7, 169.3, 161.4, 141.7, 139.6, 134.0, 130.4, 126.4, 121.8, 121.5, 115.6, 115.3, 106.7, 106.3, 66.4, 60.6, 56.6, 20.6; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{21}H_{19}NO_6$: 382.1285; found: 382.1277. Anal. Calcd for $C_{21}H_{19}NO_6 \cdot 0.5H_2O$: C, 64.61; H, 5.16; N, 3.59; found: C, 64.78; H, 5.23; N, 3.21.

By following the same procedure as that for the synthesis of (±) **30a**, the following compounds were prepared:

*4.15.1. (±)2,3-Diacetyl-4,5,6-trimethoxy-2,3-dihydro-1H-pyrido [3,2,1-de]acridin-7-one (**30b**).* Compound (±) **30b** was prepared from (±)**29b** (355 mg, 1.0 mmol), pyridine (3 mL), and acetic anhydride (3 mL). Yield, 0.39 g (90%); mp 177–178 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): 8.49–8.50 (1H, m, ArH), 7.68–7.71 (1H, m, ArH), 7.43–7.46 (1H, m, ArH), 7.30–7.33 (1H, m, ArH), 6.75 (1H, d, *J*=1.2 Hz, CH), 5.35 (1H, m, CH), 4.34 (1H, dd, *J*=5.7 and 11.0 Hz, 1/2× CH_2), 4.04–4.08 (1H, dt, *J*=6.5 and 11.0 Hz, 1/2× CH_2), 4.06 (6H, s, 2× OMe), 3.92 (3H, s, OMe), 2.15 (3H, s, OAc), 2.13 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.0, 169.5, 169.3, 156.1, 155.8, 140.8, 140.3, 136.9, 133.6, 126.3, 122.5, 121.8, 114.9, 112.9, 108.6, 66.2, 61.6, 61.5, 61.2, 61.1, 42.2, 20.7, 20.6; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{23}H_{23}NO_8$: 442.1496; found: 442.1471. Anal. Calcd for $C_{23}H_{23}NO_8 \cdot 0.5H_2O$: C, 61.33; H, 5.37; N, 3.11; found: C, 61.39; H, 5.39; N, 3.14.

*4.15.2. (±)2,3,-Diiacetyl-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**30c**).* Compound (±)**30c** was prepared form (±)**29c** (78 mg, 0.2 mmol), pyridine (0.5 mL), and acetic anhydride (0.25 mL). Yield, 79 mg (94%), mp 167–168 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.03–8.05 (1H, m, ArH), 7.22–7.25 (1H, m, ArH), 7.16–7.18 (1H, m, ArH), 6.61 (1H, s, CH), 5.34 (1H, dd, *J*=4.2 and 12.0 Hz, CH), 4.81 (1H, dd, *J*=3.0 and 12.0 Hz, 1/2× CH_2), 4.20 (1H, t, *J*=12.0 Hz, 1/2× CH_2), 4.05 (3H, s, OMe), 4.04 (3H, s, OMe), 3.96 (3H, s, OMe), 3.90 (3H, s, OMe), 2.16 (3H, s, OAc), 2.13 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.2, 169.4, 169.3, 156.4, 155.0, 149.3, 140.3, 139.0, 132.6, 126.3, 122.8, 117.9, 116.2, 112.8, 109.3, 66.7, 61.9, 61.5, 61.3, 61.1, 56.8, 46.0, 20.7, 20.6; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{24}H_{25}NO_9$: 472.1602; found: 472.1574. Anal. Calcd for $C_{24}H_{25}NO_9$: C, 61.14; H, 5.34; N, 2.97; found: C, 61.05; H, 5.65; N, 2.92.

*4.15.3. (±)2,3,10-Triacetyl-4,5,6,11-tetramethoxy-2,3-dihydro-1H-pyrido[3,2,1-de]acridin-7-one (**30d**).* Compound (±)**30d** was prepared from (±)**29d** (48 mg, 0.12 mmol), pyridine (0.5 mL), and acetic anhydride (0.5 mL). Yield, 52 mg (83%), mp 152–153 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.23 (1H, d, *J*=8.8 Hz, ArH) 7.03 (1H, d, *J*=8.8 Hz, ArH), 6.62 (1H, d, *J*=2.0 Hz, CH), 5.36 (1H, dd, *J*=4.0 and 12.0 Hz, CH), 4.91–4.93 (1H, dd, *J*=3.2 and 2.0 Hz, 1/2× CH_2), 4.10 (1H, t, *J*=12.0 Hz, 1/2× CH_2), 4.05 (6H, s, 2× OMe), 3.91 (3H, s, OMe), 3.80 (3H, s, OMe), 2.39 (3H, s, OAc), 2.15 (3H, s, OAc), 2.12 (3H, s, OAc); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.8, 169.5, 169.4, 168.5, 156.5, 155.3, 148.3, 141.0, 140.7, 138.5, 136.5, 124.2, 122.2, 118.0, 113.0, 109.5, 66.6, 62.0, 61.7, 61.6, 61.4, 61.2, 45.1, 20.7, 20.6, 20.5; HRMS (ESI) *m*/*z*: calcd for M+H$^+$ $C_{26}H_{27}NO_{11}$: 530.1657; found: 530.1629. Anal. Calcd for $C_{26}H_{27}NO_{11}$: C, 58.97; H, 5.14; N, 2.65; found: C, 58.92; H, 5.10; N, 2.60.

4.16. (±)4-Methoxy-13,13a-dihydro-3a*H*,7*H*-[1,3]dioxolo[4′,5′:4,5]pyrido[3,2,1-*de*]acridine-2,7-dione (31)

A mixture of (±)**29a** (99 mg, 0.33 mmol) and *N*,*N*′-carbonyldiimidazole (0.27 mg, 1.65 mmol) in butanone (15 mL) was heated at reflux temperature for 5 h under argon. The solvent was removed in vacuo to dryness and the residue was chromatographed on a silica gel column (2×30 cm) using $CHCl_3$ as the eluant. The

fractions containing product were combined and concentrated in vacuo. The residue was crystallized from EtOH to give (±)**31**, 30 mg (29%). Mp 205–206 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 8.62 (1H, d, J=9.0 Hz, ArH), 8.54–8.55 (1H, m, ArH), 7.72–7.76 (1H, m, ArH), 7.53–7.54 (1H, m, ArH), 7.33–7.36 (1H, m, ArH), 6.99 (1H, d, J=9.0 Hz, ArH), 6.14 (1H, d, J=7.6 Hz, CH), 5.33–5.34 (1H, m, CH), 4.51 (1H, dd, J=5.7 and 14.0 Hz, 1/2× CH_2), 4.27 (1H, dd, J=3.0 and 14.0 Hz, 1/2× CH_2) 4.06 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.4, 163.1, 154.1, 142.2, 140.6, 134.1, 130.6, 126.7, 121.9, 121.8, 115.7, 115.6, 107.0, 106.0, 72.5, 68.7, 56.7, 43.0; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{18}H_{13}NO_5$: 324.0866; found: 324.0858. Anal. Calcd for $C_{18}H_{13}NO_5 \cdot 0.5H_2O$: C, 65.06; H, 4.25; N, 4.22, found: C, 65.27; H, 4.30; N, 4.19.

By following the same procedure as that for the synthesis of (±) **31**, the following compounds were prepared:

*4.16.1. (±)4,5,6-Trimethoxy-13,13a-dihydro-3aH,7H-[1,3]dioxolo [4′,5′:4,5]pyrido[3,2,1-de] acridine-2,7-dione (**32**).* Compound (±)**32** was prepared from (±)**29b** (178 mg, 0.5 mmol) and *N,N′*-carbonyldiimidazole (405 mg, 2.5 mmol) in butanone (30 mL). Yield, 88 mg (46%); mp 233–234 °C (EtOH); ^{1}H NMR (500 MHz, $CDCl_3$): 8.45–8.48 (1H, m, ArH), 7.67–7.69 (1H, m, ArH), 7.45–7.47 (1H, m, ArH), 7.29–7.33 (1H, m, ArH), 6.19 (1H, d, J=8.1 Hz, CH), 5.32–5.37 (1H, m, CH), 4.60 (1H, dd, J=4.9 and 14.0 Hz, 1/2× CH_2), 4.18 (3H, s, OMe), 4.08 (3H, s, OMe), 4.05 (1H, dd, J=3.1 and 14.0 Hz, 1/2× CH_2), 3.93 (3H, s, OMe); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 174.9, 157.7, 156.0, 154.0, 141.4, 140.7, 138.4, 133.7, 126.6, 123.1, 121.8, 115.4, 113.2, 108.5, 72.8, 69.1, 61.7, 61.6, 61.3, 44.2; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{20}H_{17}NO_7$: 384.1078; found: 384.1067. Anal. Calcd $C_{20}H_{17}NO_7$: C, 62.66; H, 4.47; N, 3.65; found: C, 62.22; H, 4.48; N, 3.59.

*4.16.2. (±)4,5,6,11-Tetramethoxy-13,13a-dihydro-3aH,7H-[1,3]dioxolo[4′,5′:4,5] pyrido[3,2,1-de]acridine-2,7-dione (**33**).* Compound **33** was prepared from **29c** (129 mg, 0.33 mmol) and *N,N′*-carbonyldiimidazole (267 mg, 1.65 mmol) in butanone (10 mL). Yield, 93 mg (67%), mp 229–230 °C; ^{1}H NMR (500 MHz, $CDCl_3$): 7.96–7.98 (1H, m, ArH), 7.25–7.29 (1H, m, ArH), 7.17–7.20 (1H, m, ArH), 6.20 (1H, d, J=8.8 Hz, CH), 5.32–5.36 (1H, m, CH), 4.93 (1H, dd, J=4.2 and 13.0 Hz, 1/2× CH_2), 4.15 (3H, s, OMe), 4.05 (3H, s, OMe), 4.00 (3H, s, OMe), 3.93 (3H, s, OMe), 3.78 (1H, dd, J=2.8 and 13.0 Hz, 1/2× CH_2); ^{13}C NMR (500 MHz, DMSO-d_6) (δ, ppm): 175.7, 157.7, 155.4, 154.3, 149.8, 142.6, 141.1, 132.9, 127.0, 123.3, 117.8, 115.9, 114.2, 110.2, 75.1, 68.4, 61.8, 61.5, 61.3, 56.7, 50.0; HRMS (ESI) m/z: calcd for M+H$^+$ $C_{21}H_{19}NO_8$: 414.1183; found: 414.1174. Anal. Calcd for $C_{21}H_{19}NO_8$: C, 61.02; H, 4.63; N, 3.39, found: C, 61.22; H, 4.58; N, 3.49.S.

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