Aza-Annulation of 1,2,3,4-Tetrahydro-β-carboline Derived Enaminones and Nitroenamines: Synthesis of Functionalized Indolizino[8,7-b]indoles, Pyrido[1,2-a:3,4-b']diindoles, Indolo[2,3-a]quinolizidine-4-ones and Other Tetrahydro-β-carboline Fused Heterocycles

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ABSTRACT: Aza-annulation of novel 1,2,3,4-tetrahydro-β-carboline derived enaminones and nitroenamines with various 1,2- and 1,3-bis electrophiles, such as oxalyl chloride, maleic anhydride, 1,4-benzoquinone, 3-bromopropionyl chloride, itaconic anhydride, and imines (from formaldehyde and primary amines), has been investigated. These methodologies provide simple one-step pathways for efficient construction of highly functionalized tetrahydro-β-carboline 1,2-fused, five- and six-membered heterocyclic frameworks, such as indolizino[8,7-b]indoles, pyrido[1,2-a:3,4-b']-diindoles, indolo[2,3-a]quinolizidines, and pyrimido[1′,6′:1,2]-pyrido[3,4-b']indoles, which are core structures of many naturally occurring indole alkaloids with diverse bioactivity.

INTRODUCTION

The indole structure is regarded as one of the most privileged classes of heterocycles representing structural core of many natural and non-natural compounds with a range of biological activities. The indole alkaloids have been a subject of intense structural, pharmacological, biosynthetic and synthetic studies, because of the structural diversity and complexity of many of its members, along with the important physiological and medicinal properties displayed by this class of compounds.

Similarly, natural product inspired compounds based on polycyclic indole alkaloids also exhibit interesting biological activities. Therefore, the development of new synthetic methods that allow rapid and efficient access to these natural and non-natural indole-containing scaffolds has attracted much attention for several decades among organic as well as medicinal chemists.

Tetrahydro-β-carboline constitutes a recurring subunit in numerous indole alkaloids, besides, they are also templates for drug discovery and have been used as scaffolds for combinatorial libraries. Therefore, the construction of structurally novel, non-natural alkaloid type polycyclic heterocyclic scaffolds containing this subunit is a highly challenging and rewarding endeavor in the fast emerging area of oriented synthesis.

Enaminoketones, esters, and nitriles, including nitroenamines, have been shown to be versatile building blocks for the synthesis of various five- and six-membered heterocycles and are frequently used in domino and multicomponent reactions, because of the rich reactive sites present in these intermediates. However, the corresponding heterocyclic enaminones/esters derived from tetrahydro-β-carboline framework have not been much explored for the construction of indole-annulated heterocycles, despite their considerable synthetic potential, although acyclic β-enaminesters generated from the reaction of tryptamine and alkyl propiolates have been frequently employed as useful building blocks for construction of indole-annulated heterocycles via the sequential Pictet–Spengler reaction.

We have previously reported an efficient general approach for the synthesis of 6,7-dimethoxytetrahydroisoquinoline-derived push-pull enaminoes/esters/nitriles of the general structure 2 and their subsequent synthetic elaboration to tetrahydroisoquinoline-fused five- and six-membered heterocycles 3 (Scheme 1). The overall process involves the Bischler–Napieralski type cyclization of newly synthesized...
ketene $N,S$-acetals 1 derived from 3,4-dimethoxyphenylethylamine and polarized ketene dithioacetals, and subsequentaza-annulation of the resulting enaminones/nitroenamines 2 with two or three carbon 1,2- and 1,3-electrophilic species, affording highly functionalized isoquinoline-fused five- and six-membered heterocycles, such as pyrrolo[2,1-$a$]isoquinolines, indolo[2,1-$a$]isoquinolines, and substituted benzisoquinolidin-$4$-one and pyrimido[6,1-$a$]isoquinoline structural motifs present in several naturally occurring alkaloids and physiologically active drugs (Scheme 1).

Our fascination with this class of molecules prompted us to extend these studies for the synthesis of tetrahydro-$\beta$-carboline-derived functionalized push-pull enamines, as potentially useful building blocks for the synthesis of 1,2-heteroannulated tetrahydro-$\beta$-carbolines-derived 5–6 membered heterocycles and related natural products. Thus, we had previously reported the synthesis of a series of functionalized 1,2,3,4-tetrahydro-$\beta$-carboline-derived enaminones/esters/nitriles 7 via trifluoroacetic acid-induced Bischler–Napieralski type cyclization of newly prepared polarized ketene $N,S$-acetals 6 from tryptamine 4 and polarized ketene $S,S$-acetals 5 (Scheme 2).

On the basis of our previous studies, with tetrahydroisoquinoline-based enaminones (Scheme 1), we anticipated that tetrahydro-$\beta$-carboline-derived enaminones and nitroenamines such as 7 could also be employed in efficientaza-annulation reactions with various 1,2- and 1,3-biselectrophiles, leading to a variety of tetrahydro-$\beta$-carboline 1,2-annulated five- and six-membered heterocycles (Scheme 3). Also, because of our previous experience in exploring the reactivity and synthetic potential of polarized ketene $N,S$-acetals as functionalized enamines, we also envisioned the possibility of synthesizing the target tetrahydro-$\beta$-carboline-fused heterocycles, directly from acyclic $N,S$-acetals with concurrent formation of both tetrahydropridine and 5/6 membered rings in a tandem one-pot operation (Scheme 3). The results of these studies have been presented in the following section, and we now report in the present paper, one-step synthetic elaboration of a few of these enaminones/nitroenamine 7 to 1,2-tetrahydro-$\beta$-carboline-annulated heterocycles, such as substituted dihydroindolizino[8,7-$b$]indoles, pyrido[1,2-$a$:3,4-$b'$]diindole, indolo-[2,3-$a$]quinolinizidines, their benzo-fused analogues, and other novel heterocyclic scaffolds (Scheme 3).

Scheme 1. Aza-Annulation of Isoquinoline-Derived Enaminones/Nitroenamine to Tetrahydroisoquinoline-Fused Five- and Six-Membered Heterocycles

Scheme 2. Synthesis of $\beta$-Carboline-Derived Push-Pull Enaminones

Scheme 3. Synthesis of Tetrahydro-$\beta$-Carboline-Fused Five- and Six-Membered Heterocycles
RESULTS AND DISCUSSION

We first examined the cycloannulation of few β-carboline-derived enamines and nitroenamine 7, with oxalyl chloride, and maleic anhydride with a view to synthesize dihydroindolizino[8,7-b]indole derivatives (Schemes 5 and 6). Indolizino[8,7-b]indole represents an important class of the indole-containing heterocyclic core present in several naturally occurring bioactive alkaloids, such as harmicine, pegaharmamine B, and also in synthetic pharmacologically active compounds such as human CCK1 receptor antagonists (Figure 1).1,7a−c,10 Several synthetic approaches for the construction of this heterocyclic core have been reported in recent years.7−14 In most of these protocols, the pyrrole ring of the indolizino[8,7-b]indole framework has been constructed in various ways. Thus, Knolker and co-workers have reported a two-step procedure for the construction of the pyrrole ring by addition of a propargyl Grignard reagent to 3,4-dihydro-β-carboline and subsequent silver(I)-promoted oxidative cyclization of the resulting adduct.12 The pyrrole ring has also been constructed by several research groups via 1,3-dipolar cycloaddition of tetrahydro-β-carboline-derived azomethine ylides−s13a (or munchrones13b) with various dipolarophiles, including a photoredox-catalyzed oxidation/1,3-dipolar cycloaddition reported by Maurya and co-workers.13c Functionalized dihydroindolizino[8,7-b]indoles have also been obtained via a one-pot or stepwise reaction of tryptamine, alkyl propiolates, and β-nitroalkenes/α,β-unsaturated ketones via intermediary of acyclic β-enaminoesters, with concomitant formation of both tetrahydropyridine and pyrrole ring in a domino fashion.7a,b Wu and co-workers have recently reported the acid-catalyzed multicomponent cyclization protocol for the synthesis of polyfunctional dihydroindolizino[8,7-b]indoles from readily available arylglyoxal monohydrates, tryptamine, and β-nitrostyrenes or malononitrile.10,14 For our study, the desired enamines 7a−f and nitroenamine 7g were synthesized according to our earlier reported procedure,4a as shown in the Scheme 4. We first examined the reactions of enamines 7a,b,d and nitroenamine 7g with oxalyl chloride, with a view to synthesize indolizino[8,7-b]indole-2,3-diones 8 in a domino fashion, with concomitant formation of both the rings via intramolecular cyclization of the initially formed N-substituted 4-benzoyl-5-methylthiopyrrolidin-2,3-diones 9 (Scheme 5). Indeed, the reactions proceeded as expected, yielding the desired tetracyclic indolizino[8,7-b]indole-2,3-diones 8a,b,d in comparatively better yields (route b, Scheme 5). However, the corresponding cyclic nitroenamine 7g or the acyclic nitroketene N,S-acetal 6g failed to furnish the desired 1-nitroindolizino[8,7-b]indole-2,3-dione 8g under above described conditions, yielding only an intractable reaction mixture (Scheme 5).

With the successful isolation of indolizino[8,7-b]indole-2,3-diones 8 from the reactions of enamines 7 with oxalyl chloride, we next investigated aza-annulation of enamines 7 with maleic anhydride 10, with a view to synthesize functionalized indolizino[8,7-b]indoles such as 11 with an acetic acid side chain (Scheme 6). Aza-annulation of a few acyclic and cyclic enamines/esters/nitrides with maleic anhydride/maleimide has been reported in the literature affording substituted monocyclic and bicyclic pyrrolidinones,16,15 however, cycloannulation of tetrahydro-β-carboline-derived enamines such as 7 with maleic anhydride has not
been investigated. Thus, when the enaminone 7a was reacted with an equimolar quantity of maleic anhydride in solvents such as benzene, toluene, and acetonitrile under reflux conditions, the product isolated after work-up was characterized as expected 2-(1-benzoyl-3-oxo-3,5,6,11-tetrahydro-2H-indolizino[8,7-b]indol-2-yl)acetic acid 11a, with the help of spectral and analytical data (Scheme 6). However, the best yield (60%) of 11a was obtained in refluxing acetonitrile, whereas in other solvents, formation of side products was observed along with 11a. Similarly the 4-chlorobenzoyl-substituted enaminone 7b also afforded the substituted indolizino[8,7-b]indole-2-acetic acid 11b in good yield (Scheme 6). However, the corresponding nitroenamine 7g, although reacted completely with maleic anhydride under identical conditions, the products could not be isolated in their pure form, even after repeated column chromatography.

Similarly, attempted domino cyclization of N,S-acetal 6a with maleic anhydride was not successful and neither the tetracyclic product 11a nor the pyrrolidinone intermediate 12a could be isolated from the reaction mixture (Scheme 6).

We next extended our aza-annulation strategy for the synthesis of pyrido[1,2-a:3,4-b′]dindole analogues via a Nenitzescu type reaction of enaminones 7 with 1,4-benzoquinone (Scheme 7). This pentacyclic pyrido[1,2-a:3,4-b′]dindole framework constitutes the core structure of several marine alkaloids, including red pigment fascaplysin, homofascaplysins B,C, and their bromo-analogues (Figure 2). Fascaplysin displays a broad range of biological activities, such as antibacterial, antifungal, antiviral, antimarial, HIV-1-RT, and especially inhibition of cyclin-dependent kinase 4, which regulates the G0–G1/S checkpoint of the cell cycle. Therefore, there is considerable interest in the synthesis and development of fascaplysin and its analogues, as lead compounds for potential anticancer drugs and for other therapeutic applications. Similarly, naturally occurring alkaloids cladonamide G possessing an unprecedented indolotryptoline skeleton have also shown to display significant toxicity against human colon and breast cancer (Figure 2).

Although the Nenitzescu reaction for the synthesis of 5-hydroxyindole has been widely studied and various acyclic and cyclic enaminoesters/enaminones have been employed as enamine components in this reaction, the corresponding heterocyclic enaminones such as 7a–d or nitroenamine 7g derived from β-carboline have not been explored for the construction of the pyridodiindole framework. On the basis of our previous studies with tetrahydroisoquinoline-derived enaminoesters, we have developed a new one-step procedure for the synthesis of the novel pentacyclic pyrido[1,2-a:3,4-b′]dindole framework through the Nenitzescu reaction of enaminones 7 with 1,4-benzoquinone (Scheme 7). Thus, the reaction of 7a with 1,4-benzoquinone in either refluxing acetic acid or in presence of ZnCl2 catalyst (20 mol %) yielded only a complex mixture of products; however, when the enaminone 7a was stirred with 1,4-benzoquinone in nitromethane for 2 days under our earlier described conditions, the reaction mixture after a usual work-up and purification yielded a yellow solid (58%) characterized as 6,7-dihydro-2-hydroxy-13-benzoyl-12H-pyrido[1,2-a:3,4-b′]dindole 13a (Scheme 7). Similarly, the other substituted enaminones 7b,c also underwent cycloannulation with 1,4-benzoquinone under identical conditions furnishing the corresponding 2-hydroxy-13-aryldihydropyridodiindoles 13b,c in moderate to good yields (Scheme 7). Interestingly, the nitroenamine 7g could also be reacted with benzoquinone, yielding the corresponding hitherto unreported 2-hydroxy-13-
We next investigated aza-annulation of enamines 7 with 3-bromopropionyl chloride and itaconic anhydride with a view to construct indolo[2,3-a]quinolizine-4-one frameworks (Schemes 8 and 9). The indolo[2,3-a]quinolizine structural motif is of significant importance, since this privileged structure is present in a plethora of numerous naturally occurring, bioactive indole alkaloids,\textsuperscript{1,6a,19} such as deplancheine, geissoschizine, dihydrocorynantheine, including ajmalicine, and yohimbane, a potent modulator of tubulin cytoskeleton, and important anticancer drugs (Figure 3).\textsuperscript{5} Because of their complex structures and pharmacological properties, new synthetic routes for the construction of this tetracyclic indolo[2,3-a]quinoliniz-4-ones with diverse functionalities have attracted much attention, among synthetic as well as medicinal chemists.\textsuperscript{20} Some of the recent approaches for the construction of this challenging heterocyclic target involve cyclization of N-acyliminium ion on the pendant indole ring,\textsuperscript{20a,b} Bischler–Napieralski reaction,\textsuperscript{21a} and Fischer Indole synthesis.\textsuperscript{21b}

Franzen\textsuperscript{22} and Wu’s\textsuperscript{23} groups have recently developed facile organocatalytic enantioselective one-pot, three-component, cascade approaches for highly substituted indoloquinolizidines, involving a Michael addition-Pictet–Spengler sequence of β-ketoesters (or alkyl propiolates), α,β-unaturated aldehydes, and tryptamine. Muller and co-workers\textsuperscript{16} have reported a sequential, four-component synthesis of highly substituted indolo[2,3-a]quinolizidine-4-ones with diverse functionalities have attracted much attention, among synthetic as well as medicinal chemists.\textsuperscript{20} Some of the recent approaches for the construction of this challenging heterocyclic target involve cyclization of N-acyliminium ion on the pendant indole ring,\textsuperscript{20a,b} Bischler–Napieralski reaction,\textsuperscript{21a} and Fischer Indole synthesis.\textsuperscript{21b}

In our study, we first examined cycloannulation of enamines 7a, 7d, and nitroenamine 7g with 3-bromopropionyl chloride 15 with a view to synthesize 1-aryl/nitro-tetrahydroindolo[2,3-a]quinolizin-4-ones 14 (Scheme 8). Thus, under optimized reactions conditions, when 7a was reacted with 3-bromopropionyl chloride 15 in refluxing THF and triethylamine, the reaction proceeded smoothly, yielding the desired indoloquinolizidine-4-one 14a in 65% yield. Alternatively, we also attempted one-pot tandem cyclization of open-chain N,S-acetal 6a with 15, under identical conditions, and to our delight, indoloquinolizidine 14a was obtained in increased yield of 75%, without isolation of the corresponding tetrahydro-2-pyridone intermediate 16a (Scheme 8). The corresponding 1-acetyl and hitherto unreported 1-nitroindoloquinolizidinone 14d and 14g were similarly obtained in good yields from respective cyclic enamine 7d, 7g or the corresponding N,S-acetals 6d and 6g under identical conditions (Scheme 8).

With the successful synthesis of 1-substituted tetrahydroindolo[2,3-a]quinazolidones 14 by cycloannulation of enamines 7 with 3-bromopropionyl chloride, we next examined the aza-annulation of enamines 7a–c and nitroenamine 7g with itaconic anhydride 18, with anticipation to synthesize functionalized indoloquinolizidin-4-ones 17, bearing an acetic acid side chain (Scheme 9). There are very few reports of aza-annulation of enamine substrates with exocyclic anhydrides, like itaconic anhydride 18.\textsuperscript{14a,17a} Thus,
when enaminone 7a was reacted with itaconic anhydride in refluxing acetonitrile, under our previously described conditions,\textsuperscript{4a,9a} work-up and purification of the reaction mixture yielded a single product, which was found to be the expected 1-benzoyl-indolo[2,3-a]quinolizin-4-one-3-acetic acid 17a (62%) on the basis of its spectral and analytical data (Scheme 9).

Similarly, the enaminones 7b,c and the nitroenamine 7g also reacted with itaconic anhydride \textsuperscript{18} under identical conditions furnishing the corresponding 1-aroyl- and 1-nitroindolo[2.3-a]quinolizido-4-one-3-acetic acids 17b,c, 17g in good yields (Scheme 9). In an alternative procedure, the acyclic N,S-acetal 6a was reacted with itaconic anhydride \textsuperscript{18} with a view to obtain the target functionalized indolo[2,3-a]quinolizinone 17a in a tandem one-pot operation. However, when 6a was reacted with 18 in refluxing acetonitrile, the product isolated was found to be only acyclic substituted dihydropyridone 19a (70%), which did not cyclize to indoloquinolizidone 17a even on prolonged heating of the reaction mixture (Scheme 9).

However, treatment of the isolated dihydropyridone 19a with trifluoroacetic acid at room temperature furnished the quinolizidone 17a in good yield (64\%, Scheme 9). In fact, it was not necessary to purify the pyridone 19a and the crude reaction mixture after evaporation of acetonitrile (from the reaction of 6a and itaconic anhydride), affording 17a in comparable yield, on treatment with trifluoroacetyl (TFA).

We also subjected 2-chloro/bromobenzoylenaminones, such as 7c, 7e,f, to intramolecular nucleophilic aromatic substitution (S_NAr), with a view to synthesize pentacyclic dihydroindolo-[2',3'\,3,4]\,pyrido[1,2-a]quinolin-2-ones \textsuperscript{20} (Scheme 10).\textsuperscript{25} Thus, when o-chlorobenzoylenaminone 7c was heated in either dimethylformamide or dimethyl sulfoxide (DMSO) in the presence of bases like K\textsubscript{2}CO\textsubscript{3}, Cs\textsubscript{2}CO\textsubscript{3}, or sodium t-butoxide at higher temperature for a prolonged time, the desired product 20c was formed in varying yields; however, the best yield (71\%) of 20c was obtained when N,S-acetal 7c was heated in DMSO for 12h at 120 °C (Scheme 10). Similarly, the other substituted o-halobenzoyl enaminones 7e,f also underwent intramolecular nucleophilic substitution to give the corresponding indolo-fused dihydroindolopyridoquinolin-2-ones 20e,f in high yields. However, the products 20e,f were found to be highly insoluble and 20e could be characterized by \textsuperscript{1}H NMR/high-resolution mass spectrometry (HRMS) data, whereas 20f, only by HRMS.

Finally, we also synthesized a few of the 2,3,4,6,7,12-hexahydropyrimido[1',6':1,2]\,pyrido[3,4-b]indoles 21a-c via cycloannulation of enaminones and nitroenamines 7a, 7g via the double Mannich reaction with formaldehyde and primary amines (Scheme 11). Thus, when the enaminone 7a was stirred with formaldehyde and benzylamine at room temperature in solvents like THF, CH\textsubscript{2}Cl\textsubscript{2}, acetonitrile, and benzene, starting materials remained unchanged whereas in methanol as solvent, the corresponding 1-benzoyl-3-N-benzylhexahydropyrimido[1',6':1,2]\,pyrido[3,4-b]indole 21a was obtained in 65% yield. On the other hand, annulation of nitroenamine 7e with formaldehyde and benzyl or furfuryl amines was found to be very facile, providing the
corresponding, 1-nitro-3-benzyl/furfuryl-hexahydropyrimido-
[1′,6′:1,2]pyrido[3,4-b]indoles 21bc in 80 and 91% yields, respectively (Scheme 11). Some of these compounds are shown to be a potent inhibitor of lipid peroxidation.26

**CONCLUSIONS**

In summary, we have carried out a detailed study of azaan- 
notation of newly synthesized ϕ-carboline-derived enami- 
nones and nitroenamines with various 1,2- or 1,3-biscarbo- 
philic species, like oxalyl chloride, maleic anhydride, 1,4-
benzoquinone, 3-bromopropionyl chloride, itaconic anhydride, 
etc. and successfully developed convenient one-pot protocols 
for the construction of a variety of novel ϕ-carboline-1,2-fused 
highly functionalized five- and six-membered tetra- 
and pentacyclic heterocyclic motifs, in reasonable yields. It should 
be noted that, while there are few reports of azaan- 
notation of ϕ-carboline-derived enaminoesters (or in situ generated acyclic enaminoester from tryptamine and ethyl propiolate) furnishing tetrahydroindolizino[8,7-b]indoles or indolo[2,3-a]- 
quinolizidines derivatives, the synthesis and reactivity of the 
corresponding ϕ-carboline-derived enaminoesters and especially 
nitroenamines have not been explored. Also, the azaan-
nnotations of these ϕ-carboline-derived enamines with maleic 
anhydride, itaconic anhydride, and 1,4-benzoquinone have not 
been reported in the literature. These novel protocols provide 
a rapid and efficient access to biologically important non-
natural indole alkaloids in a highly concise fashion. The overall 
study reveals the possibility of construction of a range of novel 
substituted ϕ-carboline-fused heterocyclic scaffolds with 
potential biological activity employing this protocol.

**EXPERIMENTAL SECTION**

**General Information.** All reagents were purchased from 
commercial suppliers and used without further purification. 
Solvents were dried according to the standard procedures. All 
reactions were monitored by thin layer chromatography using 
standard thin-layer chromatography (TLC) Silica gel plates 
and visualized with UV light. Column chromatography was 
performed using silica gel (100–200 mesh) or neutral alumina 
wherever mentioned. Nuclear magnetic resonance spectra were 
recorded on Bruker (400 MHz) ultrasharp plus and Jeol (600 
MHz) ECZ 600R FT-NMR spectrometer with CDCl3, 
DMSO-d6 or CD3OD as solvent. Chemical shifts were 
reported in δ ppm using residual solvent protons as internal 
standard (δ 7.26 for CDCl3, δ 2.50 for DMSO-d6 and δ 3.31 
for CD3OD in 1HM NMR, δ 77.16 for CDCl3, δ 39.52 for 
DMSO-d6 and δ 49.01 for CD3OD in 13C NMR). Coupling 
constants were reported as J values in hertz (Hz). Splitting 
patterns are designated as s (singlet), d (doublet), t (triplet), q 
(quartet), dd (doublet of doublet), dt (doublet of triplet), td 
(triplet of doublet), ddd (doublet of doublet of doublet), m 
(multiplet), and br (broad). Infrared spectra of neat samples 
were recorded in attenuated total reflectance mode using 
Fourier transform infrared instrument (Agilent technologies) 
and HRMS on a 6538 UHD accurate mass Q-TOF LC/MS 
spectrometer through electrospray ionization (ESI) mode. 
Melting points were recorded using an electrothermal capillary 
melting point apparatus and are uncorrected. All tetrahydro-ϕ-
carboline derived enaminoesters 7a–f and nitroenamine 7g 
were prepared according to our earlier reported procedure from 
the respective N,4-acetals 6a–g.26 The spectral data of the known 
enaminoesters 7a–d and 7g has been reported earlier,26 whereas 
spectral and analytical data of unknown enaminoesters 7e,f, is 
given below.

1-(2,4-Dichlorobenzoyl)methylene-1,2,3,4-tetrahydro-ϕ-carboline 
(7e). Obtained from 6e; yellow solid (542 mg, 76%); mp 192–194 °C; R 0.26 (2:8 (EtOAc)/hexane); 1H NMR (600 MHz, DMSO-d6) δ 11.64 (s, 1H, NH), 10.34 (s, 1H, indole NH), 7.67 (br s, 1H, ArH), 7.61 (d, J = 7.6 Hz, 1H, ArH), 7.55 (d, J = 8.4 Hz, 1H, ArH), 7.50 (dd, J = 8.4, 1.2 Hz, 1H, ArH), 7.40 (d, J = 7.6 Hz, 1H, ArH), 7.25 (t, J = 7.6 Hz, 1H, ArH), 7.08 (t, J = 7.6 Hz, 1H, ArH), 5.90 (s, 1H, =CH2), 3.67–3.65 (m, 2H, NCH3), 3.00 (t, J = 7.0 Hz, 2H, CH2); 13C[1H] NMR (150 MHz, DMSO-d6) δ 186.7, 152.2, 140.5, 137.8, 133.8, 130.9, 130.2, 129.3, 127.2, 127.0, 125.2, 124.6, 119.8, 119.7, 116.4, 112.1, 89.3, 39.0, 19.7; IR (neat, cm–1) 3020, 1725, 740; HRMS (ESI-Q-TOF) m/z [M + H]+ calcd for C20H18BrN2O2 [M + H]+ 397.0552, found 397.0531.

1-(2-Bromo-5-methoxybenzoyl)methylene-1,2,3,4-tetrahydro-ϕ-carboline (7f). Obtained from 6f; yellow solid (416 mg, 70%); mp 198–200 °C; R 0.26 (4:6 (EtOAc)/hexane); 1H NMR (400 MHz, CDCl3) δ 10.69 (s, 1H, NH), 9.35 (s, 1H, indole NH), 7.71 (d, J = 7.2 Hz, 1H, ArH), 7.49–7.39 (m, 3H, ArH), 7.29–7.25 (m, 1H, ArH), 7.15 (d, J = 2.8 Hz, 1H, ArH), 7.79 (dd, J = 8.8, 3.2 Hz, 1H, ArH), 5.89 (s, 1H, =CH2), 3.89 (s, 3H, OCH3), 3.73 (dt, J = 7.2, 2.8 Hz, 1H, NCH3), 3.15 (t, J = 7.2 Hz, CH2); 13C[1H] NMR (100 MHz, CDCl3) δ 190.3, 158.7, 152.8, 144.3, 137.9, 133.9, 127.2, 125.9, 125.2, 120.5, 119.7, 117.5, 116.4, 114.2, 112.1, 109.9, 89.7, 55.5, 40.2, 20.3; IR (neat, cm–1) 3059, 1722, 642; HRMS (ESI-Q-TOF) m/z [M + H]+ calcd for C22H15BrN2O4 [M + H]+ 397.0552, found 397.0551.

**General Procedure for the Reaction of Enaminones 7a,b, 7d or N,4-Acetals 6a,b, 6d with Oxalyl Chloride.**

**Synthesis of 1-Aroyl/nitro-5,6-dihydro-2H-indolizino[8,7-b]indole-2,3-(11H)-diones 8.** To a stirred solution of the appropriate enaminoesters 7 (1.09 mmol) or the N,4-acetals 6 and triethylamine (0.38 mL, 2.7 mmol) in dry THF (15 mL) under a nitrogen atmosphere, oxalyl chloride (0.95 mL, 1.1 mmol) was added at 0 °C. After stirring the reaction mixture for 4 h (monitored by TLC), the solvent was evaporated under reduced pressure and the residue dissolved in CH2Cl2 and washed three times with water (3 X 10 mL). The organic layer was dried over anhydrous Na2SO4 and evaporated under reduced pressure, and the crude residue was purified by silica gel chromatography using (2:8) EtOAc/hexane as eluent to give pure 8.

1-Benzoyl-5,6-dihydro-2H-indolizino[8,7-b]indole-2,3-(11H)-dione (8a). Obtained from 6a or 7a; red solid (328 mg, 88% from 6a; 283 mg, 76% from 7a); mp 202–204 °C; R 0.2 (3.7 EtOAc/hexane); 1H NMR (600 MHz, CDCl3) δ 11.96 (s, 1H, NH), 7.73–7.71 (m, 3H, ArH), 7.59–7.56 (m, 1H, ArH), 7.53–7.51 (m, 2H, ArH), 7.48–7.44 (m, 2H, ArH), 7.24–7.22 (m, 1H, ArH), 4.16 (t, J = 7.8 Hz, 2H, NCH3), 3.42 (t, J = 7.8 Hz, 2H, CH2); 13C[1H] NMR (150 MHz, CDCl3) δ 190.4,
177.7, 159.9, 158.6, 141.1, 138.6, 132.6, 130.4, 129.3, 127.1, 125.6, 123.2, 122.1, 121.5, 113.5, 105.2, 37.8, 20.4; IR (neat, cm$^{-1}$) 3040, 1746, 1688, 1608; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ calcd for C$_{23}$H$_{18}$ClN$_2$O$_4$ [M + H]+ 421.0955, found 421.0956.

**General Procedure for the Reaction of Enaminones 7a-c and Nitroenamine 7g with 1,4-Benzoquinone.**

Synthesis of 2-Hydroxy-7,12-dihydro-6H-indolo[2,1-ajj-carbolin-13-yl-aryl]nitro Methanones 13. To a stirred solution of the appropriate enaminones 7a-c, 7g (1.6 mmol) in nitromethane, p-benzoquinone (237 mg, 2.2 mmol) was added under a nitrogen atmosphere and the reaction was stirred at 25°C for 1.5–2 days (monitored by TLC). The reaction mixture was then brought to room temperature and evaporated under reduced pressure, residue was dissolved in EtOAc, and the organic layer was washed with water (3 × 10 mL) and dried (anhydrous Na$_2$SO$_4$). The solvent was evaporated under reduced pressure to afford the crude products, which were purified by silica-gel column chromatography using (2:8) EtOAc/hexane as eluent.

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General Procedure for the Reaction of Enaminones 7a–c and Nitroenamine 7g with Itaconic Anhydride. Synthesis of 2-(1-Aryl-nitro-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic Acids 17. A solution of the appropriate enamine 7 (1.5 mmol) and itaconic anhydride (180 mg, 1.6 mmol) in dry acetonitrile (15 mL) was refluxed for 10 h (monitored by TLC). The reaction mixture was then brought to room temperature and evaporated under reduced pressure, and the residue was dissolved in EtOAc (15 mL). The organic layer was washed with water, dried (anhydrous Na$_2$SO$_4$), and evaporated to afford the crude product, which was purified by column chromatography over a neutral alumina column using (8:2) EtOAc/hexane as eluent.

2-(1-Benzoyl-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic Acid (17a). Obtained from 7b; yellow solid (200 mg, 64%); mp 170–172 °C; R$_f$ 0.18 (8:2 EtOAc/hexane); $^1$H NMR (400 MHz, DMSO-$_d_6$) $\delta$ 12.10 (br s, 1 H, NH), 10.33 (s, 1 H, CO$_2$H), 7.84 (d, J = 7.2 Hz, 2H, ArH), 7.59–7.46 (m, 4H, ArH), 7.39 (d, J = 8.0 Hz, 1H, ArH), 7.16 (t, J = 7.6 Hz, 1H, ArH), 7.03 (t, J = 7.6 Hz, 1H, ArH), 4.78 (dt, J = 12.8, 4.8 Hz, 1H, NCH$_3$H), 3.43–3.36 (m, 3H, NCH$_3$H), 3.01 (dt, J = 16.4, 4.0 Hz, 1H, ArCHH-7), 2.93–2.88 (m, 2H, ArCHH-7, H-3), 2.77–2.68 (m, 2H, CH$_2$H), 2.53–2.52 (m, merged with DMSO signal, 1H, CH$_2$CO$_2$H), 2.34 (dd, J = 16.4, 6.4 Hz, 1H, CHFCCO$_2$H); $^{13}$C{$_1$H} NMR (150 MHz, DMSO-$_d_6$) $\delta$ 195.9, 173.4, 133.7, 132.6, 128.6, 128.5, 126.7, 125.3, 120.3, 119.3, 113.8, 111.3, 40.7, 31.9, 26.0, 20.8; IR (neat, cm$^{-1}$) 2916, 1732, 1619, HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ calcd for C$_{18}$H$_{14}$N$_3$O$_3$ [M + H]$^+$ 401.1628; found 401.1607.

2-(1-(4-Chlorobenzoyl)-4-oxo-2,3,4,6,7,12-hexahydroindolo[2,3-a]quinolizin-3-yl)acetic Acid (17b). Obtained from 7b; yellow solid (617 mg, 58%); mp 217–218 °C; R$_f$ 0.18 (8:2 EtOAc/hexane); $^1$H NMR (600 MHz, DMSO-$_d_6$) $\delta$ 10.36 (s, 1 H, NH), 7.80 (d, J = 8.4 Hz, 2H, ArH), 7.50–7.47 (m, 3H, ArH), 7.32 (d, J = 8.4 Hz, 1H, ArH), 7.10 (t, J = 7.8 Hz, 1H, ArH), 6.97 (t, J = 7.8 Hz, 1H, ArH), 4.71 (dt, J = 12.0, 4.0 Hz, 1H, NCH$_3$H-6) 3.36 (td, J = 12.0, 4.1 Hz, 1H, NCH$_3$H-6), 2.96 (dt, J = 16.2, 3.8 Hz, 1H, ArCHH-7), 2.92–2.85 (m, 2H, ArCHH-7, H-3), 2.70–2.65 (m, 2H, CH$_2$H), 2.51–2.48 (dd, J = 16.8, 5.4 Hz, 1H, CHFCCO$_2$H), 2.34 (dd, J = 16.8, 7.2 Hz, 1H, CHFCCO$_2$H); $^{13}$C{$_1$H} NMR (150 MHz, DMSO-$_d_6$) $\delta$ 195.1, 173.5, 171.6, 137.9, 137.7, 137.2, 131.3, 129.0, 126.6, 125.2, 124.8, 120.1, 119.7, 117.5, 112.8, 114.7, 40.8, 37.6, 34.7, 31.8, 30.3, 20.9; IR (neat, cm$^{-1}$) 3445, 2921, 1701, 1678, 746; HRMS (ESI-Q-TOF) m/z: [M + H]$^+$ calcd for C$_{24}$H$_{20}$ClN$_4$O$_3$ [M + H]$^+$ 435.1112; found 435.1121.
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2-(1-(2-Chlorobenzoyl)-4-oxo-2,3,4,6,7,12-hexahydropyridolo[2,3-a]quinolin-3-yl)acetic Acid (17c).

Obtained from 7c; yellow solid (392 mg, 54%); mp 217–218 °C; Rf 0.18 (8:2 EtOAc/hexane); 1H NMR (400 MHz, DMSO-d6) δ 12.18 (br s, 1H, NH), 11.67 (s, 1H, CO2H), 7.62 (d, J = 8 Hz, 1H, ArH), 7.58–7.44 (m, 5H, ArH), 7.28 (t, J = 7.6 Hz, 1H, ArH), 7.10 (t, J = 7.6 Hz, 1H, ArH), 4.83 (dt, J = 12.8, 4.0 Hz, 1H, NCH=N-H), 3.52 (td, J = 12.8, 4.0 Hz, 1H, NCH=N-H), 3.05 (dt, J = 16.8, 6.0 Hz, 1H, ArCH=CH2), 2.96–2.86 (m, 2H, ArCH=CH2–H3), 2.65 (dd, J = 16.8, 6.0 Hz, 1H, CH(NH)=CH2), 2.55 (d, J = 16.8 Hz, 1H, CH(NH)=CH2), 2.45 (dd, J = 16.8, 6.8 Hz, 1H, CHCH2OOC), 2.34 (dd, J = 16.4, 6.8 Hz, 1H, CHCH2OOC); 13C{1H} NMR (100 MHz, DMSO-d6) δ 193.6, 172.7, 171.1, 140.7, 140.1, 136.6, 131.3, 129.7, 129.4, 128.9, 127.4, 126.2, 125.2, 124.5, 119.9, 119.5, 118.9, 112.6, 112.3, 41.0, 36.8, 33.8, 28.8, 20.2; IR (neat, cm−1) 3200, 2922, 1687, 1745; HRMS (ESI-Q-TOF) m/z: [M + H]+ calc for C24H20ClN2O4 [M + H]⁺ 435.0994; found 435.0966.

Conversion of 19a to 17a.

To a solution of 19a (450 mg, 1 mmol) in dichloromethane (10 mL), TFA (0.23 mL, 3 mmol) was added and the reaction mixture was stirred at room temperature for 3 h (monitored by TLC). After evaporation of solvent, it was neutralized with sat. NaHCO3 (15 mL), extracted with EtOAc (3 × 10 mL). The organic layer was washed with water, dried (anhydrous Na2SO4), and evaporated to afford the crude product, which was purified by column chromatography over a neutral-alumina column using (8:2) EtOAc/hexane as eluant to give pure 17a; (yield, 256 mg), 64%; spectral and analytical data as mentioned above.

General Procedure for Base-Mediated Intramolecular Nucleophilic Substitution of 7c, 7e, and 7f.

Synthesis of Dihydropyrido[2′,3′:3,4]pyridino[1,2-aliquinolin-2-ones 20. To a stirring solution of enamines 7 (1.0 mmol) in DMSO (10 mL) in a sealed tube, K2CO3 (414 mg, 3.0 mmol) was added and the reaction mixture was heated to 120 °C for 12 h (monitored by TLC). For the product 19f, the enamione 7f was heated in N-methylpyrrolidone, at 140 °C for 36 h in a sealed tube. The reaction mixture was cooled to room temperature and was diluted with sat. NH4Cl solution (15 mL). The precipitated product was filtered and washed with water and hexane. The crude product was purified by column chromatography using (6:4) EtOAc/hexane as eluent.

8,9-Dihydropyrido[2′,3′:3,4]pyridino[1,2-aliquinolin-2(14H)-one 20c. Obtained from 7c; yellow solid (203 mg, 71%); mp 345–357 °C; Rf 0.2 (6:4 EtOAc/hexane); 1H NMR (600 MHz, DMSO-d6) δ 11.73 (s, 1H, NH), 8.18 (dd, J = 7.8, 1.8 Hz, 1H, ArH), 7.98 (d, J = 8.4 Hz, 1H, ArH), 7.72 (dt, J = 7.8, 1.8 Hz, 1H, ArH), 7.64 (d, J = 7.8 Hz, 1H, ArH), 7.42 (d, J = 7.8 Hz, 1H, ArH), 7.32 (t, J = 7.2 Hz, 1H, ArH), 7.24 (t, J = 7.2 Hz, 1H, ArH), 7.07 (t, J = 7.8 Hz, 1H, ArH), 6.69 (s, 1H, CH=N), 4.51 (t, J = 6.6 Hz, 2H, NCH2), 3.23 (t, J = 6.6 Hz, 2H, CH2); 13C{1H} NMR (150 MHz, DMSO-d6) δ 176.1, 142.3, 142.1, 138.8, 132.8, 128.1, 126.9, 126.1, 125.7, 124.9, 123.3, 120.3, 120.2, 117.0, 114.4, 112.5, 103.8, 44.3, 20.2; IR (neat, cm−1) 3215, 1592, 1293; HRMS (ESI-Q-TOF) m/z: [M + H]+ calc for C24H23N3O5 [M + H]+ 387.1644; found 387.1634.

5-Chloro-8,9-dihydropyrido[2′,3′:3,4]pyridino[1,2-aliquinolin-2(14H)-one 20e. Obtained from 7e; yellow solid (200 mg, 73%); mp 350–352 °C; Rf 0.2 (4:6 EtOAc/hexane); 1H NMR (600 MHz, CD3OD) δ 11.75 (s, 1H, NH), 8.15 (d, J = 8.4 Hz, 1H, ArH-3), 8.09 (d, J = 1.8 Hz, 1H, ArH-6), 7.65 (d, J = 7.8 Hz, 1H, ArH), 7.41 (d, J = 8.4 Hz, 1H, ArH), 7.37 (dd, J = 8.4, 1.8 Hz, 1H, ArH-4), 7.24 (dt, J = 7.8, 1.2 Hz, 1H, ArH), 7.08 (dt, J = 7.8, 1.2 Hz, 1H, ArH), 6.65 (s, 1H, CH=N), 4.50 (t, J = 7.2 Hz, 2H, NCH2), 3.22 (t, J = 7.2 Hz, 2H, CH2); IR (neat, cm−1) 3200, 1612, 743; HRMS (ESI-Q-TOF) m/z: [M + H]+ calc for C21H16ClN3O [M + H]+ 342.0824; found 342.0818.

General Procedure for the Synthesis of 1-Benzoyl-nitro-2,3,4,6,7,12-hexahydropyridimido[1′6′:1′2′]pyrido[3,4-d]biphenyldes 21. A solution of the enamino 7a (288 mg, 1 mmol), or nitroenamine 7g (230 mg,1 mmol), formaldehyde...
Copies of 1H NMR, 13C NMR, and HRMS spectra of compounds 7e, 7f, 8a,b, 8d, 11a,b, 13a–c, 13g, 14a, 14d, 14g, 17a–c, 17g, 19a, 20c, 20e, 21a–c (PDF)

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