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Selective *N*-alkylation of isoquinolines, benzazepines and thienopyridines with aromatic aldehydes and naphthols

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ABSTRACT

The reactions of 1- or 2-naphthol, benzaldehyde or substituted benzaldehydes with tetrahydroisoquinoline, tetrahydrobenzo[*d*]azepine, tetrahydrobenzo[*c*]azepine or tetrahydrothieno[3,2-*c*]pyridine under solvent-free conditions, allowed a series of tertiary aminonaphthols to be prepared. The reactions were accelerated by the use of microwave irradiation, and the yields were also improved. As an exception, the aminoalkylation of 2-naphthol with 1,2,3,4-tetrahydroisoquinoline in the presence of benzaldehyde led to the parallel *N*-alkylation and redox α-arylation of the tetrahydroisoquinoline in a ratio of 4:1. The reaction of 1-naphthol with 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine led to the formation of the *N*-alkylated compound as a single product, illustrating that the reaction route depends on the structures of the cyclic amine and the naphthol.

1. Introduction

The Mannich reaction[1] is an important reaction involving C–C bond formation that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products.[2] In the past decade, modified three-component Mannich reactions (mMRs), based on the aminoalkylation of 2- or 1-naphthol as electron-rich aromatic compounds, have become of considerable importance for the formation of aminonaphthols under mild experimental conditions.[3,4] The compounds obtained in this way depend on the starting nitrogen source: the use of primary or secondary amines leads to secondary or tertiary aminonaphthols,[5–10] while when ammonia is used, primary aminonaphthols are obtained.[11–15]

In view of the two or more functional groups in the aminonaphthols, one of the most important areas of application is the synthesis of new heterocycles,[3,4] while enantioenriched aminonaphthol derivatives have been successfully applied in enantioselective transformations.[3,4] 1-((2-Hydroxynaphthalen-1-yl)arylmethyl)piperidin-4-ol derivatives were earlier designed and synthetized as novel selective ostrogen receptor modulators,[16,17] while 1-[(6-halo- or 4-methylbenzo[*d*]thiazol-2-ylamino)phenylmethyl]naphthalen-2-ol derivatives and 5-[(6-halo- or 4-methylbenzo[*d*]thiazol-2-ylamino) phenylmethyl]quinolin-6-ol derivatives were found to exert repellent, insecticidal and larvicidal activity against the mosquito *Anopheles arabiensis*.[18]

The importance of the aminonaphthols prepared via mMRs has recently increased because they have proved to be excellent model compounds for study of the α-arylation/*N*-alkylation of cyclic amines.[19–21] When pyrrolidine was aminoalkylated with electron-rich aromatic compounds in the presence of aromatic aldehydes, the two possible main products, i.e. α-arylated or *N*-alkylated, could be isolated only if the aldehyde component was added extremely slow to the reaction mixture containing acid as catalyst. It was also demonstrated that 2-naphthol can be sufficiently acidic to promote the required tautomerization.[20] This process, starting from 1,2,3,4-tetrahydroisoquinoline as substrate, can theoretically lead to the formation of the regioisomeric tertiary aminonaphthols (***A*** or ***B***) according to Scheme 1, where HNu is an electron-rich aromatic compound such as 2- or 1-naphthol. Our present primary aim was to investigate the application of 1,2,3,4-tetrahydroisoquinoline and analogous secondary amines such as 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine in mMRs. A further aim was a systematic investigation of the α-arylation/

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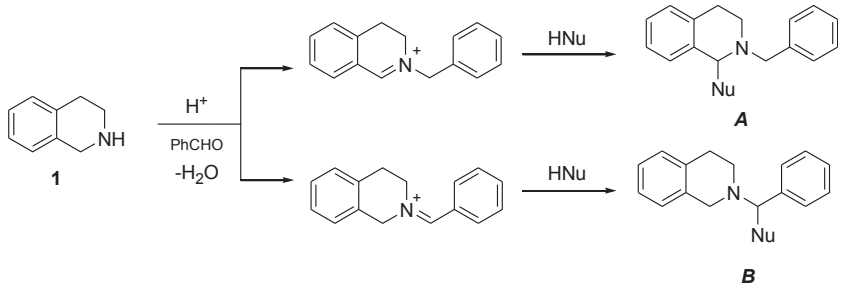


Scheme 1. Reaction pathway for the formation of the possible α-arylated (***A***) and *N*-alkylated (***B***) products starting from tetrahydroisoquinoline (**1**) (HNu=nucleophile).

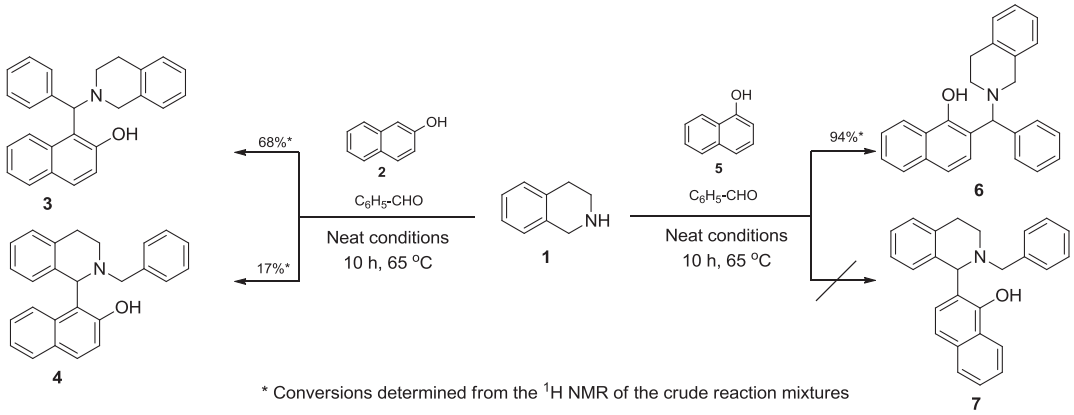
N-alkylation process starting from tetrahydroisoquinoline, tetrahydrobenzazepine or tetrahydrothieno[3,2-*c*]pyridine by using 2- or 1-naphthol as nucleophile in the presence of benzaldehyde.

2. Results and discussion

First, 1,2,3,4-tetrahydroisoquinoline (**1**), 2-naphthol (**2**) and benzaldehyde were reacted under neat conditions at 65 °C. After a reaction time of 4 h, the desired 1-[(3,4-dihydro-1*H*-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**3**, Scheme 2) was isolated by crystallization with MeOH. Since the yield of the reaction was only 28%, the reaction was repeated under microwave (MW) irradiation at 65 °C. After a relatively long reaction time (1.5 h), the ^{1}H NMR spectra of the crude reaction mixture did not reveal the formation of **3**. The synthesis of **3** was earlier performed[22] by refluxing **2**, 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde in ethanol for 12 h, **3** being isolated as a 'yellow gummy solid' in a yield of 78%.[22] However when we attempted to repeat this under the same reaction conditions, the ^{1}H NMR spectra of the crude product indicated that, the desired product **3** was formed in only trace amounts.

product formed, **3**:**4**, was found to be constant (4:1) throughout reaction (Scheme 2).

To extend this mMR, 1-naphthol (**5**) was reacted with 1,2,3,4-tetrahydroisoquinoline (**1**) in the presence of benzaldehyde, when the possible products obtained by α-arylation/*N*-alkylation of **1** were **6** and **7** (Scheme 2). For a systematic study of this reaction, the *N*-alkylated product 2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (**7**) was synthetized from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol[23] and benzyl bromide. 1-Naphthol (**5**), 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde were reacted under neat conditions, by heating at 65 °C, or under MW irradiation at the same temperature. The presence of the possible products (**6** and **7**) was followed by NMR spectroscopy, with a comparison of the relative intensities of the characteristic singlets of **6** and **7** in the crude product. Interestingly, in contrast with our expectations, the signals of the crude product indicated only the formation of **6** when classical heating was applied at 65 °C (Scheme 2). This tendency seemed to be independent of the reaction conditions (classical or MW heating): even after relatively short reaction times (1.5 h on classical heating; 0.5 h on MW) both conditions, led to the formation of **6** in excellent yields.

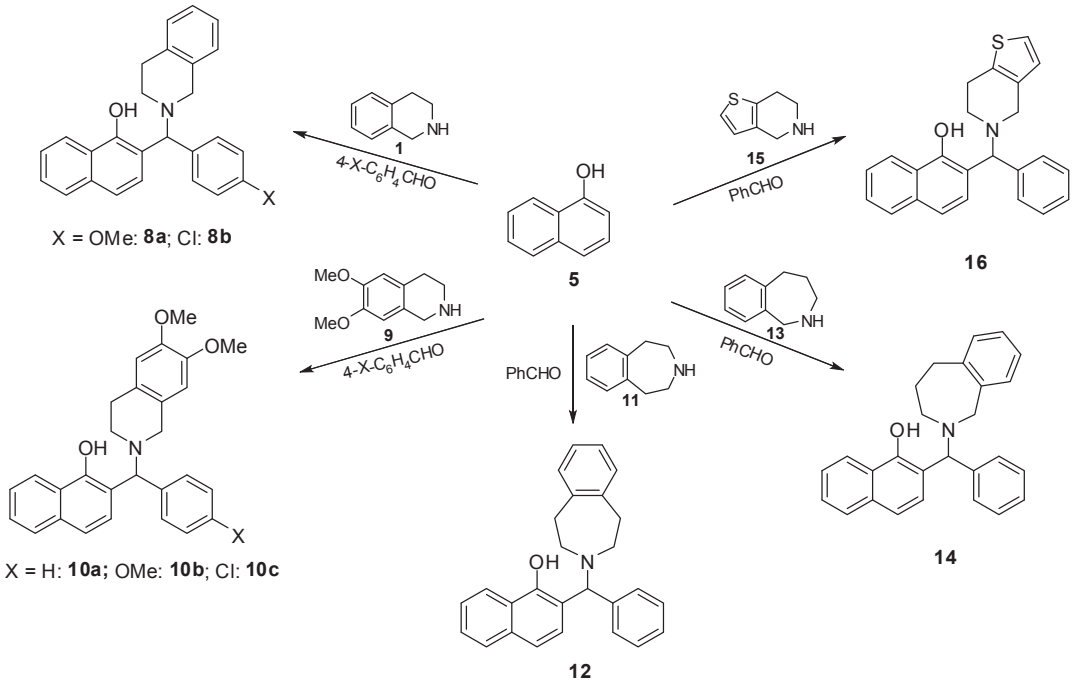


Scheme 2. Reaction of **1** with 2- or 1-naphthol in the presence of benzaldehyde.

In the above experiments, the possibility of formation of the α-arylated product **4** was not taken into account. For a systematic investigation of this reaction, **4** was synthetized from 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol[23] and benzyl bromide on the basis of the literature process.[24] 2-Naphthol (**2**), 1,2,3,4-tetrahydroisoquinoline (**1**) and benzaldehyde were reacted under neat conditions at 65 °C. The formation of the possible products (**3** and **4**) and the conversion of the reaction were followed by ^{1}H NMR spectroscopy at different reaction times up to 10 h. The ratio of the

The series of 2-substituted 1-naphthol analogs was extended by using different 4-substituted benzaldehydes such as 4-methoxybenzaldehyde or 4-chlorobenzaldehyde leading to, **8a** and **8b** (Scheme 3), while 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**) was tested as substrate with 1-naphthol and benzaldehyde or 4-substituted benzaldehydes, leading to **10a**–**c** (Scheme 3).

To test the scope and limitations of the reaction, 1-naphthol was reacted with other secondary cyclic amines, such as 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**11**), 2,3,4,5-tetrahydro-1*H*-benzo



Scheme 3. Syntheses of tertiary aminonaphthols **8**, **10**, **12**, **14** and **16** from 1-naphthol (reaction conditions and yields are listed in Table 1).

Table 1
Optimized reaction conditions for the syntheses of **6**, **8**, **10**, **12**, **14** and **16**

Product	Classical heating	Yield (%)	MW agitation	Yield (%)
6	70 °C, 12 h	58[a]	65 °C, 0.5 h	78[a]
8a	70 °C, 8 h	53[a]	65 °C, 0.5 h	72[a]
8b	70 °C, 5 h	57[a]	65 °C, 0.5 h	74[a]
10a	70 °C, 12 h	52[b]	65 °C, 1 h	73[b]
10b	70 °C, 7 h	60[b]	65 °C, 0.5 h	77[b]
10c	70 °C, 5 h	61[b]	65 °C, 0.5 h	81[b]
12	60 °C, 64 h	45[c]	55 °C, 1.5 h	55[c]
14	60 °C, 64 h	53[c]	55 °C, 1.5 h	57[c]
16	65 °C, 45 h	37[d]	60 °C, 1,5 h	48[d]

[a] Recrystallized from iPr_2O:MeOH (1:1).
[b] Recrystallized from MeOH.
[c] Recrystallized from iPr_2O:MeOH (2:1).
[d] Recrystallized from iPr_2O:MeOH (4:1).

[*c*]azepine (**13**)[25] and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**15**),[26] in the presence of benzaldehyde, leading to the formation of **12**, **14** and **16**. As concerns the aldehyde substrates, the highest yields were obtained with 4-chlorobenzaldehyde, when shorter reaction times too were needed (see the Experimental section). The yields of the formation of 1-naphthol derivatives pointed to the lower reactivity of 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**15**) versus 1,2,3,4-tetrahydroisoquinolines (**1** and **9**) or 2,3,4,5-tetrahydro-1*H*-benzazepines (**11** and **13**). When MW irradiation was applied the reaction times were in all cases shorter, while the yields were improved.

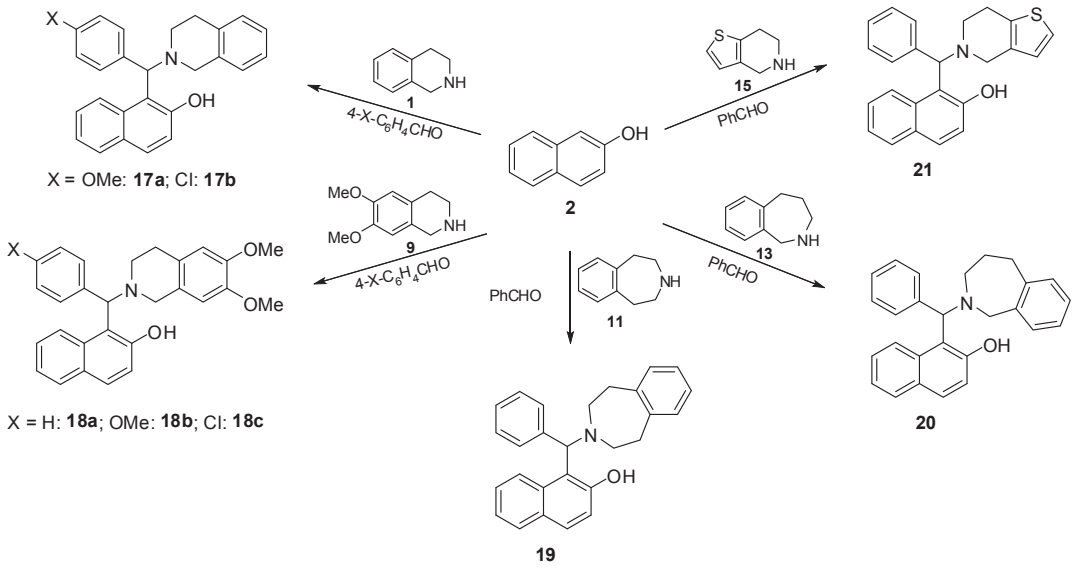
Since the solvent-free heating of 1-naphthol with different cyclic amine substrates in the presence of the above aldehydes (either by classical heating or by MW agitation) led to the formation of the desired aminonaphthols (**6**, **8**, **10**, **12**, **14** and **16**) in good yields, our attention turned back to the aminoalkylation of 2-naphthol. Thus, tetrahydroisoquinoline (**1**) was reacted with 2-naphthol and 4-methoxybenzaldehyde or 4-chlorobenzaldehyde under neat conditions. The reaction was then extended by using different cyclic amines, such as 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**), 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**11**), 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (**13**) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**15**). On the use of 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**), the aldehyde substrates were benzaldehyde, 4-methoxybenzaldehyde and 4-chlorobenzaldehyde. The structures of the tertiary aminonaphthol products **17a**–**b**, **18a**–**c** and **19**–**21** are shown in Scheme 4.

When tetrahydroisoquinoline **1** was reacted with 2-naphthol in the presence of 4-methoxybenzaldehyde or 4-chlorobenzaldehyde, relatively long reaction times (classical heating: 20 h, MW agitation: 2.5 h) were needed. In all cases, the isolated yields were sufficiently high to allow the conclusion that other α-arylated by-products were absent. When 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (**9**) was applied as starting material, a higher temperature (75 °C) was needed, a faster reaction as compared with **3** and **17** can be assumed. When 2,3,4,5-tetrahydro-1*H*-benzo[*d*]azepine (**11**), 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (**13**) and 4,5,6,7-tetrahydrothieno[3,2-*c*]pyridine (**15**) was used as cyclic amine, closely similar reaction conditions were found to be optimum (Scheme 4).

A consideration of the yields of all the product aminonaphthols (except **3** and **4**) revealed the lowest yields for those whose synthesis started from 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine (**20**). This might be due to the lower stability of the benzazepine ring system at higher temperature, or to the formation of two regioisomers (*N*-alkylation or α-substitution) during the reaction. To check on this, the syntheses of **14** and **20** were repeated and the conversion of the starting compounds was systematically followed via the NMR spectra of the crude products. The desired aminonaphthols **14** and **20** were found to be single products in the NMR spectra of the crude reaction mixtures, suggesting that the lower yields observed for **14** and **20** were due to the lower stability of the starting benzazepine (**13**).

3. Conclusions

Selective *N*-alkylations of tetrahydroisoquinolines, tetrahydrobenzo[*d*]azepine, tetrahydrobenzo[*c*]azepine and tetrahydrothieno[3,2-*c*]pyridine were achieved by using 1-naphthol and aromatic aldehydes under neat conditions. The reactions were extended to 2-naphthol, and all were accelerated by using MW agitation.



Scheme 4. Syntheses of tertiary aminonaphthols **17**–**21** from 2-naphthol (reaction conditions and yields are listed in Table 2).

Table 2
Optimized reaction conditions for the syntheses of **3**, **17**–**19**, **20** and **21**

Product	Classical heating	Yield (%)	MW agitation	Yield (%)
3	80 °C, 4 h	46[a]	65 °C, 1.5 h	—
17a	70 °C, 5 h	48[c]	65 °C, 0.5 h	71[c]
17b	70 °C, 5 h	50[c]	65 °C, 0.5 h	77[c]
18a	75 °C, 8 h	55[b]	70 °C, 1 h	82[b]
18b	75 °C, 8 h	57[b]	70 °C, 1 h	84[b]
18c	75 °C, 3.5 h	65[b]	70 °C, 0.5 h	87[b]
19	60 °C, 64 h	58[a]	60 °C, 2 h	67[a]
20	60 °C, 56 h	62[d]	60 °C, 1.5 h	70[d]
21	75 °C, 56 h	28[a]	70 °C, 1.5 h	41[a]

[a] Recrystallized from iPr$_2$O:MeOH (4:1).
[b] Recrystallized from MeOH.
[c] Recrystallized from iPr$_2$O:MeOH (1:1).
[d] Recrystallized from iPr$_2$O:MeOH (2:1).

As an exception, when a mixture of 2-naphthol, 1,2,3,4-tetrahydroisoquinoline and benzaldehyde was reacted, MW heating did not lead to the formation of the desired aminonaphthol, while classical heating resulted in two products: 1-[(3,4-dihydro-1*H*-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**3**) and 1-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol (**4**). The ratio of **3**:**4** was systematically studied at 65 °C, and was found to be 4:1, independent of the reaction time. With 1-naphthol as nucleophile in the aminoalkylation of **1** in the presence of benzaldehyde, the *N*-alkylated compound **6** was isolated as a single product. In the reactions of 2,3,4,5-tetrahydro-1*H*-benzo[*c*]azepine, benzaldehyde and 2- or 1-naphthol at 65 °C, formation of the *N*-alkylated product was assumed in each case. As a final conclusion for this three-component mMR, α-arylation and *N*-alkylation are possible, but the α-arylated product was identified only in the case of the reaction of 1,2,3,4-tetrahydroisoquinoline, 2-naphthol and benzaldehyde. Which of the two possible products is formed therefore depends on the structures of the cyclic amine and the nucleophilic partner (2-naphthol or 1-naphthol).

4. Experimental

The ^{1}H and ^{13}C NMR spectra were recorded in DMSO solutions in 5 mm tubes, at room temperature, on a Bruker spectrometer at 400 (^{1}H) and 100.6 (^{13}C) MHz, with the deuterium signal of the solvent as the lock and TMS as internal standard. Melting points were determined on a Hinotek X-4 melting point apparatus and are uncorrected. Elemental analyses were performed with a Perkin–Elmer 2400 CHNS elemental analyser. Merck Kieselgel 60F$_{254}$ plates were used for TLC. The MW reactions were performed by using a CEM Discover SP MW reactor.

4.1. General method for the synthesis of 3, 6, 8, 10, 12, 14, 16–21

The reaction mixture of 0.5 mmol secondary amine (**1**, **9**, **11**, **13** or **15**), 0.5 mmol aromatic aldehyde (benzaldehyde, 4-chlorobenzaldehyde or 4-methoxybenzaldehyde) and 0.5 mmol 2- or 1-naphthol in a 10 mL pressurized reaction vial was heated in an oil bath or in a CEM Discover SP MW reactor. After the reaction times indicated in Tables 1 and 2, MeOH (5 mL) was added. The crystals that separated out were filtered off and recrystallized.

*4.1.1. 2-[(3,4-Dihydro-1H-isoquinolin-2-yl)phenylmethyl]naphthalen-1-ol (**6**).* Mp: 138–140 °C. ^{1}H NMR: 2.80–2.96 (4H, m), 3.67 (1H, d, J=15.1 Hz), 3.78 (1H, d, J=15.1 Hz), 5.00 (1H, s), 6.94 (1H, d, J=7.4 Hz), 7.07–7.14 (1H, m), 7.14–7.19 (2H, m), 7.29 (3H, dd, J=15.7, 8.6 Hz), 7.36 (2H, t, J=7.5 Hz), 7.42–7.48 (2H, m), 7.58 (2H, d, J=7.7 Hz), 7.74–7.79 (1H, m), 8.12–8.17 (1H, m), 12.42 (1H, br s). ^{13}C NMR: 29.1, 49.2, 54.8, 74.0, 119.5, 120.3, 120.5, 122.8, 125.8, 126.7, 126.9, 127.4, 127.6, 127.8, 128.1, 128.6, 128.9 (2C), 129.3, 129.7 (2C), 134.1, 134.4, 139.0, 141.6, 152.0. IR: ν_{max} 744, 753, 1387, 3031, 3737. Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45, H, 6.34, N, 3.83. Found: C, 85.47, H, 6.35, N, 3.82.

*4.1.2. 2-[(3,4-Dihydro-1H-isoquinolin-2-yl)-(4-methoxyphenyl)methyl]naphthalen-1-ol (**8a**).* Mp: 178–179 °C. ^{1}H NMR: 2.77–2.93 (4H, m), 3.64 (1H, d, J=15.2), 3.70 (3H, s), 3.76 (2H, d, J=15.2 Hz), 4.92 (1H, s), 6.90 (2H, d, J=8.8 Hz), 6.97 (1H, d, J=7.7 Hz), 7.05–7.11 (1H, m), 7.12–7.16 (2H, m), 7.23 (2H, dd, J=29.9, 8.4 Hz), 7.39–7.47 (4H, m), 7.72–7.77 (1H, m), 8.08–8.14 (1H, m), 12.59 (1H, br s). ^{13}C NMR: 29.1, 49.1, 54.6, 55.9, 73.6, 115.1, 119.3, 120.4, 122.8, 125.7, 126.7, 126.9, 127.4, 127.6, 127.8, 128.1, 129.3, 130.2, 133.2, 134.0, 134.4, 134.5, 152.1, 159.6. IR: ν_{max} 671, 1250, 1510, 2835, 3737. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00, H, 6.37, N, 3.54. Found: C, 82.01, H, 6.35, N, 3.56.

*4.1.3. 2-[(4-Chlorophenyl)-(3,4-dihydro-1H-isoquinolin-2-yl)methyl]naphthalen-1-ol (**8b**).* Mp: 180–182 °C. ^{1}H NMR: 2.77–2.96 (4H, m),

3.66 (1H, d, *J*=15,2 Hz), 3.77 (1H, d, *J*=15.2 Hz), 5.05 (1H, s), 6.97–7.02 (1H, m), 7.07–7.13 (1H, m), 7.15–7.19 (2H, m), 7.28 (1H, d, *J*=8.5 Hz), 7.33 (1H, d, *J*=8.6), 7.40–7.49 (4H, m), 7.60 (2H, d, *J*=8.4 Hz), 7.75–7.80 (1H, m), 8.12–8.17 (1H, m), 12.18 (1H, br s). ^{13}C NMR: 29.1, 49.2, 54.7, 72.6, 119.7, 120.2, 122.5, 122.8, 125.7, 125.8, 126.7, 127.0, 127.4, 127.5, 127.6, 128.2, 129.3, 129.7, 130.7, 133.1, 134.1, 134.4, 140.7, 151.9. IR: ν_{max} 671, 747, 1093, 1491, 2837, 3737. Anal. Calcd for $C_{26}H_{22}ClNO$: C, 78.09, H, 5.54, N, 3.50. Found: C, 78.07, H, 5.56, N, 3.48.

*4.1.4. 2-[(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)phenylmethyl]naphthalen-1-ol (**10a**).* Mp: 164–166 °C. ^{1}H NMR: 2.76–2.88 (4H, m), 3.59 (1H, d, *J*=15.3 Hz), 3.63 (3H, s), 3.71 (1H, d, *J*=15.3 Hz), 3.72 (3H, s), 4.96 (1H, s), 6.59 (1H, s), 6.73 (1H, s), 7.23–7.32 (3H, m), 7.36 (2H, t, *J*=7.4 Hz), 7.42–7.48 (2H, m), 7.58 (2H, d, *J*=7.5 Hz), 7.73–7.80 (1H, m), 8.12–8.18 (1H, m), 12.61 (1H, br s). ^{13}C NMR: 28.7, 49.4, 54.5, 56.3, 56.4, 74.3, 111.1, 112.6, 119.4, 120.3, 122.8, 125.7, 126.0, 126.1, 126.9, 127.8, 128.1, 128.6, 128.9 (2C), 129.7 (2C), 134.0, 141.6 (2C), 148.1, 148.4, 152.2. IR: ν_{max} 698, 750, 1119, 1521, 2835, 3737. Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03, H, 6.40, N, 3.29. Found: C, 79.01, H, 6.42, N, 3.30.

*4.1.5. 2-[(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(4-methoxyphenyl)methyl]naphthalen-1-ol (**10b**).* Mp: 121–123 °C. ^{1}H NMR: 2.75–2.88 (4H, m), 3.57 (1H, d, *J*=14.4 Hz), 3.63 (3H, s), 3.66–3.72 (1H, m), 3.72 (6H, s), 4.90 (1H, s), 6.59 (1H, s), 6.73 (1H, s), 7.20 (1H, d, *J*=8.9 Hz), 7.28 (1H, d, *J*=8.5 Hz), 7.41–7.49 (4H, m), 7.74–7.79 (1H, m), 8.11–8.17 (1H, m), 12.79 (1H, br s).^{13}C NMR:28.8, 49.3, 54.3, 55.9, 56.3, 56.4, 73.8, 111.1, 112.6, 115.1 (2C), 119.2, 120.4, 122.8, 125.6, 125.7, 126.0, 126.2, 126.8, 127.9, 128.1, 130.2 (2C), 133.3, 134.0, 148.1, 148.4, 152.2, 159.6. IR: ν_{max} 671, 808, 1122, 1257, 1508, 2935, 3734. Anal. Calcd for $C_{29}H_{29}NO_4$: C, 76.46, H, 6.42, N, 3.07. Found: C, 76.48, H, 6.41, N, 3.09.

*4.1.6. 2-[(4-Chlorophenyl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methyl]-naphthalen-1-ol (**10c**).* Mp: 132–133 °C. ^{1}H NMR: 2.73–2.91 (4H, m), 3.58 (1H, d, *J*=15.5 Hz), 3.64 (3H, s), 3.68 (1H, d, *J*=15.5 Hz), 3.72 (3H, s), 5.01 (1H, s), 6.61 (1H, s), 6.73 (1H, s), 7.29 (2H, dd, *J*=22.0, 8.4 Hz), 7.39–7.49 (4H, m), 7.55–7.62 (2H, m), 7.75–7.8 (1H, m), 12.32–12.47 (1H, br s). ^{13}C NMR: 28.7, 49.5, 54.4, 56.3, 56.4, 73, 111.1, 112.6, 119.6, 120.1, 122.8, 125.8, 126.0, 126.1, 127.0, 127.6, 128.2, 129.2, 130.7, 133.1, 134.1, 140.7, 147.9, 148.1, 148.4, 152.0. IR: ν_{max} 671, 1120, 1520, 3737. Anal. Calcd for $C_{28}H_{26}ClNO_3$: C, 73.11, H, 5.70, N, 3.05. Found: C, 73.13, H, 5.69, N, 3.07.

*4.1.7. 2-[(4,5-Dihydro-1H-benzo[d]azepin-3(2H)-yl)-phenylmethyl]-naphthalen-1-ol (**12**).* Mp: 153–155 °C. ^{1}H NMR: 2.61–2.79 (4H, m), 2.93–3.00 (4H, m), 5.13 (1H, s), 7.06–7.10 (4H, m), 7.23–7.30 (2H, m), 7.32–7.38 (2H, m), 7.44–7.54 (5H, m), 7.74–7.79 (1H, m), 8.19–8.25 (1H, m), 13.12 (1H, br s). ^{13}C NMR: 35.9 (2C), 53.6 (2C), 74.3, 118.9, 119.5, 122.9, 125.7, 126.1, 126.9, 127.2 (2C), 127.8, 128.1, 128.6, 129.5 (2C), 129.6 (2C), 129.7 (2C), 134.1, 140.0, 142.1 (2C), 152.9. IR: ν_{max} 671, 748, 1387, 2833, 3737. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45, H, 6.64, N, 3.69. Found: C, 85.46, H, 6.66, N, 3.70.

*4.1.8. 2-[(4,5-Dihydro-1H-benzo[c]azepin-2(3H)-yl)phenylmethyl]naphthalen-1-ol (**14**).* Mp: 79–81 °C. ^{1}H NMR: 1.72 (2H, s), 2.71–2.79 (1H, m), 2.84–3.01 (3H, m), 3.87 (1H, d *J*=14.0 Hz), 4.07 (1H, d, *J*=14.0 Hz), 4.89 (1H, s), 6.48 (1H, d, *J*=7.3 Hz), 7.00–7.11 (2H, m), 7.17–7.28 (4H, m), 7.30–7.36 (2H, m), 7.41–7.47 (2H, m), 7.48–7.53 (2H, m), 7.72–7.78 (1H, m), 8.10–8.16 (1H, m), 12.46 (1H, br s). ^{13}C NMR: 26.8, 35.6, 56.9, 58.0, 71.6, 119.2, 120.3, 122.8, 124.1, 125.7, 126.7, 126.9, 127.7, 128.1 (2C), 128.5 (2C), 128.9 (2C), 129.6 (2C), 130.7, 134.0, 138.1, 141.7, 143.9, 152.4. IR: ν_{max} 671, 744, 1390, 1458, 2928, 3734. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45, H, 6.64, N, 3.69. Found: C, 85.43, H, 6.65, N, 3.71.

*4.1.9. 2-[(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)phenylmethyl]naphthalen-1-ol (**16**).* Mp: 161–162 °C. ^{1}H NMR: 2.88–2.99 (4H, m), 3.57 (1H, d, *J*=14.7 Hz), 3.67 (1H, d, *J*=14.7 Hz), 5.05 (1H, s), 6.75–6.78 (1H, m), 7.24–7.32 (4H, m), 7.33–7.38 (2H, m), 7.43–7.48 (2H, m), 7.57 (2H, d, *J*=7.6 Hz), 7.75–7.79 (1H, m), 8.13–8.19 (1H, m).^{13}C NMR: 25.5, 49.5, 52.0, 73.4, 119.5, 120.4, 122.8, 123.1, 124.4, 125.8, 126.6, 126.9, 127.7, 128.1, 128.6, 128.9 (2C), 129.7 (2C), 133.5, 133.9, 134.0, 141.7, 152.0. IR: ν_{max} 671, 698, 1506, 1558, 3737. Anal. Calcd for $C_{24}H_{21}NOS$: C, 77.59, H, 5.70, N, 3.77. Found: C, 77.61, H, 5.68, N, 3.78.

*4.1.10. 1-[(3,4-Dihydro-1H-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**3**).* Mp: 151–152 °C. ^{1}H NMR: 2.74–3.02 (4H, m), 3.62 (1H, d, *J*=14.6 Hz), 3.81 (1H, d, *J*=14.6 Hz), 5.57 (1H, s), 6.96 (1H, d, *J*=7.4 Hz), 7.07–7.13 (2H, m) 7.14–7.19 (2H, m), 7.26 (2H, t, *J*=7.4 Hz), 7.35 (2H, t, *J*=7.5 Hz), 7.42 (2H, t, *J*=7.5 Hz), 7.68–7.79 (4H, m), 8.13 (1H, d, *J*=8.6 Hz), 13.27 (1H, br s). ^{13}C NMR: 29.1, 49.5, 55.0, 70.2, 117.2, 120.5, 122.5, 123.4, 126.7, 127.3, 127.4, 127.6, 128.7, 129.1, 129.3 (2C), 129.4, 129.5, 129.7 (2C), 130.1, 132.8, 134.2, 134.3, 141.0, 155.7. IR: ν_{max} 739, 1240, 1452, 1620, 2958, 3737. Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45, H, 6.34, N, 3.83. Found: C, 85.49, H, 6.37, N, 3.80.

*4.1.11. 3,4-Dihydro-1H-isoquinolin-2-yl)-(4-methoxyphenyl)methyl]naphthalen-2-ol (**17a**).* Mp: 176–178 °C. ^{1}H NMR: 2.72–3.03 (4H, m), 3.61 (1H, d, *J*=15.4 Hz), 3.79 (1H, d, *J*=15.4 Hz), 5.51 (1H, s), 6.90 (1H, d, *J*=8.8 Hz), 6.98 (1H, d, *J*=7.5 Hz), 7.06–7.13 (2H, m), 7.14–7.19 (2H, m), 7.26 (1H, t, *J*=7.3 Hz), 7.41 (1H, t, *J*=7.5 Hz), 7.6 (2H, d, *J*=8.4 Hz), 7.73 (1H, d, *J*=8.9 Hz), 7.77 (1H, d, *J*=7.8 Hz), 8.07 (1H, d, *J*=8.7), 13.38 (1H, br s). ^{13}C NMR: 29.1, 49.4, 54.9, 55.9, 69.6, 115.1, 117.4, 120.5, 122.5, 123.3, 126.7, 127.3 (2C), 127.4, 127.6, 129.1, 129.3, 129.5, 130.0, 130.4, 130.6, 132.7, 132.8, 134.2, 134.3, 155.6, 159.6. IR: ν_{max} 757, 1228, 1512, 2958, 3737. IR: ν_{max} 757, 1228, 1512, 2958, 3737. Anal. Calcd for $C_{27}H_{25}NO_2$: C, 82.00, H, 6.37, N, 3.54. Found: C, 82.07, H, 6.42, N, 3.59.

*4.1.12. 1-[(4-Chlorophenyl)-(3,4-dihydro-1H-isoquinolin-2-yl)methyl]naphthalen-2-ol (**17b**).* Mp: 180–181 °C. ^{1}H NMR: 2.72–3.00 (4H, m), 3.61 (1H, d, *J*=15.3 Hz), 3.78 (1H, d, *J*=15.3 Hz), 5.61 (1H, s), 6.98 (1H, d, *J*=7.7 Hz), 7.06–7.12 (2H, m), 7.13–7.18 (2H, m), 7.26 (1H, t, *J*=7.7 Hz), 7.37–7.45 (3H, m), 7.68–7.8 (4H, m), 8.12 (1H, d, *J*=8.2 Hz). ^{13}C NMR: 29.1, 49.6, 54.9, 69.1, 116.9, 122.5, 123.5, 126.7, 127.4 (2C), 127.5, 127.6, 129.2, 129.3 (2C), 129.6, 129.7 (2C), 130.3, 131.2, 132.8, 133.3, 134.2, 134.3, 140.0, 155.6. IR: ν_{max} 750, 833, 1071, 1492, 3737. Anal. Calcd for $C_{26}H_{22}ClNO$: C, 78.09, H, 5.54, N, 3.50. Found: C, 78.12, H, 5.55, N, 3.52.

*4.1.13. 1-[(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)phenylmethyl]naphthalen-2-ol (**18a**).* Mp: 193–195 °C. ^{1}H NMR: 2.69–2.96 (4H, m), 3.53 (1H, d *J*=15.3 Hz), 3.63 (3H, s), 3.70 (1H, d, *J*=14.9 Hz), 3.72 (3H, s), 5.54 (1H, s), 6.57 (1H, s), 6.72 (1H, s), 7.12 (1H, d, *J*=8.8 Hz), 7.23–7.28 (2H, m), 7.34 (2H, t, *J*=7.5 Hz), 7.42 (1H, t, *J*=7.8 Hz), 7.68–7.79 (4H, m), 8.12 (1H, d, *J*=8.5 Hz), 13.42 (1H, br s). ^{13}C NMR: 28.8, 49.7, 54.7, 56.3, 56.4, 70.3, 111.0, 112.5, 117.3, 120.5, 122.4, 123.3, 125.9 (2C), 127.4, 128.7, 129.1, 129.4, 129.5 (2C), 129.7 (2C), 130.1, 132.9, 141.0, 148.1, 148.5, 155.7. IR: ν_{max} 671, 742, 1521, 3737. Anal. Calcd for $C_{28}H_{27}NO_3$: C, 79.03, H, 6.40, N, 3.29. Found: C, 79.08, H, 6.38, N, 3.26.

*4.1.14. 1-[(6,7-Dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-(4-methoxyphenyl)methyl]naphthalen-2-ol (**18b**).* Mp: 207–209 °C. ^{1}H NMR: 2.67–2.97 (4H, m), 3.52 (1H, d, *J*=14.7 Hz), 3.64 (3H, s), 3.66–3.70 (1H, m), 3.7 (3H, s), 3.72 (3H, s), 5.48 (1H, s), 6.59 (1H, s), 6.72 (1H, s), 6.90 (2H, d, *J*=8.3 Hz), 7.09 (1H, d, *J*=8.8 Hz), 7.25 (1H, t,

J=7.5 Hz), 7.41 (1H, t, J=7.7 Hz), 7.59 (2H, d, J=7.9 Hz), 7.72 (1H, d, J=8.8 Hz), 7.77 (1H, d, J=7.9 Hz), 8.06 (1H, d, J=8.4 Hz), 13.51 (1H, br s). ^{13}C NMR: 28.8, 40.4, 54.5, 55.9, 56.3, 56.4, 69.7, 111.0, 112.5, 115.0, 117.5, 120.5, 122.4, 123.3, 125.9, 126.0, 127.3, 129.1, 129.5, 129.9, 130.7, 132.7, 132.8, 148.1, 148.4, 155.7, 159.6. IR: ν_{max} 671, 1510, 1521, 3737. Anal. Calcd for $C_{29}H_{29}NO_4$: C, 76.46, H, 6.42, N, 3.07. Found: C, 76.43, H, 6.38, N, 3.12.

*4.1.15. 1-[(4-Chlorophenyl)-(6,7-dimethoxy-3,4-dihydro-1H-isoquinolin-2-yl)-methyl]-naphthalen-2-ol (**18c**).* Mp: 209–211 °C. ^{1}H NMR: 2.67–3.01 (4H, m), 3.53 (1H, d, J=15.0 Hz), 3.64 (3H,s), 3.65–3.71 (1H,m), 3.72 (3H, s), 5.59 (1H, s), 6.61 (1H, s), 6.72 (1H, s), 7.12 (1H, d, J=8.8 Hz), 7.26 (1H, t, J=7.5 Hz), 7.37–7.46 (3H, m), 7.68–7.81 (4H, m), 8.05–8.16 (1H, m), 13.32 (1H, br s). ^{13}C NMR: 28.8, 49.8, 54.5, 56.3, 56.4, 69.3, 111.1, 112.5, 116.9, 120.5, 122.4, 123.4, 125.9 (2C), 127.5, 129.1, 129.6, 129.7 (2C), 130.3 (2C), 131.3, 132.8, 133.3, 140.0, 148.2, 148.5, 155.7. IR: ν_{max} 671, 1124, 1523, 3587. Anal. Calcd for $C_{28}H_{26}ClNO_3$: C, 73.11, H, 5.70, N, 3.05. Found: C, 73.13, H, 5.71, N, 3.03.

*4.1.16. 1-[(4,5-Dihydro-1H-benzo[d]azepin-3(2H)-yl)phenylmethyl] naphthalen-2-ol (**19**).* Mp: 201–203 °C. ^{1}H NMR: 1.59–1.85 (2H, m), 2.86–3.10 (4H, m), 3.87 (1H, d J=14.7 Hz), 4.05 (1H, d J=14.7 Hz), 5.45 (1H, s), 6.37 (1H, d, J=7.5 Hz), 6.90–6.97 (1H, m), 7.07 (1H, d, J=8.7 Hz), 7.16–7.26 (4H, m), 7.27–7.38 (3H, m), 7.62 (2H, d, J=7.5 Hz), 7.73 (2H, dd, J=15.4, 9.0 Hz), 7.81–7.89 (1H, m), 13.26 (1H, br s).^{13}C NMR: 35.4, 40.6, 57.0, 58.1, 68.1, 120.4, 122.1, 123.2, 126.7, 127.2, 128.6 (2C), 129.0 (2C), 129.3 (2C), 129.5 (2C), 129.6, 130.1, 130.7, 132.6, 136.5, 141.4, 141.9, 143.9, 155.9. IR: ν_{max} 752, 1267, 1452, 2935, 3435. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45, H, 6.64, N, 3.69. Found: C, 85.48, H, 6.62, N, 3.72.

*4.1.17. 1-[(4,5-Dihydro-1H-benzo[c]azepin-2(3H)-yl)phenylmethyl] naphthalen-2-ol (**20**).* Mp: 158–160 °C. ^{1}H NMR: 2.61–2.86 (4H, m), 2.88–3.03 (4H, m), 5.56 (1H, s), 7.07–7.15 (5H, m), 7.20–7.26 (2H, m), 7.31 (2H, t, J=7.7 Hz), 7.38 (1H, t, J=7.5 Hz), 7.67 (2H, d, J=7.5 Hz), 7.74 (2H, t, J=9.7 Hz), 8.04 (1H, d, J=8.6 Hz), 13.75 (1H, br s). ^{13}C NMR: 35.3 (2C), 53.9 (2C), 69.9, 117.7, 120.6, 122.3, 123.2, 127.2 (2C), 127.3, 128.6, 129.0, 129.5 (2C), 129.6 (2C), 129.7 (2C), 130.0, 132.8, 141.1, 142.1 (2C), 142.2, 155.9. IR: ν_{max} 740, 1236, 1624, 2827, 3737. Anal. Calcd for $C_{27}H_{25}NO$: C, 85.45, H, 6.64, N, 3.69. Found: C, 85.43, H, 6.63, N, 3.70.

*4.1.18. 1-[(6,7-Dihydro-4H-thieno[3,2-c]pyridin-5-yl)phenylmethyl] naphthalen-2-ol (**21**).* Mp: 142–143 °C. ^{1}H NMR: 2.79–3.09 (4H, m), 3.51 (1H, d, J=14.4 Hz), 3.61–3.71 (1H, m), 5.62 (1H, s), 6.76 (1H, d, J=5.5), 7.11 (1H, d, J=8.8 Hz), 7.22–7.28 (2H, m), 7.29–7.36 (3H, m), 7.42 (1H, t, J=7.8 Hz), 7.67–7.8 (4H, m), 8.12 (1H, d, J=8.5 Hz), 13.23 (1H, br s). ^{13}C NMR: 25.5, 49.8, 52.2, 69.7, 117.3, 120.5, 122.5, 123.4, 124.6, 126.6, 127.4, 128.8, 129.1, 129.4, 129.5 (2C), 129.7 (2C), 130.1, 132.8, 133.4, 133.9, 141.0, 155.7. IR: ν_{max} 671, 1558, 3734. Anal. Calcd for $C_{24}H_{21}NOS$: C, 77.59, H, 5.70, N, 3.77. Found: C, 77.61, H, 5.68, N, 3.79.

4.2. Synthesis of 2-(2-benzyl-1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol (7)

A mixture of 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol[25] (50 mg, 0.183 mmol), sodium carbonate (58 mg, 0.55 mmol) and benzyl bromide (40 mg, 0.23 mmol) was stirred in acetonitrile (15 mL) in an oil bath at 70 °C for 4 h. The solvent was then evaporated off, 15 ml water was added to the residue and the solution was extracted with DCM (3×10 mL). The combined organic extracts were dried (Na_2SO_4) and concentrated in vacuum. The residue was crystallized from iPr$_2$O and recrystallized from n-hexane:EtOAc (10 mL:1 mL).

Yield: 57 mg (85%), Mp: 148–149 °C. ^{1}H NMR: 2.54–2.61 (1H, m), 2.81–2.89 (1H, m), 2.99–3.09 (1H, m), 3.17–3.24 (1H, m), 3.46 (1H,d, J=13.4 Hz), 3.97 (1H,d, J=13.4 Hz), 5.07 (1H, s), 6.87 (1H, d, J=8.0 Hz), 7.03 (1H, t, J=7.7 Hz), 7.09–7.18 (2H, m), 7.28–7.33 (3H, m), 7.35–7.41 (2H, m), 7.42–7.49 (3H, m), 7.50–7.54 (1H, m), 7.85 (1H, d J=7.8 Hz), 8.11 (1H, d, J=8.2 Hz). ^{13}C NMR: 29.1, 47.7, 59.0, 67.1, 119.2, 121.5, 122.7, 125.7, 125.8, 126.7, 127.0, 127.1, 128.2, 128.3, 128.9, 129.2 (2C), 129.4 (2C), 130.1 (2C), 134.4, 134.7, 136.9, 137.7, 152.3. IR: ν_{max} 671, 1559, 3737. Anal. Calcd for $C_{26}H_{23}NO$: C, 85.45, H, 6.34, N, 3.83. Found: C, 85.47, H, 6.32, N, 3.81.

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