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Friedel–Crafts Chemistry. Part 63. Syntheses of some *condensed N-heterocyclic* systems via combined Darzens and Friedel-Crafts approaches

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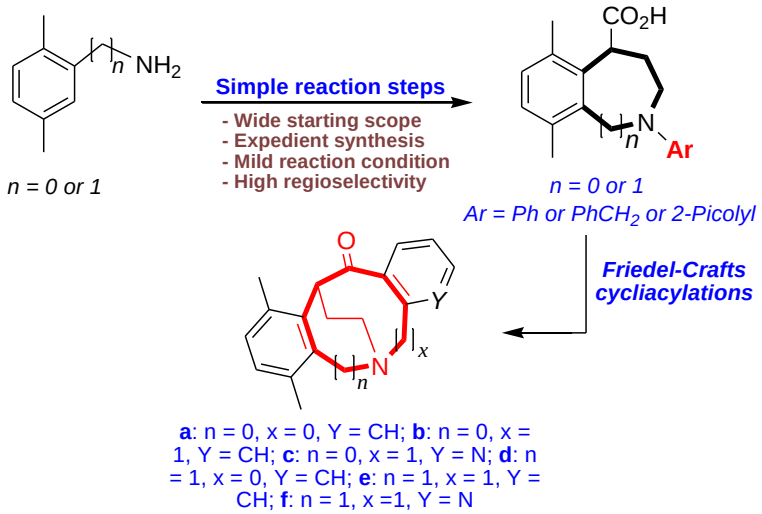
Abstract

An efficient protocol for the synthesis of novel fused *N*-heteropolycycles **10a-f** (tetracyclic-fused and bridged dibenzo-azepinone, -azocinones, -azoninone, benzo[*b*]pyrido[3,2-*f*]azocinone and benzo[*c*]pyrido[3,2-*g*]azoninones) via combined Darzens and Friedel-Crafts methodologies is described. The starting ketones **5a,b** were conveniently obtained via cyanoethylation of aminoxylenes **1a,b** followed by hydrolysis of the resulting nitriles **3a,b** to the corresponding carboxylic acids **4a,b** and were finally cycloacylated by intramolecular Friedel-Crafts reaction. The key acetylated intermediates **7a,b** were obtained by Darzens condensation. Subsequently, two steps led to substituted heterocyclic acids **9a-f** which successfully underwent Friedel–Crafts cycloacylations mediated by $AlCl_3/CH_3NO_2$, TfOH or P_2O_5 catalysts. The method offers readily access to diverse drug-like **10a-f** scaffolds in moderate to good yields.



Keywords: Friedel-Crafts cyclization, Darzens reaction, medium-sized *N*-heterocycles, azocines, azonines, Brønsted and Lewis acid catalysts

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Introduction

Polycyclic systems containing medium-sized *N*-heterocycles (e.g. benzofused and bridged-azepines and higher ring systems) are prominent scaffolds in numerous biologically active natural products[1-3] and pharmaceutically relevant compounds,[4-6] possessing a wide diversity of biologically activities (Figure1).[7-9] Given their structural complexity as well as their intriguing pharmacological activities, syntheses of these scaffolds have been subject to many synthetic endeavors.

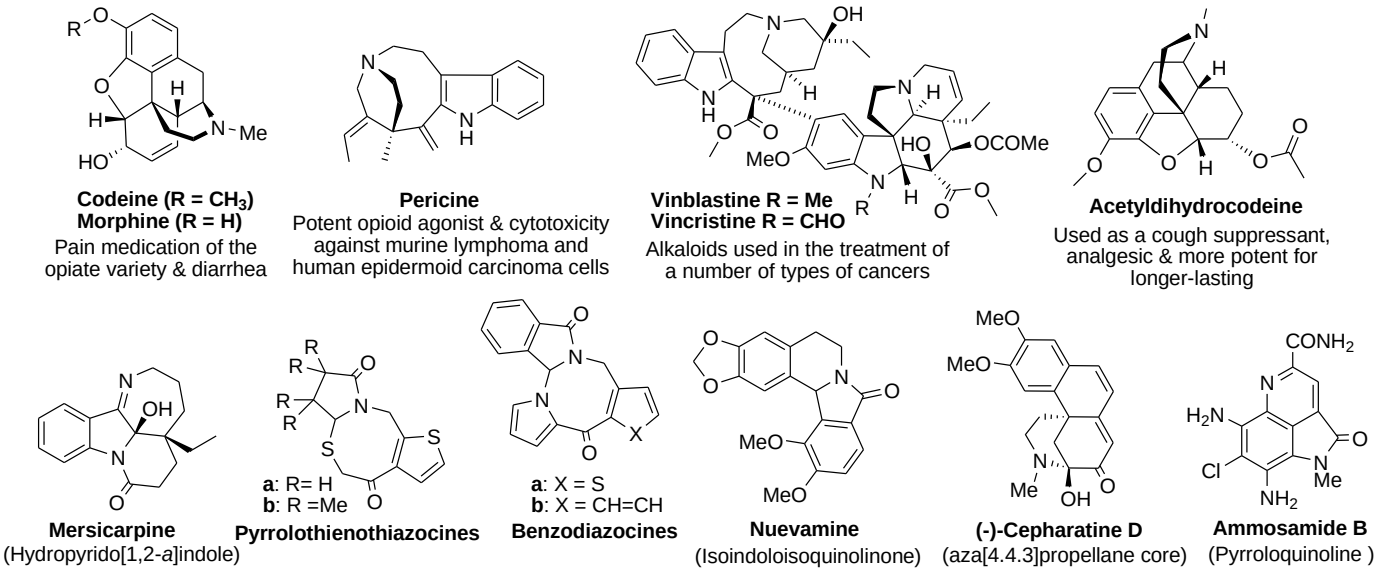

Figure 1. Some of biologically active natural alkaloids and examples of condensed heterocycles prepared by Friedel–Crafts processes.

In literature, numerous comprehensive reviews surveying their occurrence, synthetic strategies and biological activities have been published.[10,11] But up to our knowledge, even with these awesome accomplishments, there is a lack of efficient and generalized protocols for the synthesis of eight-and higher membered azahetereocycles. Only some examples of dopamine receptor antagonists have been isolated from several indole-alkaloid families, such as, Erythrina, Aspidosperma, Hasubanan and Iboga alkaloids.[12] The scarcity associated with the syntheses of condensed polycycles containing nine- and higher-membered amine containing ring systems can mainly be attributed to synthetic difficulties associated with the presence of a large number of conformations, low energetic transannular reactions[13] as well as with unfavorable entropy barriers.[14]

It is worthy of mention here that some of the successfully applied approaches to synthesize condensed azocine systems included: cycloaddition reactions between enamines and ethyl propiolate followed by electrocyclic ring-opening reaction,[15] cascade reactions of 1,2,4-triazines with enamines,[16] reductive ring-expansion reactions of aromatic cyclic ketoximes with di-isobutylaluminiumhydride,[17] intramolecular condensation of ethyl *N*-substituted-cyanomethylanthranilates using potassium tert-butoxide,[18] thermal isomerization reactions based on the *tert*-amino effect of *o,o*̀-functionalized biaryls originating from Suzuki reaction followed by the Knoevenagel condensation,[19] microwave-assisted Suzuki-Miyaura cross-coupling followed by ring-closing metathesis of various acyclic and alicyclic aminobiaryl intermediates,[20] Mo-alkylidene complexes catalyzed ring closing metathesis of appropriate diene-systems,[21] aza-Claisen rearrangement of

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substituted allylamines followed by intramolecular Heck reaction,[22] ring closing metathesis using Grubbs-catalyst derivatives of diene, enyne and amide intermediates formed by a reductive amination of 2-vinylindole carbaldehydes.[23] As a result, these pioneering syntheses proceeds from one of the following limitations: (i) limitations in substrate scope, (ii) utilizing expensive catalysts, (iii) low functional tolerance, (iv) syntheses proceeds through lengthy sequences with low overall yields.

In our previous work in this series, we developed new synthetic routes for the construction of a number of fused carbo-and heteropolycycles containing naphthalene, thiophene, quinoline and indole moieties via Friedel-Crafts cycloacylations of suitably synthesized precursors.[24-27] Herein, we extend our efforts applying some parallel facile protocols of broad applicability for the construction of a wide range of polyfunctionalized heteropolycycles including; dibenzo-azepinones, -azocinones, -azoninones, benzo[*b*]pyrido[3,2-*f*]azocinones and benzo[*c*]pyrido[3,2-*g*]azoninones, via Lewis and Brønsted acid-mediated Friedel–Crafts cycloacylations of easily prepared precursors.

Results and Discussion

Synthetically, the desired key starting bicyclic-heterocarboxylic acids **9a-f** were readily generated starting with the synthesis of propanenitriles **3a,b** (Scheme 1). These propionitriles were readily obtained in good yields via cyanoethylation[28] of the correspondingly aromatic amines **1a,b** with acrylonitrile (**2**) in the presence of $BnMe_3NOH$ (Triton B) under standard conditions. Basic hydrolysis of nitriles **3a,b** to the corresponding carboxylic acids **4a,b** using KOH in diethylene glycol, was followed by cyclization by H_2SO_4 to furnish quinolinone **5a** and benzo[*c*]azepinone **5b** in good yields. Treatment of these ketones with ethyl 2-bromopropanoate in the presence of EtONa in ether following Darzens[29] condensation yielded glycidic ester **6a,b**.

Hydrolysis of the latter esters were achieved by EtONa in ethanol, followed by decarboxylations of the resulting salts by heating with glacial acetic acid. This was accompanied by a vigorous CO_2 evolution and led to the acetyl derivatives **7a,b** in good yields. The key intermediate acids **8a,b** were obtained in 82–87% yields by the oxidative demethylation (Haloform) reactions of the resulting methyl ketones **7a,b** in the presence of iodine and KOH in dioxane. The requisite highly electrophilic precursors *N*-arylcarboxylic acids **9a-f** were readily prepared in moderate yield via Ullmann[30] coupling reactions of acids **8a,b** with various aromatic halides in presence of K_2CO_3 in DMF.

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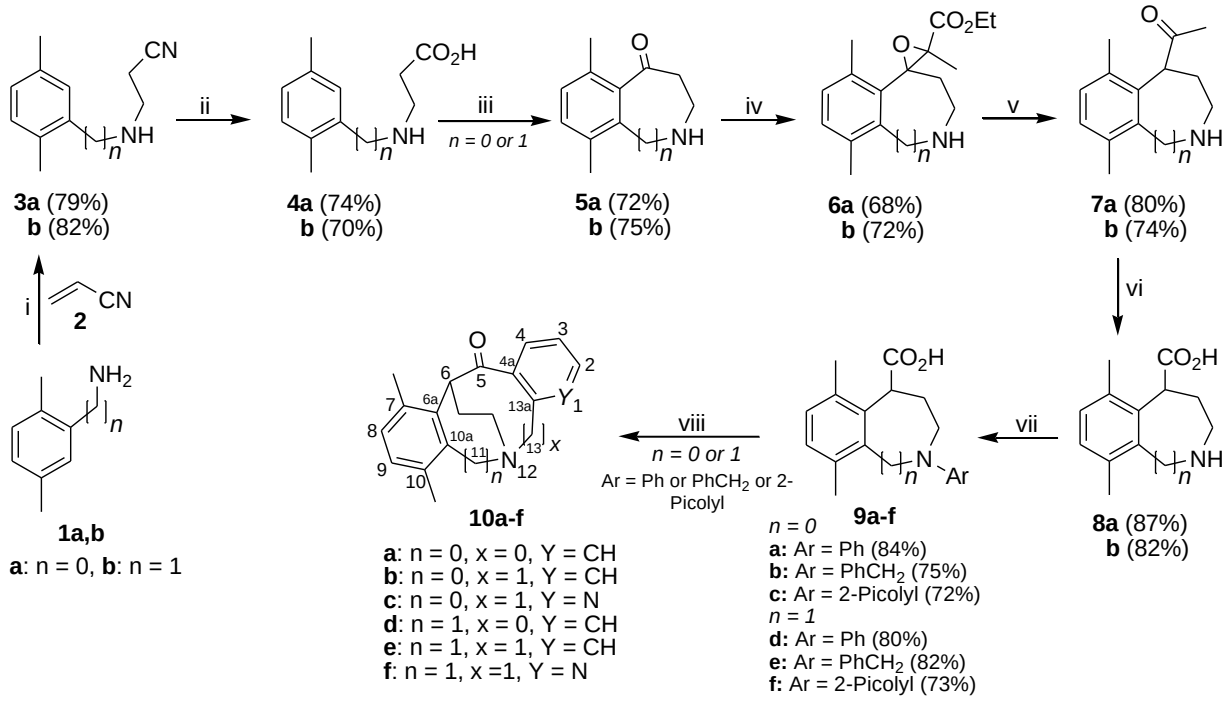

Scheme 1. Reagents and conditions: (i) Acrylonitrile (**2**)/$BnMe_3NOH$ (Triton B), dioxane, 80-90 °C, 5 h, (ii) KOH, DEG, 15h,Reflux, HCl, (iii) H_2SO_4 (85%), 90-100 °C, 6 h, (iv) $CH_3CHBrCO_2Et$/EtONa/ether, 0-5°C, 9 h, (v) *a.*EtONa/EtOH, 0-5°C, 5h, *b.* glacial AcOH, 70-80 °C, 1h, $NaHCO_3$, (vi) I_2/KOH, Dioxane, 60-70 ºC, 2 h, AcOH, (vii) Aryl halide (PhBr or $PhCH_2Cl$ or 2-Picolyl chloride), K_2CO_3/Pyridine/CuI, DMF, 110-20 °C, 10h, (viii) Cycloacylations of acids precursors mediated by $AlCl_3/CH_3NO_2$ or TfOH or P_2O_5 promoters (Table 1).

The versatility of this approach was demonstrated by the attempted cycloacylations of precursors **9a-f** to novel tetracyclic ketones **10a-f** via extensive optimization of the cyclization conditions. Therefore, several factors were considered as we further optimized the conditions to improve the effectiveness of the transformation such as the screening of more suitable acidic promoters, variations of the reaction temperature, the type of solvent and the length of the reaction time. The chosen conditions and their results are summarized in Scheme 1 and Table 1. Ring closure progress of substrates **9a-f** has been performed by using $AlCl_3/CH_3NO_2$ or TfOH (trifluoromethanesulfonic acid) or P_2O_5 catalysts as promoting Friedel-Crafts cycloacylation reactions. The structure elucidations of all new compounds were carried out by spectral and elemental analysis.

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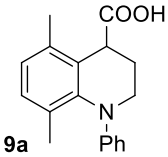
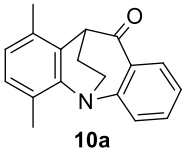
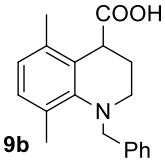
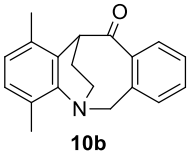
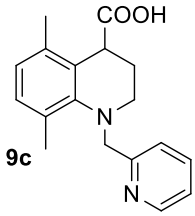
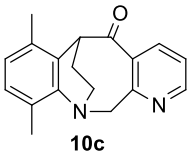
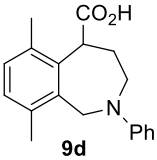
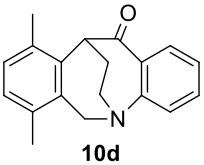
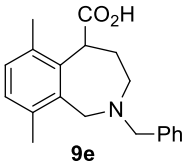
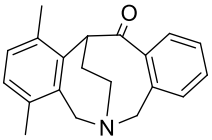
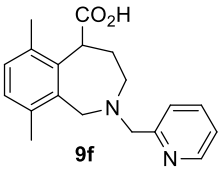
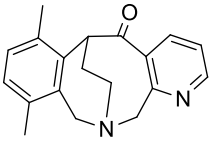
Table 1. Condition screening for intramolecular acylation of heterocyclic acids **9a–f**

Entry	Substrate	Cyclization conditions	Time, h	Product	Yield (%)
1	 **9a**	Method I*	10	 **10a**	83
		Method II**	6		75
		Method III***	12		70
2	 **9b**	Method I	11	 **10b**	86
		Method II	8		77
		Method III	15		80
3	 **9c**	Method I	18	 **10c**	82
		Method II	8		84
		Method III	16		76
4	 **9d**	Method I	14	 **10d**	78
		Method II	8		70
		Method III	18		71
5	 **9e**	Method I		 **10e**	79
		Method II	8		83
		Method III	8		75
6	 **9f**	Method I	20	 **10f**	86
		Method II	10		72
		Method III	10		70

* Method I: acids **9a**–**f** (4 mmol) in CH_2Cl_2 (10 ml), $AlCl_3$ (10 mmol), $MeNO_2$ (80 mmol), room temperature.

** Method II: acids **9a**–**f** (4 mmol), TfOH (1.6 ml, 20 mmol), 1,2-DCE (15 ml), 60–70 °C.

*** Method III: acids **9a**–**f** (4 mmol), P_2O_5 (5 g), toluene (15 mL), reflux.

The striking observations from initial examination of cyclization conditions suitable for hetero-acids **9a-f** led to the conclusion that several potentials had to be addressed for this type of cyclization reactions. In such cases, Friedel-Crafts ring closure is complicated by the continued presence of the poor leaving -OH group ability, as well as by the electrophilic inhibitions[31] of acidic promoters through their binding properties on the basic nitrogen (sp^3-hybridized) present in substrate. In an attempt to circumvent this issue, it was speculated from the classical valence bond theory[32] that the rate of the cyclization is strongly dependent on the catalyst strength, while the ease of the cyclization depends mainly on the binding activity of the acidic catalysts on the heteroatom present in the electron-rich substrate.

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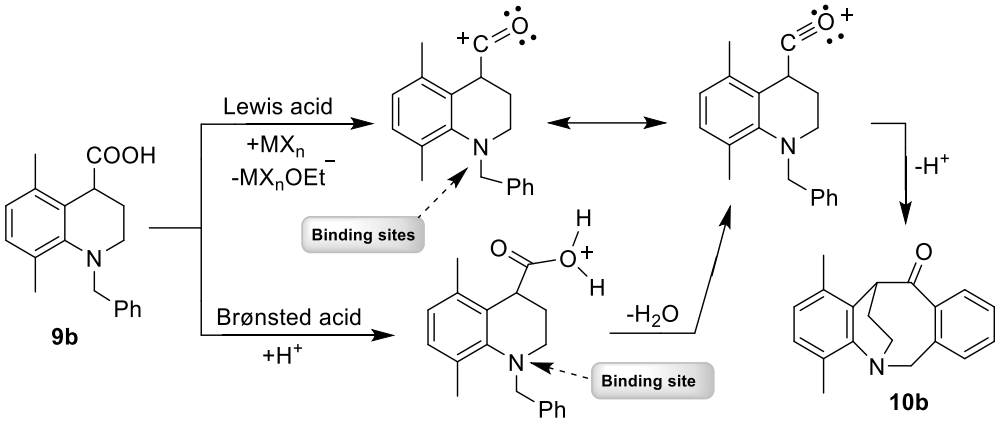
Presumably, the stronger the catalyst, the more it coordinates with the electron density of the heteroatom, leading ultimately to deactivation of its nucleophilicity and consequently, retardation of the cyclization process. Thus, mild strength catalysts favor the cyclization process in such cases. In fact, numerous literature studies on the mechanism of Friedel-Crafts acylations[33,34] have been reported and included two distinct mechanistic pathways for electrophilic aromatic substitutions depending on the nature of the acylating agent and the strength of the acidic promoters. For example, the suggested mechanistic rationalization for the formation of tetracyclic ketone **10b** from sufficiently electron rich precursor **9b** is presented in Scheme 2.

From a mechanistic point of view, acyl-cations, either a resonance stabilized σ-complex, or Wheland intermediate are generated by the treatment of heterocyclic acid **9b** with acidic promoters (Scheme 2). The catalyst-substrate σ-complex is formed using a Lewis acid, while Wheland intermediates form by the treatment of electron rich carboxylic acid with Brønsted acid, respectively. Subsequently, removal of H_2O molecules generates a free resonating acyl–carbocation σ-complex or an ion pair.[35] Electrophilic substitution reactions are taking place by loss of a ring proton to produce ketone **10b**.



Scheme 2. Proposed mechanisms for cycliacylations of heterocyclic acid **9b.**

It has been suggested[36] that a strongly electrophilic Lewis or Brønsted acid provide transition states resembling a π-complex, while the less electrophilic catalysts provide transition states similar to a stabilized polarized σ-complex. Increasingly, the electrophilicity of this complex is determined by a combination of the nature of the acylating agent and the strength of the acidic catalyst. However, the regiochemistry is determined by the nature of the transition state leading to the intermediate carbocation. These mechanistic investigations suggested that poor acid catalysts are unable to coordinate effectively with the heteroatoms. It seemed therefore that the low reactivities of the three selected catalysts we used are due to catalyst inhibition problems. Wherefore, more than stoichiometric or excess amounts of the oxophilic promoter necessary for the Friedel-Crafts cycloacylations of electron-rich arenes. Examination of the conditions suitable for the Friedel-Crafts cycloacylations proved more fruitful.

Concurrent with these studies, the literature precedents since the late 1930s showed a great effort, however exclusively on the use of the Friedel-Crafts processes for the construction of complex carbo- and heterocyclic scaffolds from highly reactive electron–deficient and electron–rich arenes (Figure 1) .[10,37-41]

The formation of cyclic products **10a-f** was proven based on the ^{1}H NMR, ^{13}C NMR and IR spectroscopic techniques. A closer look at the acetyl-intermediates **7a,b** showed that such molecules are emphasizing inequivalent protons due to the presence of chiral center and cyclic diastereotopic protons.

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For all of the acyclic precursors **9a-f** and the corresponding tetracyclic products **10a-f** involved, the generation of a stereogenic centre led to the fact that the adjacent methylene group protons become diastereotopic[42] in nature. In addition to the chirality of the carbon and nitrogen atoms, these rings have a large number of conformations[43] which collaborates with the non-bonded interactions between atoms,[44] the considerable amount of Baeyer, Pitzer and Prelog strains,[45] transannular reactions in medium-rings conformers[46] as well as the shielding effect exerted by the magnetic anisotropic effect[47] generated by heteroatoms. These effects lead to protons of the methylene group adjacent to the stereogenic center or bonded to the heteroatom, become inequivalent and are present as unresolved signals in their NMR spectrums (Figure 3).

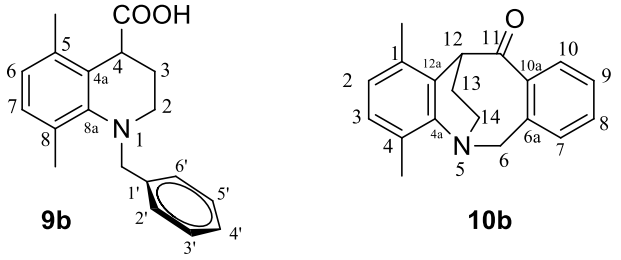

Figure 3. Diastereotopic protons containing tetracyclic structure **10b** and its acid precursor **9b.**

For example, a comparison of the spectroscopic data of heterocyclic acid **9b** and tetracyclic ketone **10b** does clearly show the disappearance of the characteristic COOH-stretch, found at 2610 cm^{-1} in the IR spectrum of acid **9b** and the appearance of the characteristic CO-stretch at 1700 cm^{-1} in the IR spectrum of ketone **10b**.

The inspection of the ^{1}H NMR spectrum of acid **9b** and ketone **10b** displays unresolved signals unlike the other multiplets of the spectrum. Thus, the ^{1}H NMR of the carboxylic acid **9b** displayed several distinct signals in which the aromatic protons appeared in the range of δ 6.43-7.27 ppm, two methyl groups appeared as singlets near δ 2.12 and 2.27 ppm, benzylic-CH_2 showed as characteristic singlet near δ 4.32 ppm and the diagnostic COOH signal at δ 10.85 ppm.

As expected, the remaining three characterized signals included two bridged diastereotopic CH_2 groups and the chiral CH proton. These appeared as a complex set of overlapped signals with different coupling constants. The upfield diastereotopic protons of C^3H_2-group (pseudo-axial & -equatorial; H_a & H_b) appeared near δ 2.09 ppm with multiplicities of doublet of doublet of doublet of doublets with different coupling constants. From the other hand, the C^4H proton appeared as doublet of doublets near δ 4.07 ppm with coupling constants, 9.8 and 4.4 Hz. The third downfield signal for N-C^2H_2 protons appeared at δ 3.24 ppm with multiplicities of doublet of doublet of doublets and three coupling constants of 13.7, 6.9 and 1.8 Hz.

In comparison, the ^{1}H NMR of azocinone skeleton **10b** showed aromatic proton signals in the range of δ 6.43-7.86 ppm, two methyl groups appeared as singlets at δ 2.10 and 2.26 ppm, cyclic N-C^6H_2 protons appeared as doublet near δ 4.46 ppm with coupling constants of 13.8 Hz. The upfield $C^{13}H_2$-protons appeared near δ 1.98 ppm with multiplicities of doublet of doublet of doublet of doublets with coupling constants 13.3, 7.9, 3.5 and 3.3 Hz. The chiral-$C^{12}H$ proton appeared as doublet of doublets near δ 4.19 ppm with coupling constants 5.1 and 1.5 Hz.

However, the downfield N-$C^{14}H_2$ protons appeared at δ 3.44 ppm as doublet of doublet of doublets with coupling constants of 14.4, 7.9 and 3.5 Hz. Also, the ^{1}H NMR spectrum of ketone **10b** indicates the

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absence of the diagnostic carboxylic acid signal shown at δ 10.85 ppm. Further, changes in the ^{13}C NMR spectra proved that the cyclization process had occurred with the disappearance of the COOH-peak at 176 ppm in the ^{13}C NMR spectrum of acid **9b** and the appearance of a new carbonyl group at 197 ppm in the ^{13}C NMR spectrum of ketone **10b**.

Conclusions

In summary, we have developed a novel easy and concise catalytic protocol for the synthesis of tetracyclic heteroaromatic scaffolds **10a-f**, in particular, dibenzo-azepinone, -azocinones, azoninone, benzo[*b*]pyrido[3,2-*f*]azocinone and benzo[*c*]pyrido[3,2-*g*]azoninones via combined Darzens condensations and Friedel-Crafts cycloacylations starting from simple readily available acyclic precursors. The operational simplicity and ready availability of all precursors should make this methodology a useful tool for the assembly of the structurally diverse fused *N*-heterocycles in very good overall yields.

Experimental Section

General. All chemicals used were of reagent grade and solvents were freshly distilled and dried by standard procedures before use. Melting points were taken on a digital Gallenkamp capillary melting point apparatus and are uncorrected. Infrared (IR) spectra were obtained on a Perkin-Elmer 1600 FT-IR spectrophotometer using KBr wafer and thin film techniques (ν cm^{-1}) and are in cm^{-1}; The NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^1H NMR, 100 MHz for ^{13}C NMR) using $CDCl_3$ solvent with tetramethylsilane (Me_4Si, TMS) as internal standard. Chemical shifts (δ) and *J* values are reported in ppm and Hz, respectively. Elemental analyses were carried out by a GmbH Vario EL III, 2400, CHNOS-elemental analyzer. The progress of reactions were monitored by thin-layer chromatography (TLC) analysis on precoated silica plates (Silufol, UV-254 TLC, aluminum sheets) and plates were visualized with UV light (at 254 and/or 360 nm). Flash column chromatography, where necessary, was performed on silica gel (230–400 mesh).

General procedure for the synthesis of substituted aryl propanenitriles 3a,b. To an ice-cold solution of aromatic amines **1a** or **1b** (35.00 mmol) and acrylonitrile **2** (3.4 g, 42.00 mmol) in dioxane (25 mL) was added triton B (1.5 ml). The reaction mixture was heated in a water bath at 80-90 °C for 5 h. The mixture was then cooled and concentrated in *vacuo*. The resultant pasty was triturated with methanol (3×5 mL) and the resultant precipitate was filtered, washed with methanol and finally dried to give the crude product **3a,b**. Crystal appearance , yields, and spectral data of acids **3a,b** are given:

3-(2,5-Dimethylphenylamino)propanenitrile (3a). White plates; 79%; mp 59-61 °C (acetone); IR (KBr, *v*, cm^{-1}): 3420 (N-H), 3045 (Ar-H), 2975 (C-H), 2250 (CN), 1600, 1585, 1480, 1445, 1375, 1245, 775. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.08 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.95 (2H, t, *J* 6.7 Hz, NH-C^3H_2), 3.23 (2H, t, *J* 6.7 Hz, -C^2H_2), 6.32 (1H, dd, *J* 1.2, 0.5 Hz), 6.64-6.84 (2H, dd, *J* 7.8, 1.2 Hz), 9.84 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.7 (1C, -*C*H_3), 18.6 (1C, -*C*H_3), 21.3 (1C, $C^{\alpha}H_2$, C-2), 39.6 (1C, $C^{\beta}H_2$, C-3), 114.4 (1C, Ar.,C-6), 118.0 (1C, -CN),129.1 (1C, Ar.,C-4), 129.9 (1C, Ar.,C-3), 130.3 (1C, Ar.,C-2), 133.7 (1C, Ar.,C-5), 140.2 (1C, Ar.,C-1). Anal. Calcd. for $C_{11}H_{14}N_2$ (174); C, 75.86; H, 8.04; N, 16.09. Found; C, 75.77; H, 8.14; N, 16.15%.

3-(2,5-Dimethylbenzylamino)propanenitrile (3b).Pale yellow plates; 82%, mp 84-86 ºC (benzene); IR (KBr, *v*, cm^{-1}): 3490 (N-H), 3020 (Ar-H), 2990 (C-H), 2235 (CN), 1600, 1590, 1480, 1440, 1370, 1250, 774. ^1H NMR (400

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MHz, $CDCl_3$, δ, ppm): 2.12 (3H, s, CH_3), 2.32 (3H, s, CH_3), 2.83 (2H, t, *J* 6.8 Hz, NH-C^3H_2), 2.89 (2H, t, *J* 6.8 Hz, -C^2H_2), 3.67 (2H, s, Ph*CH₂*), 6.77-6.99 (2H, dd, *J* 8.2, 2.5 Hz), 7.20 (1H, dd, *J* 2.5, 0.5 Hz), 9.92 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 18.6 (1C, -*C*H_3), 20.0 (1C, -*C*H_3), 21.3 (1C, $C^{\alpha}H_2$, C-2), 44.2 (1C, $C^{\delta}H_2$, C-3), 46.7 (1C, $C^{\beta}H_2$, C-3), 118.0 (1C, Ar.,C-6), 127.4 (1C, -CN), 128.9 (1C, Ar.,C-4), 129.1 (1C, Ar.,C-3), 129.8 (1C, Ar.,C-2), 134.8 (1C, Ar.,C-5), 135.3 (1C, Ar.,C-1). Anal. Calcd. for $C_{12}H_{16}N_2$ (188); C, 76.59; H, 8.51; N, 14.89. Found; C, 76.50; H, 8.60; N, 14.84 %.

General procedure for the synthesis of substituted bicyclic ketones 5a,b. These intermediate compounds were obtained in two reaction steps starting with propanenitriles **3a,b**. A summary of the steps is given in the following:

(i) To a solution of nitrile **3a** or **3b** (15.00 mmol) in diethylene glycol (30mL) was added a solution of potassium hydroxide (5.6 g, 100.00 mmol) in H_2O (6 mL) and the resulting mixture was refluxed for 15 h. The reaction mixture was then cooled and poured into ice-cold water (200 ml). The mixture was neutralized to pH 6-7 using HCl solution (5%). After standing for overnight, the resulted solid was collected, washed and dried to give crude acids **4a,b**. Further purification and yields are given in the following.

3-((2,5-dimethylphenyl)amino)propanoic acid (**4a**). Pale yellow crystals; 74 %; mp 141-43 °C (ethanol); IR (KBr, *v*, cm^{-1}): 3380 (N-H), 3050 (Ar-H), 2975 (C-H), 2560 (OH), 1715 (C=O), 1600, 1590, 1480, 1440, 1380, 1255, 1120, 784. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.08 (3H, s, CH_3), 2.26 (3H, s, CH_3), 2.50 (2H, t, *J* 6.8 Hz, NH-C^3H_2), 3.22 (2H, t, *J* 6.8 Hz, -C^2H_2), 4.45 (1H, s, NH), 6.32 (1H, dd, *J* 1.2, 0.5 Hz), 6.64-6.84 (2H, dd, *J* 7.8, 0.5 Hz), 9.97 (s, 1H, COOH). Anal. Calcd. for $C_{11}H_{15}NO_2$ (193); C, 68.39; H, 7.77; N, 7.25. Found; C, 68.27; H, 7.90; N, 7.31%.

3-((2,5-dimethylbenzyl)amino)propanoic acid (4b). Cream crystals; 70 %; mp 147-49 °C (ethanol); IR (KBr, *v*, cm^{-1}): 3420 (N-H), 3010 (Ar-H), 2988 (C-H), 2525 (OH), 1718 (C=O), 1600, 1590, 1480, 1440, 1365, 1230, 1128, 790. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.18 (6H, s, 2CH_3), 2.27 (3H, s, CH_3), 2.48 (2H, t, *J* 6.8 Hz, NH-C^3H_2), 2.85 (2H, t, *J* 6.8 Hz, -C^2H_2), 3.66 (2H, s, C^5H_2), 4.38 (1H, s, NH), 6.32 (1H, dd, *J* 1.2, 0.5 Hz), 6.60-6.84 (2H, dd, *J* 7.8, 0.5 Hz), 10.52 (s, 1H, COOH). Anal. Calcd. for $C_{12}H_{17}NO_2$ (207); C, 69.56; H, 8.21; N, 6.76. Found; C, 69.50; H, 8.34; N, 6.80%.

(ii) A mixture of carboxylic acid **4a** or **4b** (10.00 mmol) and H_2SO_4 (15 ml, 85%) was heated on a steam bath at 90-100 °C for 6 h. The resultant dark brown syrup was cooled to 0 °C and quenched by pouring into ice-cold water (150 mL) with vigorous stirring. Basification of the resulting solution with $NaHCO_3$ and the mixture was left to stand for 3h at room temperature. The oily residue was extracted with AcOEt (3×30 mL). The organic extracts was separated, washed with water, dried over $MgSO_4$ and concentrated to dryness to give the crude ketones **5a,b** as dark oil which crystallized on standing. Further purification and yields are given in the following.

2,3-Dihydro-5,8-dimethylquinolin-4(1*H*)-one (5a). Yellow crystals; 72%; mp 132–34°C (benzene); IR (KBr, ν, cm^{-1}): 3410 (N-H), 3040 (Ar-H), 2985 (C-H), 1700 (C=O), 1600, 1590, 1450, 1440, 1380, 1277, 1072, 766. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.19 (3H, s, CH_3), 2.33 (3H, s, CH_3), 2.62 (2H, ddd, *J* 14.8, 6.7, 2.4 Hz, NH-C^2H_2), 3.39 (2H, ddd, *J* 13.6, 6.7, 2.4 Hz, -C^3H_2), 6.68 (1H, d, *J* 8.1 Hz), 6.84 (1H, d, *J* 8.1 Hz), 9.74 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.7 (1C, -*C*H_3), 20.0 (1C, -*C*H_3), 39.4 (1C, C^3H_2, C-3), 41.4 (1C, C^2H_2, C-2), 113.0 (1C, Ar.,C-4a), 128.9 (1C, Ar.,C-6), 129.2 (1C, Ar.,C-8), 130.3 (1C, Ar.,C-7), 136.8 (1C, Ar.,C-5), 137.2 (1C, Ar.,C-8a), 196.2 (1C, C=O, C-4). Anal. Calcd. for $C_{11}H_{13}NO$ (175); C, 75.42; H, 7.42; N, 8.00. Found; C, 75.38; H, 7.50; N, 8.10 %.

1,2,3,4-Tetrahydro-6,9-dimethylbenzo[*c*]azepin-5-one (5b). Pale yellow needles; 75%; mp 114-16°C (ethanol); IR (KBr, ν, cm^{-1}): 3430 (N-H), 3062 (Ar-H), 2995 (C-H), 1695 (C=O), 1600, 1582, 1450, 1440, 1366, 1271, 1075, 690. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.25 (3H, s, CH_3), 2.40 (3H, s, CH_3), 2.76 (2H, ddd, *J* 15.6, 7.3, 3.7 Hz, -

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NH-C^3H_2), 3.08 (2H, ddd, *J* 9.9, 7.3, 3.7 Hz, -C^4H_2), 3.98 (2H, d, *J* 16.8 Hz, -C^1H_2), 7.02 (1H, d, *J* 8.2 Hz), 7.48 (1H, d, *J* 8.2 Hz), 10.06 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.0 (2C, 2CH_3), 40.7 (1C, C^4H_2, C-4), 41.6 (1C, C^3H_2, C-3), 46.7 (1C, C^1H_2, C-1), 126.4 (1C, Ar.,C-9), 128.8 (2C, Ar., C-7, C-8), 131.3 (1C, Ar.,C-6), 131.5 (1C, Ar.,C-9a), 136.3 (1C, Ar.,C-5a), 198.5 (1C, 1C, C=O, C-5). Anal. Calcd. for $C_{12}H_{15}NO$ (189); C, 76.19; H, 7.93; N, 7.40. Found; C, 76.15; H, 8.02; N, 7.36%.

General procedure for the synthesis of glycidic ester 6a,b.

To an ice-cold stirred mixture of ketones **5a** or **5b** (10.02 mmol) and ethyl 2-bromopropanoate (10.08 mmol) in anhydrous ether (30 ml) was added dropwise over 1.5 h a solution of freshly prepared sodium ethoxide (1g, 15 mmol) in absolute ethanol (10 ml). After complete addition, the ice-bath was removed and the mixture was allowed to stir at room temperature for 7 h. Ice water (20 ml) was then added and the mixture was neutralized by cold HCl solution (5%). After standing for 2h in refrigerator, the ether solution was separated and the mixture was extracted with ether (3×30 mL). The combined ether extracts was washed successively with water, saturated $NaHCO_3$ solution and finally with saturated NaCl solution. After drying over $MgSO_4$ and filtration, the solution was evaporated in *vacuo* to give crude glycidic ester **6a,b** as brownish viscous oil. These products were further purified by flash column chromatography (basic alumina, EtOAc/*n*–hexane, 1/1) gave pure esters as a brown oily products which crystallized on standing.

Ethyl 3,5',8'-trimethyl-2',3'-dihydro-1'*H*-spiro[oxirane-2,4'-quinoline]-3-carboxylate (6a). Brown solid; 68%; mp 64-66°C (ethanol); IR (KBr, ν, cm^{-1}): 3410 (N-H), 3010 (Ar-H), 2987 (C-H), 1745 (C=O), 1600, 1580, 1440, 1340, 1274, 1126, 794. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.31 (3H, t, *J* 7.1 Hz, $\underline{CH_3}CH_2O$), 1.58 (3H, s, C^3H_3), 1.93 (2H, ddd, *J* 14.5, 10.0, 2.0 Hz, C^3H_2), 2.10 (3H, s, $C^{5'}H_3$), 2.34 (2H, ddd, *J* 14.2, 3.5, 2.0 Hz, C^2H_2), 2.32 (3H, s, $C^{8'}H_3$), 3.12 (2H, ddd, *J* 14.9, 3.5, 2.0 Hz), 3.23 (ddd, *J* 14.9, 10.0, 2.0 Hz), 4.16 (2H, q, *J* 7.1 Hz, $CH_3\underline{CH_2O}$), 6.46 (1H, d, *J* 8.0 Hz), 6.68 (1H, d, *J* 7.0 Hz), 9.84 (s, 1H, NH). Anal. Calcd. for $C_{16}H_{21}NO_3$ (275); C, 69.81; H, 7.63; N, 5.09. Found; C, 70.05; H, 7.62; N, 4.88%.

Ethyl 3',6,9-trimethyl-1,2,3,4-tetrahydrospiro[benzo[*c*]azepine-5,2'-oxirane]-3'-carboxylate (6b). Brown crystals; 72%; mp 80-83°C (ethanol); IR (KBr, ν, cm^{-1}): 3390 (N-H), 3030 (Ar-H), 2995 (C-H), 1740 (C=O), 1600, 1580, 1445, 1377, 1250, 1145, 690. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.33 (3H, t, *J* 7.1 Hz, $\underline{CH_3}CH_2O$), 1.60 (3H, s, $C^{3'}H_3$), 2.09 (1H, ddd, *J* 14.8, 10.3, 2.8 Hz, C^4Ha), 2.23 (6H, s, C^6H_3 & C^9H_3), 2.42(1H, ddd, *J* 14.8, 2.9, 2.7 Hz, C^4Hb), 2.81 (2H, ddd, *J* 10.3, 9.9, 2.9 Hz, -N-C^3H_2), 3.82-4.04 (2H, d, *J* 15.1 Hz, C^1H_2), 4.01 (1H, d, *J* 15.1 Hz), 4.22 (2H, q, *J* 7.1 Hz, $CH_3\underline{CH_2O}$), 6.86-6.94 (2H, d, *J* 8.2 Hz), 10.24 (s, 1H, NH). Anal. Calcd. for $C_{17}H_{23}NO_3$ (289); C, 70.58; H, 7.95; N, 4.84. Found; C, 70.40; H, 7.86; N, 5.02%.

General procedure for the synthesis of bicyclic ethanone-amines 7a,b.

To an ice-cold stirred solution of sodium ethoxide (26.05 mmol, 1.78 g) in absolute ethanol (10 ml) was added water (1 ml) and the solution was stirred for 10 min. A solution of glycidic ester **6a** or **6b** (24.00 mmol) in absolute ethanol (20 ml) was added dropwise over a 10 min and the reaction was left to stir for 5 h at room temperature. The salt formed was filtered and washed with ice-cold ethanol (10 ml) to give the crude sodium salts which were used in the next transformation without further purification. The resulting crude sodium salts (15.02 mmol) was cooled in ice-bath and treated with glacial acetic acid (20 ml). A vigorous evolution of carbon dioxide occurred and after stirring at room temperature for around 20 min, the reaction had subsided. The reaction mixture was then heated on a steam-bath at 70-80 °C for 30 min or until the evolution of gases ceased. The reaction mixture was then cooled, diluted with water (150 ml), basified with $NaHCO_3$ and extracted with ether (3x30 ml). The combined organic extracts was washed with water (2x30 ml), with $NaHCO_3$ solution (10%, 30 ml), dried over $MgSO_4$. After filtration, the solution was concentrated under reduced pressure to afford crude ethanones **7a,b**.

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1-(1,2,3,4-Tetrahydro-5,8-dimethylquinolin-4-yl)ethanone (7a). Yellow crystals; 80%; mp 120–22°C (benzene); IR (KBr, ν, cm^{-1}): 4050 (N-H), 3020 (Ar-H), 2980 (C-H), 1690 (C=O), 1600, 1580, 1440, 1380, 1270, 1100, 790. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.10 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.25 (3H, s, CO*CH₃*), 2.40 (2H, dddd, *J* 13.5, 7.2, 6.9, 1.9 Hz, -NH-C^2H_2), 3.25 (2H, ddd, *J* 14.3, 6.9, 1.9 Hz, -C^3H_2), 3.65 (1H, dd, *J* 9.7, 4.6 Hz, -C^4H), 6.41 (1H, d, *J* 8.0 Hz), 6.77 (1H, d, *J* 8.0 Hz), 9.80 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.7 (1C, -*C*H_3), 20.0 (1C, -*C*H_3), 29.0 (1C, -CO*CH₃*), 29.8 (1C, CH, C-4), 41.6 (1C, C^3H_2, C-3), 54.1 (1C, C^2H_2, C-2), 128.0 (1C, Ar.,C-4a), 128.9 (1C, Ar.,C-6), 129.2 (1C, Ar.,C-7), 130.3 (1C, Ar.,C-8), 136.3 (1C, Ar.,C-5), 137.2 (1C, Ar.,C-8a), 208.4 (1C, C=O). Anal. Calcd. for $C_{13}H_{17}NO$ (203); C, 76.84; H, 8.37; N, 6.89. Found; C, 76.88; H, 8.41; N, 6.82%.

1-(2,3,4,5-Tetrahydro-6,9-dimethyl-1H-benzo[*c*]azepin-5-yl)ethanone (7b). Yellow needles; 74%, m.p. 141-43°C (AcOEt); IR (KBr, ν, cm^{-1}): 3390 (N-H), 3070 (Ar-H), 2990 (C-H), 1715 (C=O), 1600, 1580, 1440, 1330, 1275, 1155, 790. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.08 (2H, dddd, *J* 13.4, 6.6, 4.8, 2.6 Hz, C^4H_2), 2.15 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.27 (3H, s, CO*CH₃*), 2.97 (2H, ddd, *J* 9.8, 6.6, 2.6 Hz, -NH-C^2H_2), 3.82 (2H, d, *J* 14.5 Hz, C^1H_2), 3.93 (1H, dd, *J* 8.1, 1.4 Hz, C^5H), 6.72 (1H, d, *J* 8.2 Hz), 6.79 (1H, d, *J* 8.2 Hz), 9.65 (s, 1H, NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 19.9 (2C, 2*C*H_3), 29.0 (1C, -CO*CH₃*), 29.8 (1C, C^4H_2, C-4), 41.6 (1C, CH, C-5), 46.7 (1C, C^3H_2, C-3), 54.1 (1C, C^1H_2, C-1), 126.4 (1C, Ar.,C-9), 128.8 (2C, Ar., C-7, C-8), 132.9 (1C, Ar.,C-6), 136.3 (2C, Ar.,C-5a, C-9a), 210.0 (1C, C=O). Anal. Calcd. for $C_{14}H_{19}NO$ (217); C, 77.42; H, 8.75; N, 6.45. Found; C, 77.52; H, 8.68; N, 6.42%.

General procedure for the synthesis of heterocyclic acids 8a,b.

To a stirred solution of ethanone **7a** or **7b** (6.04 mmol) in dioxane (20 mL) was added KOH solution (3.5 g, 60.01 mmol) in water (10 ml). A solution of iodine (25 mmol) prepared from 6.4 g I_2 and 12.4 g KI in H_2O (30 ml) was added dropwise with stirring over 10 min at room temperature. The resulting yellow solution was left to stir at room temperature until fading the yellow color. The resultant solution was then heated on water-bath for 2 h at 60-70 ºC. The resulting solution was evaporated to dryness in vacuo, cooled and the residue dissolved in hot H_2O (50 ml). After filtration, the solution was cooled and neutralized with ice-cold AcOH solution (10%) to pH 6-7. After standing for overnight in refrigerator, the resulting light tan solid was collected, washed with water and dried to give the crude acids **8a,b.**

1,2,3,4-Tetrahydro-5,8-dimethylquinoline-4-carboxylic acid (8a). Yellow crystals; 87%; mp 110-12 °C (ethanol); IR (KBr, *ν*, cm^{-1}): 3420 (N-H), 3060 (Ar-H), 2984 (C-H), 2640 (OH), 1718 (C=O), 1600, 1585, 1470, 1440, 1363, 1185, 793. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.01 (2H, dddd, *J* 13.3, 7.2, 6.9, 1.9 Hz, C^3H_2), 2.10 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.19 (2H, ddd, *J* 13.9, 6.9, 1.9 Hz, -NH-C^2H_2), 4.02 (1H, dd, *J* 9.7, 4.6 Hz, -C^4H), 4.60 (1H, s, NH), 6.43 (1H, d, *J* 8.0 Hz), 6.77 (1H, d, *J* 8.0 Hz), 10.62 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.6 (1C, *C*H_3), 20.0 (1C, *C*H_3), 29.0 (1C, C^3H_2, C-3), 41.6 (1C, C^2H_2, C-2), 51.2 (1C, C^4H, C-4), 128.0 (1C, Ar.,C-6), 128.9 (1C, Ar.,C-4a), 129.2 (1C, Ar.,C-7), 130.3 (1C, Ar.,C-8), 136.3 (1C, Ar.,C-5), 137.2 (1C, Ar.,C-8a), 174.5 (1C, COOH). Anal. Calcd. for $C_{12}H_{15}NO_2$ (205); C, 70.24; H, 7.31; N, 6.82. Found; C, 70.32; H, 7.33; N, 6.75%.

2,3,4,5-Tetrahydro-6,9-dimethyl-1*H*-benzo[*c*]azepine-5-carboxylic acid (8b). brownish solid; 82%; mp 154-56 °C (benzene); IR (KBr, *ν*, cm^{-1}): 3390 (N-H), 3010 (Ar-H), 2975 (C-H), 2590 (OH), 1715 (C=O), 1600, 1590, 1470, 1440, 1377, 1158, 765. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.00 (2H, dddd, *J* 13.3, 6.6, 4.7, 2.6 Hz, C^4H_2), 2.15 (3H, s, CH_3), 2.23 (3H, s, CH_3), 3.00 (2H, ddd, *J* 8.7, 6.6, 2.6 Hz, -NH-C^3H_2), 3.83 (2H, d, *J* 14.5 Hz, C^1H_2), 4.09 (1H, dd, *J* 8.1, 1.4 Hz, -C^5H), 4.50 (1H, s, NH), 6.67 (1H, d, *J* 8.2 Hz), 6.76 (1H, d, *J* 8.2 Hz), 10.40 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.0 (2C, 2*C*H_3), 29.0 (1C, C^4H_2, C-4), 41.6 (1C, C^5H, C-5), 46.7 (1C, C^3H_2, C-3), 51.2 (1C, C^1H_2, C-1), 126.4 (1C, Ar.,C-6), 128.9 (2C, Ar.,C-7, C-8), 132.9 (1C, Ar.,C-9), 136.3 (2C, Ar.,C-5a, C-9a), 176.6 (1C, COOH). Anal. Calcd. for $C_{13}H_{17}NO_2$ (219); C, 71.23; H, 7.76; N, 6.39. Found; C, 71.20; H, 7.82; N, 6.34%.

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General procedure for N-arylation of heterocyclic acids 9a,b.

To a mixture of acid **8a** or **8b** (8 mmol), K_2CO_3 (20 mmol), pyridine (1 mL) and CuI (0.3 g) in DMF (30 mL) was added slowly a solution of *PhBr or PhCH₂Cl or 2-Picolyl chloride* (10 mmol) in DMF (20 mL). The reaction mixture was heated with continuous stirring for 10 h at 110-20 °C. The mixture was maintained at this temperature and monitored by TLC (30% AcOEt/hexane) until indicated that the reaction was complete. The mixture was then cooled and treated with NaOH solution (30 mL, 5%) and decolorizing carbon (1g). The mixture was then boiled for 20 min, cooled and filtered. The resulting filtrate was cooled to 0 °C and acidified using HCl solution (30 mL, 20%). After standing at refrigerator for overnight, the precipitate was filtered, washed and dried to afford the crude product **9a-d**. Further purification, yields and spectral data are given in the following:

1,2,3,4-Tetrahydro-5,8-dimethyl-1-phenylquinoline-4-carboxylic acid (9a). Pale yellow needles; 84%; mp 162-4 ºC (ethanol); IR (KBr, ν, cm^{-1}): 3390 (OH), 3035 (Ar-H), 2950 (C-H), 2520, 1720 (C=O), 1600, 1585, 1470, 1440, 1370, 1144, 777. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.10 (2H, dddd, *J* 13.1, 6.9, 6.6, 2.5 Hz, -C^3H_2), 2.16 (3H, s, CH_3), 2.29 (3H, s, CH_3), 3.48 (2H, ddd, *J* 16.7, 6.6, 2.5 Hz, -NH-C^2H_2), 3.89 (1H, dd, *J* 10.1, 3.8 Hz, -C^4H), 6.43 (1H, d, *J* 7.9 Hz), 6.52 (2H, dtd, *J* 8.2, 1.2, 0.5 Hz), 6.80 (1H, d, *J* 7.9 Hz), 6.98 (1H, tt, *J* 8.1, 1.2 Hz), 7.22 (2H, dddd, *J* 8.2, 8.1, 1.3, 0.5 Hz), 10.61 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.3 (1C, *C*H_3), 20.5 (1C, *C*H_3), 29.0 (1C, C^3H_2, C-3), 50.1 (1C, CH, C-4), 51.2 (1C, C^2H_2, C-2), 124.5 (2C, Ar., C-6, C-4'), 127.8 (1C, Ar.,C-2'), 128.0 (1C, Ar.,C-6'), 128.2 (2C, Ar.,C-7, C-8), 128.9 (1C, Ar.,C-3'), 130.3 (1C, Ar.,C-5'), 136.3 (1C, Ar.,C-4a), 137.1 (1C, Ar.,C-5), 137.7 (1C, Ar., C-8a), 148.7 (1C, Ar., C-1'), 174.5 (1C, COOH). Anal. Calcd. for $C_{18}H_{19}NO_2$ (281); C, 76.86; H, 6.76; N, 4.98. Found; C, 76.90; H, 6.82; N, 4.90%.

1-Benzyl-1,2,3,4-tetrahydro-5,8-dimethylquinoline-4-carboxylic acid (9b). Yellow crystals; 75%; mp 155-57 °C (acetone); IR (KBr, ν, cm^{-1}): 3345 (OH), 3040 (Ar-H), 2966(C-H), 2610, 1720 (C=O),, 1610, 1580, 1480, 1445, 1364, 1195, 768; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.09 (2H, dddd, *J* 13.5, 7.1, 6.9, 1.8 Hz, C^3H_2), 2.12 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.24 (2H, ddd, *J* 13.7, 6.9, 1.8 Hz, -NH-C^2H_2), 4.07 (1H, dd, *J* 9.8, 4.4 Hz, -C^4H), 4.32 (2H, s, $PhCH_2$), 6.43 (1H, d, *J* 8.0 Hz), 6.67 (1H, d, *J* 8.0 Hz), 7.19 (1H, tt, *J* 7.7, 1.3 Hz), 7.27 2H, dddd, *J* 7.9, 7.7, 1.8, 0.5 Hz), 7.27 (2H, dddd, *J* 7.9, 1.3, 1.0, 0.5 Hz), 10.85 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.7 (1C, *C*H_3), 20.0 (1C, *C*H_3), 29.0 (1C, C^3H_2, C-3), 50.1 (1C, CH, C-4), 51.2 (1C, C^2H_2, C-2), 54.7 (1C, benzylic-CH_2), 127.8 (3C, Ar.,C-4a, C-6, C-8), 128.0 (1C, Ar., C-7), 128.4 (2C, Ar.,C-3', C-5'), 128.9 (1C, Ar., C-4'), 130.3 (1C, Ar., C-2'), 136.3 (1C, Ar., C-6'), 136.6 (1C, Ar., C-5), 137.1 (1C, Ar., C-1'), 137.7 (1C, Ar., C-8a), 176.9 (1C, COOH). Anal. Calcd. for $C_{19}H_{21}NO_2$ (295); C, 77.28; H, 7.11; N, 4.74. Found; C, 77.35; H, 7.04; N, 4.76%.

1,2,3,4-Tetrahydro-5,8-dimethyl-1-((pyridin-2-yl)methyl)quinoline-4-carboxylic acid (9c). Pale yellow crystals; 72%; mp 129-31 °C (acetone); IR (KBr, *ν*, cm^{-1}): 3360 (OH),, 3065 (Ar-H), 2985 (C-H), 2690, 1719 (C=O), 1605, 1590, 1485, 1440, 1384, 1155, 768; ^{1}; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.14 (2H, dddd, *J* 13.5, 7.1, 6.9, 1.8 Hz, -C^3H_2), 2.10 (3H, s, CH_3), 2.27 (3H, s, CH_3), 3.17 (2H, ddd, *J* 13.8, 6.9, 1.8 Hz, -NH-C^2H_2), 4.07 (1H, dd, *J* 9.8, 4.4 Hz, C^4H), 4.47 (2H, s, $PyCH_2$), 6.43 (1H, d, *J* 8.0 Hz), 6.67 (1H, d, *J* 8.0 Hz), 7.20 (1H, ddd, *J* 7.4, 4.5, 1.2 Hz), 7.26 (1H, ddd, *J* 7.6, 1.2, 0.5 Hz), 7.63 (1H, ddd, *J* 7.6, 7.4, 1.9 Hz), 8.51 (1H, ddd, *J* 4.5, 1.9, 0.5 Hz), 11.20 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.5 (1C, *C*H_3), 20.4 (1C, *C*H_3), 29.0 (1C, C^3H_2, C-3), 50.1 (1C, CH, C-4), 51.2 (1C, benzylic-CH_2), 54.1 (1C, C^2H_2, C-2), 122.7 (1C, Ar., C-6), 125.1 (1C, Ar., C-4'), 128.0 (1C, Ar., C-4a), 128.9 (1C, Ar., C-6'), 130.3 (1C, Ar., C-8), 136.3 (1C, Ar., C-7), 136.7 (1C, Ar., C-5), 137.1 (1C, Ar., C-5'), 137.7 (1C, Ar., C-8a), 149.1 (1C, Ar., C-3'), 157.8 (1C, Ar., C-1'), 177.4 (1C, COOH). Anal. Calcd. for $C_{18}H_{20}N_2O_2$ (296); C, 72.97; H, 6.75; N, 9.45. Found; C, 73.04; H, 6.82; N, 8.77%.

2,3,4,5-Tetrahydro-6,9-dimethyl-2-phenyl-1*H*-benzo[*c*]azepine-5-carboxylic acid (9d). Cream crystals; 80%; mp 141-43 °C (benzene); IR (KBr, *ν*, cm^{-1}): 3380 (OH), 3030 (Ar-H), 2982 (C-H), 2650, 1720 (C=O), 1600, 1585, 1470, 1445, 1385, 1164, 775. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.04 (2H, dddd, *J* 13.3, 6.6, 4.7, 2.6 Hz, -C^4H_2),

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2.21 (3H, s, CH_3), 2.23 (3H, s, CH_3), 3.33 (2H, ddd, *J* 15.7, 6.6, 2.6 Hz, -NH-C^3H_2), 4.13 (1H, dd, *J* 8.1, 1.4 Hz, -C^5H), 4.49 (2H, d, *J* 15.6 Hz, -C^1H_2), 6.76 (1H, d, *J* 8.2 Hz), 6.87 (1H, d, *J* 8.2 Hz), 6.88 (1H, tt, *J* 8.1, 1.2 Hz), 6.92 (2H, dtd, *J* 8.3, 1.2, 0.5 Hz), 7.24 (2H, dddd, *J* 8.3, 8.1, 1.4, 0.5 Hz), 10.8 (s, 1H, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.4 (2C, 2*C*H_3), 29.0 (1C, C^4H_2, C-4), 50.1 (1C, CH, C-5), 51.2 (1C, C^1H_2, C-1), 53.5 (1C, C^3H_2, C-3), 124.5 (2C, Ar., C-2', C-6'), 126.4 (1C, Ar., C-4'), 127.8 (1C, Ar., C-8), 128.2 (2C, Ar., C-3', C-5'), 128.8 (2C, Ar., C-6, C-9), 132.9 (1C, Ar., C-7), 136.4 (2C, Ar., C-5a, C-9a), 148.3 (1C, Ar., C-1'), 175.2 (1C, COOH). Anal. Calcd. for $C_{19}H_{21}NO_2$ (295); C, 77.28; H, 7.11; N, 4.74. Found; C, 77.22; H, 7.06; N, 4.81%.

2-Benzyl-2,3,4,5-tetrahydro-6,9-dimethyl-1*H*-benzo[*c*]azepine-5-carboxylic acid (9e). White plates; 82%; mp 162-64 °C (benzene); IR (KBr, *v*, cm^{-1}): 3390 (OH), 3045 (Ar-H), 2974 (C-H), 2684, 1725 (C=O), 1590, 1575, 1470, 1440, 1381, 1145, 770. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.05 (2H, dddd, *J* 13.7, 6.6, 4.7, 2.6 Hz, -C^4H_2), 2.16 (3H, s, CH_3), 2.21 (3H, s, CH_3), 2.93 (2H, ddd, *J* 11.0, 6.6, 2.6 Hz, -NH-C^3H_2), 3.69 (2H, s, $PhCH_2$), 3.89 (2H, d, *J* 12.1 Hz, -C^1H_2), 4.12 (1H, dd, *J* 8.1, 1.4 Hz, -C^5H), 6.70 (1H, d, *J* 8.2 Hz), 6.87 (1H, d, *J* 8.2 Hz), 7.17 (1H, tt, *J* 7.7, 1.4 Hz), 7.24 (2H, dddd, *J* 7.7, 1.4, 0.9, 0.5 Hz), 7.30 (2H, tdd, *J* 7.7, 1.8, 0.5 Hz), 10.53 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.5 (2C, 2*C*H_3), 29.0 (1C, C^4H_2, C-4), 50.1 (1C, CH, C-5), 51.2 (1C, C^1H_2, C-1), 53.5 (1C, C^3H_2, C-3), 61.9 (1C, benzylic-CH_2), 126.4 (1C, Ar., C-4'), 127.8 (3C, Ar., C-3', C-5', C-8), 128.4 (2C, Ar., C-2', C-6'), 128.9 (2C, Ar., C-6, C-9), 132.9 (1C, Ar., C-7), 136.3 (2C, Ar., C-1', C-5a), 136.6 (1C, Ar., C-9a), 178.8 (1C, COOH). Anal. Calcd. for $C_{20}H_{23}NO_2$ (309); C, 77.66; H, 7.44; N, 4.53. Found; C, 77.74; H, 7.46; N, 4.45%.

2,3,4,5-Tetrahydro-6,9-dimethyl-2-((pyridin-2-yl)methyl)-1*H*-benzo[*c*]azepine-5-carboxylic acid (9f). Pale yellow needles; 73%; mp 172 ºC *dec.* (acetone); IR (KBr, *v*, cm^{-1}): 3410 (OH), 3080 (Ar-H), 2960 (C-H), 2510, 1715 (C=O), 1600, 1570, 1455, 1330, 1245, 1158, 779. ^1H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.07 (2H, dddd, *J* 13.7, 6.6, 4.7, 2.6 Hz, -C^4H_2), 2.18 (3H, s, CH_3), 2.20 (3H, s, CH_3), 2.88 (2H, ddd, *J* 9.8, 6.6, 2.6 Hz, -NH-C^3H_2), 3.89 (2H, d, *J* 13.1 Hz, -C^1H_2), 3.94 (2H, s, $PyCH_2$), 4.12 (1H, dd, *J* 8.1, 1.4 Hz, -C^5H), 6.74 (1H, d, *J* 8.2 Hz), 6.87 (1H, d, *J* 8.2 Hz), 7.11 (1H, ddd, *J* 7.4, 4.6, 1.2 Hz), 7.25 (1H, ddd, *J* 7.7, 1.2, 0.5 Hz), 7.60 (1H, ddd, *J* 7.7, 7.4, 1.9 Hz), 8.51 (1H, ddd, *J* 4.6, 1.9, 0.5 Hz), 10.41 (1H, s, COOH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.7 (2C, 2*C*H_3), 29.0 (1C, C^4H_2, C-4), 50.1 (1C, CH, C-5), 51.2 (1C, C^1H_2, C-1), 53.5 (1C, C^3H_2, C-3), 54.1 (1C, benzylic-CH_2), 122.7 (1C, Ar., C-4'), 125.1 (1C, Ar., C-6'), 126.4 (1C, Ar., C-6), 128.8 (2C, Ar., C-7, C-8), 132.9 (1C, Ar., C-9), 136.3 (2C, Ar., C-5a, C-5'), 136.7 (1C, Ar., C-9a), 149.1 (1C, Ar., C-3'), 157.8 (1C, Ar., C-1'), 180.6 (1C, COOH). Anal. Calcd. for $C_{19}H_{22}N_2O_2$ (310); C, 73.54; H, 7.09; N, 9.03. Found; C, 73.51; H, 7.14; N, 8.96%.

General procedure for ring closure of heterocyclic acids 9a-f.

Method I. A solution of acid **9a-f** (4.00 mmol) in DCM (10 mL) was added dropwise to $AlCl_3$ (10.00 mmol) in CH_3NO_2 (80.00 mmol) over 10 min at ambient temperature. The mixture was stirred for the time given in Table1. Afterwards, the mixture was quenched with ice–cold HCl solution (20 mL, 10%) and finally extracted with ether (3×20 mL). The combined organic layer was washed with H_2O and Na_2CO_3 solution (20 mL, 10%). After drying over $MgSO_4$ and filtration, the solvent was evaporated under reduced pressure to give the crude products **10a-f**.

Method II. TfOH (1.6 ml, 20.00 mmol) was added dropwise to a cooled (0 °C) solution of acid **9a-f** (4.00 mmol) in 1,2–Dichloroethane (15 mL) and the mixture was stirred at the required temperature for the time given in Table 1. Thereafter, the mixture was quenched by aqueous $NaHCO_3$ solution (30 ml, 50%) at 0 °C and the product was extracted with EtOAc (3×30 mL). The combined organic extracts were washed with H_2O, dried over anhydrous $MgSO_4$ and evaporated in *vacuo* to give the crude products **10a-f**.

Method III. A mixture of acid **9a-f** (4.00 mmol) and P_2O_5 (5 g) in toluene (15 mL) was refluxed for the time given in Table 1. Completion of the reaction was monitored by TLC-analysis (15% AcOEt/hexane). Afterwards, the mixture was cooled to room temperature and aqueous $NaHCO_3$ solution (30 ml, 50%) was added at 0 °C. The product was then extracted with EtOAc (3×30 mL). The combined organic extracts were washed with H_2O,

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dried over anhydrous $MgSO_4$ filtered, and concentrated under reduced pressure to afford the desired product **10a-f**.

In all procedures, the crude residue was subjected to flash chromatography (basic alumina, 25%, EtOAc/hexane) to afford the pure tetracyclic products **10a-f**. Further purification and yields of the products from the given methods are illustrating in the following.

6,9-Dimethyl-5,10-ethanodibenzo[*b,f*]azepin-11(10*H*)-one (10a). Yield 0.87 g (83%, method I), 0.79 g (75%, method II), 0.73 g (70%, method III), Pale yellow crystals; mp 140-143 ºC (acetone); IR (KBr, *v*, cm^{-1}): 3030 (Ar-H), 2955 (C-H), 1690 (C=O), 1600, 1590, 1440, 1377, 1275,1180, 795; ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.04 (2H, dddd, *J* 13.8, 7.9, 4.1, 3.1 Hz, $C^{12}H_2$), 2.16 (3H, s, CH_3), 2.28 (3H, s, CH_3), 3.99 (2H, ddd, *J* 12.8, 7.9, 4.1 Hz, $C^{13}H_2$), 4.28 (1H, dd, *J* 4.6, 1.6 Hz, C^5H_2), 6.48 (1H, d, *J* 8.0 Hz), 6.77 (1H, d, *J* 8.0 Hz), 7.09 (1H, ddd, *J* 8.4, 1.3, 0.5 Hz), 7.26 (1H, ddd, *J* 7.9, 7.4, 1.3 Hz), 7.36 (1H, ddd, *J* 7.9, 1.3, 0.5 Hz), 7.62 (1H, ddd, *J* 8.4, 7.4, 1.3 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.1 (1C, -*C*H_3), 20.6 (1C, -*C*H_3), 29.0 (1C, *bridged*-CH_2, C-12), 50.1 (1C, CH, C-10), 54.1 (1C, *bridged*-CH_2, C-13), 116.0 (1C, Ar., C-2), 121.9 (1C, Ar., C-8), 127.2 (1C, Ar., C-4), 128.0 (1C, Ar., C-11a), 128.2 (1C, Ar., C-9a), 128.4 (1C, Ar., C-7), 128.9 (1C, Ar., C-6), 130.3 (1C, Ar., C-1), 136.3 (1C, Ar., C-9), 137.1 (1C, Ar., C-3), 137.7 (1C, Ar., C-4a), 141.5 (1C, Ar., C-5a), 197.7 (1C, C=O, C-11). Anal. Calcd. for $C_{18}H_{17}NO$ (263); C, 82.13; H, 6.46; N, 5.32. Found; C, 82.20; H, 6.49; N, 5.28%.

1,4-Dimethyl-6*H*-5,12-ethanodibenzo[*b,f*]azocin-11(12*H*)-one (10b). Yield 0.95 g (86%, method I), 0.85 g (77%, method II), 0.88 g (80%, method III), Yellow solid; mp 154-57 ºC (acetone); IR (KBr, *v*, cm^{-1}): 3040 (Ar-H), 2977 (C-H), 1700 (C=O), 1600, 1585, 1480, 1440, 1381, 1285, 1158, 786. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 1.98 (2H, dddd, *J* 13.3, 7.9, 3.5, 3.3 Hz, $C^{13}H_2$), 2.1 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.44 (2H, ddd, *J* 14.4, 7.9, 3.5 Hz, $C^{14}H_2$), 4.19 (1H, dd, *J* 5.1, 1.5 Hz, $C^{12}H$), 4.46 (2H, d, *J* 13.8 Hz, C^6H_2), 6.43 (1H, d, *J* 7.9 Hz), 6.67 (1H, d, *J* 7.9 Hz), 7.29 (1H, ddd, *J* 7.9, 1.4, 0.5 Hz), 7.37 (1H, ddd, *J* 7.9, 7.5, 1.4 Hz), 7.49 (1H, ddd, *J* 7.9, 7.5, 1.4 Hz), 7.86 (1H, ddd, *J* 7.9, 1.4, 0.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.7 (1C, -*C*H_3), 20.4 (1C, -*C*H_3), 29.0 (1C, *bridged*-CH_2, C-13), 50.1 (1C, CH, C-12), 53.5 (1C, *bridged*-CH_2, C-14), 54.1 (1C, CH_2, C-6), 126.4 (1C, Ar., C-2), 126.7 (1C, Ar., C-4), 128.0 (1C, Ar., C-12a), 128.5 (2C, Ar., C-3, C-7), 128.9 (1C, Ar., C-9), 129.8 (1C, Ar., C-10), 130.3 (1C, Ar., C-6a), 133.0 (1C, Ar., C-10a), 136.3 (1C, Ar., C-1), 137.1 (1C, Ar., C-8), 137.7 (1C, Ar., C-4a), 199.3 (1C, C=O, C-11). Anal. Calcd. for $C_{19}H_{19}NO$ (277); C, 82.31; H, 6.85; N, 5.05. Found; C, 82.30; H, 6.92; N, 4.97%.

7,10-Dimethyl-6,12-dihydro-5*H*-6,11-ethanobenzo[*b*]pyrido[3,2-*f*]azocin-5-one (10c). Yield 0.91 g (82%, method I), 0.93 g (84%, method II), 0.84 g (76%, method III), White crystals; mp 170-173 ºC (ethanol); IR (KBr, *v*, cm^{-1}): 3070 (Ar-H), 2995 (C-H), 1688 (C=O), 1600, 1590, 1470, 1440, 1361, 1274, 1136, 765. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.09 (2H, dddd, *J* 13.3, 7.9, 3.5, 3.3 Hz, $C^{14}H_2$), 2.10 (3H, s, CH_3), 2.26 (3H, s, CH_3), 3.59 (2H, ddd, *J* 14.3, 7.9, 3.5 Hz, $C^{13}H_2$), 4.33 (1H, dd, *J* 5.1, 1.5 Hz, C^6H), 4.63 (2H, d, *J* 13.3 Hz, $C^{12}H_2$), 6.43 (1H, d, *J* 7.9 Hz), 6.67 (1H, d, *J* 7.9 Hz), 7.26 (1H, dd, *J* 7.8, 4.6 Hz), 7.88 (1H, dd, *J* 7.8, 1.9 Hz), 8.78 (1H, dd, *J* 4.6, 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 17.2 (1C, -*C*H_3), 21.1 (1C, -*C*H_3), 29.0 (1C, *bridged*-CH_2, C-14), 50.1 (1C, CH, C-6), 54.1 (2C, *bridged*-CH_2, C-12, C-13), 123.4 (1C, Ar., C-8), 128.0 (1C, Ar., C-3), 128.3 (1C, Ar., C-6a), 128.9 (1C, Ar., C-10), 130.3 (1C, Ar., C-9), 135.4 (1C, Ar., C-4a), 136.3 (1C, Ar., C-7), 137.1 (1C, Ar., C-4), 137.7 (1C, Ar., C-10a), 149.1 (1C, Ar., C-2), 155.8 (1C, Ar., C-12a), 199.0 (1C, C=O, C-5). Anal. Calcd. for $C_{18}H_{18}N_2O$ (278); C, 77.69; H, 6.47; N, 10.07. Found; C, 77.76; H, 6.43; N, 10.02%.

7,10-Dimethyl-6*H*-5,11-ethanodibenzo[*b,f*]azocin-12(11*H*)-one (10d). Yield 0.86 g (78%, method I), 0.77 g (70%, method II), 0.78 g (71%, method III), Yellow crystals, mp 160-63 °C (benzene); IR (KBr, ν, cm^{-1}): 3020 (Ar-H), 2978 (C-H), 1690 (C=O), 1600, 1585, 1500, 1440, 1329, 1245, 1171, 790. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.15 (2H, dddd, *J* 13.7, 6.9, 4.3, 1.9 Hz, $C^{13}H_2$), 2.21 (3H, s, CH_3), 2.25 (3H, s, CH_3), 3.61 (2H, ddd, *J* 13.2, 6.9, 1.9 Hz, $C^{14}H_2$), 4.47 (1H, dd, *J* 6.9, 1.7 Hz, C^6H), 4.79 (2H, d, *J* 13.9 Hz, $C^{11}H_2$), 6.67 (1H, d, *J* 8.2 Hz), 6.73 (1H, d, *J* 8.2 Hz), 6.85 (1H, ddd, *J* 8.1, 1.2, 0.5 Hz), 7.29 (1H, ddd, *J* 7.9, 7.4, 1.2 Hz), 7.62 (1H, ddd, *J* 8.1, 7.4, 1.4 Hz), 7.70

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(1H, ddd, *J* 7.9, 1.4, 0.5 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.2 (2C, 2*C*H_3), 29.0 (1C, *bridged*-CH_2, C-13), 50.1 (1C, CH, C-11), 53.5 (1C, *bridged*-CH_2, C-14), 54.1 (1C, CH_2, C-6), 116.0 (1C, Ar., C-4), 121.9 (1C, Ar., C-12a), 126.4 (1C, Ar., C-2), 127.2 (1C, Ar., C-9), 128.2 (1C, Ar., C-8), 128.4 (1C, Ar., C-1), 128.8 (2C, Ar., C-7, C-10), 132.9 (1C, Ar., C-6a), 136.3 (2C, Ar., C-3, C-10a), 141.5 (1C, Ar., C-4a), 202.6 (1C, C=O, C-12). Anal. Calcd. for $C_{19}H_{19}NO$ (277); C, 82.31; H, 6.86; N, 5.05. Found; C, 82.24; H, 6.80; N, 5.11%.

8,11-Dimethyl-7,12-dihydro-6,12-ethanodibenzo[*c,g*]azonin-13(5*H*)-one (10e). Yield 0.91 g (79%, method I), 0.95 g (83%, method II), 0.87 g (75%, method III), Yellow needles, mp 150-52 °C (AcOEt); IR (KBr, *v*, cm^{-1}): 3010 (Ar-H), 2965 (C-H), 1700 (C=O), 1600, 1585, 1470, 1440, 1362, 1245, 1149, 792. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.17 (3H, s, CH_3), 2.23 (3H, s, CH_3), 2.42 (2H, dddd, *J* 13.8, 6.7, 3.6, 2.7 Hz, $C^{14}H_2$), 2.91 (2H, ddd, *J* 11.3, 6.7, 2.7 Hz, $C^{15}H_2$), 3.97 (2H, d, *J* 15.7 Hz, C^5H_2), 4.06 (2H, d, *J* 14.1 Hz, C^7H_2), 4.23 (1H, dd, *J* 5.8, 1.5 Hz, $C^{12}H$), 6.74 (1H, d, *J* 8.2 Hz), 6.88 (1H, d, *J* 8.2 Hz), 7.37 (1H, ddd, *J* 7.9, 7.5, 1.9 Hz), 7.48 (1H, ddd, *J* 8.1, 7.5, 1.3 Hz), 7.50 (1H, ddd, *J* 8.1, 1.9, 0.6 Hz), 7.83 (1H, ddd, *J* 7.9, 1.3, 0.6 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.0 (2C, 2*C*H_3), 29.0 (1C, *bridged*-CH_2, C-14), 50.1(1C, CH, C-12), 53.5 (1C, CH_2, C-7), 54.1 (1C, *bridged*-CH_2, C-15), 55.2 (1C, CH_2, C-5), 126.5 (2C, Ar., C-1, C-9), 126.7 (1C, Ar., C-4), 128.3 (2C, Ar., C-2, C-10), 128.9 (2C, Ar., C-3, C-11), 129.8 (1C, Ar., C-4a), 132.8 (2C, Ar., C-8, C-13a), 136.4 (2C, Ar., C-7a, C-11a), 200.2 (1C, C=O, C-13). Anal. Calcd. for $C_{20}H_{21}NO$ (291); C, 82.47; H, 7.21; N, 4.81. Found; C, 82.44; H, 7.30; N, 4.76%.

7,10-Dimethyl-11,13-dihydro-6,12-ethanobenzo[*c*]pyrido[3,2-*g*]azonin-5(6*H*)-one (10f). Yield 1.0 g (86%, method I), 0.84 g (72%, method II), 0.81 g (70%, method III), White crystals; mp 142-44 ºC (acetone); IR (KBr, *v*, cm^{-1}): 3050 (Ar-H), 2978 (C-H), 1690 (C=O), 1600, 1480, 1440, 1395, 1238, 1182, 765. ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 2.25 (3H, s, CH_3), 2.27 (3H, s, CH_3), 2.42 (2H, dddd, *J* 13.8, 6.7, 3.6, 2.7 Hz, $C^{15}H_2$), 2.96 (2H, ddd, *J* 11.3, 6.7, 2.7 Hz, $C^{14}H_2$), 4.03 (2H, d, *J* 14.1 Hz, $C^{11}H_2$), 4.25 (1H, dd, *J* 5.8, 1.5 Hz, C^6H), 4.36 (2H, d, *J* 15.7 Hz, $C^{13}H_2$), 6.74 (1H, d, *J* 8.5 Hz), 6.88 (1H, d, *J* 8.5 Hz), 7.20 (1H, dd, *J* 7.8, 4.5 Hz), 7.89 (1H, dd, *J* 7.8, 1.9 Hz), 8.89 (1H, dd, *J* 4.5, 1.9 Hz). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 20.1 (2C, 2*C*H_3), 29.0 (1C, *bridged*-CH_2, C-15), 50.1 (1C, CH, C-6), 53.5 (1C, CH_2, C-13), 54.1 (2C, *bridged*-CH_2, C-11, C-14), 123.4 (1C, Ar., C-3), 126.4 (1C, Ar., C-9), 128.3 (1C, Ar., C-8), 128.9 (2C, Ar., C-7, C-10), 132.9 (1C, Ar., C-4a), 135.4 (1C, Ar., C-10a), 136.3 (2C, Ar., C-4, C-6a), 149.1 (1C, Ar., C-2), 155.8 (1C, Ar., C-13a), 199.7 (1C, C=O, C-5). Anal. Calcd. for $C_{19}H_{20}N_2O$ (292); C, 78.08; H, 6.84; N, 9.58. Found; C, 78.11; H, 6.79; N, 9.64%.

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Supplementary Material

Supplementary data associated with this article is available in the Supplementary Material.

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