The synthesis of pyrido(2,3,4-*kl*)acridine unit of some marine alkaloids

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Abstract: A simple and convenient synthesis of pyrido(2,3,4-*kl*)acridine (**1**), the main skeleton of some marine alkaloids, via cyclization and intramolecular nitrene insertion, is described. The importance of the planarity of the molecule during the nitrene insertion is explained.

Key words: pyridoacridine, marine alkaloids, nitrene insertion, quinoline, quinolinone.

Résumé : On décrit une synthèse simple et pratique de la pyrido(2,3,4-*kl*)acridine (**1**), le squelette fondamental de quelques alcaloïdes marins; elle implique une cyclisation et une insertion intramoléculaire de nitrène. On explique l'importance de la planéité de la molécule au cours de l'insertion du nitrène.

Mots clés : pyridoacridine, alcaloïdes marins, insertion de nitrène, quinoléine, quinoléinone.

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Introduction

Recently, many polycyclic fused-ring alkaloids containing pyrido(2,3,4-*kl*)acridine (**1**) skeleton have been isolated from a variety of marine sources such as sponges, molluscs, and tunicates, most of which have been reported to have cytotoxic, antitumor, and antiviral activities (1). Calliactine (2), 2-bromoleptoclinidinone (3), ascididemin (4), cystodytins A, B, and C (5), petrosamine (6), diplamine (7), varamines (8), dercitin (9), cyclodercitin (10), segolines A (11, 12) and B (12), isosegoline A (11, 12), norsegoline (11, 12), shermilamines A (12), B (13, 14), C (5*b*), D and E (15), styelsamine A, B, C, and D (16), arnoamine A and B (17), kuanoniamine A, B, C, and D (13, 5*b*), eilatin (12), amphimedine (18), neoamphimedine (19), pantherinine (20), lissoclin A and B (21), are among this type of alkaloid. Although elegant synthetic methodologies for most of these alkaloids have been developed and total synthesis of many of these natural products have been achieved, such alkaloids are still continuing to be the focus of many synthetic groups (1, 22). This is due to their interesting biological activities and challenging structures. It seems that any contribution toward the synthesis of pyridoacridine units is worthwhile since most of the strategies involve the synthesis of such units. The route we present here involves two important key steps, cyclization to form the quinolinone moiety and intramolecular nitrene insertion to build a tetracyclic system.

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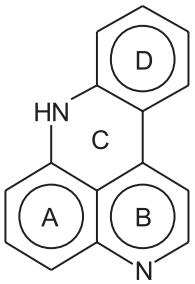

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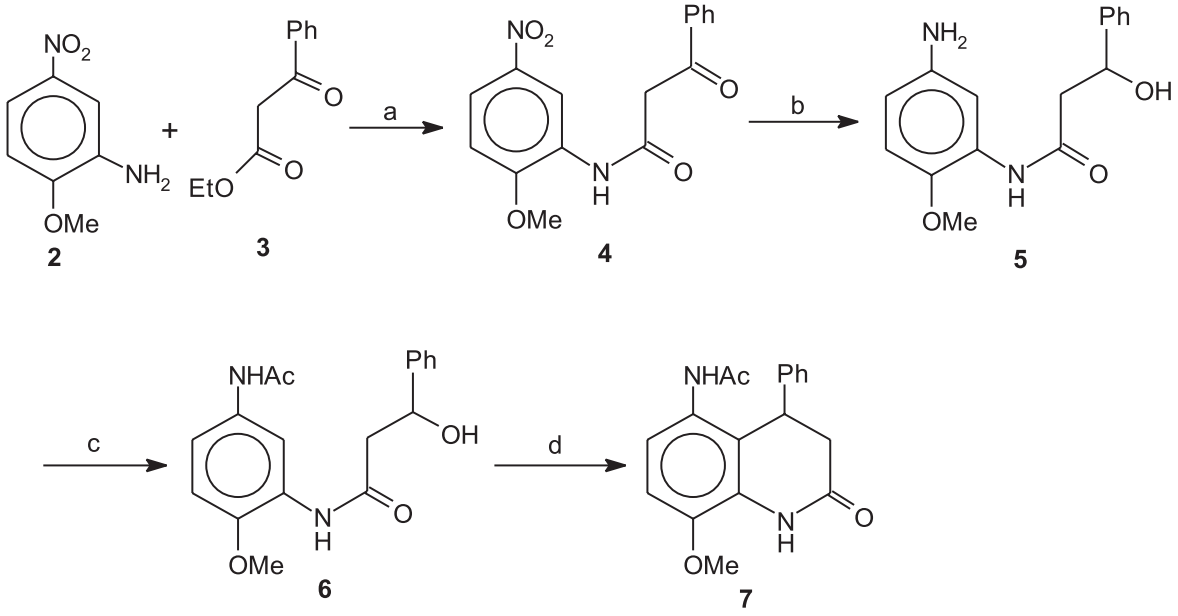
This approach may also be utilized as an easy access for the synthesis of ring B-modified analogues of this type of alkaloid.

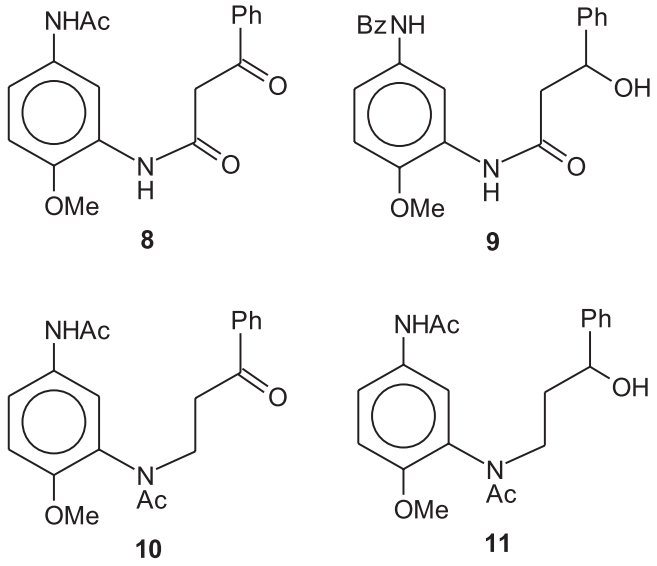
Results and discussion

The synthesis of this important pyridoacridine intermediate **21** has been achieved in 10 steps with overall 13.5% yield. Our synthesis started with the condensation of the commercially available reagents 2-methoxy-5-nitroaniline (**2**) and ethyl benzoylacetate (**3**) in toluene, which led to the formation of the amide **4** in 75% yield (Scheme 1) (22*c*). Hydrogenation of the nitro and keto groups of **4**, over palladium on charcoal at room temperature in ethanol, took place at the same time with a 90% yield. Acetylation of the amino group of **5** with acetyl chloride was followed by the cyclization of the corresponding product **6** with 80% H_2SO_4, which smoothly yielded the quinolinone **7** in 92% yield. Unfortunately, our other cyclization attempts with various amides such as **8**, **9**, **10**, and **11** to obtain such an important intermediate were not successful. Although these attempts were carried out in various reagents, conc. H_2SO_4, H_3PO_4, poly.H_3PO_4, $POCl_3$, HCl, and 80% H_2SO_4, in almost all reactions, intractable products or starting materials were obtained, except **8** and **9** which gave hydrolysis of the amide

Scheme 1. (a) Toluene, reflux, 75%; (b) Pd/C, H_2, ethanol, rt, 90%; (c) AcCl, pyridine, 75%; (d) H_2SO_4 (80%), 92%.



when treated with HCl or 80% H_2SO_4, and dehydration with 80% H_2SO_4, respectively.

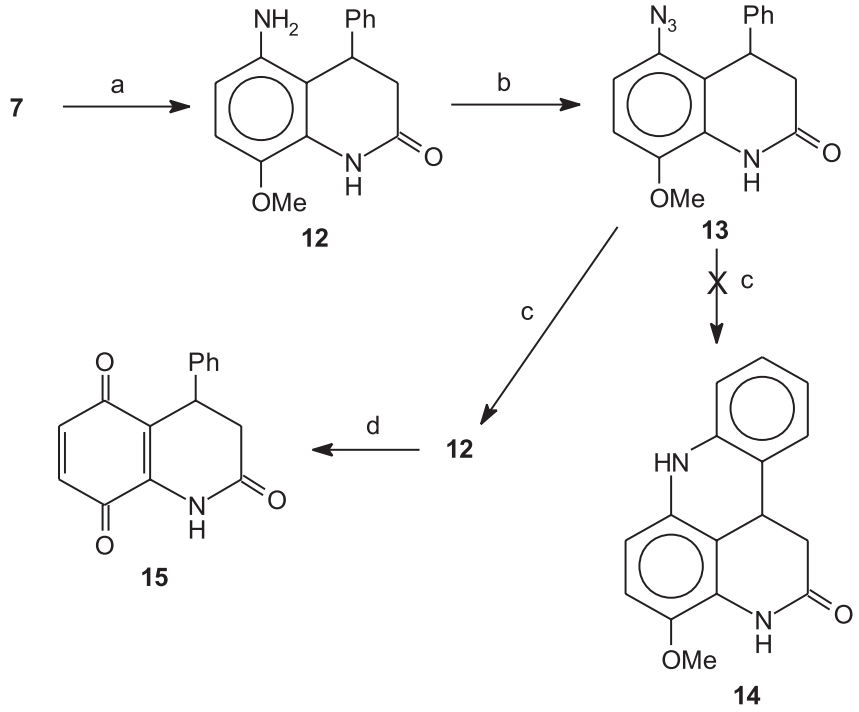


After constructing the quinolinone ring successfully, we concentrated on building the last ring, utilizing the intramolecular nitrene insertion methodology. Initially, deacetylation of **7** was performed, and after some exploratory work, it was found that deacetylation of **7** to **12** best took place in hot 45% sulphuric acid, and **12** was obtained in a very satisfactory, 88% yield (Scheme 2). Conversion of **12** to the corresponding azide **13** was then carried out by the classical nitrous acid followed by sodium azide combination of reactions. With the azide **13** available, conversion to the tetracyclic system **14** was attempted. Thus, **13** was heated in refluxing xylene until no starting material remained in the reaction mixture, as shown by TLC. Examination of the NMR spectrum of the product, however, showed that it was the amine **12**. Further confirmation that **12** had been obtained, was provided by oxidative demethylation with manganese dioxide, which gave the trione **15** in 78% yield, and the analytical and spectroscopic data for **15** were fully consistent with the assigned structure.

In this attempted cyclization of **13** to **14** via the nitrene insertion, which was carried out in xylene, both in the presence and absence of a nitrogen atmosphere, it was assumed that conversion of the nitrene **13** to the aniline **12** was the result of hydrogen abstraction from the solvent. In an attempt to circumvent this, the azide **13** was carefully melted and the liquid azide was stirred under nitrogen in the absence of solvent. After 30 min, NMR and TLC examination of the crude product showed the same result as previously, that is, formation of the amine **12**. Hydrogen abstraction in this case could involve the benzylic hydrogen atom at the 4-position of the dihydroquinolinone ring. Moreover, the stereochemical situation in **13** is probably less than ideal as far as the intended intramolecular cyclisation is concerned. The phenyl group is not on the same plane with the azide, and this is obviously one of the driving forces in such cyclizations (22*g*, *j*, *k*, 23).

To circumvent the problem encountered during intramolecular nitrene insertion, it was decided to introduce a double bond to the system to bring the phenyl group to the same plane with the azide. Then, employment of the one of the most common dehydrogenation reagents DDQ (2,3-dichloro-5,6-dicyanobenzoquinone), unfortunately, did not give any result, only starting material was recovered. This is perhaps not too surprising in view of the large steric bulk of the reagent and the relative steric shielding of the hydrogen atoms at the 3- and 4-positions of the dihydroquinolinone by the 4-phenyl substituent. Then, the conventional method, palladium on charcoal in diphenyl ether, yielded the quinolinone **16** in 65% yield together with 20% of the starting material (Scheme 3). Hydrolysis of the amide group using 45% sulphuric acid proceeded smoothly to give the aminoquinolinone **17** in 96% yield, and conversion of the

Scheme 2. (a) H_2SO_4 (45%), reflux, 2 h, 88%; (b) (*i*) $NaNO_2$, 0–5°C; (*ii*) NaN_3, 0–5°C, 86%; (c) xylene, reflux; (d) MnO_2, H_2SO_4 (35%), 78%.



amino to the azide group, as usual, presented no difficulties. The crude azide **18**, which showed only one spot on TLC, was obtained in 93% yield. It proved to be sensitive to both heat and light and hence no attempt to obtain an analytical sample was made.

The next step in the synthesis was the key intramolecular nitrene insertion reaction. Azide **18** was heated under reflux in xylene for 1.5 h. In contrast to the complete failure to achieve cyclization with the dihydro derivative **13**, the azide **18** reacted quite smoothly to give the required tetracyclic material **19** in 78% yield. Use of the azidoquinolinone rather than the dihydroquinolinone had proved successful, therefore, and would seem to imply that the controlling feature in the reaction as far as nitrene insertion is concerned is sterochemistry.

The synthesis of the tetracyclic compound **19** constitutes achievement of one of the major objectives, namely the synthesis of an advanced tetracyclic intermediate in which the B ring is functionalized. Analogues of natural products containing pyridoacridine units could be available from it by manipulation of the quinolinone ring.

The key compound **21** was then easily prepared from **19** by conversion to the chloroquinoline **20** in 83% yield by reaction with hot phosphorus oxychloride, followed by reductive removal of the chlorine on charcoal in triethylamine in 79% yield.

Experimental

Melting points were determined on a Kofler hotstage microscope melting point apparatus and are uncorrected. Microanalysis were performed with a Carlo Erba 1106 elemental analyzer. Infrared spectra were recorded on Perkin–Elmer 257, 297 grating infrared spectrophotometers using the standard Nujol mull or liquid film techniques between sodium chloride plates. Proton NMR spectra were recorded on JEOL PMX 60 MHz and JEOL GX-400 MHz spectrometers. The ^{13}C NMR spectra were recorded on a JEOL EX-90Q 24 MHz spectrometer. Tetramethylsilane (TMS) was used as the internal standard in all NMR spectra run in $CDCl_3$, DMSO-d_6. Mass spectra were recorded on a Kratos MS-25 mass spectrometer with an ionization potential of 70 eV at 200°C. All column chromatography was performed on silica gel (Merck, Kieselgel 60H, Art 7736) and Merck aluminum oxide 60 PF_{24k}.

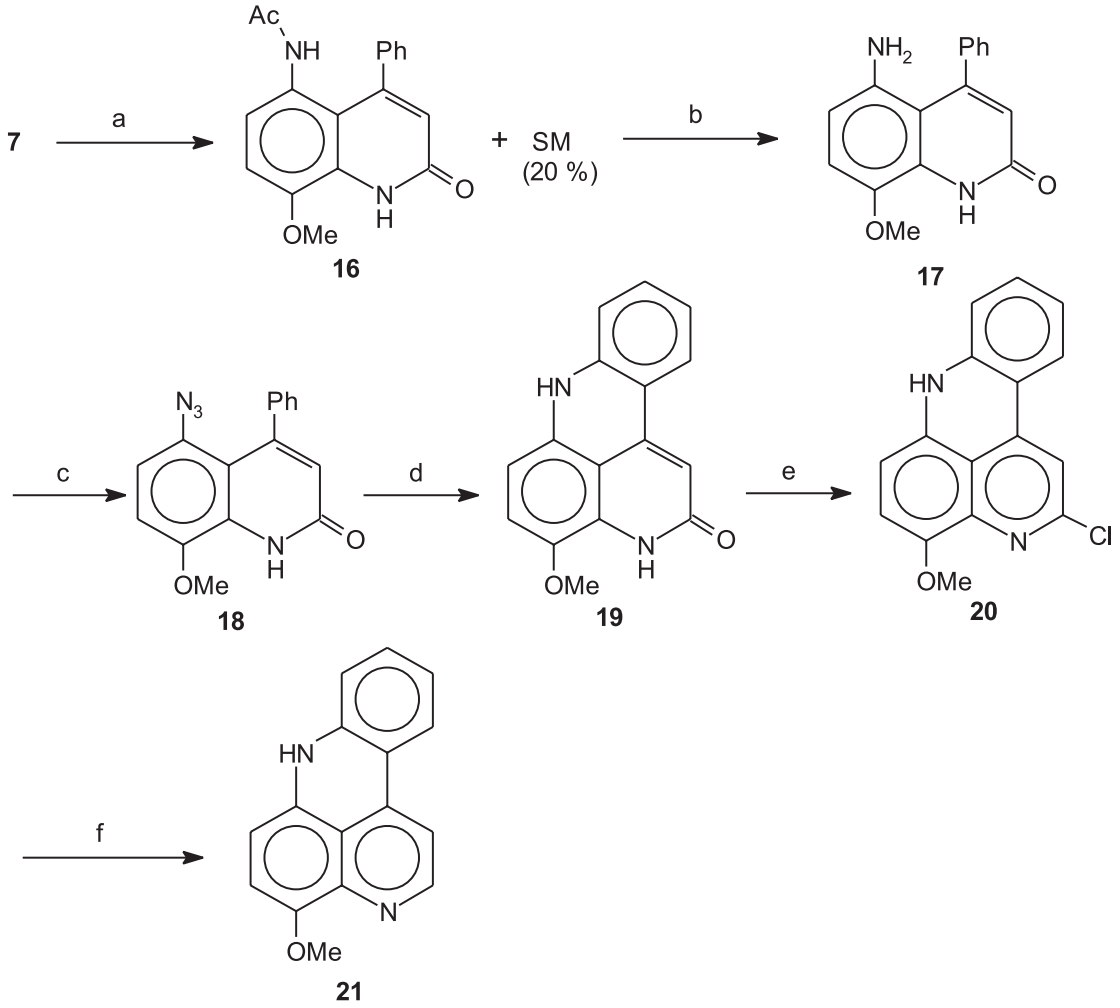
N-(2-Methoxy-5-nitrophenyl)-3-oxo-3-phenylpropanamide (4)

2-Methoxy-5-nitroaniline (**2**) (15 g, 90 mmol) and ethyl benzoylacetate (**3**) (17.29 g, 90 mmol) were condensed in toluene (400 mL) using a Dean and Stark's apparatus for 6 h, and the mixture was then left overnight at room temperature. The solid, which separated, was collected by filtration and recrystallized from ethanol. Yield: 21.9 g, 75%. Light yellow crystals, mp 183–185°C. MS: *m*/*z* 314 (M^+). ^1H NMR ($CDCl_3$) δ: 4.02 (s, 3H), 4.08 (s, 2H), 6.86 (d, J = 8.4 Hz, 1H), 7.60 (s, 5H), 8.0 (m, 2H). Anal. calcd. for $C_{16}H_{14}N_2O_5$: C 61.14, H 4.46, N 8.91; found: C 61.12, H 4.15, N 8.91.

N-(5-Amino-2-methoxyphenyl)-3-hydroxy-3-phenylpropanamide (5)

Compound **4** (6 g, 19 mmol) and C/Pd (0.21 g, 5%) were hydrogenated in ethanol (100 mL) at room temperature until the disappearance of the starting material (TLC). The

Scheme 3. (a) Pd/C, diphenyl ether, reflux, 65%, 20% (starting material); (b) H_2SO_4 (45%), reflux, 96%; (c) (*i*) $NaNO_2$; (*ii*) NaN_3, 93%; (d) xylene, reflux, 78%; (e) $POCl_3$, reflux, 83%; (f) Pd/C, H_2, Et_3N, 79%.



catalyst was filtered off through kieselguhr under suction and the kieselguhr was washed with acetone. After evaporation of the solvent, the crude solid was recrystallized from toluene. Yield: 4.89 g, 90%. Light yellow needles, mp 155–158°C. MS: *m*/*z* 286 (M^+). IR (Nujol) (cm^{-1}): 3420, 3360, 3100–3480, 1654. ^1H NMR ($CDCl_3$) δ: 2.68 (d, *J* = 2.9 Hz, 2H), 3.28 (s, 2H), 3.68 (s, 3H), 5.08 (t, *J* = 2.9 Hz, 1H), 6.26 (dd, *J* = 10.1, 1.2 Hz, 1H), 6.64 (d, *J* = 9.7 Hz, 1H), 7.26 (s, 5H), 7.82 (d, *J* = 1.2 Hz, 1H), 8.06 (s, 1H). Anal. calcd. for $C_{16}H_{18}N_2O_3$: C 67.43, H 6.29, N 9.79; found: C 67.43, H 6.40, N 9.58.

N-(5-Acetamido-2-methoxyphenyl)-3-hydroxy-3-phenylpropanamide (6)

To compound **5** (3 g, 10 mmol), dissolved in pyridine (25 mL) and cooled in an ice bath, was added dropwise freshly distilled acetyl chloride (0.80 mL, 110 mmol). The mixture was stirred for 2 h at room temperature and then poured into water (50 mL). The resulting mixture was extracted with CH_2Cl_2 (3 × 40 mL), dried over Mg_2SO_4. The solvent was evaporated under reduced pressure. Yield: 2.46 g, 75%. Colorless crystalline solid, mp 79–82°C. MS: *m*/*z* 328 (M^+). IR (Nujol) (cm^{-1}): 3110–3400, 1630–1680. ^1H NMR ($CDCl_3$) δ: 2.04 (s, 3H), 2.68 (d, *J* = 3.0 Hz, 2H), 3.00 (s, 3H), 4.04 (s, 1H), 5.08 (t, *J* = 3.0 Hz, 1H), 6.66 (d, *J* = 10.0 Hz, 1H), 7.24 (s, 5H), 7.44 (dd, *J* = 10.0, 1.1 Hz, 1H), 8.20 (d, *J* = 1.0 Hz, 1H), 8.25 (s, 1H). Anal. calcd. for $C_{18}H_{20}N_2O_4$: C 65.85, H 6.09, N 8.53; found: C 65.24, H 6.18, N 8.21.

5-Acetamido-3,4-dihydro-8-methoxy-4-phenylquinolin-2(1*H*)-one (7)

Compound **6** (0.50 g) was stirred in H_2SO_4 (80%, 100 mL) at 80°C for 1 h. The reaction mixture was cooled to room temperature and poured into ice water. The resulting solution was then neutralized with Na_2CO_3 and the Na_2SO_4 which separated was removed by filtration and washed with CH_2Cl_2 (3 × 40 mL) and the combined extracts were dried (Mg_2SO_4) and the solvent was evaporated under reduced pressure. The crude product was recrystallized from toluene. Yield: 0.42 g, 92%. Colorless crystalline solid, mp 218–220°C. MS: *m*/*z* 310 (M^+), 311. IR (Nujol) (cm^{-1}): 3200–3440, 1656, 1650. ^1H NMR ($CDCl_3$) δ: 1.91 (s, 3H), 2.63 (d, *J* = 15.7 Hz, 1H), 2.89 (dd, *J* = 16.1, 6.9 Hz, 1H), 3.80

(s, 3H), 4.53 (d, J = 5.9 Hz, 1H), 6.93 (d, J = 8.8 Hz, 1H), 6.98 (d, J = 8.8 Hz, 1H), 7.02–7.29 (m, 5H), 9.21 (s, 1H), 9.25 (s,1H). Anal. calcd. for $C_{18}H_{18}N_2O_3$: C 69.67, H 5.80, N 9.03; found: C 69.73, H 5.92, N 8.93.

5-Amino-3,4-dihydro-8-methoxy-4-phenylquinolin-2(1*H*)-one (12)

Compound **7** (0.5 g, 1.6 mmol) was refluxed in H_2SO_4 (25 mL, 45%) for 2 h. The mixture was cooled down to room temperature and poured into water (50 mL). The resulting solution was then neutralized with Na_2CO_3, and the aqueous mixture was extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were dried over Mg_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude solid was recrystallized from ethanol. Yield: 0.41 g, 88%. Colorless crystalline solid, mp 225–228°C. MS: m/z 268 (M^+). IR (Nujol) (cm^{-1}): 3460, 3380, 1700. ^{1}H NMR (DMSO-d_6) δ: 2.49 (d, J = 15.7 Hz, 1H), 2.87 (dd, J = 16.1, 6.9 Hz, 1H), 3.71 (s, 3H), 4.40 (d, J = 6.2 Hz, 1H), 4.57 (s, 2H), 6.21 (d, J = 8.4 Hz, 1H), 6.70 (d, J = 8.4 Hz, 1H), 7.09–7.25 (m, 5H), 9.85 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 35.7, 38.4, 55.7, 102.8, 109.7, 109.8, 126.4, 127.0, 128.3, 132.1, 134.7, 142.1, 142.4, 168.0. Anal. calcd. for $C_{16}H_{16}N_2O_2$: C 71.64, H 5.97, N 10.44; found: C 71.45, H 6.05, N 10.15.

5-Azido-3,4-dihydro-8-methoxy-4-phenylquinolin-2(1*H*)-one (13)

To concentrated H_2SO_4 (1.72 mL) dissolved in water (5.7 mL) was added **12** (1.90 g, 7 mmol). The mixture was stirred for 10 min at room temperature, then more water (3 mL) was added and the mixture was cooled to 0–5°C in an ice water bath. A solution of sodium nitrite (0.63 g, 10 mmol) in water (5 mL) was carefully added dropwise and the mixture was stirred for 45 min. With strong stirring, a solution of sodium azide (0.7 g, 10 mmol) in water (5 mL) was then added dropwise and stirring was continued for a further 40 min. The light yellow solid, which separated, was collected by filtration and washed with plenty of water. The crystalline solid was dried under vacuum, mp 134–137°C. Yield: 1.80 g, 86%. MS: m/z 294 (M^+). IR (Nujol) (cm^{-1}): 2120, 1656. ^{1}H NMR (DMSO-d_6) δ: 2.60 (d, J = 16.2 Hz, 1H), 2.96 (dd, J = 16.2, 7.3 Hz, 1H), 3.82 (s, 3H), 4.43 (d, J = 6.4 Hz, 1H), 6.91 (d, J = 8.8 Hz, 1H), 7.05 (d, J = 8.5 Hz, 1H), 7.08–7.26 (m, 5H), 9.44 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 36.2, 36.8, 56.0, 111.4, 112.3, 117.7, 126.7, 128.4, 128.6, 129.5, 141.6, 143.0, 143.8, 168.1. Anal. calcd. for $C_{16}H_{14}N_4O_2$: C 65.30, H 4.76, N 19.04; found: C 65.07, H 4.72, N 18.76.

Compound **13** was dissolved in xylene (750 mL) and refluxed for 4 h until the disappearance of the starting material (TLC). Then the reaction mixture was left in the refrigerator for overnight and the formed deep brown solid was filtered and washed with petroleum ether (bp 49–60°C). The crude material was chromatographed using ethyl acetate as an eluent and a brown crystalline solid was then obtained. Its TLC, NMR, and mass analysis showed that the product was indeed 5-amino-3,4-dihydro-8-methoxy-4-phenylquinolin-2(1*H*)-one (**12**).

Compound **13** (1 g) was melted and kept stirring at 150°C under nitrogen atmosphere for 30 min. Examination of the NMR and TLC of the crude product showed that the product is **12**.

3,4-Dihydro-4-phenylquinolin-2(1*H*),5,8-trione (15)

To a stirred solution of the product obtained from attempted insertion reaction of **13** (0.38 g, 1.4 mmol) dissolved in H_2SO_4 (59 mL, 35%) was added activated MnO_2 (0.46 g) portionwise at 0°C. Stirring was carried out 1 h longer, then the mixture was diluted with CH_2Cl_2 (30 mL), neutralized with Na_2CO_3, and filtered. The filtrate was washed with water and the CH_2Cl_2 phase was separated, dried over Mg_2SO_4, filtered, and the solvent was evaporated under reduced pressure. The crude product was crystallized from toluene. Yield: 0.27 g, 78%. Red needles, mp 154–156°C. MS: m/z 253 (M^+). IR (Nujol) (cm^{-1}): 3340, 1740, 1654, 1640. ^{1}H NMR ($CDCl_3$) δ: 2.88 (m, 2H), 4.44 (m, 1H), 6.66 (s, 2H), 7.22 (s, 5H), 8.22 (s, 1H). Anal. calcd. for $C_{15}H_{11}NO_3$: C 71.14, H 4.34, N 5.53; found: C 70.90, H 4.04, N 5.30.

5-Acetamido-8-methoxy-4-phenylquinolin-2(1*H*)-one (16)

A mixture of compound **7** (0.30 g, 1 mmol) and Pd/C (10%, 53 mg) in diphenyl ether (30 mL) was refluxed for 48 h. The reaction mixture was cooled to room temperature, filtered through kiselguhr under suction, and the kiselguhr washed with CH_2Cl_2 (50 mL). The dichloromethane solution was evaporated under reduced pressure and the resulting diphenyl ether solution was poured into petroleum ether (bp 40–60°C, 100 mL). The solid, which separated, was collected by filtration and washed with petroleum ether (25 mL). The crude solid was chromatographed on silica, using ethyl acetate as the first eluent to remove starting material (20%) and then ethanol–ethyl acetate (1:6) to obtain the product. Yield: 0.2 g, 65%. Colorless crystalline solid, mp 193–196°C. MS: m/z 308 (M^+). IR (Nujol) (cm^{-1}): 1615–1654. ^{1}H NMR (DMSO-d_6) δ: 1.12 (s, 3H), 3.93 (s, 3H), 6.22 (s, 1H), 6.84 (d, 1H, J = 8.2 Hz, 1H), 7.18 (d, J = 8.2 Hz, 1H), 7.21–7.41 (m, 5H), 8.81 (s, 1H), 10.88 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 21.8, 56.4, 110.9, 115.1, 121.6, 124.3, 127.1, 127.3, 127.5, 127.7, 129.9, 139.4, 144.2, 151.1, 159.9, 168.1. Anal. calcd. for $C_{18}H_{16}N_2O_3$: C 70.12, H 5.19, N 9.09; found: C 70.50, H 5.41, N 8.96.

5-Amino-8-methoxy-4-phenylquinolin-2(1*H*)-one (17)

The same reaction conditions and work-up were applied as in the preparation of **12** for the deacetylation of **16** to obtain **17**. The crude product was recrystallized from toluene. Yield: 96%. Yellow needles, mp 216–218°C. MS: m/z 266 (M^+). IR (nujol) (cm^{-1}): 3480, 3440,1650. ^{1}H NMR (DMSO-d_6) δ: 3.80 (s, 3H), 4.12 (s, 2H), 6.05 (s, 1H), 6.30 (d, J = 8.4 Hz, 1H), 7.03 (d, J = 8.8 Hz, 1H), 7.38–7.51 (m, 5H), 10.39 (s, 1H). ^{13}C NMR DMSO-d_6 δ: 56.9, 105.4, 107.1, 114.7, 121.0, 127.5, 128.4, 128.6, 130.1, 137.0,139.4, 139.7, 151.2, 159.9. Anal. calcd. for $C_{16}H_{14}N_2O_2$: C 72.14, H 5.26, N 10.52; found: C 72.14, H 5.19, N 10.29.

5-Azido-8-methoxy-4-phenylquinolin-2(1*H*)-one (18)

Using the same reaction conditions as in the preparation of **13**, compound **17** was converted to the azide **18**. Instead of filtering the precipitate, which formed after the addition of NaN_3, the reaction mixture was poured into water (30 mL), and the resulting solution neutralized with Na_2CO_3

and extracted with CH_2Cl_2 (3 × 40 mL). The organic extracts were dried (Mg_2SO_4), filtered, and the solvent was evaporated under reduced pressure. The yellow crystalline solid, which was obtained in 93% yield, was used directly for the next insertion step. IR (Nujol) (cm^{-1}): 2120, 1640. ^1H NMR ($CDCl_3$) δ: 4.0 (s, 3H), 6.44 (s, 1H), 6.84 (s, 1H), 6.86 (s, 1H), 7.12–7.24 (m, 5H), 9.16 (s, 1H).

3,7-Dihydro-4-methoxy-2-oxo-pyrido(2,3,4-*kl*)acridine (19)

Compound **18** (0.60 g, 2 mmol) was refluxed in xylene (750 mL) for 1.5 h. The reaction mixture was cooled to room temperature and left overnight. The solid, which separated, was collected by filtration and washed with petroleum ether (bp 40–60°C, 25 mL). This crude product was chromatographed on silica using ethyl acetate–ethanol (4:2) as eluent. Yield: 0.41 g, 78%. Brown crystalline solid, mp 270°C (decomp.). MS: *m*/*z* 264 (M^+). IR (Nujol) (cm^{-1}): 1610–1650. ^1H NMR (DMSO-d_6) δ: 3.83 (s, 3H), 6.44 (s, 1H), 6.56 (d, *J* = 8.7 Hz, 1H), 6.97 (t, *J* = 7.1 Hz, 1H), 7.07 (d, *J* = 8.2 Hz, 1H), 7.18 (d, *J* = 8.7 Hz, 1H), 7.41 (t, *J* = 7.3 Hz, 1H), 7.93 (d, *J* = 7.8 Hz, 1H), 10.01 (s, 1H), 10.42 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 56.7, 101.8, 102.6, 108.2, 114.1, 115.8, 115.9, 120.1, 124.4, 129.6, 131.6, 131.7, 137.5, 139.2, 142.3, 162.4. Anal. calcd. for $C_{16}H_{12}N_2O_2$: C 72.72, H 4.54, N 10.60; found: C 72.39, H 4.56, N 10.34.

2-Chloro-4-methoxy-7*H*-pyrido(2,3,4-*kl*)acridine (20)

Compound **19** (0.20 g, 0.75 mmol) was refluxed in $POCl_3$ (30 mL) for 1 h. The reaction mixture was cooled to room temperature and poured into water (50 mL). The resulting solution was neutralized with Na_2CO_3 and the solid, which separated, was collected by filtration. This gave 0.17 g (83%) of crude red crystalline solid which showed one spot on the TLC and was used directly for the next step. A sample was crystallized from toluene for the analysis, mp 202°C (decomp.). MS: *m*/*z* 282 (M^+). ^1H NMR (DMSO-d_6) δ: 3.85 (s, 3H), 6.69 (d, *J* = 8.4 Hz, 1H), 6.92–7.41 (m, 5H), 7.99 (d, *J* = 8.0 Hz, 1H), 10.57 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 56.1, 113.6, 114.3, 115.6, 117.9, 120.2, 124.6, 128.1, 128.8, 131.9, 132.4, 139.8, 140.1, 143.7, 144.8, 151.8, 1H. Anal. calcd. for $C_{16}H_{11}ClN_2O$: C 67.97, H 3.92, N 9.91, Cl 12.54; found: C 67.84, H 4.05, N 9.66, Cl 12.20.

4-Methoxy-7*H*-pyrido(2,3,4-*kl*)acridine (21)

Compound **20** (0.50 g, 2 mmol) was catalytically hydrogenated with 10% Pd/C (50 mg) in ethyl alcohol (40 mL) in the presence of triethylamine (0.25 g, 2.7 mmol) for 6 h at room temperature. The catalyst was filtered off through kieselguhr under suction, and then the solvent was evaporated under reduced pressure. This gave 0.34 g (79%) of red crystalline product, which showed one spot on TLC, mp 224°C (decomp.). MS: *m*/*z* 248 (M^+). ^1H NMR (DMSO-d_6) δ: 3.84 (s, 3H), 6.58 (d, *J* = 8.9 Hz, 1H), 6.90 (t, *J* = 8.3 Hz, 1H), 6.95 (d, *J* = 8.3 Hz, 1H), 7.1 (d, *J* = 8.3 Hz, 1H), 7.33 (t, *J* = 7.6 Hz, 1H), 7.41 (d, *J* = 4.9 Hz, 1H), 7.93 (d, *J* = 7.3 Hz, 1H), 8.48 (d, *J* = 4.9 Hz, 1H), 10.30 (s, 1H). ^{13}C NMR (DMSO-d_6) δ: 56.2, 101.5, 107.1, 112.3, 115.1, 119.2, 119.8, 124.0, 130.8, 131.7, 132.1, 139.6, 140.2, 141.1, 145.7, 150.7. Anal. calcd. for $C_{16}H_{12}N_2O$: C 77.42, H 4.48, N 11.29; found: C 77.21, H 4.84, N 11.24.

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