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Tandem Synthesis of Pyrroloacridones via [3 + 2] Alkyne Annulation/Ring-Opening with Concomitant Intramolecular Aldol Condensation

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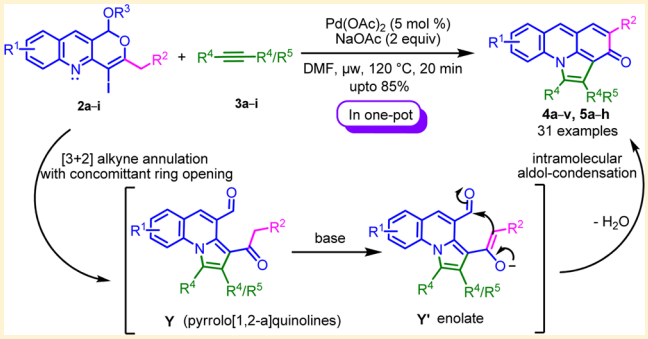
Supporting Information

ABSTRACT: An efficient cascade strategy for the direct synthesis of pyrrolo[3,2,1-*de*]acridones **4a−v, 5a−h** from iodopyranoquinolines **2a−i** by the palladium-catalyzed regioselective [3 + 2] alkyne annulation/ring-opening followed by intramolecular aldol condensation under microwave irradiation is described. The chemistry involves the in situ formation of pyrroloquinolines **Y**, via palladium-catalyzed selective [3 + 2] annulation of iodopyranoquinolines and internal akynes with ring-opening and successive intramolecular cross-aldol condensation. Both the symmetrical and unsymmetrical internal alkynes were reacted smoothly to provide the desired pyrroloacridones in good yields. This methodology provides the facile conversion of easily accessble iodopyranoquinoline into highly functionalized biologically important pyrroloacridones in a single process.



INTRODUCTION

The substituted acridines represent an important class of compounds that exhibit a wide spectrum of biological activities.[1] Some of their derivatives inhibit the growth of cancerous cells via binding to DNA.[2] Amsacrine[3] is one acridine-based drug that is in clinical use to cure acute lymphoblastic leukemia (Figure 1, **I**). Significantly, the nucleus of pyrroloacridones and pyrroloacridines family is associated with a wide range of biological activities including anti-helmintic,[4] antitumor[5] and antifungal activity.[6] The tetracyclic core of these compounds enhances their DNA intercalation[7] and topoisomerase I and II inhibition[8] properties, providing the potential lead frameworks for the development of novel anticancer drugs. The majority of these compounds were found in metabolites from marine sources such as plakinidines (Figure 1, **II** and **III**) and alpkinidine (Figure 1, **IV**).[9] Plakinidine A exhibited in vitro activity against *Nippostrongylus brastiliensis*.[4] In recent years, marine sponges have received considerable attention due to the production of secondary metabolites, with numerous studies focusing on culturing these microorganisms and screening them for the production of bioactive compounds.[10] Despite their significant biological activities, less attention has been paid for the synthesis of pyrroloacridones;[11,12] therefore, the development of efficient and concise protocols for the synthesis of these heterocyclic cores represents a major challenge for the organic chemist.

In the past decade, palladium-catalyzed reactions[13] became known for the synthesis of fused carbocyclic compounds and natural-product-like scaffolds[14] because of their high reactivity, tolerance toward many functional groups[15] and excellent ability to trigger the π-systems, toward C−C and C−N bond formations. Among various reactions, tandem cyclization[16] has received a considerable interest as these reactions can quickly synthesize the complex molecules from simple starting materials in an iterative manner.

In 2012, Shi and co-workers[17] reported an interesting domino approach for the synthesis of pyrrolo[2,3,4-*kl*]acridin-1-one from isatin using L-proline. In continuation of our ongoing work on the synthesis of heterocyclic scaffolds from alkynes,[18] recently we have reported the first silver-catalyzed/iodine-mediated tandem synthesis of pyrrolo[1,2-*a*]quinolines (**Q**) from iodopyranoquinolines (**P**) via site-selective electrophilic cyclization (preferential attack of the pyridyl nitrogen over aryl ring) and subsequent opening of pyran ring under mild reaction conditions (Scheme 1, i). The formation of 5-*endo-dig* cyclized products **Q** over 6-*endo-dig* cyclized products **R** was supported by the quantum chemical calculations.[19] Encouraged by the above finding, we have extended this interesting chemistry for the direct synthesis of pyrrolo[1,2-

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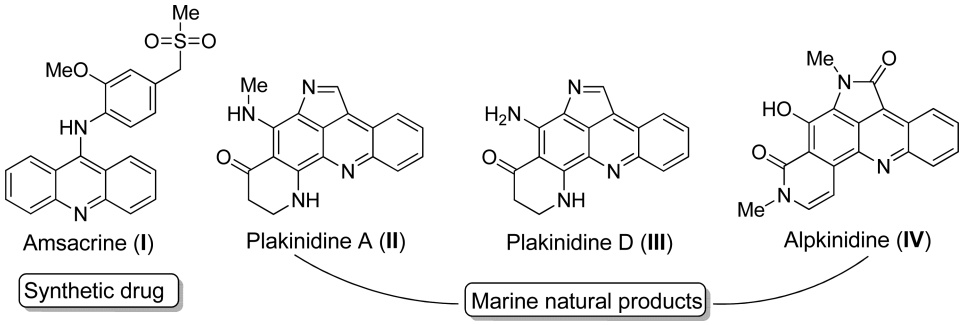
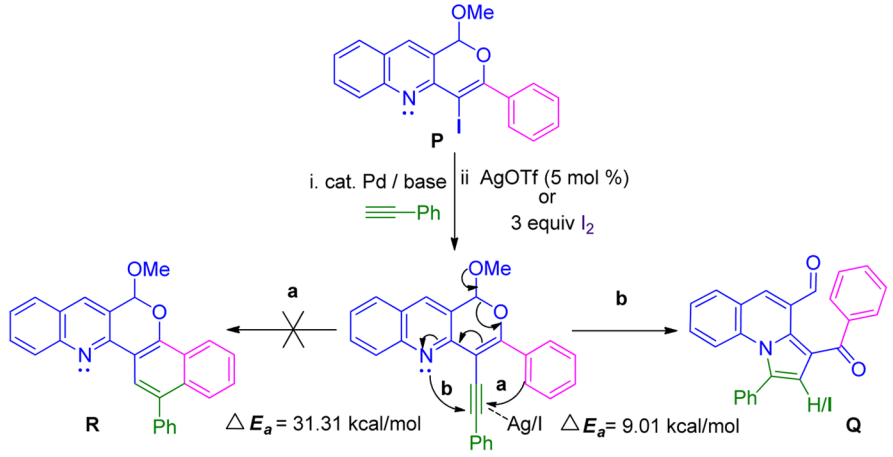


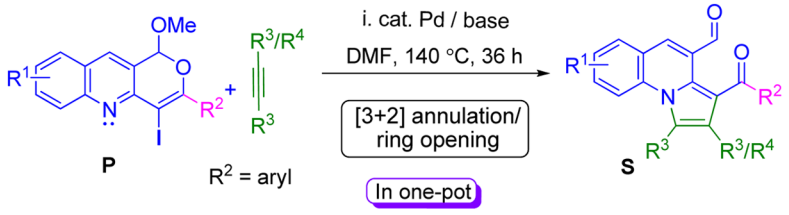
Figure 1. Biologically and medicinally important substituted acridines.

Scheme 1. Previous Work of Our Laboratory

i. Synthesis of pyrrolo[1,2-*a*]quinolines via site-selective electrophilic cyclization and subsequent ring opening.



ii. Synthesis of pyrrolo[1,2-*a*]quinolines via palladium-catalyzed regioselective [3 + 2] alkyne annulation with concomitant ring opening.



a]quinolines via palladium-catalyzed regioselective [3 + 2] alkyne annulation with concomitant ring-opening (Scheme 1, ii).[20] During the course of our study, we have also observed that the pyrrolo[1,2-*a*]quinolines having α-H (R^2 = alkyl) were in situ converted in to pyrroloacridones via successive intramolecular aldol condensation. Herein, we wish to report the full details of our study on the palladium-catalyzed tandem synthesis of highly functionalized pyrrolo[3,2,1-*de*]acridones **4a**–**v**, **5a**–**h** from iodo-pyranoquinolines **2a**–**i** by the [3 + 2] alkyne annulations/ring-opening with concomitant intramolecular cross aldol condensation. We have explored various iodopyranoquinolines with a variety of symmetrical and unsymmetrical internal alkynes for the designed reaction.

The designed tandem process for the direct sythesis of pyrroloacridones is advantageous in improving the efficiency, atom economy, and modularity of the synthesis (Scheme 2).

RESULTS AND DISCUSSION

Preparation of 4-Iodopyrano[4,3-*b*]quinolines. The substrates 4-iodopyranoquinolines **2a**–**i**, required for the designed approach, were prepared in good yields by the electrophilic iodocyclization of 2-(alkynyl)quinoline-3-carbaldehydes **1a**–**i** using standard procedures developed in our laboratory (Scheme 3).[21]

To identify the optimal reaction conditions for the synthesis of pyrroloacridones, we examined the reaction of 4-iodo-1-

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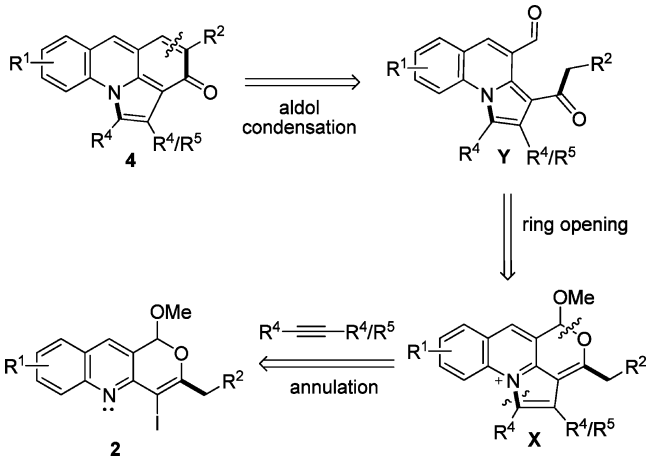
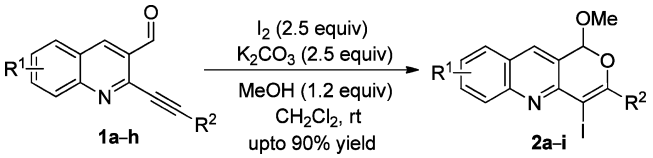
Scheme 2. Designed Retrosynthetic Approach for the Tandem Synthesis of Pyrrolo[3,2,1-*de*]acridones



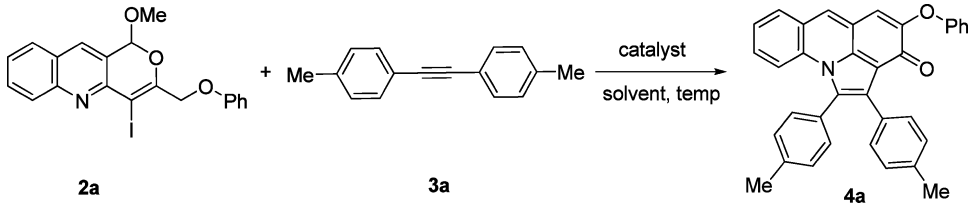
Scheme 3. Synthesis of 4-Iodopyrano[4,3-*b*]quinolines 2a−i



methoxy-3-(phenoxymethyl)-1*H*-pyrano[4,3-*b*]quinoline (**2a**) with 1,2-di-*p*-tolylethyne (**3a**) using 3.0 equiv of LiCl and 2.0 equiv of NaOAc with 5 mol % of $Pd(OAc)_2$ in DMF at 120 °C for 10 min under microwave irradiation, and the desired product **4a** was obtained in only 45% (Table 1, entry 1). When the reaction was allowed to run for 15 and 20 min, the desired product **4a** was obtained in 60 and 78% yields, respectively (entries 2 and 3). When the reaction was further allowed to run for 30 min, no significant improvement in the yield was observed (entry 4). The efficiency of this organic transformation was affected when the catalyst loading was decreased from 5 to 3 mol % (entry 5). When 5 mol % of $PdCl_2$ was used, the desired product **4a** was obtained in 72% yield (entry 6). The Pd-complexes such as $PdCl_2(PPh_3)_2$, $Pd(PPh_3)_4$ and $Pd_2(dba)_3$ were also found to be effective and afforded the desired products in 74, 70 and 65% yields, respectively (entries 7−9). From entries 10 to 12, it is noticeable that other solvents like DMSO, DMA and toulene afforded the desired product **4a** in lower yields. Use of KOAc as a base provided the product **4a** in 70% yield (entry 13), while significant decrease in the yield was observed with K_2CO_3 and Na_2CO_3 (entries 14 and 15). Lowering the reaction temperature leads to incomplete conversion of the substrates (entries 16 and 17).

Synthesis of Pyrrolo[3,2,1-*de*]acridones (4a−v) Using Symmetrical Internal Alkynes. With this standard protocol in hand, we examined the scope and generality of the reaction by employing a vide variety of iodopyranoquinolines **2a−i** and alkynes **3a−e**. Reaction of phenoxy-substituted iodopyranoquinolines **2a−b**, **2e**, **2h** with internal alkynes **3a−e** afforded the desired pyrrolo[3,2,1-*de*]acridones **4a−d**, **4k,l** and **4o−s** in good yields (entries 1−5, 12, 13 and 16−20). However, reaction of benzyl substituted iodopyranoquinolines **2c**, **2g** and **2i** with alkynes **3a−e** afforded the desired products **4e−i**, **4n**, **4t−v** comparatively in lower yields (entries 6−10, 15, 21−23 vs 1−5, 12−13, 16−20). The reaction of alkynes **3e** and **3a** with substrates **2d** and **2f** bearing aliphatic substitutents at R^2 provided the desired products **4j** and **4m** in 68 and 72%

Table 1. Optimization of the Reaction Conditions[a]



entry	solvent	base	catalyst	mol %	*t* (min)	yield[b]
1	DMF	NaOAc	$Pd(OAc)_2$	5	10	45
2	DMF	NaOAc	$Pd(OAc)_2$	5	15	60
3	**DMF**	NaOAc	**$Pd(OAc)_2$**	**5**	**20**	**78**
4	DMF	NaOAc	$Pd(OAc)_2$	5	30	78
5	DMF	NaOAc	$Pd(OAc)_2$	3	20	60
6	DMF	NaOAc	$PdCl_2$	5	20	72
7	DMF	NaOAc	$Pd(PPh_3)_2Cl_2$	5	20	74
8	DMF	NaOAc	$Pd(PPh_3)_4$	5	20	70
9	DMF	NaOAc	$Pd_2(dba)_3$	5	20	65
10	DMSO	NaOAc	$Pd(OAc)_2$	5	20	62
11	DMA	NaOAc	$Pd(OAc)_2$	5	20	58
12	toulene	NaOAc	$Pd(OAc)_2$	5	20	50
13	DMF	KOAc	$Pd(OAc)_2$	5	20	70
14	DMF	K_2CO_3	$Pd(OAc)_2$	5	20	20
15	DMF	Na_2CO_3	$Pd(OAc)_2$	5	20	30
16	DMF	NaOAc	$Pd(OAc)_2$	5	20	65[c]
17	DMF	NaOAc	$Pd(OAc)_2$	5	20	50[d]

[a]Reactions were performed using 0.25 mmol of **2a**, 2.0 equiv of NaOAc, 3.0 equiv of LiCl, catalyst in 3.0 mL solvent at 120 °C under microwave irradiation. [b]Isolated yield. [c]At 110 °C. [d]At 100 °C.

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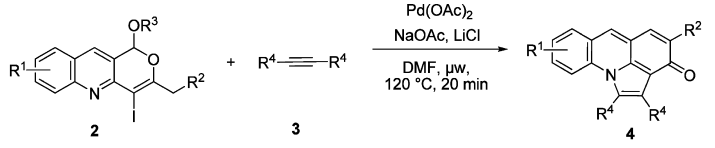
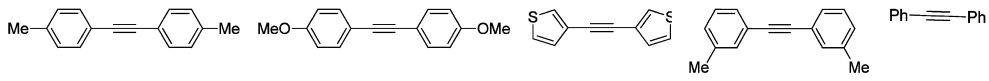
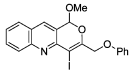
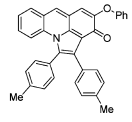
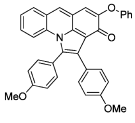
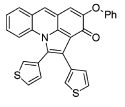
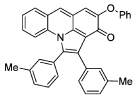
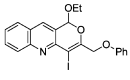
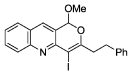
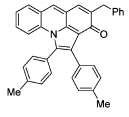
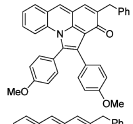
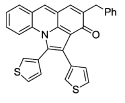
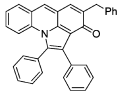
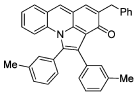
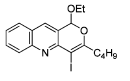
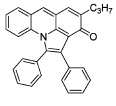
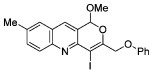
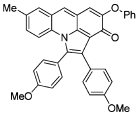
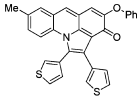
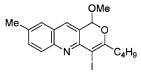
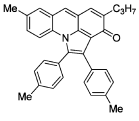
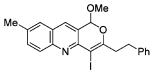
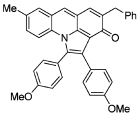
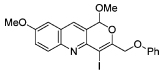
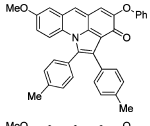
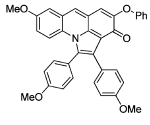
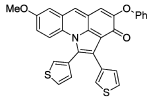
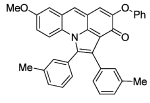
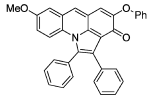
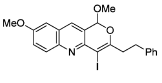
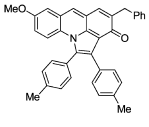
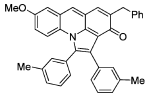
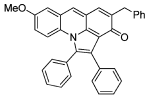
Table 2. Synthesis of Pyrrolo[3,2,1-*de*]acridones Using Developed Tandem Strategy[a]





3a **3b** **3c** **3d** **3e**

entry	substrate	alkyne	product	yield[b]
1		**2a** **3a**		**4a** 78
2		**2a** **3b**		**4b** 80
3		**2a** **3c**		**4c** 74
4		**2a** **3d**		**4d** 70
5		**2b** **3b**		**4b** 70[c]
6		**2c** **3a**		**4e** 76
7		**2c** **3b**		**4f** 78
8		**2c** **3c**		**4g** 72
9		**2c** **3e**		**4h** 75
10		**2c** **3d**		**4i** 68
11		**2d** **3e**		**4j** 68[c]
12		**2e** **3b**		**4k** 80
13		**2e** **3c**		**4l** 75
14		**2f** **3a**		**4m** 72[d]
15		**2g** **3b**		**4n** 78
16		**2h** **3a**		**4o** 82
17		**2h** **3b**		**4p** 85
18		**2h** **3c**		**4q** 76
19		**2h** **3d**		**4r** 72
20		**2h** **3e**		**4s** 75
21		**2i** **3a**		**4t** 78
22		**2i** **3d**		**4u** 70
23		**2i** **3e**		**4v** 74

[a]Reactions were performed using 0.25 mmol of **2**, 1.2 equiv of **3**, 5 mol % of $Pd(OAc)_2$, 3.0 equiv of LiCl and 2.0 equiv of NaOAc in 3.0 mL of DMF at 120 °C under microwave irradiation for 20 min unless otherwise noted. [b]Isolated yield. [c]For 50 min. [d]For 25 min.

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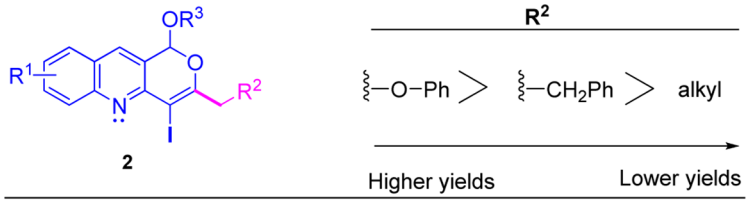
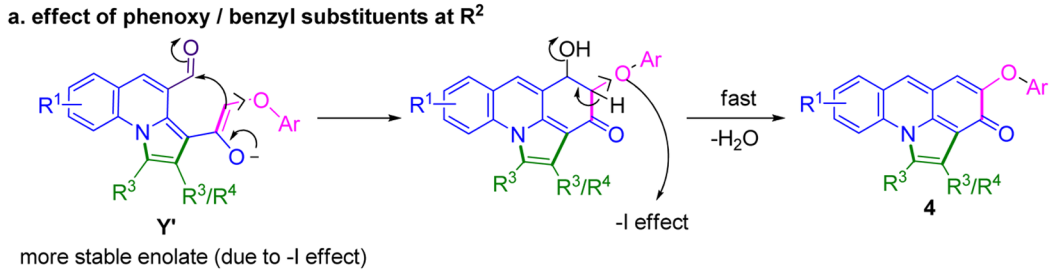
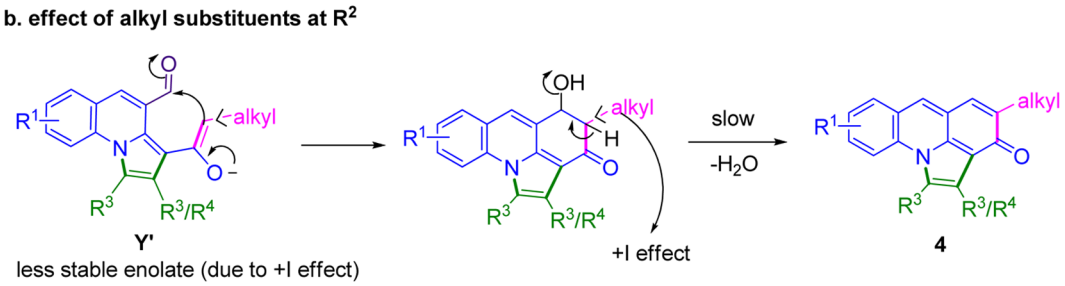
Scheme 4. Effect of Substituent R^2 on the Reaction







yields, respectively (entries 11 and 14). A marginal improvement in the yields of the products was observed with substrates bearing methyl and methoxy substituents at R^1 (entries 12−23 vs 1−11). Substrates **2b** and **2d** bearing an ethyl group at R^3 afforded the desired products **4b** and **4j** comparatively in lower yields and required 50 min for completion of the reaction (entries 5 and 11). Electron-rich heterocyclic internal alkyne 1,2-di(thiophen-3-yl)ethyne (**3c**) afforded the desired products **4c**, **4g**, **4l** and **4q** in good yields (entries 3, 8, 13 and 18). The products of the reaction were fully characterized by ^{1}H and ^{13}C NMR and mass spectroscopic data.

It is evident from Table 2 that products were obtained in good yields with the presence of phenoxy and benzyl group at R^2. The presence of phenoxy and benzyl group (-I effect) at R^2 increases the acidity of α-hydrogen of the pyrroloquinoline intermediate **Y** (generated in situ by the [3 + 2] alkyne annulations followed by the ring-opening) and generates stable enolate **Y′** (Scheme 4a); however, presence of an alkyl group (+ I effect) decreases the acidity and generates the less stable enolate (Scheme 4b). Thus, the attack of more stable enolate (nucleophile) to the carbonyl carbon of the adjacent aldehydic group is faster and leads to the higher yield of the product.

Synthesis of Pyrrolo[3,2,1-*de*]acridones (5a−h) Using Unsymmetrical Internal Alkynes. With our successful results on the symmetrical internal alkynes, next we employed the unsymmetrical alkynes for this tandem transformation. A variety of unsymmetrical internal alkynes **3f−i** exhibiting different electronic properties at aryl substituents was evaluated (Table 3, entries 1−8). The reaction of alkynes bearing a phenyl, 4-methoxyphenyl and thienyl moiety at one end of the alkyne and electron-withdrawing *p*-substituted nitro aryl group at the other end afforded the mixture of regioisomers in 60−72% yield (entries 2−8). This study proved that the regioselectivity of the reaction was independent of electronic effects, as most of the alkynes gave mixtures of regioisomers of pyrroloacridones. The ratio of regioisomers was obtained on the basis of their ^{1}H NMR data analysis. The formation of major product was analyzed on the basis of steric effect of substituents attached on the alkyne as previously reported by the Larock.[22]

After obtaining a mixture of regioisomers with unsymmetrical alkynes, we have separated the regioisomers **5c**,**d**, **5f** and **6c**,**d**, **6f** by HPLC to confirm their structures. We analyzed ^{1}H and NOESY NMR data of products **5f** and **6f** to uncover the major isomer. However, because of the spatial arrangement of bulky aryl group, no interaction between $\mathbf{H_a}$ and $\mathbf{H_b}$ was observed in NOESY (Figure 2). Therefore, we have performed the 1D-NOE experiment by irradiating various protons. The weak enhancement of $\mathbf{H_b}$ by the irradiation of $\mathbf{H_a}$ supported our concept that the bulky group is adjacent to nitrogen at R^4 (see Supporting Information).

To validate our hypothesis, we next employed the TMS-substituted unymmetrical alkynes. Because of the basic conditions employed in the reaction, TMS group was removed during the course of reaction and we obtained selectively single isomer **7a**,**b** (Scheme 5). The reaction underwent smoothly with substrates **2a** and **2e** and afforded the desired single isomers **7a**,**b** in good yields. The structure of the products **7a**,**b** was confirmed by their spectral data ^{1}H, ^{13}C and NOESY analysis. The NOESY spectrum of **7a** shows the interaction of

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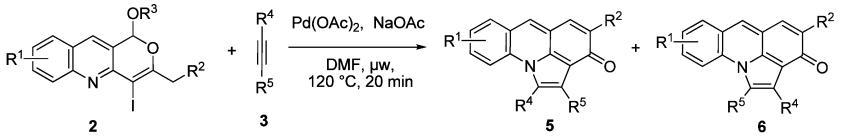
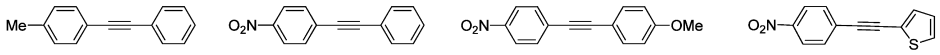
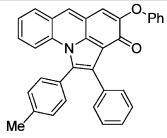
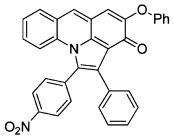
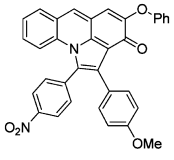
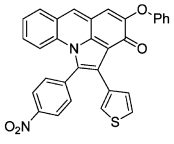
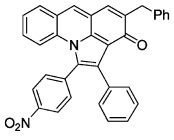
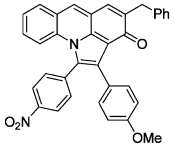
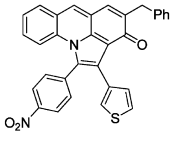
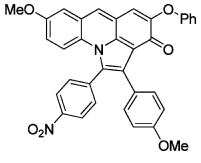
Table 3. Synthesis of Pyrrolo[3,2,1-*de*]acridones 5a–h Using Unsymmetrical Alkynes[a]





entry	substrate	alkyne	product (major)		ratio **5**/**6**	yield[b]
1	**2a**	**3f**		**5a**	53/47	70
2	**2a**	**3g**		**5b**	72/28	68
3	**2a**	**3h**		**5c**	66/34[c]	65
4	**2a**	**3i**		**5d**	53/47[c]	62
5	**2b**	**3g**		**5e**	73/27	60
6	**2b**	**3h**		**5f**	64/36[c]	61
7	**2b**	**3i**		**5g**	50/49	60
8	**2h**	**3h**		**5h**	50/50	72

[a]All reactions were performed using pyranoquinolines **2** (0.25 mmol), 1.2 equiv of internal alkynes **3**, 5 mol % of $Pd(OAc)_2$, 3.0 equiv of LiCl and 2.0 equiv of NaOAc in 3.0 mL of DMF at 120 °C under microwave irradiation. [b]Isolated yields. [c]Separated by HPLC.

H present on the pyrrole ring with proton present on the adjacent aryl ring as shown in Scheme 5. (see Supporting Information).

A detailed study of ^{1}H NMR revealed a significant shift of the H_a peak of the acridone ring (from ~8.09 to ~7.27 ppm) (Figure 3), which could be attributed to the anisotropic effect of the aryl ring, which is believed to be perpendicular to this proton (For details see Supporting Information).

To further validate the anisotropic effect, the reaction of pyranopyridine **2j** with alkyne **3e** under optimized conditions

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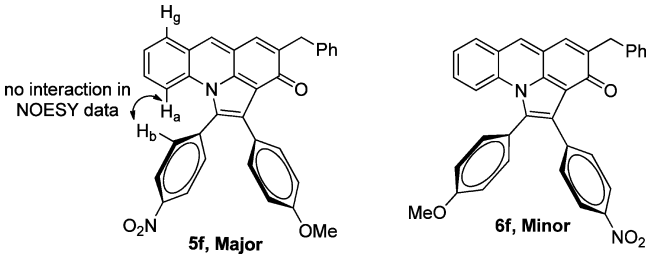


Figure 2. Spatial rearrangement of compound **5f** and **6f**.

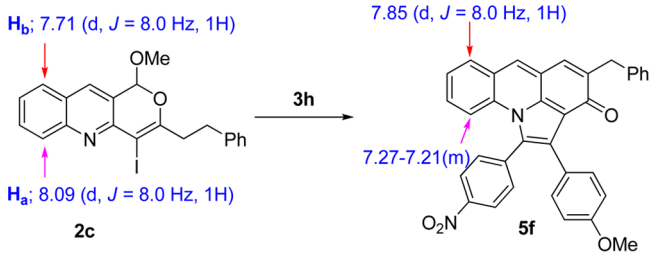


Figure 3. Study of the anisotropic effect in ^{1}H NMR. Because of the anisotropic effect, the proton H_a moved upfield in the product **5f** and merged with other aromatic protons appearing as multiplet.

was carried out to obtain pyrroloquinoline **8** (Scheme 6). The structure of compound **8** was confirmed by its ^{1}H and ^{13}C NMR. The thorough study of NMR data indicates that no anisotropic effect was observed in pyrroloquinoline, which might be due to the absence of one ring in the starting substrate **2j** (Scheme 6).

A plausible mechanism was proposed on the basis of our previously reported mechanism[20] (Scheme 7). The substrate **2** forms a vinyl palladium intermediate **X** with internal alkyne **3** in the presence of $Pd(OAc)_2$. The attack of nitrogen lone pair on the vinyl palladium followed reductive elimination, and subsequent opening of the pyran ring forms the [3 + 2] annulated product **Y**. The base CH_3COONa present in the reaction abstracts the α-hydrogen and generates enolate **Y′**, which on successive intramolecular aldol condensation leads to the generation of unstable β-hydroxy carbonyl intermediate **Z**. The instability of the intermediate **Z** subsequently leads to the loss of water molecule and provides the stable aromatic product **4**.

CONCLUSIONS

In summary, we have demonstrated a direct one-pot approach for the tandem synthesis of pharmaceutically important pyrrolo[3,2,1-*de*]acridones by [3 + 2] alkyne annulation with successive opening of the pyran ring followed by intramolecular cross-aldol condensation under microwave irradiation. This developed chemistry accommodates a variety of functional groups present on the alkynes as well on the substrates. From a synthetic point of view, this organic transformation involves a one-step conversion of easily acessble iodo-pyranoquinolines into an interesting class of natural-product-like heterocyclic compounds. Further investigation of the scope and synthetic applications of the developed strategy are currently underway and will be reported in due course.

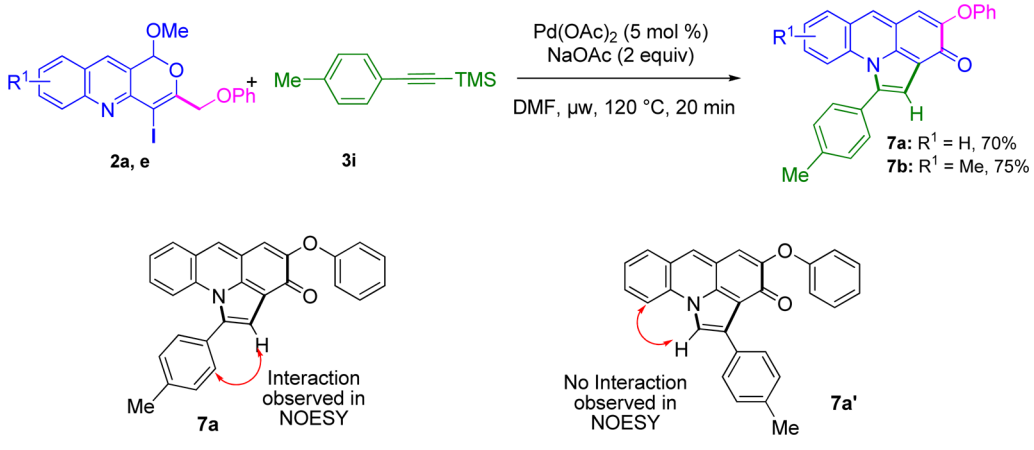
EXPERIMENTAL SECTION

General Method. ^{1}H NMR (400 MHz) and ^{13}C NMR (100 MHz) spectra were recorded in $CDCl_3$. Chemical shifts for carbons are reported in ppm from tetramethylsilane and are referenced to the carbon resonance of the solvent. Data are reported as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, dd = doublet of doublet), coupling constants in Hertz, and integration. High-resolution mass spectra were recorded on (QqTOF) LC–MS/MS system with electrospray mass spectrometer. TLC analysis was performed on commercially prepared 60 F254 silica gel plates and visualized by either UV irradiation or by staining with I_2. All purchased chemicals were used as received. A CEM Discover microwave synthesizer (Model No: 908010) operating at 180/264 V and 50/60 Hz with microwave power maximum level of 300 W and frequency of 2455 MHz was employed for the microwave-assisted experiments .

The starting material **1** was prepared by the Sonogashira coupling,[21a,b] and the substrates **2** were synthesized by the electrophilic iodocyclization using reported procedure.[21] All the symmetrical and unsymmetrical internal alkynes **3** were either commercially available or synthesized by using reported methodology.[23]

HPLC Conditions. A high-performance liquid chromatography (HPLC) system consisted of Dionex instruments equipped with a quaternary pump and a PDA detector. The analytical column used was C_{18} reversed-phase column (4.6 mm × 250 mm) packed with 5 μm particles. The column temperature was maintained at the room temperature (25 °C). The mobile phase consisted of acetonitrile and water in gradient manner. The solution was filtered and degassed by vacuum filtration through a 0.22 μm membrane filter before use. The flow rate of the mobile phase was adjusted to 1.3 mL/min.

Scheme 5. Regioselective Synthesis of Pyrrolo[3,2,1-*de*]acridones 7a–b Using TMS Substituted Unsymmetrical Alkynes



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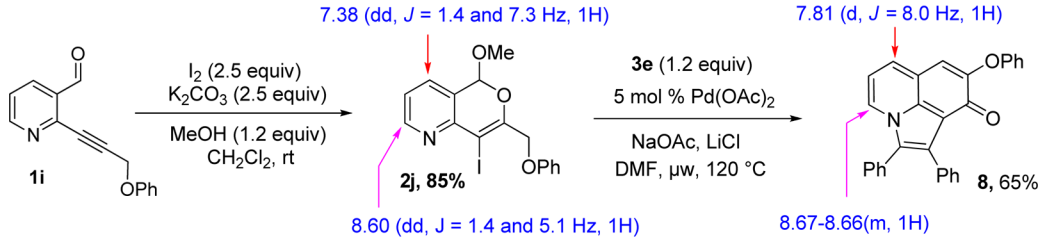
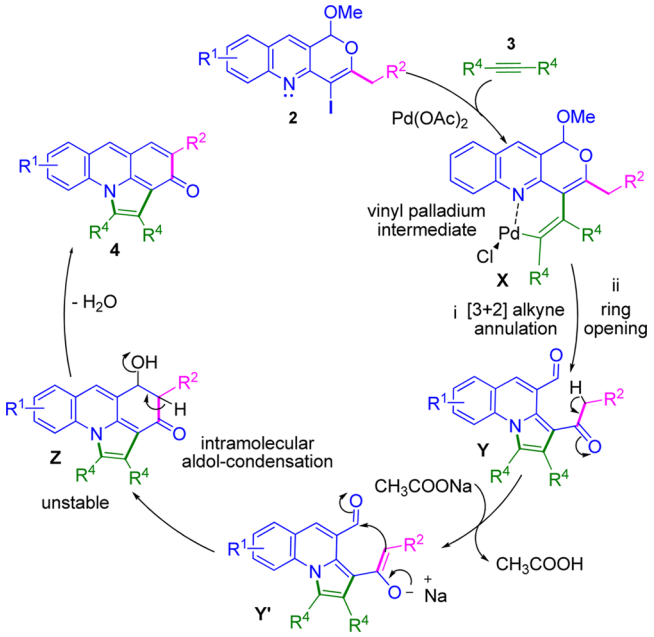
Scheme 6. Synthesis of Pyrrolo[3,2,1-*ij*]quinolin-9-one 8 from 2-(Phenoxyethynyl) nicotinaldehyde 2j



Scheme 7. Plausible Mechanism



2-(4-Phenylbut-1-yn-1-yl)quinoline-3-carbaldehyde (1b). The product was obtained as off-white crystals (1.18 g, 80%): mp 66–68 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.65 (s, 1H), 8.10 (d, J = 8.8 Hz, 1H), 7.90 (d, J = 8.8 Hz, 1H), 7.83–7.79 (m, 1H), 7.59–7.55 (m, 1H), 7.33–7.30 (m, 2H), 7.27–7.24 (m, 3H), 3.01 (t, J = 7.3 Hz, 2H), 2.88 (t, J = 7.3 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 149.8, 144.0, 139.9, 136.8, 132.9, 129.6, 129.0, 128.7, 128.6, 128.4, 128.0, 126.6, 126.3, 97.1, 78.0, 34.3, 21.8; HRMS (ESI) calcd for [$C_{20}H_{15}NO$] requires [M]$^+$ 285.1154, found [M]$^+$ 285.1153.

6-Methyl-2-(3-phenoxyprop-1-yn-1-yl)quinoline-3-carbaldehyde (1d). The product was obtained as white crystals (1.09 g, 75%): mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.39 (s, 1H), 8.52 (s, 1H), 7.94 (d, J = 9.2 Hz, 1H), 7.61–7.58 (m, 2H), 7.28–7.24 (m, 2H), 7.00–6.93 (m, 3H), 4.98 (s, 2H), 2.48 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 157.4, 148.6, 142.0, 138.9, 136.2, 135.5, 129.6, 129.0, 128.2, 126.6, 121.9, 115.0, 89.8, 83.3, 56.3, 21.6; HRMS (ESI) calcd for [$C_{20}H_{15}NO_2$] requires [M]$^+$ 301.1103, found [M]$^+$ 301.1102.

6-Methyl-2-(4-phenylbut-1-yn-1-yl)quinoline-3-carbaldehyde (1f). The product was obtained as off-white crystals (1.12 g, 77%): mp 98–100 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.55 (s, 1H), 7.99 (d, J = 8.8 Hz, 1H), 7.65–7.63 (m, 2H), 7.33–7.30 (m, 2H), 7.27–7.22 (m, 3H), 3.01 (t, J = 7.3 Hz, 2H), 2.87 (t, J = 7.3 Hz, 2H), 2.52 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.1, 148.2, 143.0, 139.9, 138.4, 136.3, 135.5, 128.7, 128.6, 128.4, 128.2, 126.6, 126.4, 97.2, 34.3, 21.8, 21.6; HRMS (ESI) calcd for [$C_{21}H_{17}NO$] requires [M]$^+$ 299.1310, found [M]$^+$ 299.1311.

6-Methoxy-2-(3-phenoxyprop-1-yn-1-yl)quinoline-3-carbaldehyde (1g). The product was obtained as white crystals (1.18 g, 83%): mp 120–122 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1H), 8.55 (s, 1H), 8.00 (d, J = 8.8 Hz, 1H), 7.49–7.46 (m, 1H), 7.33–7.29 (m, 2H), 7.13–7.12 (m, 1H), 7.04–6.98 (m, 3H), 5.03 (s, 2H), 3.92 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.6, 159.2, 157.4, 146.2, 140.3, 135.3, 130.7, 129.6, 129.1, 128.0, 126.4, 121.9, 115.0, 106.1, 89.6, 83.1, 56.3, 55.8; HRMS (ESI) calcd for [$C_{20}H_{15}NO_3$] requires [M]$^+$ 317.1052, found [M]$^+$ 317.1053.

6-Methoxy-2-(4-phenylbut-1-yn-1-yl)quinoline-3-carbaldehyde (1h). The product was obtained as off-white crystals (1.14 g, 80%): mp 112–114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.36 (s, 1H), 8.52 (s, 1H), 7.98 (d, J = 9.5 Hz, 1H), 7.45 (dd, J = 2.9, 9.5 Hz, 1H), 7.34–7.30 (m, 2H), 7.27–7.24 (m, 3H), 7.10 (d, J = 2.9 Hz, 1H), 3.92 (s, 3H), 3.00 (t, J = 8.0 Hz, 2H), 2.87 (t, J = 6.5 Hz, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 191.5, 158.7, 146.4, 141.8, 140.0, 135.0, 130.6, 129.0, 128.5, 128.4, 127.5, 126.6, 126.1, 106.1, 95.8, 78.0, 55.7, 34.4, 21.7; HRMS (ESI) calcd for [$C_{21}H_{17}NO_2$] requires [M]$^+$ 315.1259, found [M]$^+$ 315.1260.

2-(3-Phenoxyprop-1-yn-1-yl)nicotinaldehyde (1i). The product was obtained as a white solid (500 mg, 82%): mp 100–102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.35 (s, 1H), 8.78–8.76 (m, 1H), 8.17–8.15 (m, 1H), 7.42–7.39 (m, 1H), 7.35–7.31 (m, 2H), 7.05–7.02 (m, 3H), 5.02 (s, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 190.4, 157.3, 154.3, 144.9, 134.7, 132.2, 129.6, 123.7, 121.9, 114.9, 90.9, 82.3, 56.1; HRMS (ESI) calcd for [$C_{15}H_{11}NO_2$] requires [M]$^+$ 237.0790, found [M]$^+$ 237.0790.

4-Iodo-1-methoxy-3-(phenoxymethyl)-1*H*-pyrano[4,3-*b*]-quinoline (2a). The product was obtained as a brown solid (1.39 g, 90%): mp 116–118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (d, J = 8.7 Hz, 1H), 7.82 (s, 1H), 7.71 (d, J = 8.0 Hz, 1H), 7.65 (t, J = 7.3 Hz, 1H), 7.42 (t, J = 7.3 Hz, 1H), 7.27–7.24 (m, 2H), 6.98 (d, J = 8.8 Hz, 2H), 6.95–6.91 (m, 1H), 6.03 (s, 1H), 5.24 (d, J = 13.2 Hz, 1H), 5.03 (d, J = 12.4 Hz, 1H), 3.38 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 154.6, 148.6, 146.2, 133.2, 130.3, 129.5, 129.4, 127.5, 126.5, 122.0, 121.4, 114.8, 99.7, 80.3, 70.5, 56.0; HRMS (ESI) calcd for [$C_{20}H_{16}INO_3$] requires [M]$^+$ 445.0175, found [M]$^+$ 445.0176.

1-Ethoxy-4-iodo-3-(phenoxymethyl)-1*H*-pyrano[4,3-*b*]-quinoline (2b). The product was obtained as a brown solid (1.18 g, 77%): mp 114–116 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.11 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.72 (d, J = 8.0 Hz, 1H), 7.66–7.62 (m, 1H), 7.43–7.40 (m, 1H), 7.25–7.21 (m, 2H), 6.96–6.88 (m, 3H), 6.13 (s, 1H), 5.22 (d, J = 13.1 Hz, 1H), 5.01 (d, J = 13.2 Hz, 1H), 3.78–3.70 (m, 1H), 3.62–3.55 (m, 1H), 1.00 (t, J = 7.2 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.2, 155.1, 148.4, 146.4, 133.2, 130.4, 129.6, 129.4, 127.6, 127.5, 126.5, 122.4, 121.4, 114.8, 98.6, 79.9, 70.5, 64.5, 14.7; HRMS (ESI) calcd for [$C_{21}H_{18}INO_3$] requires [M]$^+$ 459.0331, found [M]$^+$ 459.0330.

4-Iodo-1-methoxy-3-phenethyl-1*H*-pyrano[4,3-*b*]quinoline (2c). The product was obtained as a brown solid (1.36 g, 88%): mp 118–120 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09 (d, J = 8.0 Hz, 1H), 7.83 (s, 1H), 7.71 (d, J = 8.4 Hz, 1H), 7.65–7.60 (m, 1H), 7.42–7.38 (m, 1H), 7.25–7.24 (m, 4H), 7.17–7.14 (m, 1H), 6.00 (s, 1H), 3.51 (s, 3H), 3.08–3.03 (m, 2H), 2.98–2.93 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.4, 148.7, 147.2, 140.6, 133.0, 130.2, 129.5, 129.4, 128.5, 128.4, 127.4, 126.3, 126.1, 121.5, 99.8, 78.1, 56.1, 40.1, 33.2; HRMS (ESI) calcd for [$C_{21}H_{18}INO_2$] requires [M]$^+$ 443.0382, found [M]$^+$ 443.0381.

3-Butyl-1-ethoxy-4-iodo-1*H*-pyrano[4,3-*b*]quinoline (2d). The product was obtained as a brown semisolid (1.29 g, 75%): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.13 (d, J = 8.0 Hz, 1H), 7.86 (s, 1H), 7.76 (d, J = 8.0 Hz, 1H), 7.69–7.64 (m, 1H), 7.46–7.42 (m, 1H), 6.16

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(s, 1H), 4.03−3.97 (m, 1H), 3.83−3.75 (m, 1H), 2.90−2.72 (m, 2H), 1.73−1.61 (m, 2H), 1.48−1.39 (m, 2H), 1.25 (t, J = 6.6 Hz, 3H), 0.95 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 162.1, 148.4, 147.5, 133.0, 130.1, 129.1, 127.4, 127.2, 126.0, 121.8, 98.5, 64.4, 37.8, 29.3, 22.2, 15.0, 14.0; HRMS (ESI) calcd for $[C_{18}H_{20}INO_2]$ requires $[M]^+$ 409.0539, found $[M]^+$ 409.0540.

4-Iodo-1-methoxy-8-methyl-3-(phenoxymethyl)-1*H*-pyrano-[4,3-*b*]quinoline (2e). The product was obtained as a brown solid (1.29 g, 85%): mp 134−136 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.7 Hz, 1H), 7.81 (s, 1H), 7.55−7.53 (m, 2H), 7.31−7.27 (m, 2H), 7.03−6.95 (m, 3H), 6.09 (s, 1H), 5.28 (d, J = 12.0 Hz, 1H), 5.07 (d, J = 12.0 Hz, 1H), 3.43 (s, 3H), 2.50 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 154.1, 147.3, 145.5, 136.6, 132.7, 132.6, 129.6, 129.2, 127.6, 126.4, 122.1, 121.4, 114.9, 99.9, 80.5, 70.6, 56.0, 21.6; HRMS (ESI) calcd for $[C_{21}H_{18}INO_3]$ requires $[M]^+$ 459.0331, found $[M]^+$ 459.0330.

4-Iodo-1-methoxy-8-methyl-3-phenethyl-1*H*-pyrano[4,3-*b*]-quinoline (2g). The product was obtained as brown solid (1.24 g, 82%): mp 108−110 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (d, J = 8.8 Hz 1H), 7.73 (s, 1H), 7.47−7.45 (m, 2H), 7.26−7.23 (m, 4H), 7.17−7.13 (m, 1H), 5.94 (s, 1H), 3.51 (s, 3H), 3.04−3.03 (m, 2H), 2.97−2.95 (m, 2H), 2.44 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 160.0, 147.2, 146.4, 140.6, 136.1, 132.5, 132.4, 129.0, 128.5, 128.4, 127.3, 126.4, 126.3, 121.5, 100.0, 78.1, 56.0, 40.1, 33.2, 21.6; HRMS (ESI) calcd for$[C_{22}H_{20}INO_2]$ requires $[M + H]^+$ 458.0617, found $[M + H]^+$ 458.0617.

4-Iodo-1,8-dimethoxy-3-(phenoxymethyl)-1*H*-pyrano[4,3-*b*]quinoline (2h). The product was obtained as a brown solid (1.37 g, 92%): mp 112−114 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 9.5 Hz, 1H), 7.79 (s, 1H), 7.36 (dd, J = 2.9, 9.5 Hz, 1H) 7.31−7.27 (m, 2H), 7.04−7.01 (m, 3H), 6.99−6.95 (m, 1H), 6.08 (s, 1H), 5.27 (d, J = 13.2 Hz, 1H), 5.06 (d, J = 13.2 Hz, 1H), 3.89 (s, 3H), 3.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 158.3, 157.9, 153.6, 144.6, 144.1, 132.1, 130.8, 129.5, 128.6, 123.1, 122.4, 121.4, 114.9, 105.1, 99.8, 80.2, 70.6, 55.9, 55.5; HRMS (ESI) calcd for$[C_{21}H_{18}INO_4]$ requires $[M]^+$ 475.0281, found $[M]^+$ 475.0281.

4-Iodo-1,8-dimethoxy-3-phenethyl-1*H*-pyrano[4,3-*b*]-quinoline (2i). The product was obtained as a brown solid (1.35 g, 90%): mp 110−112 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.05 (d, J = 9.6 Hz, 1H), 7.78 (s, 1H), 7.35 (dd, J = 2.2, 8.8 Hz, 1H), 7.32−7.30 (m, 4H), 7.25−7.20 (m, 1H), 7.03 (d, J = 2.2 Hz, 1H), 6.05 (s, 1H), 3.90 (s, 3H), 3.58 (s, 3H), 3.15−3.09 (m, 2H), 3.05−3.01 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 157.5, 145.0, 144.4, 140.6, 132.0, 130.5, 128.5, 128.4, 128.2, 126.2, 122.8, 121.7, 105.2, 99.9, 77.6, 56.1, 55.5, 40.0, 33.2; HRMS (ESI) calcd for$[C_{22}H_{20}INO_3]$ requires $[M]^+$ 473.0488, found $[M]^+$ 473.0490.

8-Iodo-5-methoxy-7-(phenoxymethyl)-5*H*-pyrano[4,3-*b*]-pyridine (2j). The product was obtained as a white solid (700 mg, 85%): mp 120−122 °C, ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.60 (dd, J = 1.4, 5.1 Hz, 1H), 7.38 (dd, J = 1.4, 7.3 Hz, 1H), 7.27−7.23 (m, 2H), 7.16−7.13 (m, 1H), 6.98−6.91 (m, 3H), 5.93 (s, 1H), 5.23−5.19 (m, 1H), 4.99−4.95 (m, 1H), 3.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 157.9, 152.8, 150.4, 146.2, 133.3, 129.3, 122.5, 121.1, 114.5, 99.0, 78.7, 69.9, 60.0, 55.5. HRMS (ESI) calcd for $[C_{16}H_{14}INO_3]$ requires $[M]^+$ 395.0018, found $[M]^+$ 395.0019.

General Procedure for the Synthesis of Substituted Substituted Pyrrolo[3,2,1-*de*]acridones (4a−v, 5a−h, 7 and 8) Using Microwave Reactor. In an oven-dried, 10-mL reaction vial containing a stirring bar, pyranoquinoline/pyridine **2** (0.25 mmol), 1.2 equiv of internal alkyne **3**, 2.0 equiv of NaOAc, 3.0 equiv of LiCl, and 5 mol % of Pd $(OAc)_2$ were added in 3 mL of DMF. The vial was sealed tightly with a Teflon cap. The reaction mixture was irradiated for 20 min at 120 °C, with an irradiation power of 100 W in microwave. After completion of the reaction monitored by the TLC, the reaction mixture was cooled and diluted with H_2O and then extracted with EtOAc. The combined organic layers were dried over Na_2SO_4, concentrated, and purified by column chromatography using ethyl acetate/hexane as eluent to afford the corresponding products.

4-Phenoxy-1,2-di-*p*-tolyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4a). The product was obtained as brown crystals (95 mg, 78%): mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, J = 8.0 Hz, 1H), 7.76 (s, 1H), 7.37−7.34 (m, 4H), 7.31−7.27 (m, 5H), 7.25−7.24 (m, 2H), 7.15−7.12 (m, 3H), 7.00 (d, J = 8.0 Hz, 2H), 6.84 (s, 1H), 2.44 (s, 3H), 2.26 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 156.4, 156.0, 139.3, 139.0, 136.5, 133.8, 131.7, 131.5, 130.7, 130.1, 129.8, 129.3, 128.8, 128.0, 127.0, 125.7, 124.3, 124.0, 123.9, 121.2, 119.5, 117.4, 114.0, 112.8, 111.5, 21.5, 21.3; HRMS (ESI) calcd for $[C_{35}H_{25}NO_2]$ requires $[M]^+$ 491.1885, found $[M]^+$ 491.1886.

1,2-Bis(4-methoxyphenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4b). The product was obtained as brown crystals (104 mg, 80%): mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79−7.74 (m, 1H), 7.70 (s, 1H), 7.35−7.19 (m, 5H), 7.08−7.06 (m, 3H), 6.95−6.85 (m, 4H), 6.79−6.85 (m, 1H), 6.68 (d, J = 8.8 Hz, 2H), 6.57−6.54 (m, 1H), 6.41 (d, J = 8.8 Hz, 1H), 3.81 (s, 3H), 3.67 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 160.0, 158.4, 156.3, 156.0, 133.7, 133.2, 132.0, 131.5, 130.4, 130.1, 129.8, 129.6, 129.4, 127.0, 125.7, 124.8, 124.6, 124.4, 124.0, 121.0, 119.5, 117.3, 114.5, 113.2, 112.8, 111.4, 55.3, 55.0; HRMS (ESI) calcd for $[C_{35}H_{25}NO_4]$ requires $[M]^+$ 523.1784, found $[M]^+$ 523.1781.

4-Phenoxy-1,2-di(thiophen-3-yl)-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4c). The product was obtained as brown crystals (88 mg, 74%): mp 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 7.3 Hz, 1H), 7.79 (s, 1H), 7.71 (s, 1H), 7.60 (t, J = 3.6 Hz, 1H), 7.42−7.40 (m, 2H), 7.38−7.36 (m, 4H), 7.26−7.22 (m, 2H), 7.18−7.14 (m, 2H), 7.11 (s, 2H), 6.84 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 156.2, 156.0, 139.3, 133.6, 133.0, 132.1, 130.2, 129.9, 129.8, 129.3, 128.1, 127.5, 127.2, 126.0, 125.7, 124.9, 124.6, 124.2, 124.0, 123.4, 123.3, 121.0, 119.6, 116.9, 114.05, 111.3; HRMS (ESI) calcd for $[C_{29}H_{17}NO_2S_2]$ requires $[M]^+$ 475.0701, found $[M]^+$ 475.0701.

4-Phenoxy-1,2-di-*m*-tolyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4d). The product was obtained as brown crystals (86 mg, 70%): mp 144−146 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.95 (m, 1H), 7.77 (d, J = 7.3 Hz, 1H), 7.73−7.69 (m, 1H), 7.33−7.27 (m, 4H), 7.25−7.21 (m, 3H), 7.23−7.17 (m, 2H), 7.10−7.08 (m, 3H), 7.02−6.98 (m, 2H), 6.93−6.91 (m, 1H), 6.74−6.70 (m, 1H), 2.28 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.3, 156.2, 138.6, 136.5, 133.7, 132.7, 132.4, 132.1, 131.7, 131.1, 130.0, 129.9, 129.8, 129.7, 129.3, 129.0, 128.8, 127.8, 127.7, 127.1, 126.9, 125.8, 124.4, 124.1, 121.3, 119.9, 117.5, 116.9, 116.8, 112.8, 110.9, 21.4; HRMS (ESI) calcd for $[C_{35}H_{25}NO_2]$ requires $[M]^+$ 491.1885, found $[M]^+$ 491.1886.

4-Benzyl-1,2-di-*p*-tolyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4e). The product was obtained as dark-brown crystals (93 mg, 76%): mp 168−170 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 7.3 Hz, 1H), 7.69 (s, 1H), 7.30−7.28 (m, 1H), 7.26−7.25 (m, 4H), 7.23−7.21 (m, 5H), 7.17−7.15 (m, 4H), 7.06 (s, 1H), 6.98 (d, J = 8.0 Hz, 2H), 3.95 (s, 2H), 2.37 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 145.7, 140.1, 138.8, 136.4, 134.1, 132.6, 131.7, 130.6, 130.4, 130.3, 129.8, 129.7, 129.6, 129.5, 128.9, 128.5, 128.4, 128.1, 127.2, 126.1, 125.7, 124.2, 121.9, 117.4, 114.1, 112.3, 36.0, 21.5, 21.3; HRMS (ESI) calcd for$[C_{36}H_{27}NO]$ requires $[M]^+$ 489.2093, found $[M]^+$ 489.2093.

4-Benzyl-1,2-bis(4-methoxyphenyl)-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4f). The product was obtained as orange crystals (101 mg, 78%): mp 182−184 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.84 (d, J = 7.3 Hz, 1H), 7.76 (s, 1H), 7.40−7.35 (m, 2H), 7.32−7.30 (m, 5H), 7.29−7.26 (m, 1H), 7.24−7.19 (m, 4H), 7.14 (s, 1H), 6.97−6.95 (m, 2H), 6.79−6.77 (m, 2H), 4.02 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 159.9, 158.4, 145.6, 140.1, 139.3, 134.1, 133.2, 132.5, 131.9, 130.5, 129.6, 128.6, 128.5, 128.3, 127.3, 126.1, 125.8, 125.1, 124.9, 124.2, 121.8, 117.3, 115.9, 114.4, 112.9, 112.1, 55.3, 55.0, 36.0; HRMS (ESI) calcd for $[C_{36}H_{27}NO_3]$ requires $[M]^+$ 521.1991, found $[M]^+$ 521.1992.

4-Benzyl-1,2-di(thiophen-3-yl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4g). The product was obtained as brown crystals (85 mg, 72%): mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82−7.79 (m, 1H), 7.73 (s, 1H), 7.53−7.51 (m, 2H), 7.33−7.30 (m, 4H), 7.28−7.26 (m, 3H), 7.20−7.18 (m, 2H), 7.16−7.14 (m, 1H), 7.12−7.08 (m, 3H), 3.99 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 145.5, 140.0, 134.0, 133.0, 132.6, 130.5, 130.2, 129.9, 129.6, 129.2, 128.7,

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128.5, 127.9, 127.4, 127.2, 126.1, 125.6, 125.5, 124.8, 124.5, 123.3, 121.7, 116.9, 36.2; HRMS (ESI) calcd for $[C_{30}H_{19}NOS_2]$ requires $[M]^+$ 473.0908, found $[M]^+$ 473.0909.

4-Benzyl-1,2-diphenyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4h). The product was obtained as orange crystals (86 mg, 75%): mp 166−168 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.0 Hz, 1H), 7.71 (s, 1H), 7.40−7.34 (m, 4H), 7.33−7.30 (m, 3H), 7.28−7.21 (m, 6H), 7.19−7.12 (m, 5H), 7.08 (s, 1H), 3.96 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 145.7, 140.0, 134.0, 132.7, 131.9, 130.8, 130.5, 129.6, 129.2, 129.0, 128.9, 128.6, 128.5, 127.4, 127.3, 126.9, 126.1, 125.8, 124.3, 121.9, 117.4, 112.2, 36.0; HRMS (ESI) calcd for $[C_{34}H_{23}NO]$ requires $[M]^+$ 461.1780, found $[M]^+$ 461.1781.

4-Benzyl-1,2-di-*m*-tolyl-3-pyrrolo[3,2,1-*de*]acridin-3-one (4i). The product was obtained as brown crystals (83 mg, 68%): mp 100−102 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 7.3 Hz, 1H), 7.69 (s, 1H), 7.31−7.29 (m, 1H), 7.26−7.23 (m, 7H), 7.22−7.20 (m, 2H), 7.17−7.12 (m, 4H), 7.09−7.06 (m, 2H), 6.93 (d, J = 7.3 Hz, 1H), 3.96 (s, 2H), 2.22 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 145.7, 140.1, 138.5, 136.5, 134.1, 132.7, 132.6, 132.4, 131.5, 130.9, 130.7, 130.4, 129.7, 129.5, 129.2, 129.0, 128.7, 128.5, 128.3, 128.1, 127.9, 127.7, 127.2, 126.5, 126.1, 125.8, 124.2, 121.9, 117.4, 116.3, 112.3, 36.0, 21.5, 21.4; HRMS (ESI) calcd for $[C_{36}H_{27}NO]$ requires $[M]^+$ 489.2093, found $[M]^+$ 489.2091.

1,2-Diphenyl-4-propyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4j). The product was obtained as orange crystals (70 mg, 68%): mp 160−162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, J = 8.0 Hz, 1H), 7.84 (s, 1H), 7.45−7.40 (m, 5H), 7.39−7.36 (m, 3H), 7.31−7.28 (m, 1H), 7.25−7.22 (m, 2H), 7.20−7.18 (m, 2H), 7.09 (s, 1H), 2.66 (t, J = 8.0 Hz, 2H), 1.73−1.63 (m, 2H), 1.00 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.5, 146.2, 133.9, 132.9, 132.8, 132.7, 131.9, 130.8, 130.4, 130.23, 130.18, 129.4, 129.1, 128.9, 128.8, 127.7, 127.5, 127.3, 126.8, 126.6, 125.8, 124.2, 122.2, 117.3, 112.3, 32.6, 22.3, 14.1; HRMS (ESI) calcd for $[C_{30}H_{23}NO]$ requires $[M]^+$ 413.1780, found $[M]^+$ 413.1780.

1,2-Bis(4-methoxyphenyl)-8-methyl-4-phenoxy-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (4k). The product was obtained as brown crystals (107 mg, 80%): mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.55 (s, 1H), 7.31−7.24 (m, 6H), 7.19−7.18 (m, 1H), 7.09−7.06 (m, 4H), 6.91 (d, J = 8.7 Hz, 2H), 6.78 (s, 1H), 6.68 (d, J = 8.8 Hz, 2H), 3.81 (s, 3H), 3.68 (s, 3H), 2.35 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 160.0, 158.4, 156.5, 155.9, 134.0, 133.2, 132.0, 131.9, 131.2, 131.0, 130.2, 129.7, 129.5, 128.4, 126.9, 125.8, 124.8, 124.7, 123.8, 121.0, 119.4, 117.1, 114.4, 112.8, 112.6, 111.7, 55.3, 55.0, 20.8; HRMS (ESI) calcd for $[C_{36}H_{27}NO_4]$ requires $[M]^+$ 537.1940, found $[M]^+$ 537.1941.

8-Methyl-4-phenoxy-1,2-di(thiophen-3-yl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4l). The product was obtained as orange crystals (92 mg, 75%): mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (m, 2H), 7.62−7.58 (m, 2H), 7.40−7.36 (m, 3H), 7.26−7.21 (m, 3H), 7.18−7.14 (m, 3H), 7.12−7.09 (m, 2H), 6.84 (s, 1H), 2.43 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.3, 155.9, 134.4, 133.0, 132.2, 131.8, 131.6, 131.3, 130.2, 129.8, 129.6, 129.3, 128.0, 127.3, 127.0, 125.9, 125.7, 124.7, 124.0, 123.2, 120.9, 119.5, 116.6, 112.4, 111.6, 20.8; HRMS (ESI) calcd for $[C_{30}H_{19}NO_2S_2]$ requires $[M]^+$ 489.0857, found $[M]^+$ 489.0858.

8-Methyl-4-propyl-1,2-di-*p*-tolyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4m). The product was obtained as brown crystals (82 mg, 72%): mp 152−154 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.70 (s, 1H), 7.61 (s, 1H), 7.32 (s, 1H), 7.23−7.21 (m, 4H), 7.18−7.14 (m, 3H), 7.06 (dd, J = 2.2, 9.5 Hz, 1H), 6.97 (d, J = 8.0 Hz, 2H), 2.58 (t, J = 8.0 Hz, 2H), 2.37 (s, 6H), 2.22 (s, 3H), 1.63−1.57 (m, 2H), 0.93 (t, J = 8.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.4, 146.2, 139.3, 138.7, 136.2, 133.8, 132.2, 131.8, 130.9, 130.7, 130.0, 129.9, 129.60, 129.59, 128.7, 128.1, 127.4, 126.3, 126.1, 126.0, 122.1, 117.3, 114.0, 31.9, 22.7, 22.4, 21.5, 21.3, 14.1; HRMS (ESI) calcd for $[C_{33}H_{29}NO]$ requires $[M]^+$ 455.2249, found $[M]^+$ 455.2250.

4-Benzyl-1,2-bis(4-methoxyphenyl)-8-methyl-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (4n). The product was obtained as orange crystals (105 mg, 78%): mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.69 (s, 1H), 7.61 (s, 1H), 7.34 (s, 1H), 7.32−7.30 (m, 5H), 7.29−7.26 (m, 2H), 7.24−7.20 (m, 2H), 7.14−7.11 (m, 2H), 6.95 (d, J = 8.6 Hz, 2H), 6.78 (d, J = 9.1 Hz, 2H), 4.02 (s, 2H), 3.87 (s, 3H), 3.76 (s, 3H), 2.41 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 159.9, 158.3, 145.5, 140.2, 139.3, 133.9, 133.2, 132.4, 132.0, 131.2, 129.9, 129.6, 128.6, 128.4, 127.1, 126.0, 125.8, 125.2, 125.0, 123.9, 123.4, 121.7, 117.1, 115.9, 114.3, 114.0, 112.9, 112.0, 55.3, 55.1, 36.0, 22.7; HRMS (ESI) calcd for $[C_{37}H_{29}NO_3]$ requires $[M]^+$ 535.2147, found $[M]$ 535.2149.

8-Methoxy-4-phenoxy-1,2-di-*p*-tolyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4o). The product was obtained as brown crystals (107 mg, 82%): mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1H), 7.37 (t, J = 8.04 Hz, 2H), 7.32−7.29 (m, 4H), 7.27−7.25 (m, 3H), 7.23 (d, J = 2.9 Hz, 1H), 7.17−7.13 (m, 3H), 7.02 (d, J = 8.0 Hz, 2H), 6.92 (dd, J = 2.9, 9.5 Hz, 1H), 6.84 (s, 1H), 3.86 (s, 3H), 2.46 (s, 3H), 2.28 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.5, 156.2, 155.8, 139.0, 136.4, 132.8, 131.8, 130.9, 130.8, 130.7, 130.5, 129.8, 128.6, 128.1, 127.0, 126.4, 126.0, 123.9, 121.5, 119.5, 118.7, 114.2, 112.6, 111.4, 110.5, 55.6, 21.6, 21.3; HRMS (ESI) calcd for $[C_{36}H_{27}NO_3]$ requires $[M]^+$ 521.1991, found $[M]^+$ 521.1992.

8-Methoxy-1,2-bis(4-methoxyphenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4p). The product obtained as orange crystals (117 mg, 85%): mp 188−190 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.63 (s, 1H), 7.32−7.28 (m, 2H), 7.28−7.25 (m, 3H), 7.24−7.23 (m, 2H), 7.15 (d, J = 2.9 Hz, 1H), 7.10−7.06 (m, 3H), 6.91 (d, J = 8.8 Hz, 2H), 6.86 (dd, J = 2.9, 9.5 Hz, 1H), 6.76 (s, 1H), 6.68 (d, J = 9.5 Hz, 2H), 3.81 (s, 3H), 3.78 (s, 3H), 3.68 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 160.0, 158.4, 156.4, 156.1, 155.8, 133.2, 132.0, 130.8, 130.1, 129.8, 128.6, 128.4, 127.0, 126.5, 124.8, 124.7, 123.9, 121.4, 119.5, 118.8, 118.6, 114.5, 112.8, 112.4, 111.4, 110.5, 55.5, 55.3, 55.0; HRMS (ESI) calcd for $[C_{36}H_{27}NO_5]$ requires $[M]^+$ 553.1889, found $[M]^+$ 553.1890.

8-Methoxy-4-phenoxy-1,2-di(thiophen-3-yl)-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (4q). The product was obtained as dark-brown crystals (96 mg, 76%): mp 190−192 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73−7.71 (m, 1H), 7.69 (s, 1H), 7.60−7.58 (m, 1H), 7.40−7.34 (m, 3H), 7.29−7.25 (m, 1H), 7.22−7.19 (m, 2H), 7.17−7.13 (m, 3H), 7.10−7.09 (m, 2H), 6.97 (dd, J = 2.3, 8.8 Hz, 1H), 6.82 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 156.2, 156.0, 139.3, 133.6, 133.0, 132.1, 130.2, 130.0, 129.8, 129.3, 128.0, 127.4, 127.2, 126.0, 125.6, 124.9, 124.6, 124.1, 123.9, 123.4, 123.3, 121.0, 119.6, 116.9, 114.1, 111.3, 55.6; HRMS (ESI) calcd for $[C_{30}H_{19}NO_3S_2]$ requires $[M]^+$ 505.0806, found $[M]^+$ 505.0807.

8-Methoxy-4-phenoxy-1,2-di-*m*-tolyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4r). The product was obtained as brown crystals (93 mg, 72%): mp 116−118 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1H), 7.34−7.30 (m, 2H), 7.27−7.25 (m, 2H), 7.22−7.21 (m, 1H), 7.168−7.161 (m, 4H), 7.12−7.07 (m, 4H), 7.00 (t, J = 8.0 Hz, 1H), 6.93−6.91 (m, 1H), 6.84 (dd, J = 2.9, 9.6 Hz, 1H), 6.73 (s, 1H), 3.79 (s, 3H), 2.28 (s, 3H), 2.19 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 155.9, 145.5, 136.6, 133.1, 132.5, 131.7, 131.0, 130.9, 130.8, 129.9, 129.8, 129.7, 129.1, 128.8, 128.6, 128.1, 127.8, 127.7, 127.1, 126.3, 125.2, 124.1, 123.1, 121.6, 119.8, 118.8, 118.7, 112.5, 110.8, 110.5, 55.6, 22.6, 21.4; HRMS (ESI) calcd for $[C_{36}H_{27}NO_3]$ requires $[M]^+$ 521.1991, found $[M]^+$ 521.1992.

8-Methoxy-4-phenoxy-1,2-diphenyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4s). The product was obtained as brown crystals (92 mg, 75%): mp 184−186 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.41−7.27 (m, 9H), 7.17−7.06 (m, 8H), 6.83−6.80 (m, 1H), 6.74 (s, 1H), 3.76 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.3, 156.1, 155.8, 132.6, 132.3, 131.9, 130.9, 130.8, 130.5, 129.8, 129.1, 128.9, 128.5, 128.4, 127.2, 127.0, 126.9, 126.6, 124.0, 121.5, 119.5, 118.7, 118.5, 112.5, 111.2, 110.5, 55.5; HRMS (ESI) calcd for $[C_{34}H_{23}NO_3]$ requires $[M]^+$ 493.1678, found $[M]^+$ 493.1679.

4-Benzyl-8-methoxy-1,2-di-*p*-tolyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (4t). The product was obtained as brown crystals (101 mg, 78%): mp 180−182 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.59 (s, 1H), 7.28−7.24 (m, 3H), 7.22−7.19 (m, 4H), 7.17−7.15 (m, 3H), 7.14−7.13 (m, 3H), 7.04 (s, 1H), 6.98 (d, J = 8.0 Hz, 2H), 6.83 (dd, J = 2.9, 9.5 Hz, 1H), 3.95 (s, 2H), 3.77 (s, 3H), 2.36 (s, 3H), 2.22 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 155.6, 145.8, 140.2,

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138.8, 136.3, 132.0, 131.8, 130.6, 130.0, 129.9, 129.8, 129.7, 129.6, 129.4, 128.9, 128.4, 128.38, 128.1, 127.0, 126.6, 126.0, 122.2, 118.8, 118.6, 112.0, 110.9, 55.5, 36.0, 21.5, 21.3; HRMS (ESI) calcd for $[C_{37}H_{29}NO_2]$ requires $[M]^+$ 519.2198, found $[M]^+$ 519.2199.

4-Benzyl-8-methoxy-1,2-di-*m*-tolyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4u). The product was obtained as light-brown crystals (90 mg, 70%): mp 102−104 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.25−7.22 (m, 5H), 7.18−7.14 (m, 8H), 7.08−7.04 (m, 2H), 6.93 (d, J = 7.3 Hz, 1H), 6.84 (d, J = 8.8 Hz, 1H), 6.85−6.83 (m, 1H), 3.97 (s, 2H), 3.79 (s, 3H), 2.26 (s, 3H), 2.18 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 155.7, 145.8, 140.2, 135.6, 134.2, 134.0, 132.4, 131.5, 130.9, 130.8, 129.7, 129.2, 129.0, 128.7, 128.5, 128.4, 128.1, 128.0, 127.6, 127.1, 126.7, 126.5, 126.4, 126.1,123.0, 121.1, 118.7, 116.1, 110.9, 55.6, 36.0, 21.5, 21.4; HRMS (ESI) calcd for $[C_{37}H_{29}NO_2]$ requires $[M]^+$ 519.2198, found $[M]^+$ 519.2199.

4-Benzyl-8-methoxy-1,2-diphenyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (4v). The product was obtained as brown crystals (90 mg, 74%): mp 192−194 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (s, 1H), 7.39−7.37 (m, 1H), 7.35−7.33 (m, 1H), 7.33−7.29 (m, 5H), 7.25−7.24 (m, 3H), 7.17−7.15 (m, 4H), 7.13−7.11 (m, 3H), 7.06 (s, 1H), 6.82 (dd, J = 2.9, 9.5 Hz, 1H), 3.96 (s, 2H), 3.77 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.8, 155.8, 145.8, 140.1, 139.2, 132.83, 132.78, 132.1, 131.9, 130.8, 130.1, 129.6, 129.0, 128.9, 128.8, 128.6, 128.4, 127.3, 127.0, 126.8, 126.1, 122.2, 118.8, 118.5, 114.2, 112.1, 111.0, 55.6, 36.1; HRMS (ESI) calcd for $[C_{35}H_{25}NO_2]$ requires $[M]^+$ 491.1885, found $[M]^+$ 491.1885.

4-Phenoxy-2-phenyl-1-(*p*-tolyl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (5a and 6a). The product was obtained as a brown solid (83 mg, 70%) in the mixture of regioisomers (53:47): mp 220−222 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.0 Hz, 2H), 7.69 (s, 2H), 7.42−7.34 (m, 5H), 7.32−7.27 (m, 8H), 7.24−7.21 (m, 5H), 7.19−7.15 (m, 3H), 7.13−7.06 (m, 8H), 6.93 (d, J = 8.0 Hz, 2H), 6.77 (d, J = 5.8 Hz, 2H), 2.37 (s, 3H), 2.19 (s, 2.64H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 174.2, 156.3, 156.0, 136.5, 133.7, 133.6, 132.8, 132.4, 132.0, 131.7, 131.54, 131.49, 131.0, 130.8, 130.7, 130.14, 130.11, 129.8, 129.7, 129.5, 129.4, 129.1, 129.0, 128.9, 128.7, 128.0, 127.3, 127.1, 127.0, 126.9, 125.7, 124.4, 124.1, 124.0, 121.2, 119.6, 119.5, 117.4, 117.3, 112.8, 112.7, 111.5, 111.3, 21.5, 21.2; HRMS (ESI) calcd for $[C_{34}H_{23}NO_2]$ requires $[M]^+$ 477.1729, found $[M]^+$ 477.1730.

1-(4-Nitrophenyl)-4-phenoxy-2-phenyl-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (5b and 6b). The product was obtained as a yellow solid (86 mg, 68%) in the mixture of regioisomers (72:28): mp 274−276 °C;^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.96 (d, J = 8.8 Hz, 1H), 7.85−7.74 (m, 3H), 7.54 (d, J = 8.8 Hz, 2H), 7.50−7.47 (m, 1H), 7.46−7.40 (m, 1H), 7.38−7.29 (m, 6H), 7.28−7.21 (m, 4H), 7.18−7.13 (m, 4H), 7.11−7.06 (m, 3H), 6.80−6.76 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.3, 174.2, 156.2, 156.0, 147.8, 146.5, 139.7, 139.5, 133.1, 132.8, 132.2, 131.9, 131.8, 131.7, 131.6, 131.5, 130.7, 130.6, 130.4, 130.3, 129.9, 129.8, 129.6, 129.4, 127.9, 127.7, 127.5, 127.3, 125.94, 125.91, 124.9, 124.4, 124.3, 124.0, 122.5, 121.4, 121.2, 119.8, 117.3, 117.1, 111.2, 111.1; HRMS (ESI) calcd for $[C_{33}H_{20}N_2O_4]$ requires $[M]^+$ 508.1423, found $[M]^+$ 508.1424.

2-(4-Methoxyphenyl)-1-(4-nitrophenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (5c and 6c). The product was obtained as brown solid in the mixture of regioisomers (66:34), which was separated by HPLC. The yield of compound **5c** (major) (43 mg, 66%): mp 218−220 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.55 (d, J = 8.8 Hz, 2H), 7.40−7.27 (m, 4H), 7.24−7.22 (m, 1H),7.19−7.18 (m, 2H), 7.14−7.08 (m, 3H), 6.80 (s, 1H), 6.71 (d, J = 8.8 Hz, 2H), 3.71 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 173.0, 156.2, 156.1, 133.2, 132.8, 132.0, 131.9, 130.5, 130.1, 129.9, 129.6, 129.3, 128.9, 127.2, 127.1, 125.9, 125.6, 124.9, 124.3, 124.1, 121.4, 119.7, 119.5, 117.2, 113.2, 111.3, 107.9, 55.1; HRMS (ESI) calcd for $[C_{34}H_{22}N_2O_5]$ requires $[M]^+$ 538.1529, found $[M]^+$ 538.1530.

1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (6c) (Minor). The product was obtained as a brown solid (22 mg, 34%): mp >280 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.0 (d, J = 8.7 Hz, 2H), 7.83 (d, J = 7.3 Hz, 1H), 7.77 (s, 1H), 7.51 (d, J = 8.7 Hz, 2H), 7.39−7.31 (m, 5H), 7.29−7.26 (m, 2H), 7.15−7.09 (m, 3H), 6.95 (d, J = 8.0 Hz, 2H), 6.79 (s, 1H), 3.85 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 160.6, 156.0, 146.5, 139.9, 133.8, 133.0, 131.7, 130.7, 130.4, 129.9, 129.8, 127.8, 126.5, 124.9, 124.4, 123.9, 123.7, 122.6, 121.3, 119.8, 117.4, 114.8, 112.3, 111.1, 55.3; HRMS (ESI) calcd for $[C_{34}H_{22}N_2O_5]$ requires $[M]^+$ 538.1529, found $[M]^+$ 538.1530.

1-(4-Nitrophenyl)-4-phenoxy-2-(thiophen-3-yl)-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (5d and 6d). The product was obtained as a yellow solid in the mixture of regioisomers (53:47). The yield of compound **5d** (major) (33 mg, 53%): mp 115−120 °C; ^{1}H NMR(400 MHz, $CDCl_3$) δ 8.03 (d, J = 8.7 Hz, 2H), 7.84 (d, J = 8.0 Hz, 1H), 7.78 (s, 1H), 7.54−7.52 (m, 3H), 7.42−7.40 (m, 1H), 7.38−7.36 (m, 2H), 7.34−7.32 (m, 2H), 7.28−7.27 (m, 1H), 7.17−7.13 (m, 2H), 7.10 (d, J = 8.7 Hz, 2H), 6.79 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.2, 156.1, 156.0, 146.7, 139.7, 133.7, 131.5, 130.3, 130.1, 130.0, 129.9, 128.3, 127.9, 127.7, 127.5, 126.3, 125.9, 125.1, 124.4, 122.6, 121.2, 121.1, 119.8, 117.0, 112.4, 111.1; HRMS (ESI) calcd for $[C_{31}H_{18}N_2O_4S]$ requires $[M]^+$ 514.0987, found $[M]^+$ 514.0988.

2-(4-Nitrophenyl)-4-phenoxy-1-(thiophen-3-yl)-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (6d). The product was obtained as a brown solid (29 mg, 47%): mp >280 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.8 Hz, 2H), 7.85 (d, J = 8.0 Hz, 1H), 7.77 (s, 1H), 7.62 (d, J = 8.8 Hz, 2H), 7.40−7.36 (m, 2H), 7.34−7.33 (m, 2H), 7.31−7.26 (m, 2H), 7.17−7.14 (m, 2H), 7.11−7.08 (m, 2H), 6.93 (d, J = 5.1 Hz, 1H), 6.80 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 171.5, 140.1, 132.9, 130.6, 130.3, 129.9, 129.7, 129.4, 128.4, 127.3, 127.2, 126.4, 125.9, 125.7, 125.5, 125.1, 125.0, 124.4, 124.3, 124.1, 121.8, 121.7, 121.3, 119.8, 117.0; HRMS (ESI) calcd for $[C_{31}H_{18}N_2O_4S]$ requires $[M]^+$ 514.0987, found $[M]^+$ 514.0988.

4-Benzyl-1-(4-nitrophenyl)-2-phenyl-3*H*-pyrrolo[3,2,1-*de*]-acridin-3-one (5e and 6e). The product was obtained as a yellow solid (68 mg, 60%) in the mixture of regioisomers (73:27): mp 276−278 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, J = 8.0 Hz, 2H), 8.06 (d, J = 8.8 Hz, 1H), 7.92−7.87 (m, 1H), 7.83−7.82 (m, 1H), 7.56 (d, J = 8.8 Hz, 2H), 7.54−7.50 (m, 1H), 7.48−7.44 (m, 1H), 7.42−7.40 (m, 1H), 7.39−7.34 (m, 1H), 7.33−7.30 (m, 6H), 7.30−7.27 (m, 4H), 7.27−7.24 (m, 4H), 7.24−7.21 (m, 2H), 7.17 (s, 1H), 4.01 (s, 0.8H), 4.00 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 179.9, 147.7, 145.8, 139.8, 139.7, 133.4, 132.7, 132.5, 132.0, 131.9, 131.7, 131.6, 130.9, 130.7, 130.6, 130.5, 130.4, 130.0, 129.8, 129.65, 129.60, 129.5, 129.3, 128.9, 128.8, 128.5, 128.1, 127.7, 127.6, 127.5, 127.4, 126.2, 125.9, 124.8, 123.9, 122.6, 122.0, 117.3, 117.1, 112.7, 36.0, 35.9; HRMS (ESI) calcd for $[C_{34}H_{22}N_2O_3]$ requires $[M]^+$ 506.1630, found $[M]^+$ 506.1631.

4-Benzyl-1-(4-nitrophenyl)-2-(4-methoxyphenyl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (5f and 6f). The product was obtained as a yellow solid in the mixture of regioisomers (64:36). The yield of compound **5f** (major) (39 mg, 64%): mp 172−175 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.22 (d, J = 8.8 Hz, 2H), 7.85 (d, 8.0 Hz, 1H), 7.76 (s, 1H), 7.51 (d, J = 8.8 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.31−7.29 (m, 1H), 7.27−7.23 (m, 4H), 7.19−7.17 (m, 2H), 7.15 (d, J = 8.8 Hz, 2H), 7.11 (s, 1H), 6.74 (d, J = 8.8 Hz, 2H), 3.95 (s, 2H), 3.72 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 180.0, 158.9, 147.7, 145.8, 139.9, 133.4, 132.7, 131.9, 131.4, 130.9, 130.3, 129.8, 129.6, 128.9, 128.5, 127.6, 127.2, 126.2, 125.9, 124.8, 124.0, 123.4, 122.0, 117.2, 113.3, 112.7, 55.1, 36.0; HRMS (ESI) calcd for $[C_{35}H_{24}N_2O_4]$ requires $[M]^+$ 536.1736, found $[M]^+$ 536.1737.

1-(4-Methoxyphenyl)-2-(4-nitrophenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (6f). The product was obtained as a brown solid (22g, 36%): mp 264−266 °C; ^{1}H NMR (400 MHz, CDCl3) δ 8.03 (d, J = 8.8 Hz, 2H), 7.84−7.82 (m, 1H), 7.78 (s, 1H), 7.49 (d, J = 8.8 Hz, 2H), 7.37−7.34 (m, 2H), 7.31−7.28 (m, 1H), 7.27−7.26 (m, 4H), 7.19 (s, 3H), 7.15 (s,1H), 6.93 (d, J = 8.0 Hz, 2H), 3.96 (s, 2H), 3.83 (s, 3H); ^{13}C NMR (100 MHz, CDCl3) δ 178.4, 146.5, 145.5, 138.5, 137.6, 134.6, 134.2, 133.0, 131.7, 131.5, 131.2, 130.8, 130.0, 129.6, 129.1, 128.9, 128.6, 128.1, 126.6, 126.2, 124.3, 122.6, 120.6, 117.3, 114.7, 55.4, 36.1; HRMS (ESI) calcd for $[C_{35}H_{24}N_2O_4]$ requires $[M]^+$ 536.1736, found $[M]^+$ 536.1737.

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4-Benzyl-1-(4-nitrophenyl)-2-(thiophen-3-yl)-3*H*-pyrrolo-[3,2,1-*de*]acridin-3-one (5g and 6g). The product was obtained as a yellow solid (77 mg, 60%) in the mixture of regioisomers (50:50): mp 278−280 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.28 (d, J = 8.8 Hz, 2H), 8.05 (d, J = 8.8 Hz, 2H), 7.86−7.83 (m, 2H), 7.77 (d, J = 6.6 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H), 7.51−7.49 (m, 3H), 7.39−7.36 (m, 4H), 7.30−7.23 (m, 13H), 7.16−7.12 (m, 4H), 6.98−6.96 (m, 1H), 3.97 (s, 2H), 3.95 (s, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 179.9, 179.8, 149.6, 148.3, 148.0, 146.8, 146.7, 146.6, 146.5, 145.7, 145.5, 144.6, 140.2, 140.1, 139.8, 139.7, 134.5, 134.0, 133.4, 132.8, 131.6, 131.4, 131.0, 130.7, 130.3, 130.0, 129.9, 129.6, 128.90, 128.5, 128.2, 127.7, 127.5, 127.2, 126.6, 126.3, 126.2, 125.9, 124.9, 124.8, 124.2, 124.1, 122.6, 121.9, 117.0, 36.1, 36.0; HRMS (ESI) calcd for $[C_{32}H_{20}N_2O_3S]$ requires $[M]^+$ 512.1195, found $[M]^+$ 512.1197.

8-Methoxy-2-(4-methoxyphenyl)-1-(4-nitrophenyl)-4-phenoxy-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (5h and 6h). The product was obtained as a yellow solid (102 mg, 72%) in the mixture of regioisomers (50:50): mp 258−260 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.23 (d, J = 8.8 Hz, 2H), 7.99 (d, J = 8.8 Hz, 2H), 7.70−7.69 (m, 2H), 7.54−7.49 (m, 4H), 7.35−7.30 (m, 4H), 7.29−7.25 (m, 3H), 7.21−7.20 (m, 1H), 7.17−7.15 (m, 2H), 7.13−7.12 (m, 2H), 7.10−7.07 (m, 6H), 6.95−6.89 (m, 4H), 6.78 (s, 2H), 6.69 (d, J = 8.8 Hz, 2H), 3.84 (s, 3H), 3.82 (s, 3H), 3.81 (s, 3H), 3.70 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 174.0, 160.5, 158.9, 156.1, 156.0, 147.7, 146.4, 140.0, 139.8, 133.0, 132.8, 132.0, 131.7, 129.9, 127.8, 127.3, 127.23, 127.20, 126.7, 124.3, 124.2, 124.1, 123.6, 122.6, 121.7, 121.5, 119.7, 119.6, 119.1, 118.9, 118.6, 118.4, 114.8, 114.5, 113.2, 112.9, 111.3, 111.1, 111.0, 110.8, 55.7, 55.6, 55.4, 55.1; HRMS (ESI) calcd for $[C_{35}H_{26}N_2O_5]$ requires $[M]^+$ 568.1634, found $[M]^+$ 568.1635.

4-Phenoxy-1-(*p*-tolyl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (7a). The product was obtained as a brown solid (70 mg, 70%): mp 180−185 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 1H), 8.03−7.99 (m, 3H), 7.88 (d, J = 7.3 Hz, 1H), 7.76−7.71 (m, 2H), 7.50 (t, J = 6.8 Hz, 1H), 7.41−7.37 (m, 2H), 7.24−7.19 (m, 3H), 7.17−7.15 (m, 2H), 6.80 (s, 1H), 2.37 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.7, 156.6, 156.2, 137.7, 132.1, 131.7, 131.1, 130.9, 130.3, 130.0, 129.8, 129.0, 128.7, 126.0, 125.0, 124.5, 124.1, 121.2, 119.7, 114.8, 113.5, 112.5, 111.0, 21.3; HRMS (ESI) calcd for $[C_{28}H_{19}NO_2]$ requires $[M]^+$ 401.1416, found $[M]^+$ 402.1470.

8-Methyl-4-phenoxy-1-(*p*-tolyl)-3*H*-pyrrolo[3,2,1-*de*]acridin-3-one (7b). The product was obtained as a brown solid (75 mg, 75%): mp 192−196 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98−7.93 (m, 3H), 7.65−7.62 (m, 2H), 7.52 (d, J = 8.8 Hz, 1H), 7.33 (t, J = 8.4 Hz, 2H), 7.20−7.19 (m, 4H), 7.13−7.09 (m, 2H), 6.77 (s, 1H), 2.48 (s, 3H), 2.33 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 174.1, 156.5, 156.4, 140.5, 138.5, 137.7, 131.9, 130.02, 129.97, 129.8, 129.5, 129.0, 128.8, 128.7, 125.9, 124.1, 121.2, 119.7, 114.6, 113.5, 112.3, 111.1, 21.3, 21.2; HRMS (ESI) calcd for $[C_{29}H_{21}NO_2]$ requires $[M]^+$ 415.1572, found $[M + H]^+$ 416.1625.

8-Phenoxy-1,2-diphenyl-9*H*-pyrrolo[3,2,1-*ij*]quinolin-9-one (8). The product was obtained as a white solid (67 mg, 65%): mp 150−155 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.67−8.65 (m, 1H), 7.81 (d, J = 8.08 Hz, 1H), 7.61 (s. 1H), 7.38−7.34 (m, 2H), 7.33−7.26 (m, 1H), 7.19−7.13 (m, 3H), 7.09−7.05 (m, 3H), 7.04−7.02 (m, 2H), 7.00−6.97 (m, 2H), 6.89−6.84 (m, 1H), 6.43 (d, J = 8.08 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.8, 150.1, 148.7, 146.7, 145.6, 135.3, 134.0, 130.9, 130.8, 130.2, 129.7, 129.3, 129.2, 128.6, 128.2, 127.6, 124.8, 123.4, 122.4, 120.9, 119.7, 119.0, 115.6, 114.8, 113.5, 111.8, 111.7; HRMS (ESI) calcd for $[C_{29}H_{19}NO_2]$ requires $[M]^+$ 413.1416, found $[M]^+$ 413.1415.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and copies of HRMS, ^{1}H and ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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■ REFERENCES

(1) (a) El-Sabbagh, O. I.; Rady, H. M. *Eur. J. Med. Chem.* **2009**, *44*, 3680. (b) Demeunynck, M.; Charmantray, F.; Martelli, A. *Curr. Pharm. Des.* **2001**, *7*, 1703. (c) Charmantray, F.; Demeunynck, M.; Carrez, D.; Croisy, A.; Lansiaux, A.; Bailly, C.; Colson, P. *J. Med. Chem.* **2003**, *46*, 967. (d) Pinskaya, M.; Romanova, E.; Volkov, E.; Deprez, E.; Leh, H.; Brochon, J.-C.; Mouscadet, J.-F.; Gottikh, M. *Biochemistry* **2004**, *43*, 8735. (e) Wainwright, M. J. *Antimicrob. Chemother.* **2001**, *47*, 1.

(2) (a) Charmantray, F.; Demeunynck, M.; Carrez, D.; Croisy, A.; Lansiaux, A.; Bailly, C.; Colson, P. *J. Med. Chem.* **2003**, *46*, 967. (b) Shochet, N. R.; Rudi, A.; Kashman, Y.; Hod, Y.; El-Maghrabi, M. R.; Spector, I. *J. Cell. Physiol.* **1993**, *157*, 481.

(3) (a) Chilin, A.; Marzaro, G.; Marzano, C.; Via, L. D.; Ferlin, M. G.; Pastorini, G.; Guiotto, A. *Bioorg. Med. Chem.* **2009**, *17*, 523. (b) Atwell, G. J.; Cain, B. F.; Seelye, R. N. *J. Med. Chem.* **1972**, *15*, 611. (c) Denny, W. A.; Atwell, G. J.; Baguley, B. C. *J. Med. Chem.* **1983**, *26*, 1625.

(4) Inman, W. D.; O'Neill-Johnson, M.; Crews, P. *J. Am. Chem. Soc.* **1990**, *112*, 1.

(5) Gimenez-Arnau, E.; Missailidis, S.; Stevens, M. F. G. *Anti-Cancer Drug Des.* **1998**, *13*, 431.

(6) McCarthy, P. J.; Pitts, T. P.; Gunawardana, G. P.; Kelly-Borges, M.; Pomponi, S. A. *J. Nat. Prod.* **1992**, *55*, 1664.

(7) (a) Tasdemir, D.; Marshall, K. M.; Mangalindan, G. C.; Concepción, G. P.; Barrows, L. R.; Harper, M. K.; Ireland, C. M. *J. Org. Chem.* **2001**, *66*, 3246. (b) McDonald, L. A.; Eldredge, G. S.; Barrows, L. R.; Ireland, C. M. *J. Med. Chem.* **1994**, *37*, 3819. (c) Matsumoto, S.; Biggs, J.; Copp, B. R.; Holden, J. A.; Barrows, L. R. *Chem. Res. Toxicol.* **2003**, *16*, 113.

(8) Dias, N.; Vezin, H.; Lansiaux, A.; Bailly, C. *Top. Curr. Chem.* **2005**, *253*, 89.

(9) (a) West, R. R.; Mayne, C. L.; Ireland, C. M.; Brinen, L. S.; Clardy, J. *Tetrahedron Lett.* **1990**, *31*, 3271. (b) Smith, C. J.; Venables, D. A.; Hopmann, C.; Salomon, C. E.; Jompa, J.; Tahir, A.; Faulkner, D. J.; Ireland, C. M. *J. Nat. Prod.* **1997**, *60*, 1048. (c) Ford, P. W.; Davidson, B. S. *J. Nat. Prod.* **1997**, *60*, 1051. (d) Thale, Z.; Johnson, T.; Tenney, K.; Wenzel, P. J.; Lobkovsky, E.; Clardy, J.; Media, J.; Pietraszkiewicz, H.; Valeriote, F. A.; Crews, P. *J. Org. Chem.* **2002**, *67*, 9384. (e) Ralifo, P.; Sanchez, L.; Nadine, C. G.; Karen, T.; Scott Lokey, R.; Theodore, R. H.; Frederick, A. V.; Crews, P. *J. Nat. Prod.* **2007**, *70*, 95.

(10) (a) Hentschel, U.; Schmid, M.; Wagner, M.; Fieseler, L.; Gernert, C.; Hacker, J. *FEMS Microbiol. Ecol.* **2001**, *35*, 305. (b) Kennedy, J.; Baker, P.; Piper, C.; Cotter, P. D.; Walsh, M.; Mooij, M. J.; Bourke, M. B.; Rea, M. C.; O'Connor, P. M.; Ross, R. P.; Hill, C.; O'Gara, F.; Marchesi, J. R.; Dobson, A. D. W. *Mar. Biotechnol.* **2009**, *11*, 384. (c) Muscholl-Silberhorn, A.; Thiel, V.; Imhoff, J. F. *Microb. Ecol.* **2008**, *55*, 94.

(11) (a) Munawar, M. A.; Groundwater, P. W. *Bull. Korean Chem. Soc.* **1999**, *20*, 456. (b) Gellerman, G.; Rudi, A.; Kashman, Y. *Tetrahedron* **1994**, *50*, 12959. (c) Wardani, A.; Lhomme, J. *Tetrahedron Lett.* **1993**, *34*, 6411.

(12) (a) Matesic, L.; Locke, J. M.; Vine, K. L.; Ranson, J. M.; Bremner, B.; Skropeta, D. *Tetrahedron* **2012**, *68*, 6810. (b) Feng, S.; Panetta, C. A.; Graves, D. E. *J. Org. Chem.* **2001**, *66*, 612. (c) Meesala,

R.; Nagarajan, R. *Tetrahedron Lett.* **2010**, *51*, 422. (d) Kefayati, H.; Narchin, F.; Rad-Moghadam, K. *Tetrahedron Lett.* **2012**, *53*, 4573.
(13) (a) Zeni, G.; Larock, R. C. *Chem. Rev.* **2006**, *106*, 4644. (b) Cacchi, S.; Fabrizi, G. *Chem. Rev.* **2011**, *111*, PR215. (c) Hamada, Y. *Chem. Pharm. Bull.* **2012**, *60*, 1. (e) Hartwig, J. F. In *Palladium-Catalyzed Synthesis of Aryl Ethers and Related Compounds Containing S and Se*; John Wiley & Sons, Inc.: Hoboken, NJ, 2002; Vol. *1*, p 1097. (f) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147.
(14) (a) Cadierno, V.; Crochet, P.; Francos, J.; Garcia-Garrido, S. E.; Gimeno, J.; Nebra, N. *Green Chem.* **2009**, *11*, 1992. (b) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (c) Ramirez, J.; Lillo, V.; Segarra, A. M.; Fernandez, E. *Curr. Org. Chem.* **2008**, *12*, 405. (d) Zanardi, A.; Mata, J. A.; Peris, E. *J. Am. Chem. Soc.* **2009**, *131*, 14531. (e) Smith, A. M. R.; Hii, K. K. *Chem. Rev.* **2011**, *111*, 1637. (f) Krause, N.; Winter, C. *Chem. Rev.* **2011**, *111*, 1994.
(15) (a) Worlikar, S. A.; Larock, R. C. *Org. Lett.* **2009**, *11*, 2413. (b) Cacchi, S.; Fabrizi, G.; Goggiamani, A.; Perboni, A.; Sferrazza, A.; Stabile, P. *Org. Lett.* **2010**, *12*, 3279. (c) Seel, S.; Thaler, T.; Takatsu, K.; Zhang, C.; Zipse, H.; Straub, B. F.; Mayer, P.; Knochel, P. *J. Am. Chem. Soc.* **2011**, *133*, 4774. (d) Della, C. N.; Motti, E.; Mega, A.; Catellani, M. *Adv. Synth. Catal.* **2010**, *352*, 1451. (e) Ackermann, L.; Sandmann, R.; Song, W. *Org. Lett.* **2011**, *13*, 1784. (f) Motti, E.; Faccini, F.; Ferrari, I.; Catellani, M.; Ferraccioli, R. *Org. Lett.* **2006**, *8*, 3967. (g) Takemiya, A.; Hartwig, J. F. *J. Am. Chem. Soc.* **2006**, *128*, 14800. (h) Majumdar, K. C.; Samanta, S.; Sinha, B. *Synthesis* **2012**, *44*, 817. (i) Alberico, D.; Paquin, J.-F.; Lautens, M. *Tetrahedron* **2005**, *61*, 6283. (j) Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775. (k) Thansandote, P.; Gouliaras, C.; Turcotte-Savard, M.-O.; Lautens, M. *J. Org. Chem.* **2009**, *74*, 1791. (l) Schulman, J. M.; Friedman, A. A.; Panteleev, J.; Lautens, M. *Chem. Commun.* **2012**, *48*, 55. (m) Newman, S. G.; Howell, J. K.; Nicolaus, N.; Lautens, M. *J. Am. Chem. Soc.* **2011**, *133*, 14916. (n) Fayol, A.; Fang, Y.-Q.; Lautens, M. *Org. Lett.* **2006**, *8*, 4203. (o) Newman, S. G.; Aureggi, V.; Bryan, C. S.; Lautens, M. *Chem. Commun.* **2009**, 5236. (p) Ackermann, L. *Angew. Chem., Int. Ed.* **2011**, *50*, 3842. (q) Ackermann, L.; Kapdi, A. R.; Fenner, S.; Kornhaaß, C.; Schulzke, C. *Chem.—Eur. J* **2011**, *17*, 2965. (r) Ackermann, L.; Kornhaass, C.; Zhu, Y. *Org. Lett.* **2012**, *14*, 1824.
(16) (a) Schreiber, S. L. *Science* **2000**, *287*, 1964. (b) Arya, P.; Chou, D. T. H.; Baek, M. G. *Angew. Chem., Int. Ed.* **2001**, *40*, 339. (c) Walsh, D. P.; Chang, Y. T. *Chem. Rev.* **2006**, *106*, 2476. (d) Wasilke, J. C.; Obrey, S. J.; Baker, R. T.; Bazan, G. C. *Chem. Rev.* **2005**, *105*, 1001.
(17) Wang, H.; Li, L.; Lin, W.; Xu, P.; Huang, Z.; Shi, D. *Org. Lett.* **2012**, *14*, 4598.
(18) (a) Verma, A. K.; Jha, R. R.; Chaudhary, R.; Tiwari, R. K.; Kotla, S. K. R.; Danodia, A. *J. Org. Chem.* **2012**, *77*, 8191. (b) Joshi, M.; Patel, M.; Tiwari, R.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 5633. (c) Shukla, S. P.; Tiwari, R. K.; Verma, A. K. *Tetrahedron* **2012**, *68*, 9035. (d) Rustagi, V.; Aggarwal, T.; Verma, A. K. *Green Chem.* **2011**, *13*, 1640. (e) Verma, A. K.; Kesharwani, T.; Singh, J.; Tandon, V.; Larock, R. C. *Angew. Chem., Int. Ed.* **2009**, *48*, 1138.
(19) Aggarwal, T.; Kumar, S.; Dhaked, D. K.; Tiwari, R. K.; Bharatam, P. V.; Verma, A. K. *J. Org. Chem.* **2012**, *77*, 8562.
(20) Aggarwal, T.; Jha, R. R.; Tiwari, R. K.; Kumar, S.; Kotla, S. K. R.; Kumar, S.; Verma, A. K. *Org. Lett.* **2012**, *14*, 5184.
(21) (a) Verma, A. K.; Rustagi, V.; Aggarwal, T.; Singh, A. P. *J. Org. Chem.* **2010**, *75*, 7691. (b) Verma, A. K.; Aggarwal, T.; Rustagi, V.; Larock, R. C. *Chem. Commun.* **2010**, *46*, 4064. (c) Aggarwal, T.; Imam, M.; Kaushik, N. K.; Chauhan, V. S.; Verma, A. K. *ACS Comb. Chem.* **2011**, *13*, 530.
(22) (a) Livecchi, M.; Calvet, G.; Schmidt, F. *J. Org. Chem.* **2012**, *77*, 5006. (b) Larock, R. C.; Yum, E. K.; Refvik, M. D. *J. Org. Chem.* **1998**, *63*, 7652. (c) Larock, R. C.; Doty, M. J.; Tian, Q.; Zenner, J. M. *J. Org. Chem.* **1997**, *62*, 7536.
(23) (a) Thorwirth, R.; A. Stolle, A.; B. Ondruschka, B. *Green Chem.* **2010**, *12*, 985. (b) Verma, A. K.; Joshi, M.; Singh, V. P. *Org. Lett.* **2011**, *7*, 1630. (c) Susanto, W.; Chu, C. Y.; Ang, W. J.; Chou, T. C.; Lo, L. C.; Lam, Y. *J. Org. Chem.* **2012**, *77*, 2729.