Friedel-Crafts chemistry. Part 40. An expedient novel synthesis of some dibenz-azepines, -azocines, 11*H*-benzo[*f*]pyrido[2,3-*b*]azepines and 6*H*-benzo[*g*]pyrido[2,3-*c*]azocines

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Abstract

A new synthetic approach for the synthesis of novel 5*H*-dibenz[*b*,*f*]azepine, 5*H*-dibenz[*b*,*f*]-azocine, 11*H*-benzo[*f*]pyrido[2,3-*b*]azepine and 6*H*-benzo[*g*]pyrido[2,3-*c*]azocine derivatives is reported. The key step of this methodology is based on Friedel-Crafts ring closure of nitrogen containing carboxylic acids and alkanols in the presence of $AlCl_3$, P_2O_5 or PPA catalysts in overall high yields. The starting carboxylic acids were prepared *via* an unequivocal synthetic pathway by the basic hydrolysis of trimethyloxindole followed by *N*-arylation reactions.

Keywords: *o*-Arylaminophenylacetic acids; 11*H*-benzo[*f*]pyrido[2,3-*b*]azepine; 5*H*-dibenz[*b*,*f*]-azepine; 5*H*-dibenz[*b*,*f*]azocine; Friedel-Crafts ring closure

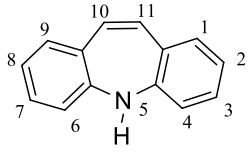
Introduction

Seven and eight-membered nitrogen frameworks in particularly dibenzo-fused azocines and azepines occupies a special place in the history of nitrogen heterocycles not only to their presence in a large array of natural products[1-3] but also to a wide diversity of biological activity[4-6], industrial application[7-10] and pharmacological effects.[11-14]

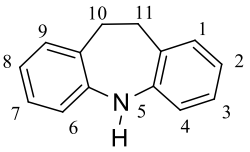
These polycyclic compounds are also identified as vital structural constituents useful intermediates in organic synthesis.[15-17] Moreover, they exhibit diverse medical functions as antidepressant, antiviral, antiepileptic, antiseizure, anticonvulsant, antimicrobial, antimalarial, anticancer, antioxidant antitumor, antibiotics and sirtuin-2 inhibitory activities.[18-20]

Full literature survey for the applied methodologies in the synthesis of 5*H*-dibenz[*b*,*f*]azepine, dihydrodibenzazepine and tetrahydro-5*H*-dibenz[*b*,*f*]azocine systems revealed that synthesis of such heterocycles has been a prominent research objective for over a century and a variety of well established methods have been developed to access 5*H*-dibenzo[*b*,*f*]azepine derivatives.[21-24] However, only a limited number of strategies have been

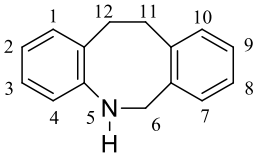
reported for the synthesis of 10,11-dihydro-5*H*-dibenz[*b,f*]azepine[25-27] and 5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocine[28-32] skeletons.



5*H*-dibenz[*b,f*]azepine



10,11-dihydro-5*H*-dibenz[*b,f*]azepine
(Iminodibenzyl)



5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocine

Figure 1

The latter dibenzazocine skeleton was developed in 1963 by Monro and coworkers.[28] They were disclosed a convenient one-step regioselective synthesis of 5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocine derivatives via Beckmann rearrangement of the dibenzosuberone oxime followed by reduction with $LiAlH_4$. Kisel *et al.*[29] achieved the synthesis of 5-acetyl- and 5-trifluoroacetyl-12-hydroxy-11-cyano-5,6-dihydrodibenz[*b,f*]azocines by intramolecular cyclo-condensation of ethyl *N*-acetyl and *N*-trifluoroacetyl-*N*-[1-(cyanomethyl)benzyl]anthranilates. Polonka-Bálint and coworkers[30] demonstrated the use of tert-amino effect to produce fused azocines. They reported that the syntheses of such azocines derivatives were accessed in three steps utilizing the Suzuki reaction, the Knoevenagel condensation reaction and the thermal isomerization.

More recently Cho *et al.*[31] in an alternative strategy reported that treating of cyclic ketoximes fused to aromatic rings with diisobutylaluminum hydride (DIBALH) resulted in reductive ring-expansion reaction leading to a variety of five- to eight-membered bicyclic heterocycles. Majumdar *et al.*[32] synthesized several coumarin, pyrimidine and quinoline annulated-benzazocine derivatives from substituted allylamines via sequential aza-Claisen rearrangement and intramolecular Heck reactions.

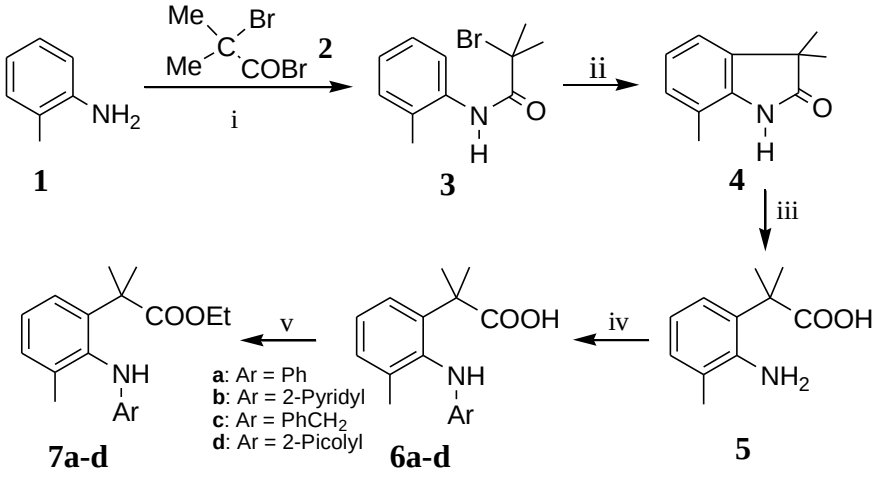
Owing to the remarkable biological activities of dibenzfusedazepines and azocines there has been increasing interest in the development of easy, economic and efficient construction strategies of this class of heterocycles.

In recent years, we devoted a part of our interest in Friedel-Crafts ring closure[33-35] to develop facile alternative routes to the building up of novel and known homo- and heterocyclic systems. [36-41] In our previous work[41] we developed a synthetic methodology for the construction of nine substituted 5,6-dihydrobenzo[*b*][1]benzazepines (iminodibenzyls) via Friedel-Crafts ring closure of suitable synthesized nitrogen containing carboxylic acids and alcohols. This inspired us to apply the same approach for the synthesis of some new substituted dibenzazepines, dibenzazocines, 11*H*-benzo[*f*]pyrido[2,3-*b*]azepines and 6*H*-benzo[*g*]pyrido[2,3-*c*]azocines via ring closure of easily obtained precursors.

Results and Discussion

Our first task was to synthesize the key intermediate 2-(2-amino-3-methylphenyl)-2-methylpropanoic acid (**5**) which in turn was obtained via three consecutive steps starting from *o*-toluidine (**1**) as depicted in Scheme 1. Thus, we first prepared the starting 2-bromo-2-methyl-*N*-*o*-tolylpropanamide (**3**) from the reaction of *o*-toluidine (**1**) and 2-bromo-2-methylpropanoyl bromide (**2)** as an acylating agent, in boiling dioxane in the presence of K_2CO_3 in good yield under standard conditions.[42]

In the next step, the bromoamide **3** was cyclized into the corresponding 3,3,7-trimethylindolin-2-one (**4**) in the presence of $AlCl_3$.[43] Hydrolysis of the oxindole **4** by refluxing with EtOH and NaOH afforded 2-(2-amino-3-methylphenyl)-2-methylpropanoic acid (**5**). This acid was then used in the catalyzed Ullmann[44] *N*-coupling reaction with different aromatic halides to give the corresponding *N*-arylpropanoic acids (**6a-d**) which in turn esterified[45] in the presence of ethanol and H_2SO_4 under reflux conditions to get the corresponding ethyl 2-(2-(arylamino)-phenyl)propionates **7a-d**.

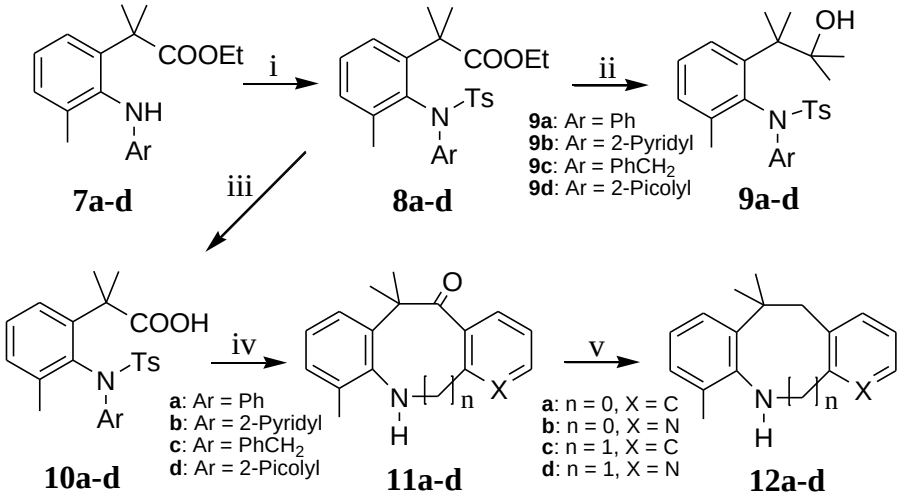


Scheme 1. Reagents and conditions: (i) K_2CO_3/dioxane, 3 h, (ii) $AlCl_3$, 1 h, (iii) EtOH/NaOH, 8 h, reflux, (iv) Aromatic halide (PhBr or 2-bromopyridine or $PhCH_2Cl$ or 2-picolyl chloride), K_2CO_3/pyridine/CuI/DMSO, 110 °C, 10 h, reflux, (v) EtOH/H_2SO_4, 9 h, reflux.

The latter esters were converted to the *N*-tosylated esters **8a-d** by reaction with tosyl chloride in pyridine (Scheme 2). The resulting tosylated esters **8a-d** were converted to the corresponding 3-[2-(*N*-aryl-*N*-tosylamino)-3-methylphenyl]-2,3-dimethylbutan-2-ols (**9a-d**) by addition of two equivalents of methylmagnesium iodide[46] in THF/Et_2O.

The ^{1}H NMR data allowed an unambiguous statement of the formation of the heterocyclic alkanols. Thus, the ^{1}H NMR spectrum for alcohol **9a** displayed five signals in which aromatic

protons appeared at δ 6.45-7.7. The gem-dimethyls at C-1 and C-2 appeared as two singlets at δ 1.1 and δ 1.35, respectively. Additionally the third singlet at δ 2.36 was assigned to the down-field proton of two methyl-groups attached to the phenyl and *p*-TosCl groups. A broad singlet showed at δ 2.1 was assigned to OH group. However, in all IR spectra, the characteristic peaks of carbonyl groups were absent.

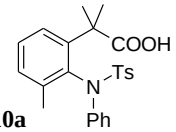
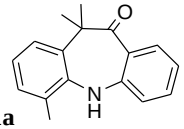
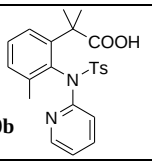
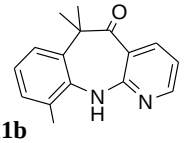
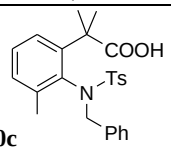
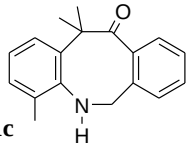
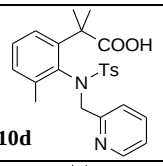
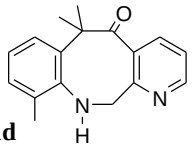
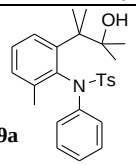
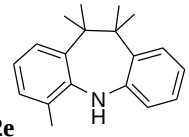
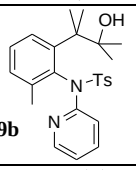
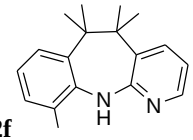
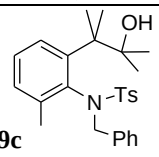
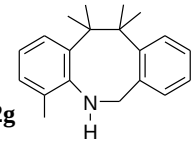
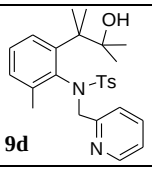
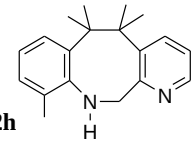


Scheme 2. Reagents and conditions: (i) *p*-TosCl/pyridine/CH_2Cl_2, 80-90 °C, 11 h, (ii) MeMgI, THF/Et_2O, rt, 6 h, NH_4Cl soln, (iii) KOH/MeOH, rt, 15 h, HCl, (iv) $AlCl_3$, P_2O_5 or PPA catalysts (Table 1), (v) $N_2H_4.H_2O$ /KOH/DEG, 10 h, reflux.

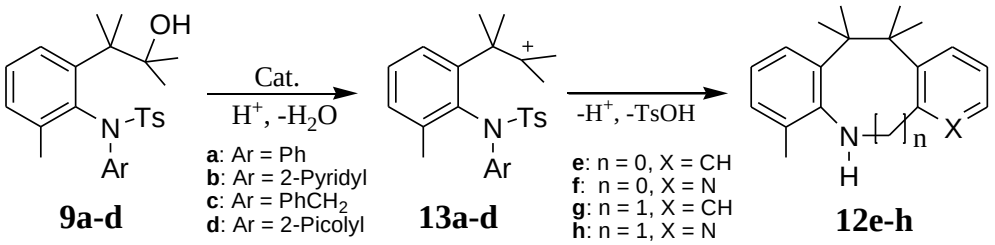
In order to obtain the tricyclic amines **12a-d**, however, the best results obtained by the cycliacylation of the corresponding 2-[2-(*N*-aryl-*N*-tosylamino)-3-methylphenyl]-2-methylpropanoic acids (**10a-d**). Thus, the tosylated esters **8a-d** were hydrolyzed with KOH in methanol furnished acids **10a-d**. Ring closures of the latter tosylated acids to dibenzazepinones and dibenzazocinones **11a-d** carried out in presence of $AlCl_3$, P_2O_5 or PPA[36-39] followed by Wolff Kishner reduction[47] of the resulting ketones to give **12a-d** in a high yields. The conditions and results for the cyclialkylation of alkanols **9a-d** and acids **10a-d** are depicted in Table 1 and Schemes 2 and 3. The structures of all new alcohols were appropriately established by both elemental and spectral analyses.

On the other hand, cyclialkylations of alcohols **9a-d** to substituted azepines and azocines **12e-h** were carried out in the presence of the same catalysts under varying conditions. A plausible mechanism accounted for the results is realized on the generation of tertiary carbocation by loss of water upon treatment of such alcohols with acidic catalysts. The resulting carbocation underwent ring closure to pentamethyl-substituted dibenzazepines and azocines (**12e-h**) in overall high reaction yields. The removal of the tosyl group occurred concurrently with the closure step as noted in other reported cases.[48] In almost all cases, yields were over 80%.

Table 1. Friedel-Crafts ring closures producing substituted dibenzazepines and azocines

Entry	Substrate	Product	Conditions	Product (%)[a]
1	 **10a**	 **11a**	$AlCl_3$[b], DCM[c], 5 h, reflux	**11a** (86)
			P_2O_5[d], toluene, 9 h, rt	**11a** (90)
			PPA[e], 2 h, 220 °C	**11a** (79)
2	 **10b**	 **11b**	$AlCl_3$, DCM, 7h, reflux	**11b** (92)
			P_2O_5, toluene, 8 h, rt	**11b** (85)
			PPA, 2 h, 220 °C	**11b** (82)
3	 **10c**	 **11c**	$AlCl_3$, DCM, 8 h, rt	**11c** (88)
			P_2O_5, toluene, 5 h, rt	**11c** (84)
			PPA, 2 h, 220 °C	**11c** (81)
4	 **10d**	 **11d**	$AlCl_3$, DCM, 8 h, rt	**11d** (88)
			P_2O_5, toluene, 5 h, rt	**11d** (91)
			PPA, 3h, 220 °C	**11d** (83)
5	 **9a**	 **12e**	$AlCl_3$, DCM, 2 h, reflux	**12e** (89)
			P_2O_5, toluene, 4 h, rt	**12e** (85)
			PPA, 1h, 230 °C	**12e** (82)
6	 **9b**	 **12f**	$AlCl_3$, DCM, 2 h, rt	**12f** (93)
			P_2O_5, toluene, 5 h, rt	**12f** (91)
			PPA, 2h, 210 °C	**12f** (80)
7	 **9c**	 **12g**	$AlCl_3$, DCM, 3 h, rt	**12g** (86)
			P_2O_5, toluene, 4 h, rt	**12g** (87)
			PPA, 1h, 220 °C	**12g** (85)
8	 **9d**	 **12h**	$AlCl_3$, DCM, 4 h, reflux	**12h** (90)
			P_2O_5, toluene, 3 h, rt	**12h** (89)
			PPA, 2h, 230 °C	**12h** (86)

[a] Isolated yield refer to substrate. [b] With $AlCl_3$ catalyst reactant proportions were: carbinol or acid (3 mmol), $AlCl_3$ (6 mmol) and solvent (10 ml). [c] Dichloromethane. [d] With P_2O_5 catalyst reactant proportions were: carbinol or acid (0.4 g) and P_2O_5 (4 g) in anhydrous toluene (15 mL). [e] With PPA catalyst reactant proportions were: carbinol or acid (0.5 g) and PPA (5 g).



Scheme 3. Cyclialkylations of alkanols **9a-d** under Friedel-Crafts conditions

Conclusions

In conclusion, the results presented here provide a novel, very attractive route to unknown tricyclic azepines and azocines were made accessible in excellent yields by short and convenient synthetic pathways. This reaction will be applicable to the synthesis of various organic compounds of medicinal interest. The simplicity of the processes, moderate cost and the results of this study proved that the development of Friedel-Crafts cyclialkylations in heterocyclic chemistry can be considered as one of the most useful pathways to the synthesis of such heteropolycycles.

Experimental Section

General. All reagents were purchased from Merck, Sigma or Aldrich Chemical Co. and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus and are uncorrected. The IR spectra were determined with a Shimadzu 470 Infrared spectrophotometer using KBr wafer and thin film techniques (ν cm^{-1}). The ^{1}H NMR and ^{13}C NMR spectra were recorded on JEOL LA 400 MHz FT-NMR (400 MHz for ^{1}H, 100 MHz for ^{13}C) and on a Varian NMR (90 MHz) spectrometers using $CDCl_3$ solvent with TMS as internal standard. Chemical shifts (δ) and J values are reported in ppm and Hz, respectively. Elemental analyses were performed on a Perkin-Elmer 2400 Series II analyzer. The mass spectra were performed by JEOL JMS 600 spectrometer at an ionizing potential of 70 eV using the direct inlet system. Reactions were monitored by thin layer chromatography (TLC) using precoated silica plates visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

Synthesis of 2-(2-amino-3-methylphenyl)-2-methylpropanoic acid (5). This acid was obtained in a series of three consecutive steps starting with commercial available *o*-toluidine. A summary of the steps and of the involved product intermediates is given in the following:

(i) To an ice-cold stirred mixture of *o*-toluidine **1** (3.2 g, 30 mmol), anhydrous K_2CO_3 (12.5 g, 90 mmol) in dioxane (35 mL) was added a solution of 2-bromo-2-methylpropanoyl bromide **2** (7.6 g, 33 mmol) in dioxane (15 mL) over a period of 30 min. The reaction mixture was left to stir for 2 hr at room temperature and then heated in a steam bath at 80-90 °C for additional 1 h. Afterwards, the reaction mixture was treated as in standard procedure to give (7.2 g, 94 %) of crude oily amide. Purification by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) gave (6.8 g, 89 %) of pure **2-bromo-2-methyl-*N*-*o*-tolylpropanamide (3)** in the form of pale yellow oil; n_D^{25} 1.577; IR (Film) ν_{max} 3350, 3105, 2920, 1675, 1605, 1560, 1490, 1455, 1340, 1170, 745, 716, 670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 2.20 (6H, s, $2CH_3$), 2.42 (3H, s, CH_3), 6.7-7.5 (4H, m, Ar-H) and 11.6 (1H, s, NH). Anal. Calcd. for $C_{11}H_{14}BrNO$ (256); C, 51.56; H, 5.46; Br, 31.25; N, 5.46. Found; C, 51.37; H, 5.25; Br, 31.52; N, 5.42%.

(ii) A mixture of amide **3** (6.4 g, 25 mmol) and anhydrous $AlCl_3$ (6.6 g, 50 mmol) was stirred for 1h at room temperature. After the evolution of HCl gas has been ceased, the reaction mixture was heated on a water bath for 1h, cooled to 0 °C and quenched with ice-cold HCl solution (30 mL, 10%). Separation of the product following literature standard procedure gave (3.9 g, 89 %) of crude product. Crystallization from ethanol gave (3.6 g, 84 %) of pure **3,3,7-trimethylindolin-2-one (4)** as white crystals; mp 105 °C; IR (KBr) ν_{max}: 3310, 3065, 2970, 1663, 1611, 1489, 1360, 1189, 1102, 1027, 814, 716, 703, 658 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.45 (6H, s, $2CH_3$), 2.38 (3H, s, CH_3), 6.6-7.5 (3H, m, Ar-H) and 10.8 (1H, s, NH). Anal. Calcd. for $C_{11}H_{13}NO$ (175); C, 75.42; H, 7.42; N, 8.00. Found; C, 75.45; H, 7.38; N, 8.26%.

(iii) A mixture of the oxindole **4** (3.5 g, 20 mmol) in ethanol (20 mL, 80%) and sodium hydroxide solution (10 N, 3.5 mL) was stirred under reflux for 8 h. The excess alcohol was removed by distillation and the residue was diluted with water (50 mL). The clear solution was cooled to 0 °C and adjusted to pH 6-7 with HCl solution (40 mL, 20 %) and then left to stand at refrigerator for overnight. The precipitated acid was collected, washed and dried to give (3.4 g, 88 %) of crude acid. Crystallization from methanol gave (3.1 g, 80 %) of pure acid **5** as white crystals; mp 85 °C; IR (KBr) ν_{max} 3425, 3380, 3090, 2980, 2750, 1720,1605, 1585, 1460, 1435, 1395, 1225, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.55 (6H, s, $2CH_3$), 2.40 (3H, s, CH_3), 4.10 (2H, s, NH_2), 6.4-7.2 (3H, m, Ar-H) and 11.5 (1H, s, COOH). Anal. Calcd. for $C_{11}H_{15}NO_2$ (193); C, 68.39; H, 7.77; N, 7.25. Found; C, 68.12; H, 7.90; N, 7.33%.

Arylation of 2-(2-amino-3-methylphenyl)-2-methylpropanoic acid (6a-d). A mixture of amino acid **5** (2 g, 10 mmol), K_2CO_3 (4.1 g, 30 mmol), aryl halide (PhBr or 2-bromopyridine or $PhCH_2Cl$ or 2-picolyl chloride) (10 mmol), pyridine (1 mL) and CuI (0.3 g) in anhydrous DMSO (15 mL) was heated with continuous stirring for 10 h at 100-10 °C. Once the reaction was cooled, just enough NaOH solution (25 mL, 5%) was added to completely dissolve the product. Decolorizing carbon (5 g) was added and the mixture was boiled for 20 min and filtered by suction. The resulting filtrate was acidified using HCl solution (30 mL, 20%) until the pH 1-2. The resultant yellow precipitate was then filtered and recrystallized from ethanol gave the pure product. The yields and spectral data are given in the following:

2-Methyl-2-[3-methyl-2-(phenylamino)phenyl]propanoic acid (6a). Yellow crystals; 82 %; mp 164 °C; IR (KBr) ν_{max} 3370, 3085, 2950, 2540, 1720, 1610, 1580, 1460, 1445, 1335, 1180, 742 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.52 (6H, s, $2CH_3$), 2.40 (3H, s, CH_3), 4.35 (1H, s, NH), 6.3-7.4 (8H, m, Ar-H) and 10.7 (1H, s, COOH). Anal. Calcd. for $C_{17}H_{19}NO_2$ (269); C, 75.83; H, 7.06; N, 5.20. Found; C, 75.92; H, 7.24; N, 5.41%.

2-Methyl-2-[3-methyl-2-(pyridin-2-ylamino)phenyl]propanoic acid (6b). Greenish plates; 75%; mp 138 °C; IR (KBr) ν_{max} 3345, 3090, 2988, 2490, 1715, 1605, 1590, 1475, 1450, 1340, 1165, 748 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.50 (6H, s, $2CH_3$), 2.42 (3H, s, CH_3), 4.5 (1H, s, NH), 6.40-7.90 (7H, m, Ar-H) and 10.4 (1H, s, COOH). Anal. Calcd. for $C_{16}H_{18}N_2O_2$ (270); C, 71.11; H, 6.66; N, 10.37. Found; C, 71.38; H, 6.39; N, 10.55%.

2-[2-(Benzylamino)-3-methylphenyl]-2-methylpropanoic acid (6c). White needles; 80 %; mp 152 °C; IR (KBr) ν_{max} 3410, 3105, 2995, 2520, 1718, 1600, 1585, 1473, 1440, 1360, 1140, 755 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.53 (6H, s, $2CH_3$), 2.40 (3H, s, CH_3), 4.20 (2H, s, CH_2), 4.5 (1H, s, NH), 6.5-7.8 (8H, m, Ar-H) and 11.2 (1H, s, COOH). Anal. Calcd. for $C_{18}H_{21}NO_2$ (283); C, 76.32; H, 7.42; N, 4.94. Found; C, 76.30; H, 7.22; N, 5.15%.

2-[2-[(Pyridin-2-yl)methylamino]-3-methylphenyl]-2-methylpropanoic acid (6d). White needles; 72 %; mp 164 °C IR (KBr) ν_{max} 3385, 3065, 2977, 2560, 1715, 1590, 1575, 1450, 1440, 1380, 1130, 749 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.53 (6H, s, $2CH_3$), 2.40 (3H, s, CH_3), 4.20 (1H, s, NH), 4.41 (2H, s, CH_2), 6.3-8.0 (7H, m, Ar-H) and 10.7 (1H, s, COOH). Anal. Calcd. for $C_{17}H_{20}N_2O_2$ (284); C, 71.83; H, 7.04; N, 9.85. Found; C, 71.80; H, 7.19; N, 9.90%.

General procedure for the synthesis of *N*-arylpropanoic acid esters 7a-d. Esterification of *N*-arylpropanoic acids (**6a** or **b** or **c** or **d)** were carried out with ethanol and H_2SO_4 following standard procedures. Purification of the crude esters by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) gave pure esters **7a-d** whose analytical, physical and spectroscopic data were as follows:

Ethyl 2-methyl-2-[3-methyl-2-(phenylamino)phenyl]propanoate (7a). Reddish viscous oil; 85%; n_D^{25} 1.625; IR (Film) ν_{max} 3355, 3070, 2965, 1740, 1610, 1585, 1490, 1440, 1340, 1230, 1180, 745 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.31 (3H, t, *J* 7.5 Hz, CH_3), 1.55 (6H, s, $2CH_3$), 2.35 (3H, s, CH_3), 4.0 (2H, s, *J* 7.5 Hz, CH_2), 4.85 (1H, s, NH) and 6.20-7.40 (8H, m, Ar-H). Anal. Calcd. for $C_{19}H_{23}NO_2$ (297); C, 76.76; H, 7.74; N, 4.71. Found; C, 76.50; H, 7.94; N, 4.64%.

Ethyl 2-methyl-2-[3-methyl-2-(pyridin-2-ylamino)phenyl]propanoate (7b). Brownish viscous oil; 84%; n_D^{25} 1.592; IR (Film) ν_{max} 3360, 3083, 2980, 1745, 1605, 1585, 1460, 1455, 1330, 1275, 745 cm^{-1}. ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.32 (3H, t, *J* 7.5 Hz, CH_3), 1.55 (6H, s, $2CH_3$), 2.35 (3H, s, CH_3), 4.20 (2H, s, *J* 7.5 Hz, CH_2), 4.52 (1H, s, NH) and 6.50-8.10 (7H, m, Ar-H). Anal. Calcd. for $C_{18}H_{22}N_2O_2$ (298); C, 72.48; H, 7.38; N, 9.39. Found; C, 72.44; H, 7.52; N, 9.61%.

Ethyl 2-[2-(benzylamino)-3-methylphenyl]-2-methylpropanoate (7c). Yellowish viscous oil; 88%; n_D^{25} 1.586; IR (Film) ν_{max} 3340, 3055, 2964, 1735, 1590, 1550, 1460, 1450, 1335, 1285,

750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.30 (3H, t, *J* 7.5 Hz, CH_3), 1.52 (6H, s, $2CH_3$), 2.40 (3H, s, CH_3), 4.15 (2H, s, *J* 7.5 Hz, CH_2), 4.40 (2H, s, CH_2), 4.85 (1H, s, NH) and 6.40-7.45 (8H, m, Ar-H). Anal. Calcd. for $C_{20}H_{25}NO_2$ (311); C, 77.17; H, 8.03; N, 4.50. Found; C, 77.06; H, 8.25; N, 4.66%.

Ethyl 2-[2-[(pyridin-2-yl)methylamino]-3-methylphenyl]-2-methylpropanoate (7d). Reddish viscous oil; 85%; n_D^{25} 1.598; IR (Film) ν_{max} 3385, 3105, 2985, 1742, 1600, 1560, 1485, 1440, 1370, 1220, 747 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.35 (3H, t, *J* 7.5 Hz, CH_3), 1.50 (6H, s, $2CH_3$), 2.35 (3H, s, CH_3), 4.15 (2H, s, *J* 7.5 Hz, CH_2), 4.58 (2H, s, CH_2), 5.0 (1H, s, NH) and 6.40-8.20 (7H, m, Ar-H). Anal. Calcd. for $C_{19}H_{24}N_2O_2$ (312); C, 73.07; H, 7.69; N, 8.97. Found; C, 72.82; H, 7.52; N, 8.90%.

General procedure for the tosylation of esters 7a-d. To a cold solution of ester (**7a**, **b**, **c** or **d)** (10 mmol) and pyridine (10 ml) in dichloromethane (30 ml) was added *p*-toluenesulfonyl chloride (4.7 g, 25 mmol) slowly in small portions over 10 minutes. The reaction mixture was stirred at room temperature for 10 h and then heated for 1h on water bath at 80-90 °C. The reaction mixture was concentrated on water bath to ca. 15 ml, cooled to room temperature, diluted with water (100 mL) and extracted with AcOEt (3 × 30 mL). The combined organic layers were washed with HCl (2 × 30 mL, 5%), with $NaHCO_3$ soln (3 × 30 mL) and finally with water. The organic layer was dried over anhydrous $MgSO_4$, filtered, and evaporated to afford crude residue. Purification of the residue by flash column chromatography (basic alumina, EtOAc/n-hexane, 3/1) provided the corresponding pure tosylated esters **8a-d**. The yields and spectral data are given in the following:

Ethyl 2-[2-(*N*-phenyl-*N*-tosylamino)-3-methylphenyl]-2-methylpropanoate (8a). White crystals; 93%; mp 115 ºC (cyclohexane); IR (KBr) ν_{max} 3082, 2990, 1743, 1585, 1540, 1470, 1440, 1380, 1335, 1184, 747 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.35 (3H, t, *J* 7.5 Hz, CH_3), 1.58 (6H, s, $2CH_3$), 2.38 (6H, s, $2CH_3$), 4.20 (2H, s, *J* 7.5 Hz, CH_2) and 6.45-7.90 (12H, m, Ar-H). Anal. Calcd. for $C_{26}H_{29}NO_4S$ (451); C, 69.17; H, 6.43; N, 3.10; S, 7.09. Found; C, 69.24; H, 6.29; N, 3.10; S, 7.15%.

Ethyl 2-[[2-(*N*-pyridin-2-yl)-*N*-tosylamino]-3-methylphenyl]-2-methylpropanoate (8b). Yellowish viscous oil; 89%; n_D^{25} 1.592; IR (Film) ν_{max} 3090, 2965, 1740, 1590, 1540, 1450, 1440, 1390, 1330, 1165, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.32 (3H, t, *J* 7.5 Hz, CH_3), 1.58 (6H, s, $2CH_3$), 2.30 (6H, s, $2CH_3$), 4.25 (2H, s, *J* 7.5 Hz, CH_2) and 6.50-8.20 (11H, m, Ar-H). Anal. Calcd. for $C_{25}H_{28}N_2O_4S$ (452); C, 66.37; H, 6.19; N, 6.19; S, 7.07. Found; C, 66.32; H, 6.20; N, 6.24; S, 6.85 %.

Ethyl 2-[2-(*N*-benzyl-*N*-tosylamino)-3-methylphenyl]-2-methylpropanoate (8c). Pale yellow crystals; 84%; mp 128 °C (benzene); IR (KBr) ν_{max} 3105, 2995, 1738, 1600, 1580, 1465, 1435, 1390, 1355, 1145, 747 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.33 (3H, t, *J* 7.5 Hz, CH_3), 1.60 (6H, s, $2CH_3$), 2.40 (6H, s, $2CH_3$), 4.20 (2H, s, *J* 7.5 Hz, CH_2), 4.35 (2H, s, CH_2) and 6.40-7.60 (12H, m, Ar-H). Anal. Calcd. for $C_{27}H_{31}NO_4S$ (465); C, 69.67; H, 6.66; N, 3.01; S, 6.88. Found; C, 69.99; H, 6.38; N, 3.20; S, 7.10%.

Ethyl 2-[2-(*N*-[(pyridin-2-yl)methyl]-*N*-tosylamino]-3-methylphenyl)-2-methylpropanoate (8d). Reddish viscous oil; 85%; n_D^{25} 1.588; IR (Film) ν_{max} 3078, 2955, 1750, 1585, 1560, 1450, 1440, 1385, 1340, 1170, 745 cm^{-1}; ^{1}H NMR (90 MHz, $CDCl_3$, ppm), δ 1.35 (3H, t, *J* 7.5 Hz, CH_3), 1.56 (6H, s, $2CH_3$), 2.37 (6H, s, $2CH_3$), 4.10 (2H, s, *J* 7.5 Hz, CH_2), 4.62 (2H, s, CH_2) and 6.40-8.50 (11H, m, Ar-H). Anal. Calcd. for $C_{26}H_{30}N_2O_4S$ (466); C, 66.95; H, 6.43; N, 6.00; S, 6.86. Found; C, 66.75; H, 6.52; N, 5.82; S, 6.80 %.

General procedure for the synthesis of alcohols 10a-d. To an ice-cold Grignard reagent solution obtained as usual from Mg turnings (0.32 g, 13 mmol), alkyl or aryl halide (13 mmol) in ether (30 mL), was added a solution of esters (**8a** or **b** or **c** or **d**) (5 mmol) in THF (20 mL). The reaction mixture was stirred for 6 h at room temperature followed by decomposition with sat. aq. NH_4Cl soln. The product was extracted with ether (3 × 30 mL) and the combined organic phases were washed with water, dried over anhydrous $MgSO_4$. The solvent was removed in *vacuo* and the residue was purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) resulting the pure alcohols **9a-h**. The yields and spectral data are given in the following:

3-[2-(*N*-Phenyl-*N*-tosylamino)-3-methylphenyl]-2,3-dimethylbutan-2-ol (9a). White needles; 88%; mp 92 ºC (ethanol); IR (KBr) ν_{max} 3370, 3095, 2988, 1745, 1595, 1580, 1460, 1445, 1390, 1360, 1150, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.10 (6H, s, $2CH_3$), 1.35 (6H, s, $2CH_3$), 2.10 (1H, s, OH exchangeable with D_2O), 2.36 (6H, s, $2CH_3$) and 6.45-7.70 (12H, m, Ar-H). Anal. Calcd. for $C_{26}H_{31}NO_3S$ (437); C, 71.39; H, 7.09; N, 3.20; S, 7.32. Found; C, 71.44; H, 6.94; N, 3.37; S, 7.51%.

3-[2-[*N*-[(pyridin-2-yl)]-*N*-tosylamino]-3-methylphenyl]-2,3-dimethylbutan-2-ol (9b). White plates; 92%; mp 104 ºC (benzene); IR (KBr) ν_{max} 3385, 3085, 2975, 1610, 1560, 1470, 1440, 1375, 1330, 760 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.10 (6H, s, $2CH_3$), 1.32 (6H, s, $2CH_3$), 2.20 (1H, s, OH exchangeable with D_2O), 2.35 (6H, s, $2CH_3$) and 6.40-8.30 (11H, m, Ar-H). Anal. Calcd. for $C_{25}H_{30}N_2O_3S$ (438); C, 68.49; H, 6.84; N, 6.39; S, 7.30. Found; C, 68.65; H, 6.72; N, 6.45; S, 7.10 %.

3-[2-(*N*-Benzyl-*N*-tosylamino)-3-methylphenyl]-2,3-dimethylbutan-2-ol (9c). Pale yellow viscous oil; 87%; n_D^{25} 1.584; IR (Film) ν_{max} 3340, 3035, 2970, 1600, 1580, 1455, 1445, 1390, 1330, 745 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.15 (6H, s, $2CH_3$), 1.30 (6H, s, $2CH_3$), 2.39 (6H, s, $2CH_3$), 2.55 (1H, s, OH exchangeable with D_2O), 4.25 (2H, s, CH_2) and 6.45-7.60 (12H, m, Ar-H). Anal. Calcd. for $C_{27}H_{33}NO_3S$ (451); C, 71.84; H, 7.31; N, 3.10; S, 7.09. Found; C, 71.85; H, 7.30; N, 3.22; S, 7.15%.

3-[2-[*N*-[(Pyridin-2-yl)methyl]-*N*-tosylamino]-3-methylphenyl]-2,3-dimethylbutan-2-ol (9d). Cream plates; 86%; mp 92 ºC (methanol); IR (KBr) ν_{max} 3450 , 3075, 2974, 1605, 1480, 1460, 1445, 1370, 1340, 745cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.10 (6H, s, $2CH_3$), 1.35 (6H, s, $2CH_3$), 2.35 (6H, s, $2CH_3$), 2.70 (1H, s, OH exchangeable with D_2O), 4.50 (2H, s, CH_2) and 6.50-8.40 (11H, m, Ar-H). Anal. Calcd. for $C_{26}H_{32}N_2O_3S$ (452); C, 69.02; H, 7.07; N, 6.19; S, 7.07. Found; C, 69.13; H, 7.28; N, 6.05; S, 6.84%.

General procedure for the synthesis of tosylated propanoic acids 10a-d. To a solution of tosylated ester (**8a** or **b** or **c** or **d)** (8 mmol) in methanol (25 mL) was added in small increments

with swirling KOH solution (10 mL, 10%). After 15 h at room temperature, the clear solution was diluted with water (100 mL) and then poured with stirring into an ice-cold diluted HCl solution (25 mL, 15%). The solid acid was filtered off and dissolved with slight warming in $NaHCO_3$ solution (40 mL, 20 %), filtered and acidified. The precipitated acid was filtered, washed and dried to afford crude acid (**10a or b or c or d**). Purifications, yields and spectral data are given in the following:

2-[2-(*N*-Phenyl-*N*-tosylamino)-3-methylphenyl]-2-methylpropanoic acid (**10a**). White crystals; 86%, mp 182 ºC (benzene); IR (KBr) ν_{max} 3085, 2975, 2580, 1720, 1590, 1460, 1435, 1395, 1230, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.50 (6H, s, $2CH_3$), 2.35 (6H, s, $2CH_3$), 6.40-7.75 (12H, m, Ar-H) and 11.4 (s, 1, COOH). Anal. Calcd. for $C_{24}H_{25}NO_4S$ (423); C, 68.08; H, 5.91; N, 3.30; S, 7.56. Found; C, 68.31; H, 5.90; N, 3.50; S, 7.27%.

2-[2-[*N*-(Pyridin-2-yl)-*N*-tosylamino]-3-methylphenyl]-2-methylpropanoic acid (**10b**). White crystals; 82%, mp 140 ºC (acetone); IR (KBr) ν_{max} 3090, 2980, 2760, 1718, 1600, 1520, 1430, 1370, 1235, 750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.55 (6H, s, $2CH_3$), 2.42 (6H, s, $2CH_3$), 6.40-8.20 (11H, m, Ar-H) and 11.7 (s, 1, COOH). Anal. Calcd. for $C_{23}H_{24}N_2O_4S$ (424); C, 65.09; H, 5.66; N, 6.60; S, 7.54. Found; C, 65.11; H, 5.64; N, 6.44; S, 7.60%.

2-[2-(*N*-Benzyl-*N*-tosylamino)-3-methylphenyl]-2-methylpropanoic acid (**10c**). White plates; 80%, mp 110 ºC (benzene); IR (KBr) ν_{max} 3074, 2983, 2565, 1715, 1595, 1560, 1480, 1440, 1385, 1240, 748 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.55 (6H, s, $2CH_3$), 2.42 (6H, s, $2CH_3$), 4.30 (2H, s, CH_2), 6.40-7.50 (12H, m, Ar-H) and 10.8 (s, 1, COOH). Anal. Calcd. for $C_{25}H_{27}NO_4S$ (437); C, 68.64; H, 6.17; N, 3.20; S, 7.32. Found; C, 68.74; H, 6.08; N, 3.41; S, 7.38%.

2-[2-[*N*-[(Pyridin-2-yl)methyl]-*N*-tosylamino]-3-methylphenyl]-2-methylpropanoic acid (**10d**). White crystals; 84%, mp 95 ºC (n-hexane); IR (KBr) ν_{max} 3095, 2960, 2620, 1720, 1600, 1580, 1460, 1440, 1370, 1250, 750 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.52 (6H, s, $2CH_3$), 2.42 (6H, s, $2CH_3$), 4.50 (2H, s, CH_2), 6.40-8.50 (11H, m, Ar-H) and 11.6 (s, 1, COOH). Anal. Calcd. for $C_{24}H_{26}N_2O_4S$ (438); C, 65.75; H, 5.93; N, 6.39; S, 7.30. Found; C, 65.92; H, 5.73; N, 6.66; S, 7.35%.

Friedel-Crafts cyclialkylation and cycliacylation procedures. The procedures described for cyclialkylation of heteroarylalkanols with $AlCl_3$, P_2O_5 or PPA were essentially followed. In all reactions, the crude oily or solid products were purified by flash column chromatography (basic alumina, EtOAc/*n*-hexane, 1/1) to give the pure products 11a-d and 12e-h. The conditions and yields for the cyclic products are shown in Table 1 while the physical and spectral data of the products are given in the following:

4,11,11-Trimethyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepin-10-one (11a). White needles; 82%; mp 112 ºC (acetone); IR (KBr) ν_{max} 3450, 3065, 2990, 1742, 1600, 1585, 1480, 1450, 1385, 1280, 1075, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.52 (6H, s, $2CH_3$), 2.34 (3H, s, CH_3), 6.41-7.72 (7H, m, Ar-H) and 9.96 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 28.6 ($2CH_3$), 45.5, 119.2, 119.7, 120.5, 122.8, 124.2, 127.8, 129.6, 131.7, 133.6, 137.2, 138.5, 142.8, 205.4; MS (EI, 70 eV) *m/z* (%), 252 (M^++1, 10), 251 (M^+, 100), 250 (80), 236 (82), 221 (32),

206 (25), 183 (50), 169 (27), 151 (25), 109 (18), 91 (33), 77 (12). Anal. Calcd. for $C_{17}H_{17}NO$ (251); C, 81.27; H, 6.77; N, 5.57. Found; C, 81.37; H, 6.74; N, 5.70%.

6,6,10-Trimethyl-5,6-dihydro-11*H*-benzo[*f*]pyrido[2,3-*b*]azepin-5-one (11b). Pale yellow crystals; 88%; mp 135 ºC (PE 60-80 °C/benzene); IR (KBr) ν_{max} 3420, 3060, 2970, 1745, 1600, 1590, 1475, 1440, 1380, 1270, 1130, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.53 (6H, s, $2CH_3$), 2.35 (3H, s, CH_3), 6.45-8.41 (6H, m, Ar-H) and 10.41 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 26.4 ($2CH_3$), 45.2, 115.2, 118.5, 119.8, 124.4, 127.6, 128.6, 129.5, 136.5, 140.7, 148.5, 168.6, 207.2; MS (EI, 70 eV) *m/z* (%), 252 (M^+, 100), 251 (69), 237 (62), 222 (19), 207 (33), 195 (25), 182 (37), 168 (22), 151 (15), 109 (12), 91 (32), 77 (9). Anal. Calcd. for $C_{16}H_{16}N_2O$ (252); C, 76.19; H, 6.34; N, 11.11. Found; C, 76.30; H, 6.42; N, 10.92%.

4,12,12-Trimethyl-5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocin-11-one (11c). Yellow needles; 88%; mp 138 ºC (acetone); IR (KBr) ν_{max} 3390, 3070, 2970, 1740, 1585, 1463, 1450, 1385, 1275, 1130, 1075, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.63 (6H, s, $2CH_3$), 2.37 (3H, s, CH_3), 4.42 (2H, s, CH_2), 6.49-7.62 (6H, m, Ar-H) and 10.56 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 17.6, 28.4 ($2CH_3$), 44.8, 117.6, 119.8, 127.5, 126.4, 126.7, 126.9, 128.6, 129.2, 132.8, 134.0, 138.6, 148.4, 204.5; MS (EI, 70 eV) *m/z* (%), 265 (M^+, 72), 264 (100), 250 (82), 235 (65), 220 (34), 207 (20), 195 (15), 180 (47), 165 (31), 151 (18), 109 (22), 91 (12), 77 (8). Anal. Calcd. for $C_{18}H_{19}NO$ (265); C, 81.50; H, 7.16; N, 5.28. Found; C, 81.64; H, 7.10; N, 5.27%.

6,6,10-Trimethyl-5,6,11,12-tetrahydro-6*H*-benzo[*g*]pyrido[2,3-*c*]azocin-5-one (11d). White needles; 90%; mp 122 ºC (acetone); IR (KBr) ν_{max} 3385, 3040, 2955, 1735, 1580, 1480, 1450, 1435, 1370, 1285, 1070, 748 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.64 (6H, s, $2CH_3$), 2.35 (3H, s, CH_3), 4.51 (2H, s, CH_2), 6.52-8.15 (6H, m, Ar-H) and 10.52 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 26.4 ($2CH_3$) 44.5, 50.7, 117.6, 118.4, 120.8, 126.7, 127.8, 130.8, 134.8, 138.4, 145.8, 152.7, 165.1, 205.4; MS (EI, 70 eV) *m/z* (%), 266 (M^+, 100), 265 (20), 251 (85), 236 (74), 221 (28), 208 (42), 196 (21), 181 (40), 167 (25), 150 (12), 109 (24), 91 (15), 77 (11). Anal. Calcd. for $C_{17}H_{18}N_2O$ (266); C, 76.69; H, 6.76; N, 10.52. Found; C, 76.91; H, 6.52; N, 10.65%.

4,10,10,11,11-Pentamethyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (12e). Yellowish viscous oil; 86%; n_D^{25} 1.584; IR (film) ν_{max} 3450, 3084, 2970, 1600, 1575, 1460, 1445, 1348, 747 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.37 (12H, s, $4CH_3$), 2.34 (3H, s, CH_3) 6.41-7.25 (7H, m, Ar-H) and 9.82 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 24.8 ($4CH_3$), 45.8, 48.1, 117.8, 117.9, 120.6, 124.0, 126.6, 127.5, 128.4, 129.6, 132.4, 134.8, 140.3, 142.2; MS (EI, 70 eV) *m/z* (%), 266 (M^++1, 40), 265 (M^+, 100), 250 (71), 220 (42), 205 (19), 190 (49), 177 (27), 167 (18), 151 (15), 109 (28), 105 (35), 90 (26), 77 (15). Anal. Calcd. for $C_{19}H_{23}N$ (265); C, 86.03; H, 8.67; N, 5.28. Found; C, 86.18; H, 8.55; N, 5.27%.

5,5,6,6,10-Pentamethyl-5,6-dihydro-11*H*-benzo[*f*]pyrido[2,3-*b*]azepine (12f). Yellow crystals; 85%; mp 105 ºC (methanol); IR (KBr) ν_{max} 3465, 3090, 2965, 1600, 1590, 1482, 1455, 1440, 1338, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.36 (12H, s, $4CH_3$), 2.34 (3H, s, CH_3), 6.42-8.20 (6H, m, Ar-H) and 10.20 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.4, 25.8 ($4CH_3$), 45.8, 48.1, 115.2, 120.3, 122.9, 125.8, 127.8, 130.6, 135.2, 137.4, 138.5, 150.2, 162.8;

MS (EI, 70 eV) *m/z* (%), 267 (M^++1, 31), 266 (M^+, 100), 251 (64), 236 (32), 221 (18), 206 (35), 191 (21), 178 (41), 166 (24), 151 (17), 109 (33), 104 (15), 90 (12), 76 (8). Anal. Calcd. for $C_{18}H_{22}N_2$ (266); C, 81.20; H, 8.27; N, 10.52. Found; C, 81.50; H, 8.01; N, 10.48%.

4,11,11,12,12-Pentamethyl-5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocine (12g). White needles; 84%; mp 95 ºC (methanol); IR (KBr) ν_{max} 3390, 3065, 2935, 1595, 1566, 1475, 1440, 1375, 1285, 746 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.34 (12H, s, $4CH_3$), 2.36 (3H, s, CH_3), 4.10 (2H, s, CH_2), 6.46-7.12 (7H, m, Ar-H) and 9.72 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.9, 24.8 ($2CH_3$), 26.4 ($2CH_3$), 46.4, 48.4, 55.4, 118.7, 122.9, 124.9, 125.5, 125.8, 126.4, 127.8, 128.4, 134.6, 139.1, 145.2, 155.6; MS (EI, 70 eV) *m/z* (%), 280 (M^++1, 15), 279 (M^+, 100), 264 (52), 249 (45), 234 (22), 219 (21), 195 (44), 177 (24), 166 (33), 150 (20), 109 (25), 104 (18), 90 (15), 76 (11). Anal. Calcd. for $C_{20}H_{25}N$ (279); C, 86.02; H, 8.96; N, 5.01. Found; C, 85.63; H, 9.20; N, 5.16%.

5,5,6,6,10-Pentamethyl-5,6,11,12-tetrahydro-6*H*-benzo[*g*]pyrido[2,3-*c*]azocine (12h). White needles; 89%; mp 136 ºC (acetone); IR (KBr) ν_{max} 3417, 3066, 2978, 1600, 1582, 1480, 1440, 1384, 1245, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.36 (12H, s, $4CH_3$), 2.35 (3H, s, CH_3), 4.17 (2H, s, CH_2), 6.41-8.27 (6H, m, Ar-H) and 10.25 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 25.6 ($2CH_3$), 28.2 ($2CH_3$), 43.4, 47.4, 54.8, 118.7, 121.8, 124.9, 126.8, 128.4, 132.6, 136.4, 139.5, 145.2, 147.7, 162.6; MS (EI, 70 eV) *m/z* (%), 281 (M^++1, 32), 280 (M^+, 100), 265 (70), 250 (31), 235 (40), 220 (15), 195 (14), 178 (36), 168 (38), 151 (18), 108 (40), 105 (28), 90 (19), 76 (14). Anal. Calcd. for $C_{19}H_{24}N_2$ (280); C, 81.42; H, 8.57; N, 10.00. Found; C, 81.55; H, 8.62; N, 9.82%.

General procedure for the synthesis of tricyclic compounds 12a-d. A mixture of ketone (11a or b or c or d) (5 mmol), absolute ethyl alcohol (6 mL), hydrazine hydrate (5 mL, 90%) and diethylene glycol (15 mL) was refluxed for 10 h. Afterwards, the cooled concentrated residue (*ca.* 15 mL) was treated with KOH (0.8 g, 12 mmol) and refluxed for additional 5 h. Cold water (40 mL) was added with shaking and the product was extracted with ether (50 mL), washed with water and dried over $MgSO_4$. The solvent was evaporated in *vacuo* and the crude residues were subjected to flash column chromatography (basic alumina, EtOAc/n-hexane, 1/1) to give the pure products 12a-d. The yields and spectral data are given in the following:

4,11,11-Trimethyl-10,11-dihydro-5*H*-dibenz[*b,f*]azepine (12a). White needles; 88%; mp 142 ºC (benzene); IR (KBr) ν_{max} 3465, 3080, 2975, 1600, 1480, 1460, 1440, 1365, 1230, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.40 (6H, s, $2CH_3$), 2.36 (3H, s, CH_3), 2.74 (2H, s, CH_2), 6.45-7.28 (7H, m, Ar-H) and 9.82 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 29.8 ($2CH_3$), 32.4, 46.6, 117.8, 118.4, 120.8, 125.0, 126.9, 127.0, 128.6, 129.1, 130.6, 134.4, 139.7, 142.2; MS (EI, 70 eV) *m/z* (%), 237 (M^+, 100), 222 (91), 207 (58), 192 (36), 192 (19), 190 (62), 176 (15), 165 (12), 150 (10), 109 (25), 105 (35), 91 (11), 77 (8). Anal. Calcd. for $C_{17}H_{19}N$ (237); C, 86.07; H, 8.01; N, 5.90. Found; C, 86.21; H, 7.92; N, 5.86%.

6,6,10-Trimethyl-5,6-dihydro-11*H*-benzo[*f*]pyrido[2,3-*b*]azepine (12b). White plates; 86%; mp 136 ºC (methanol); IR (KBr) ν_{max} 3480, 3090, 2985, 1600, 1585, 1460, 1435, 1375, 750 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.39 (6H, s, $2CH_3$), 2.38 (3H, s, CH_3), 2.82 (2H, s, CH_2),

6.45-8.18 (6H, m, Ar-H) and 9.88 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.8, 29.8 ($2CH_3$), 31.8, 45.6, 115.2, 120.3, 124.9, 125.4, 127.8, 128.6, 133.8, 135.4, 142.5, 147.2, 162.8; MS (EI, 70 eV) *m/z* (%), 238 (M^+, 100), 223 (84), 208 (40), 193 (32), 191 (47), 177 (22), 165 (15), 151 (14), 109 (20), 105 (18), 91 (15), 76 (14). Anal. Calcd. for $C_{16}H_{18}N_2$ (238); C, 80.67; H, 7.56; N, 11.76. Found; C, 80.80; H, 7.37; N, 11.82%.

4,12,12-Trimethyl-5,6,11,12-tetrahydro-5*H*-dibenz[*b,f*]azocine (12c). White crystals; 90%; mp 115 ºC (ethanol); IR (Film) ν_{max} 3385, 3066, 2950, 1595, 1494, 1475, 1440, 1355, 748 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.40 (6H, s, $2CH_3$), 2.37 (3H, s, CH_3), 2.92 (2H, s, CH_2), 4.40 (2H, s, CH_2), 6.52-7.24 (7H, m, Ar-H) and 10.46 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 16.4, 29.6 ($2CH_3$), 29.8, 47.2, 56.4, 118.7, 124.9, 125.4, 125.8, 125.9, 126.1, 126.8, 128.4, 134.6, 136.1, 144.2, 147.2; MS (EI, 70 eV) *m/z* (%), 252 (M^++1, 40), 251 (M^+, 100), 236 (55), 221 (28), 205 (33), 190 (29), 176 (39), 166 (30), 148 (20), 109 (14), 104 (22), 90 (12), 77 (9). Anal. Calcd. for $C_{18}H_{21}N$ (251); C, 86.05; H, 8.36; N, 5.57. Found; C, 86.25; H, 8.17; N, 5.58%.

6,6,10-Trimethyl-5,6,11,12-tetrahydro-6*H*-benzo[*g*]pyrido[2,3-*c*]azocine (12d). White crystals; 88%; mp 96 ºC (ethanol); IR (KBr) ν_{max} 3420, 3035, 2960, 1605, 1582, 1490, 1460, 1345, 750 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, ppm), δ 1.38 (6H, s, $2CH_3$), 2.36 (3H, s, CH_3), 2.85 (2H, s, CH_2), 4.52 (2H, s, CH_2), 6.48-8.20 (6H, m, Ar-H) and 9.66 (1H, s, NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 15.8, 28.8 ($2CH_3$), 29.8, 46.2, 56.8, 118.7, 121.8, 124.9, 125.8, 128.8, 133.2, 134.6, 136.4, 145.4, 149.7, 160.6; MS (EI, 70 eV) *m/z* (%), 252 (M^+, 100), 237 (65), 222 (44), 207 (35), 195 (36), 183 (34), 178 (20), 167 (19), 149 (33), 109 (19), 105 (25), 90 (17), 77 (12). Anal. Calcd. for $C_{17}H_{20}N_2$ (252); C, 80.95; H, 7.93; N, 11.11. Found; C, 80.94; H, 7.85; N, 11.20%.

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References

1. Naik, N.; kumar, H. V.; Shubhavathi, T. *Int J. Curr. Pharm. Res.* **2011**, *3*, 109.
2. Bräse, S.; Gil, C.; Knepper, K. *Bioorg. Med. Chem.* **2002**, *10*, 2415. http://dx.doi.org/10.1016/S0968-0896(02)00025-1
3. David, E.; Rangheard, C.; Pellet-Rostaing, S.; Lemaire, M. *Synlett* **2006**, 2016.
4. Groth, C.; Alvord, W. G.; Quinõnes, O. A.; Fortini, M. E. *M. Pharmacol.* **2010**, *77*, 67.
5. Rao, G. K.; Kaur, R.; Pai, P. N. S. *J. Chem. Pharm. Res.* **2010**, *2*, 489.

6. Oetken, M.; Nentwig, G.; Lçffler, D.; Ternes, T.; Oehlmann, *J. Arch. Environ. Contam. Toxicol.* **2005**, *49*, 353.
http://dx.doi.org/10.1007/s00244-004-0211-0
PMid:16177879
7. Pauli, J.; Vag, T.; Haag, R.; Spieles, M.; Wenzel, M.; Kaiser, W. A.; Resch-Genger, U.; Hilger, I. *Eur. J. Med. Chem.* **2009**, *44*, 3496.
http://dx.doi.org/10.1016/j.ejmech.2009.01.019
PMid:19269067
8. Forte-Tavčer, P. *Dyes Pig*. **2004**, *63*, 181.
http://dx.doi.org/10.1016/j.dyepig.2004.02.009
9. Roberts, R. J.; Payne, R. S.; Rowe, R. C. *Eur. J. Pharm. Sci.* **2000**, *9*, 277.
http://dx.doi.org/10.1016/S0928-0987(99)00065-2 1
10. Bolten, D.; Türk, M. *J. Supercritical Fluids* **2012**, *66*, 389.
http://dx.doi.org/10.1016/j.supflu.2012.04.010
11. Black, P. N.; Sandova, A.; Arias-Barrau, E.; DiRusso, C. C. *Immun. Endoc. Metab. Agents Med. Chem*. **2009**, *9*, 11.
http://dx.doi.org/10.2174/187152209788009850
12. La Roche, S. M.; Helmers,S. L. *J. Am. Med. Assoc.* **2004**, *291*, 605.
http://dx.doi.org/10.1001/jama.291.5.605
PMid:14762040
13. Arnold, L. A.; Guy, R. K. *Bioorg. Med. Chem. Lett.* **2006**, *16*, 5360.
http://dx.doi.org/10.1016/j.bmcl.2006.07.078
PMid:16890431
14. Casadio, S.; Pala, G.; Crescenzi, E.; Marazzi-Uberti, E.; Coppi, G. and Turba, C. *J. Med. Chem.* **1968**, *11*, 97.
http://dx.doi.org/10.1021/jm00307a022
15. Balaure, P. C.; Costea, I.; Iordache, F.; Drăghici, C.; Enache, C. *Rev. Roum. Chim.* **2009**, *54*, 935.
16. Righi, M.; Bedini, A.; Piersanti, G.; Romagnoli, F.; Spadoni, G. *J. Org. Chem.* **2011**, *76*, 704.
http://dx.doi.org/10.1021/jo102109f
PMid:21175194
17. Hartwig, J. F. *Synlett* **2006**, 1283.
http://dx.doi.org/10.1055/s-2006-939728
18. Vijay Kumar, H.; Kishor Kumar, C.; Nagaraja, N. *Med. Chem. Res.* **2011**, *20*, 101.
http://dx.doi.org/10.1007/s00044-009-9292-7
19. López-Muñoz, F.; Alamo, C. *Cur. Pharm. Des.* **2009**, *15*, 1563.
http://dx.doi.org/10.2174/138161209788168001
20. Wesnes, K. A.; Edgar, C.; Dean, A. D.; Wroe, S. J. *Epilepsy Behav*. **2009**, *14*, 522.
http://dx.doi.org/10.1016/j.yebeh.2008.11.012
PMid:19111629

21. MacNeil, S. L.; Gray, M.; Briggs, L. E.; Li, J. J.; Snieckus, V. *Synlett* **1998**, 419**.** http://dx.doi.org/10.1055/s-1998-1654
22. Haasz, F.; Galamb, V. *Synth. Commun*. **1994**, *24*, 683. http://dx.doi.org/10.1080/00397919408012646
23. Belluci, G.; Berti, G.; Chiappe, C.; Lippi, A.; Marioni, F. *J. Med.Chem*. **1987**, *30*, 768. http://dx.doi.org/10.1021/jm00388a004
24. Bergmann, E. D.; Shahak, L; Aizenshtat, Z. *Tetrahedron Lett.* **1968**, *31*, 3469. http://dx.doi.org/10.1016/S0040-4039(01)99085-9
25. Lohse, O.; Beutler, U.; Fűnfschilling, P.; Furet, P.; France, J.; Kaufmann, D.; Penn, G.; Zaugg, W. *Tetrahedron Lett.* **2001**, *42*, 385. http://dx.doi.org/10.1016/S0040-4039(00)01981-X
26. MacNeil, S. L.; Gray, M.; Gusev, D. G.; Briggs, L. E.; Snieckus, V. *J. Org. Chem.* **2008**, *73*, 9710. http://dx.doi.org/10.1021/jo801856n PMid:19053602
27. Palma, A.; Galeano, N.; Bahsas, A. *Synthesis* **2010**, 1291. http://dx.doi.org/10.1055/s-0029-1218674
28. Monro, A. M.; Quinton, R. M.; Wrigley, T. I. *J. Med. Chem.* **1963**, *6*, 255. http://dx.doi.org/10.1021/jm00339a009
29. Kisel, V. M.; Kovtunenko, V. A.; Turov, A. V.; Tyltin, A. K.; Babichev, F. S. *Chem. Heterocyc Compd.* **1991** *27*, 92. http://dx.doi.org/10.1007/BF00633227
30. Polonka-Bálint, Á.; Saraceno, C.; Ludányi, K.; Bényei, A. and Mátyus, P. *Synlett* **2008**, *18*, 2846.
31. Cho, H.; Iwama, Y.; Sugimoto, K.; Mori, S.; Tokuyama, H. *J. Org. Chem.* **2010**, *75*, 627. http://dx.doi.org/10.1021/jo902177p PMid:20039606
32. Majumdar, K. C.; Nandi, R. K.; Samanta, S.; Chattopadhyay, B. *Synthesis* **2010**, 985. http://dx.doi.org/10.1055/s-0029-1218630
33. Olah, G. A. *Friedel–Crafts Chemistry*; Wiley: NewYork, NY, 1973.
34. Roberts, R. M.; Khalaf, A. A. *Friedel-Crafts Chemistry: A Century of Discovery*; Marcel Dekker: New York, NY, 1984.
35. Poulsen, T. B.; Jørgensen, K. A. *Chem. Rev*. **2008**, *108*, 2903. http://dx.doi.org/10.1021/cr078372e PMid:18500844
36. Khalaf, A. A.; Roberts, R. M. *J. Org. Chem.* **1973**, *38*, 1388. http://dx.doi.org/10.1021/jo00947a032
37. Khalaf, A. A.; Awad, I. M.; El-Emary, T. I.; Abd El-Aal, H. A. K. J. *Indian Chem. Soc*. **2010**, *87*, 595.

38. Khalaf, A. A.; El-Khawaga, A. M.; Awad, I. M.; Abd El-Aal, H. A. K. *Arkivoc* **2009**, (*xiv*), 314.
39. Khalaf, A. A.; El-Khawaga, A. M.; Awad, I. M.; Abd El-Aal, H. A. K. *Arkivoc* **2010**, (*x*), 338.
http://dx.doi.org/10.3998/ark.5550190.0011.a28
40. Abd El-Aal, H. A. K.; Khalaf, A. A.; El-Emary, T. I. *Arkivoc* **2012**, *(ix)* 122.
http://dx.doi.org/10.3998/ark.5550190.0013.911
41. Abd El-Aal, H. A. K.; Khalaf, A. A. *Aust. J. Chem.* **2013**, *66*, 635.
42. Dorokhov, V. A.; Gordeev, M. F.; Demyanets, Z. K.; Vorontsova, L. G.; Kurella, M. G.; Andrianov, V. I.; Rekhlova, O. A. *Izv. Akad. Nauk SSSR, Seri. Khim*. **1991**, *11*, 2587; *Chem. Abstr*. **1992**, *117*, 26477.
43. Granoth, I.; Pownall, H. J., *J. Org. Chem*. **1975**, *40*, 2088.
http://dx.doi.org/10.1021/jo00902a017
44. Cano, R.; Ramön, D. J.; Yus, M. *J. Org. Chem*. **2011**, *76*, 654.
http://dx.doi.org/10.1021/jo1022052
PMid:21175155
45. Jones, R. G.; Soper, Q. F.; Behrens, O. K.; Corse, J. W. *J. Am. Chem. Soc*. **1948**, *70*, 2843.
http://dx.doi.org/10.1021/ja01189a002
46. Perold, G. W.; Steyn, A. P.; Von Reiche, F. V. K. *J. Am. Chem. Soc*. **1957**, *79*, 462.
http://dx.doi.org/10.1021/ja01559a063
47. Bosch, A.; Brown, R. K. *Can. J. Chem*. **1968**, *46*, 715.
http://dx.doi.org/10.1139/v68-121
48. Johnson, S. W; Woroch, L. E; Buell, G, B, *J. Am. Chem. Soc*. **1949**, *71*, 1901.
http://dx.doi.org/10.1021/ja01174a001

