Modern Friedel–Crafts Chemistry. Part 37. Efficient Syntheses of Some New Julolidines via Cyclialkylations of Heteroaryl Carbinols

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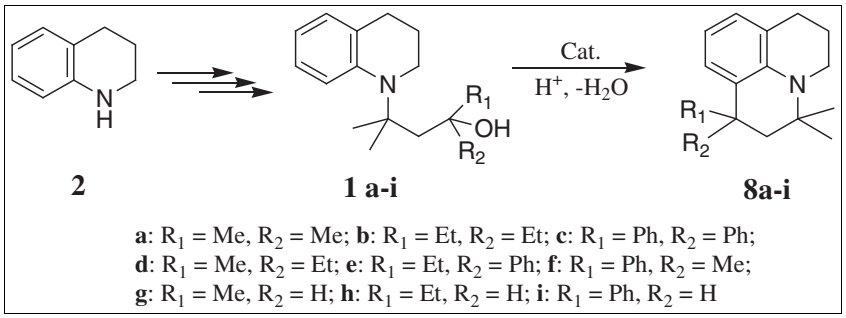

A simple and convenient procedure for the synthesis of some novel alkyl-substituted and aryl-substituted julolidines is reported. Julolidines were smoothly synthesized in excellent isolated yields via Friedel–Crafts intramolecular alkylations of heteroarylalkanols in the presence of both Brønsted (PPA) and Lewis ($AlCl_3/CH_3NO_2$) acid catalysts. The precursors alkanols, **1a–i**, were readily prepared both by reaction of selectively synthesized carboxylic acid esters and ketones with different Grignard reagents and also by reduction of the synthesized ketones with LAH. A plausible carbocation mechanism is proposed to account for the results. The structures of the compounds are established using both spectral and analytical data.

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INTRODUCTION

The chemistry of julolidine (2,3,6,7-tetrahydro-1*H*, 5*H*-pyrido[3,2,1-*ij*]quinoline) as well as lilolidine has been the focus of interest of many investigations during recent years. This growing interest can be explained because of their importance as synthetic intermediates [1–6] and as the key structural element exhibit interesting biological activities [7–9] in several natural products and fluorescent dyes [10–13]. Moreover, julolidines are the core structures of many pharmacological agents and drug molecules such as anticancer drugs [14], antidiabetic or cardiovascular agents [15], pesticides [16], and potential antidepressants [17]. Consequently, synthetic methodologies for preparing julolidine derivatives have attracted considerable interest; however, few methods offering good results have been reported for the synthesis of julolidines [18] and julolidinones [19] and to generate bicyclic systems with one ring junction nitrogen atom [20,21] (Fig. 1).

Despite numerous advances in the field of synthetic organic chemistry, the developments of valuable and efficient strategies for the construction of these ring systems remain as a significant challenge. Among these methods, intramolecular Friedel–Crafts cyclialkylations [22–27] promoted by both Brønsted and Lewis acid catalysts is promising as an efficient method to prepare substituted julolidines.

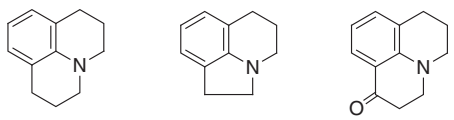


Figure 1. Heterocycles containing tetrahydroquinoline scaffold.

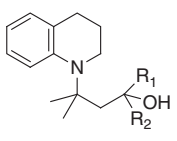
In our previous work, we developed a synthetic pathway for the construction of seven nitrogen and nitrogen–sulfur polycycles [28] containing quinoline, tetrahydroquinoline, acridine, phenothiazine, and indole moieties via Friedel–Crafts cyclialkylations of suitable synthesized alcohols. The results showed that a number of difficult substituted heterocycles can be easily obtained with the advantages of short reaction time and high yield.

This prompted us to apply these procedures in developing the synthesis of nine julolidines substituted from tetrahydroquinoline via Friedel–Crafts cyclialkylation of suitable synthesized heteroarylalkanols **1a–i** (Scheme 1).

RESULTS AND DISCUSSION

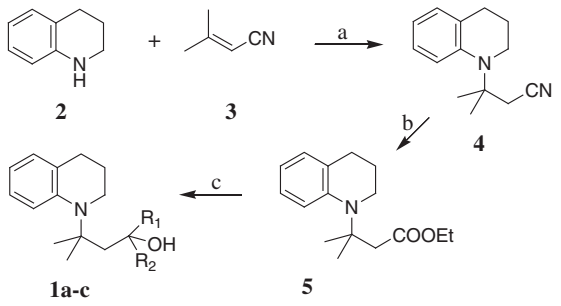
Synthesis of heteroarylalkanols 1a–i. The required 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-methylbutanenitrile (**4**)

Scheme 1. Heteroarylalkanols **1a–i**.

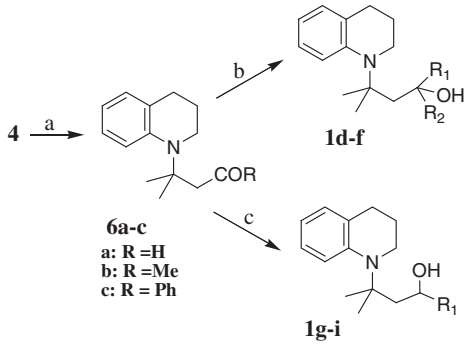


	R_1	R_2		R_1	R_2
a	Me	Me	**f**	Ph	Me
b	Et	Et	**g**	Me	H
c	Ph	Ph	**h**	Et	H
d	Me	Et	**i**	Ph	H
e	Et	Ph			

Scheme 2. Reagents and conditions: (a) $BnMe_3NOH$, dioxane, 90°C, 4 h, 86%; (b) H_2SO_4, EtOH, reflux 7 h, 82%; (c) 2RMgX, Et_2O, NH_4Cl soln, Table 1.



Scheme 3. Reagents and conditions: (a) RMgX, PhH/Et_2O, HCl; (b) RMgX, Et_2O, NH_4Cl soln; (c) LAH, E_2O, rt, Table 1.

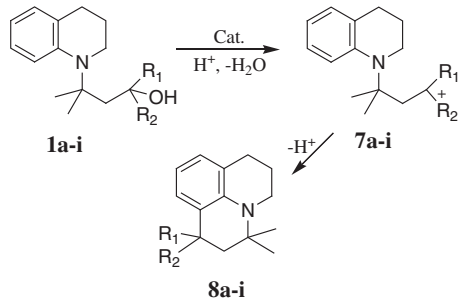


was readily synthesized in one step by the reaction of tetrahydroquinoline (**2**) with 3-methylcrotononitrile (**3**) in the presence of a catalytic amount of Triton B; **4** was successively converted to its ethyl ester **5**. The ethyl 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-methylbutanoate (**5**) was finally reacted with two equivalents of Grignard reagents to afford alcohols **1a–c**. The results are presented in Scheme 2 and Table 1 (Entries 1–3).

Two-step syntheses of alcohols **1–f** and **1g–i** are outlined in Scheme 3 and Table 1 (Entries 4–6 and 7–9). These alcohols were prepared separately via two routes starting with nitrile **4**. The nitrile **4** was allowed to react with Grignard reagents affording the corresponding ketones **6a–c**. The resulting ketones were further reacted by two different routes, (i) addition of Grignard reagents to yield alcohols **1d–f** and (ii) reduction with LAH to afford alcohols **1g–i**. The structures of all new alcohols were appropriately established by the usual spectroscopic methods.

The structural elucidation of alcohols **1a–c** was mainly based on IR, ^{1}H NMR, MS, and elemental analyses. The IR spectra of alcohols **1a–c** showed absorption bands for an OH groups as broad bands in the range 3780–3250 cm^{-1}. The ^{1}H NMR data allowed an unambiguous statement of the heterocyclic alkanols formation. Thus, the ^{1}H NMR spectrum

Scheme 4. Cyclialkylations of heteroarylalkanols **1a–i**.



displayed eight signals for compound **1a**, the four aromatic protons at δ 6.8–7.4. The aliphatic acyclic protons of the methylenes and four methyl groups of the new alcohol appeared as three singlets: thus, the gem-dimethyls at C-2 and C-4 appear at δ 1.1 and δ 1.3, respectively. A third singlet at δ 1.6 was assigned to the up-field proton CH_2. A broad singlet at δ 2.2 was assigned to OH. In all IR spectra of the synthesized carbinols, the characteristic peak of carbonyl groups was absent.

Cyclialkylations of heteroaryl alcohols to substituted julolidine. The cyclialkylations of alcohols **1a–i** were carried out in the presence of both $AlCl_3/CH_3NO_2$

Table 1

Synthesis of heteroarylalkanols (**1a–i**).

Entry	Substrate	R_1	R_2	Conditions[a]	mp (°C)	Product (%)[b]
1	**5**	Me	Me	MeMgI, Et_2O, rt, 10 h	112	**1a** (91)
2	**5**	Et	Et	EtMgBr, Et_2O, rt, 12 h	90	**1b** (89)
3	**5**	Ph	Ph	PhMgBr, Et_2O, rt, 10 h	153	**1c** (84)
4	**6a**	Me	Et	EtMgBr, Et_2O, rt, 5 h	75	**1** (85)
5	**6b**	Et	Ph	PhMgBr, Et_2O, rt, 8 h	89	**1e** (90)
6	**6c**	Ph	Me	MeMgI, Et_2O, rt, 6 h	122	**1f** (88)
7	**6a**	Me	H	LAH, Et_2O, rt, 2 h	136	**1g** (82)
8	**6b**	Et	H	LAH, Et_2O, rt, 2 h	105	**1h** (87)
9	**6c**	Ph	H	LAH, Et_2O, rt, 3 h	132	**1i** (93)

[a]All reactions were performed using (0.1 equiv) excess of RMgX and LAH than calculated.
[b]Isolated yield refers to substrate.

Table 2

Cyclialkylation conditions and results of heteroarylalkanols **1a–f**.

Entry	Substrate	Catalyst type	Solvent	Temperature (°C)	Time (h)	Product (%)[a]
1	**1a**	$AlCl_3/CH_3NO_2$[b]	DCM[c]	RT	2	**8a** (84)
2	**1a**	PPA[d]	—	160	1	**8a** (75)
3[c]	**1b**	$AlCl_3/CH_3NO_2$	PE[e]	RT	2	**8b** (86)
4	**1b**	PPA	—	160	1	**8b** (73)
5	**1c**	$AlCl_3/CH_3NO_2$	DCM	RT	50	**8c** (81)
6	**1c**	PPA	—	250	14	**8c** (75)
7[e]	**1d**	$AlCl_3/CH_3NO_2$	PE	RT	2	**8d** (82)
8	**1d**	PPA	—	160	2	**8d** (74)
9	**1e**	$AlCl_3/CH_3NO_2$	DCM	RT	2	**8e** (78)
10	**1e**	PPA	—	160	4	**8e** (76)
11	**1f**	$AlCl_3/CH_3NO_2$	PE	RT	4	**8f** (79)
12	**1f**	PPA	—	160	4	**8f** (76)

[a]Isolated yield refers to substrate.
[b]With $AlCl_3/CH_3NO_2$ catalyst, reactant proportions were as follows: carbinol (0.002 mole), $AlCl_3$ (0.0024 mole), CH_3NO_2 (0.024 mole), and solvent (10 mL).
[c]Dichloromethane.
[d]With PPA catalyst, reactant proportions were as follows: carbinol (0.5 g) and PPA (3 g).
[e]Petroleum ether (60–80°).

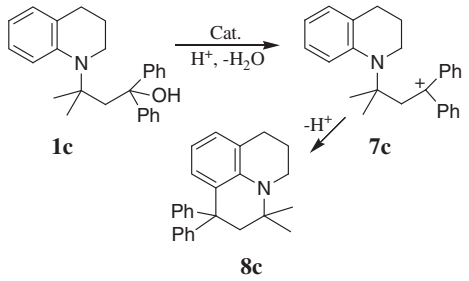
and PPA catalysts (Scheme 4). Under mild conditions, cyclialkylations of carbinols **1a,b,d–i** proceeded smoothly in the presence of $AlCl_3/CH_3NO_2$ and PPA catalysts under different reaction conditions gave substituted 2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinolines, **8a,b,d–i** in good overall yields (Table 2).

Cyclialkylations of 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-methyl-1,1-diphenylbutan-1-ol (**1c**) required more severe reaction conditions compared with their methyl substituted analog **1a** (Scheme 5; Table 2, Entry 6). Accordingly, the best results were obtained by promoted cyclialkylation under more strenuous conditions in the presence of PPA for 14 h at 250°C and with $AlCl_3/CH_3NO_2$ for 50 h in DCM at room temperature to yield 3,3-dimethyl-1,1-diphenyl-2,3,6,7-tetrahydro-1*H*,5*H*-pyrido[3,2,1-*ij*]quinoline (**8c**) as the sole product.

The results reflect that the steric interaction exerted by two phenyl groups encountered in ring closure of tertiary benzylic carbocation [29,30].

On the other hand, cyclialkylations of secondary alcohols **1g–i** required less strenuous reaction conditions in the ring

Scheme 5. Cyclialkylations of heteroarylalkanol **1c**.



Scheme 6. Cyclialkylation of heteroarylalkanols **1g–i**.

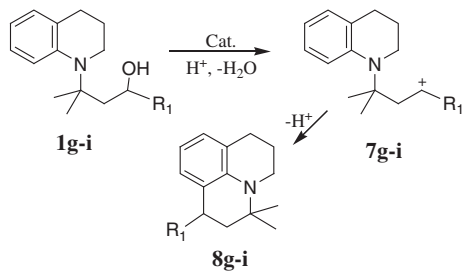


Table 3

Cyclialkylation conditions and results of heteroarylalkanols **1g–i**.

Entry	Substrate	Catalyst type	Solvent	Temperature (°C)	Time (h)	Product (%)
1	**1g**	$AlCl_3/CH_3NO_2$	DCM	RT	6	**8g** (82)
2	**1g**	PPA	—	160	4	**8g** (76)
3	**1h**	$AlCl_3/CH_3NO_2$	DCM	RT	6	**8h** (82)
4	**1h**	PPA	—	160	4	**8h** (76)
5	**1i**	$AlCl_3/CH_3NO_2$	DCM	RT	6	**8i** (77)
6	**1i**	PPA	—	160	8	**8i** (75)

closure step than alcohol **1c**. Thus, upon treatment of **1g–i** with acidic catalysts, the products were solely the julolidines **8g–i** (Table 3). The results can be explained in terms of less stability of the secondary than tertiary carbocation intermediates (Scheme 6).

CONCLUSIONS

In summary, we have developed a concise and catalytic protocol for the synthesis of alkyl-substituted and aryl-substituted julolidines that had not been reported before, via direct intramolecular Friedel–Crafts cyclization reaction of heteroaryl alkanols **1a–i** catalyzed by $AlCl_3/CH_3NO_2$ and PPA. The simplicity of the processes, moderate cost, and the results of this study proved that the development of Friedel–Crafts cyclialkylation reactions in heterocyclic chemistry can be considered as one of the most useful pathways to the synthesis of heteropolycycles.

EXPERIMENTAL

General. All reagents were purchased from Merck (Merck KGaA, Darmstadt, Germany), Sigma, or Aldrich Chemical Co. (New Road, Gillingham, Dorset, SP8 4XT, UK) and were used without further purification. Melting points were measured on a digital Gallenkamp capillary melting point apparatus (London, England) at Assiut university, and are uncorrected. The IR spectra were determined with a Shimadzu 470 Infrared spectrophotometer (3. Kanda-Nishikicho 1-chome, Chiyoda-ku, Tokyo 101-8448, Japan) at the Faculty of Science, Assiut university, Assiut, Egypt, using KBr wafer and thin film techniques (ν cm^{-1}). The ^1H NMR spectra were recorded on Jeol LA 400 MHz FT-NMR (400 MHz) (1-2, Musashino 3-chome Akishima, Tokyo 196-8558, Japan) and Varian 90 MHz NMR (Palo Alto, California USA) spectrometers at Assiut university, 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 (Waltham, MA 02451 USA) at the Faculty of Science, Assiut university, Assiut, Egypt. 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 TLC using precoated silica plates visualized with UV light. Flash column chromatography was performed on silica gel and basic alumina.

Synthesis of 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-methylbutanenitrile (4). A solution of tetrahydroquinoline **2** (6.9 g, 40 mmol) and β-methylcrotononitrile **3** (3.4 g, 42 mmol) in dioxane (30 mL) was cooled in ice bath and treated with 0.5 mL of Triton B. The reaction mixture was then heated in water bath for 4 h and then concentrated *in vacuo*. The pasty product triturated with methanol (3 × 10 mL) portions and the resulting orange precipitate was filtered off, washed excessively with methanol, and dried to yield the crude nitrile **4** (9.5 g, 92.5%), which was crystallized from acetone (8.9 g, 86.6%) as pale yellow crystals: mp 138°C; IR (KBr) ν_{max} 3070, 2950, 2260, 1595, 1480, 1455, 1340, 1170, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.82 (2H, m, $J = 7.5$ Hz, C^3H_2), 2.44 (2H, m, $J = 7.5$ Hz, C^4H_2), 2.55 (2H, m, $J = 9$ Hz, CH_2), 3.2 (2H, m, $J = 9$ Hz, C^2H_2), and 6.9–7.5 (4H, m, Ar–H). *Anal*. Calcd for $C_{14}H_{18}N_2$ (214); C, 78.5; H, 8.14; N, 13.08. Found; C, 78.9; H, 8.62; N, 12.75.

Synthesis of ethyl 3-(3,4-dihydroquinolin-1(2*H*)-yl)-3-methylbutanoate (5). A mixture of 3-(9*H*-carbazol-9-yl)-3-methylbutanenitrile **4** (5 g, 20 mmol), absolute ethanol (40 mL), and concentrated sulfuric acid (5 mL) was refluxed for 7 h. The excess alcohol is removed by distillation, and the residue was diluted with water (50 mL), basified with Na_2CO_3 solution (20 mL, 30%), and extracted with ether. The ethereal layer was separated, washed, and dried to give **5** (5 g, 85.7%). The crude yellow oil was subjected to flash column chromatography by using light petroleum and DCM as eluents to yield ethyl 3-(9*H*-carbazol-9-yl)-3-methylbutanoate **5** (4.8 g, 82.3%) in the form of a pale yellowish oil: n_D^{25} 1.572; IR (film) ν_{max} 3070, 2985, 1750, 1610, 1570, 1485, 1450, 1320, 1170, 745 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.22–1.45 (3H, t, $J = 7.5$ Hz, CH_3), 1.75 (2H, m, $J = 7.5$ Hz, C^3H_2), 2.4 (2H, s, $J = 9$ Hz, CH_2), 2.5 (2H, t, $J = 7.5$ Hz, C^4H_2), 3.25 (2H, t, $J = 7.5$ Hz, C^2H_2), 3.9 (2H, m, $J = 7.5$ Hz, CH_2), and 6.8–7.6 (4H, m, Ar–H). *Anal*. Calcd for $C_{16}H_{23}NO_2$ (261); C, 73.56; H, 8.81; N, 5.36. Found; C, 73.22; H, 8.85; N, 5.42.

General procedures for synthesis of heteroaryl ketones 6a–c. A solution of nitrile **4** (2.5 g, 10 mmol) in benzene (20 mL) was added rapidly with stirring to an ice-cold Grignard reagent obtained as usual [27] from Mg turnings (15 mmol) and alkyl or aryl halide (15 mmol) in ether (40 mL). After refluxing for 12 h, the reaction mixture was stirred into ice-cold hydrochloric acid (100 mL, 30%) followed by removal of the solvents *in vacuo*. The crude ketimine was hydrolyzed by refluxing with a mixture of (benzene, 20 mL; HCl, 10 mL; AcOH, 10 mL) until the ketimine disappeared (6–8 h) as monitored by TLC. The solution was cooled, and benzene layer was separated, whereas the aqueous layer was basified by addition of solid Na_2CO_3 with stirring and finally extracted with benzene (3 × 20 mL). The combined organic phases were washed with water, dried over $MgSO_4$, and the solvent was evaporated *in vacuo*. The crude mixture was purified by flash column chromatography (ethyl acetate–hexane 3:7) to afford the pure products **6a–c**.

4-(3,4-Dihydroquinolin-1(2H)-yl)-4-methylpentan-2-one (6a). Brown viscous oil (75%); n_D^{25} 1.588; R_f 0.43 (1:3, EtOAc/hexane); IR (film) ν_{max} 3065, 2990, 1740, 1580, 1480, 1440, 1370, 1270, 1020, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.75 (2H, m, $J = 7.5$ Hz, C^3H_2), 2.1 (3H, s, CH_3), 2.45 (2H, t, $J = 7.5$ Hz, C^4H_2), 2.6 (2H, s, CH_2), 3.3 (2H, t, $J = 7.5$ Hz, C^2H_2), 3.9 (2H, m, $J = 9$ Hz, CH_2), and 7.1–7.6 (4H, m, Ar–H). *Anal*. Calcd for $C_{15}H_{21}NO$ (231); C, 77.92; H, 9.09; N, 6.06. Found; C, 77.6; H, 8.85; N, 5.82.

5-(3,4-Dihydroquinolin-1(2H)-yl)-5-methylhexan-3-one (6b). Reddish viscous oil (77%); n_D^{25} 1.592; R_f 0.46 (1:3, EtOAc/hexane); IR (film) ν_{max} 3060, 2990, 2910, 1745, 1580, 1470, 1450, 1360, 1250, 1030, 680 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.9 (3H, t, $J = 9$ Hz, CH_3), 1.2 (6H, s, $2CH_3$), 1.8 (2H, m, C^3H_2), 2.4–2.7 (4H, m, C^4H_2, CH_2), 2.65 (2H, s, CH_2), 3.2 (2H, t, $J = 7.5$ Hz, C^2H_2), and 7.0–7.6 (4H, m, Ar–H). *Anal*. Calcd for $C_{16}H_{23}NO$ (245); C, 78.3; H, 9.38; N, 5.71. Found; C, 78.5; H, 9.33; N, 5.84.

3-(3,4-Dihydroquinolin-1(2H)-yl)-3-methyl-1-phenylbutan-1-one (6c). Pale yellow viscous oil (72%); n_D^{25} 1.605; R_f 0.34 (1:3, EtOAc/hexane); IR (KBr) ν_{max} 3040, 3000, 2970, 1750, 1580, 1480, 1450, 1375, 1275, 1060, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.3 (6H, 2s, $2CH_3$), 1.75 (2H, m,

C^3H_2), 2.4 (2H, t, $J = 7.5$, C^4H_2), 2.7 (2H, s, CH_2), 3.25 (2H, t, $J = 7.5$ Hz, C^2H_2), and 7.15–7.7 (9H, m, Ar–H). *Anal*. Calcd for $C_{20}H_{23}NO$ (293); C, 81.9; H, 7.85; N, 4.77. Found; C, 82.3; H, 7.45; N, 4.4.

General procedure for the synthesis of alcohols 1a–f. To an ice-cold Grignard reagent obtained as usual [26] from Mg turnings (0.2 g, 8 mmol) and alkyl or aryl halide (8 mmol) in ether (25 mL) was added with ester **5** (1.0 g, 3.6 mmol) and/or ketone **6a–c** (7.3 mmol). The reaction mixture was stirred at required temperature for the appointed time (Table 1) and decomposed by sat. aq. NH_4Cl soln. The product was extracted with ether (3×15 mL), and the combined organic phases were washed with water, dried over anhydrous Na_2SO_4, and the solvent was evaporated *in vacuo*. The residue was purified by flash column chromatography (basic alumina, ethyl acetate/hexane, 2:3) to afford the desired pure product **1a–f**. The conditions and yields are shown in Table 1 (Entries 1–6), and spectral data are given in the following.

4-(3,4-Dihydroquinolin-1(2H)-yl)-2,4-dimethylpentan-2-ol (1a). This compound was obtained as white crystals in yield, 84%, mp 112°C (ethanol), R_f 0.62 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3360, 3070, 2950, 1590, 1485, 1450, 1440, 1340, 1145, 750, 670 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.1 (6H, 2s, $2CH_3$), 1.3 (6H, 2s, $2CH_3$), 1.6 (2H, s, CH_2), 1.8 (2H, m, C^3H_2), 2.2 (1H, s, OH exchangeable with D_2O) 2.45 (2H, t, $J = 7.5$, C^4H_2), 3.1 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.8–7.4 (4H, m, Ar–H). *Anal*. Calcd for $C_{16}H_{25}NO$ (247); C, 77.7; H, 10.1; N, 5.66. Found; C, 78.1; H, 9.85; N, 5.4.

3-Ethyl-5-(3,4-dihydroquinolin-1(2H)-yl)-5-methylhexan-3-ol (1b). This compound was obtained as white crystals in yield, 80%, mp 90°C (ethanol), R_f 0.58 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3570, 3060, 2970, 2850, 1590, 1480, 1460, 1450, 1340, 1230, 1120, 720 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.85 (6H, m, $2CH_3$), 1.1 (6H, 2s, $2CH_3$), 1.25 (6H, 2s, $2CH_3$), 1.4 (4H, m, $2CH_2$), 1.55 (2H, s, CH_2), 1.75 (2H, m, C^3H_2), 2.35 (1H, s, OH exchangeable with D_2O) 2.6 (2H, t, $J = 7.5$, C^4H_2), 3.2 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.8–7.7 (4H, m, Ar–H). *Anal*. Calcd for $C_{18}H_{29}NO$ (275); C, 78.54; H, 10.54; N, 5.09; Found; C, 78.82; H, 10.36; N, 5.25.

3-(3,4-Dihydroquinolin-1(2H)-yl)-3-methyl-1,1-diphenylbutan-1-ol (1c). This compound was obtained as pale yellow crystals in yield, 75%, mp 153 °C (methanol), R_f 0.28 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3380, 3060, 2990, 1580, 1555, 1445, 1370, 1220, 1120, 730 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, 2s, $2CH_3$), 1.85 (2H, m, C^3H_2), 2.1 (2H, s, CH_2), 2.55 (2H, t, $J = 7.5$, C^4H_2), 3.3 (2H, t, C^2H_2), 4.2 (1H, s, OH exchangeable with D_2O), and 7.1–7.9 (14H, m, Ar–H). *Anal*. Calcd for $C_{26}H_{29}NO$ (371); C, 84.09; H, 7.81; N, 3.77. Found; C, 84.4; H, 7.45; N, 3.9.

5-(3,4-Dihydroquinolin-1(2H)-yl)-3,5-dimethylhexan-3-ol (1d). This compound was obtained as white crystals in yield, 77%, mp 75°C (ethanol), R_f 0.4 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3530, 3050, 2990, 1740, 1600, 1465, 1445, 1340, 1190, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.9 (3H, t, $J = 9$ Hz, CH_3), 1.15 (6H, 2s, $2CH_3$), 1.3 (3H, s, CH_3), 1.5 (2H, q, $J = 9$ Hz, CH_2), 1.6 (2H, s, CH_2), 1.8 (2H, m, C^3H_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.3 (2H, t, $J = 7.5$ Hz, C^2H_2), 4.5 (1H, s, OH exchangeable with D_2O), and 7.0–7.6 (4H, m, Ar–H). *Anal*. Calcd for $C_{17}H_{27}NO$ (261): C, 78.16; H, 10.34; N, 5.36. Found: C, 78.5; H, 10.25; N, 5.6.

5-(3,4-Dihydroquinolin-1(2H)-yl)-5-methyl-3-phenylhexan-3-ol (1e). This compound was obtained as creamy plates in yield, 79%, mp 89°C (ethanol), R_f 0.45 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3450, 3055, 2985, 1600, 1486, 1440, 1370, 1210, 1180, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.9 (3H, t, $J = 9$ Hz, CH_3), 1.6 (2H, q, $J = 9$ Hz, CH_2), 1.2 (6H, 2s, $2CH_3$), 1.65–1.8 (2H, m, C^3H_2), 1.8 (2H, d, $J = 6$ Hz, CH_2), 2.55 (2H, t, $J = 7.5$, C^4H_2), 3.32 (2H, t, $J = 7.5$ Hz, C^2H_2), 4.2 (1H, s, OH exchangeable with D_2O), and 6.8–7.7 (9H, m, Ar–H). *Anal*. Calcd for $C_{22}H_{29}NO$ (323): C, 81.73; H, 8.98; N, 4.33. Found: C, 81.6; H, 8.68; N, 4.75.

4-(3,4-Dihydroquinolin-1(2H)-yl)-4-methyl-2-phenylpentan-2-ol (1f). This compound was obtained as white crystals in yield, 78%, mp 122°C (ethanol), R_f 0.41 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3570, 3120, 2970, 1605, 1550, 1520, 1480, 1365, 1145, 950, 740 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, 2s, $2CH_3$), 1.5 (3H, s, CH_3), 1.6–1.8 (2H, m, C^3H_2), 1.85 (2H, d, $J = 6$ Hz, CH_2), 2.6 (2H, t, $J = 7.5$, C^4H_2), 2.9 (1H, s, OH exchangeable with D_2O), 3.4 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.9–7.7 (9H, m, Ar–H). *Anal*. Calcd for $C_{21}H_{27}NO$ (309): C, 81.55; H, 8.73; N, 4.53. Found: C, 81.3; H, 8.9; N, 4.75.

General procedure for the synthesis of heteroaryl alcohols 1g–i. To an ice-cold (0°C) stirred solution of LAH (0.1 g, 2.7 mmol) in 25 mL of ether, a solution of ketone **6a–c** (2.5 mmol) in THF (15 mL) was added dropwise over 10 min. The reduction was complete after stirring for appointed time and temperature (monitored by TLC, 20% ethyl acetate/hexane). The cold reaction mixture was quenched at (0°C) by the sequential addition of distilled water (2 mL), NaOH solution (4 mL, 20%), and distilled water (4 mL); then, it was warmed to room temperature. Suction filtration removed the white precipitate of aluminum compounds, which were thoroughly triturated with ethyl acetate. Evaporation of the organic phase afforded crude alcohols **1g–i**. The products were purified by flash column chromatography (hexane/ethyl acetate, 3:2) to afford the desired pure product. The conditions and yields are shown in Table 1 (Entries 7–9), and spectral data are given in the following.

4-(3,4-Dihydroquinolin-1(2H)-yl)-4-methylpentan-2-ol (1g). This compound was obtained as white crystals in yield, 70%, mp 136°C (methanol), R_f 0.63 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3380, 3055, 2980, 1610, 1480, 1460, 1370, 1210, 740, 690 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.1 (3H, s, $J = 9$ Hz, CH_3), δ 1.3 (6H, s, $2CH_3$), 1.5 (3H, s, CH_3), 1.6 (2H, d, $J = 7.5$ Hz, CH_2), 1.8 (2H, m, C^3H_2), 2.55 (2H, t, $J = 7.5$, C^4H_2), 2.8 (1H, s, OH exchangeable with D_2O), 3.2–3.45 (3H, m, C^2H_2, CH), and 6.8–7.5 (4H, m, Ar–H). *Anal*. Calcd for $C_{15}H_{23}NO$ (233): C, 77.25; H, 9.87; N, 6.0. Found: C, 77.56; H, 9.6; N, 5.85.

5-(3,4-Dihydroquinolin-1(2H)-yl)-5-methylhexan-3-ol (1h). This compound was obtained as white plates in yield, 74%, mp 105°C (ethanol), R_f 0.67 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3640, 3070, 2980, 1595, 1460, 1450, 1370, 1220, 1175, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 0.9 (3H, t, $J = 9$ Hz, CH_3), 1.2 (6H, s, $2CH_3$), 1.4 (2H, q, $J = 9$ Hz, CH_2),), 1.55 (2H, d, $J = 9$ Hz, CH_2), 1.8 (2H, m, C^3H_2), 2.3 (1H, s, OH exchangeable with D_2O), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.4 (2H, t, $J = 7.5$, C^2H_2), and 6.8–7.7 (4H, m, Ar–H). *Anal*. Calcd for $C_{16}H_{25}NO$ (247): C, 77.73; H, 10.1; N, 5.66. Found: C, 77.8; H, 9.84; N, 5.7.

3-(3,4-Dihydroquinolin-1(2H)-yl)-3-methyl-1-phenylbutan-1-ol (1i). This compound was obtained as faintly yellow crystals in yield, 80%, mp 132°C (benzene), R_f 0.36 (1:4, EtOAc/hexane); IR (KBr) ν_{max} 3440, 3085, 2975, 1600, 1475, 1450, 1375, 1210, 1180, 740, 695 cm^{-1}; ^1H NMR (90 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.85 (2H, m, C^3H_2), 2.0 (2H, d, $J = 7.5$ Hz, CH_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.4 (2H, t, $J = 7.5$, C^2H_2), 4.2 (1H, s,

OH exchangeable with D_2O), 4.5 (H, m, CH), and 6.9–7.6 (9H, m, Ar–H). *Anal*. Calcd for $C_{20}H_{25}NO$ (295): C, 81.35; H, 8.47; N, 4.74. Found: C, 81.7; H, 8.3; N, 4.38.

Cyclialkylation procedures. The procedures described earlier for cyclialkylations of arylalkanols with $AlCl_3/CH_3NO_2$ [23] and PPA [26] were essentially followed. The conditions and yields are shown in Tables 2 and 3, whereas the physical constants and spectral data of the products **8a–i** are given in the following.

1,1,3,3-Tetramethyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij] quinoline (8a). This product was isolated as white-yellow crystals in yields indicated earlier, mp 82°C (benzene); IR (KBr) ν_{max} 3060, 2980, 1600, 1560, 1480, 1450, 1420, 1330, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.25 (6H, s, $2CH_3$), 1.5 (6H, 2s, $2CH_3$), 1.6 (2H, s, CH_2), 1.8 (2H, m, C^3H_2), 2.4 (2H, t, $J = 7.5$, C^4H_2), 3.3 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.7–7.5 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 229 (M^+, 8.5), 214 (M^+-CH_3, 100), 199 (65.8), 184 (M^+-2CH_3, 22.8), 165 (25.3), 168 (44.3), 151 (5.4), 132 (9.5), 109 (6.5), 90 (3.3), 78 (5.4), 77 (6.5), 66 (2.2). *Anal*. Calcd for $C_{16}H_{23}N$ (229): C, 83.8; H, 10.0; N, 6.1. Found: C, 84.2; H, 9.75; N, 5.88.

1,1-Diethyl-3,3-dimethyl-2,3,6,7-tetrahydro-1H,5H-pyrido [3,2,1-ij]quinoline (8b). This product was isolated as brownish viscous oil in yields indicated earlier, n_D^{25} 1.615; IR (film) ν_{max} 3070, 2995, 1615, 1550, 1450, 1410, 1330, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.95 (6H, t, $J = 9$ Hz, $2CH_3$), 1.2 (6H, s, $2CH_3$), 1.5 (4H, t, $J = 9$ Hz, $2CH_2$), 1.7 (2H, s, CH_2), 1.8 (2H, m, C^3H_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.4 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.9–7.6 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 257 (M^+, 6.8), 241 (34), 242 (M^+-CH_3, 77.4), 228 ($M^+-CH_3CH_2$,100), 213 ($M^+-CH_3-CH_3CH_2$, 83.8), 199 (46.5), 185 (25.5), 173 (26.4), 169 (15.3), 151 (25.5), 132 (13.6), 109 (10.3), 91 (3.4), 78 (2.4), 78 (6.1), 77 (3.7), 67 (2.2). *Anal*. Calcd for $C_{18}H_{27}N$ (257): C, 84.0; H, 10.5; N, 5.44. Found: C, 84.32; H, 9.82; N, 5.5.

3,3-Dimethyl-1,1-diphenyl-2,3,6,7-tetrahydro-1H,5H-pyrido [3,2,1-ij]quinoline (8c). This product was isolated as white-yellow solid in yields indicated earlier, mp 92°C (benzene); IR (KBr) ν_{max} 3055, 2974, 1605, 1570, 1465, 1440, 1420, 1335, 1060 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.8 (2H, m, C^3H_2), 2.2 (2H, s, CH_2), 2.6 (2H, t, $J = 7.5$, C^4H_2), 3.45 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.8–7.4 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 353 (M^+, 17.2), 352 (M^+-H, 82.5), 338 (M^+-CH_3, 100), 323 (13.8), 246 (M^+-2CH_3-Ph, 45.8), 245 (19.3), 184 (14.7), 178 (11.2), 169 (62.5), 155 (7.6), 132 (18.0), 90 (14.3), 78 (7.5), 77 (6.3), 66 (2.3). *Anal*. Calcd for $C_{26}H_{27}N$ (353): C, 88.38; H, 7.64; N, 3.96. Found: C, 88.5; H, 7.33; N, 4.2.

1-Ethyl-1,3,3-trimethyl-2,3,6,7-tetrahydro-1H,5H-pyrido [3,2,1-ij]quinoline (8d). This product was isolated as white crystals in yields indicated earlier, mp 68°C (benzene/PE 60–80°C); IR (KBr) ν_{max} 3060, 2985, 1615, 1580, 1460, 1440, 1335, 1050 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.95 (3H, t, $J = 9$ Hz, CH_3), 1.2 (6H, s, $2CH_3$), 1.4 (3H, s, CH_3), 1.57 (2H, m, CH_2), 1.61–1.83 (2H, m, CH_2), 1.85 (2H, m, C^3H_2), 2.59 (2H, t, $J = 7.5$, C^4H_2), 3.43 (2H, t, $J = 7.5$ Hz, C^2H_2), and 7.1–7.5 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 243 (M^+, 14.2), 242 (M^+-H, 100), 228 (M^+-CH_3, 92.5), 214 (38.5), 213 (66.8), 191 (4.7), 184 (22.5), 178 (5.4), 168 (13.3), 150 (2.6), 132 (11.8), 109 (4.3), 91 (4.3), 78 (3.1). *Anal*. Calcd for $C_{17}H_{25}N$ (243): C, 83.95; H, 10.28; N, 5.76. Found: C, 83.9; H, 10.6; N, 5.95.

1-Ethyl-3,3-dimethyl-1-phenyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij]quinoline (8e). This product was isolated as white solid in yields indicated earlier, mp 76°C (benzene/PE 60–80°C); IR (KBr) ν_{max} 3070, 2980, 1600, 1550, 1455, 1442, 1320, 743 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.9 (3H, t, $J = 9$ Hz, CH_3), 1.21 (6H, s, $2CH_3$), 1.8 (2H, m, C^3H_2), 2.0 (2H, m, CH_2), 1.9–2.2 (2H, m, CH_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.35 (2H, t, $J = 7.5$ Hz, C^2H_2), and 7.0–7.6 (8H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 305 (M^+, 12.4), 304 80.2), 290 (M^+-CH_3, 75.2), 276 ($M^+-CH_3CH_2$,100), 275 (45.3), 246 ($M^+-2CH_3-C_2H_5$, 38.4), 228 (18.3), 213 (15.3), 198 (26.2), 199 (5.7), 169 (14.3), 151 (2.6), 132 (14.2), 90 (2.8), 77 (4.2), 66 (1.8). *Anal*. Calcd for $C_{22}H_{27}N$ (305): C, 86.55; H, 8.85; N, 4.6. Found: C, 86.75; H, 8.55; N, 4.82.

1,3,3-Trimethyl-1-phenyl-2,3,6,7-tetrahydro-1H,5H-pyrido [3,2,1-ij]quinoline (8f). This product was isolated as pale yellow crystals in yields indicated earlier, mp 64°C (benzene/PE 60–80°C); IR (KBr) ν_{max} 3085, 2990, 1605, 1560, 1455, 1440, 1330, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.21 (6H, s, $2CH_3$), 1.65 (3H, s, CH_3), 1.8 (2H, m, C^3H_2), 1.9–2.1 (2H, m, CH_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 3.35 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.9–7.4 (8H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 291 (M^+, 13.5), 290 (66.8), 276 (M^+-CH_3, 72.3), 261 (M^+-2CH_3, 100), 245 (M^+-3CH_3-H, 49.0), 214 (11.3), 199 (12.6), 169 (24.4), 151 (4.6), 132 (15.4), 91 (4.3), 78 (5.3). *Anal*. Calcd for $C_{21}H_{25}N$ (291): C, 86.59; H, 8.59; N, 4.8. Found: C, 86.82; H, 8.38; N, 5.2.

1,3,3-Trimethyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij] quinoline (8g). This product was isolated as white solid in yields indicated earlier, mp 52°C (PE 60–80°C); IR (KBr) ν_{max} 3080, 2983, 1600, 1553, 1450, 1440, 1325, 740 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.21 (6H, s, $2CH_3$), 1.32 (3H, m, $J = 6$ Hz, CH_3), 1.6–1.8 (2H, m, CH_2), 1.86 (2H, m, C^3H_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 2.86 (1H, m, CH), 3.4 (2H, t, $J = 7.5$ Hz, C^2H_2), and 6.8–7.4 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 215 (M^+, 100), 214 (82), 200 (M^+-CH_3, 75.4),185 (66.2), 170 (M^+-3CH_3, 35.8), 169 (21.3), 158 (14.3), 132 (21.3), 91 (3.3), 77 (3.6). *Anal*. Calcd for $C_{15}H_{21}N$ (215): C, 83.7; H, 9.76; N, 6.5. Found: C, 83.5; H, 10.12; N, 6.47.

1-Ethyl-3,3-dimethyl-2,3,6,7-tetrahydro-1H,5H-pyrido[3,2,1-ij] quinoline (8h). This product was isolated as reddish viscous oil in yields indicated earlier, n_D^{25} 1.592; IR (film) IR (film) ν_{max} 3055, 2986, 1600, 1550, 1445, 1450, 1330, 744 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 0.85 (3H, t, $J = 9$ Hz, CH_3), 1.2 (6H, s, $2CH_3$), 1.56 (2H, m, CH_2), 1.62–1.82 (2H, m, CH_2), 1.86 (2H, m, C^3H_2), 2.5 (2H, t, $J = 7.5$, C^4H_2), 2.72 (1H, m, CH), 3.32 (2H, t, $J = 7.5$ Hz, C^2H_2), and 7.2–7.5 (3H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 229 (M^+, 16.2), 228 (M^+-H, 100), 214 ((M^+-CH_3, 74.6), 200 ($M^+-CH_3-C_2H_5$, 32.2), 199 (18.4), 185 (36.4), 190 (3.7), 170 (4.7), 169 (12.4), 166 (11.3), 155 (5.7), 132 (10.2), 90 (4.3), 77 (2.3). *Anal*. Calcd for $C_{16}H_{23}N$ (229): C, 83.84; H, 10.0; N, 6.1. Found: C, 83.85; H, 10.2; N, 5.82.

3,3-Dimethyl-1-phenyl-2,3,6,7-tetrahydro-1H,5H-pyrido [3,2,1-ij]quinoline (8i). This product was isolated as white needless in yields indicated earlier, mp 56°C (hexane); IR (KBr) ν_{max} 3074, 2970, 1615, 1470, 1450, 1335, 745 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, ppm), δ 1.2 (6H, s, $2CH_3$), 1.82 (2H, m, C^3H_2), 1.96–2.2 (2H, m, CH_2), 2.52 (2H, t, $J = 7.5$, C^4H_2), 3.35 (2H, t, $J = 7.5$ Hz, C^2H_2), 3.9 (1H, m, CH), and 7.2–7.6 (8H, m, Ar–H); MS (EI, 70 eV) *m/z* (%), 277 (M^+, 9.3), 261 (M^+-CH_3-H, 100), 247 (55.8), 246 (M^+-2CH_3-H, 34.5), 200

(12.3), 185 (26.4), 190 (4.7), 170 (13.2), 167 (6.1), 158 (6.6), 131 (2.6), 90 (4.1), 78 (3.5). *Anal*. Calcd for $C_{20}H_{23}N$ (277): C, 86.64; H, 8.3; N, 5.05. Found: C, 86.7; H, 8.1; N, 5.2.

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