



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 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.

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1. Introduction

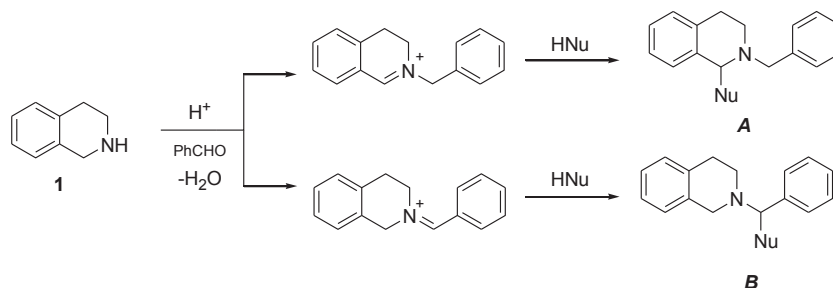
The Mannich reaction¹ is an important reaction involving C–C bond formation that is widely used in the syntheses of secondary and tertiary amine derivatives and as a key step in the syntheses of many bioactive molecules and complex natural products.² In the past decade, modified three-component Mannich 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 synthesized as novel

selective estrogen 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).

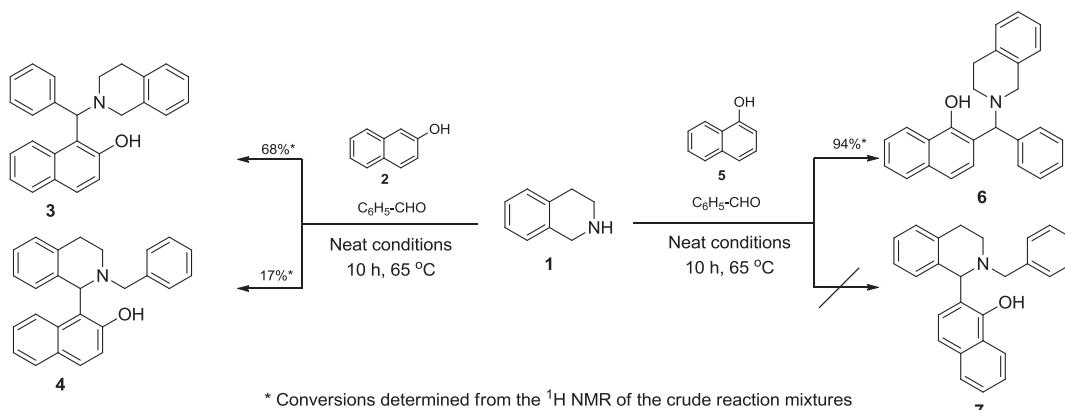
N-alkylation process starting from tetrahydroisoquinoline, tetrahydrobenzazepine or tetrahydrothieno[3,2-c]pyridine by using 2- or 1-naphthol as nucleophile in the presence of benzaldehyde.

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 1H NMR spectra of the crude reaction mixture did not reveal the formation of 3. The synthesis of 3 was earlier performed²² 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 1H 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 synthesized from 2-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-1-ol²³ 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.

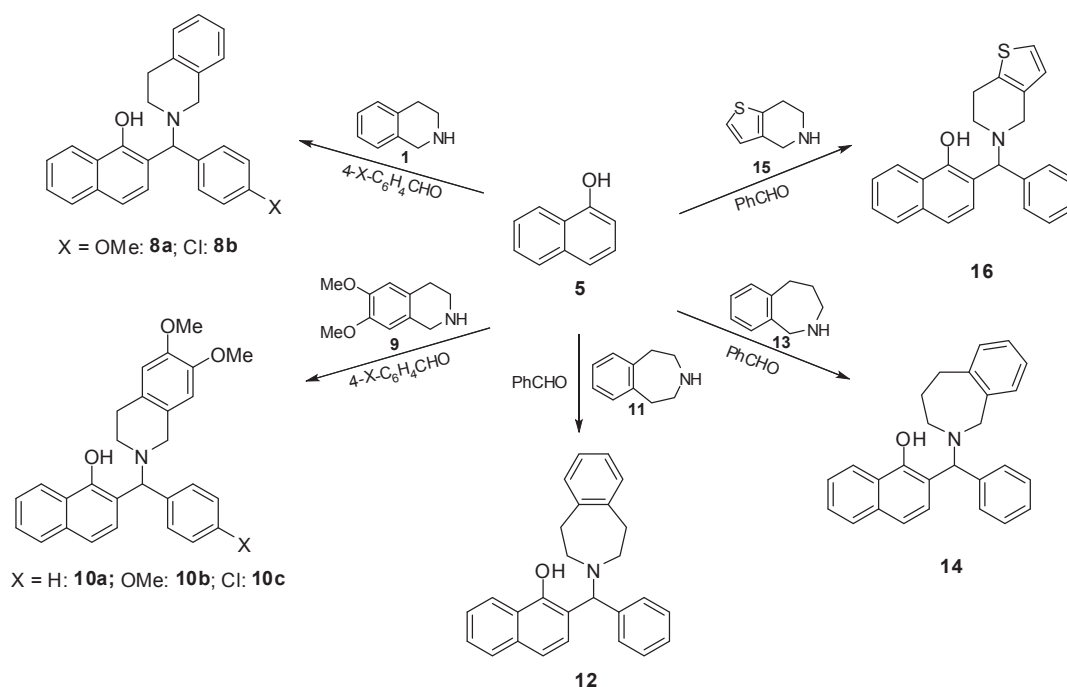


* Conversions determined from the 1H NMR of the crude reaction mixtures
Scheme 2. Reaction of 1 with 2- or 1-naphthol in the presence of benzaldehyde.

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 synthesized from 1-(1,2,3,4-tetrahydroisoquinolin-1-yl)naphthalen-2-ol²³ 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 1H 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 *i*Pr₂O:MeOH (1:1).

^b Recrystallized from MeOH.

^c Recrystallized from *i*Pr₂O:MeOH (2:1).

^d Recrystallized from *i*Pr₂O: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-

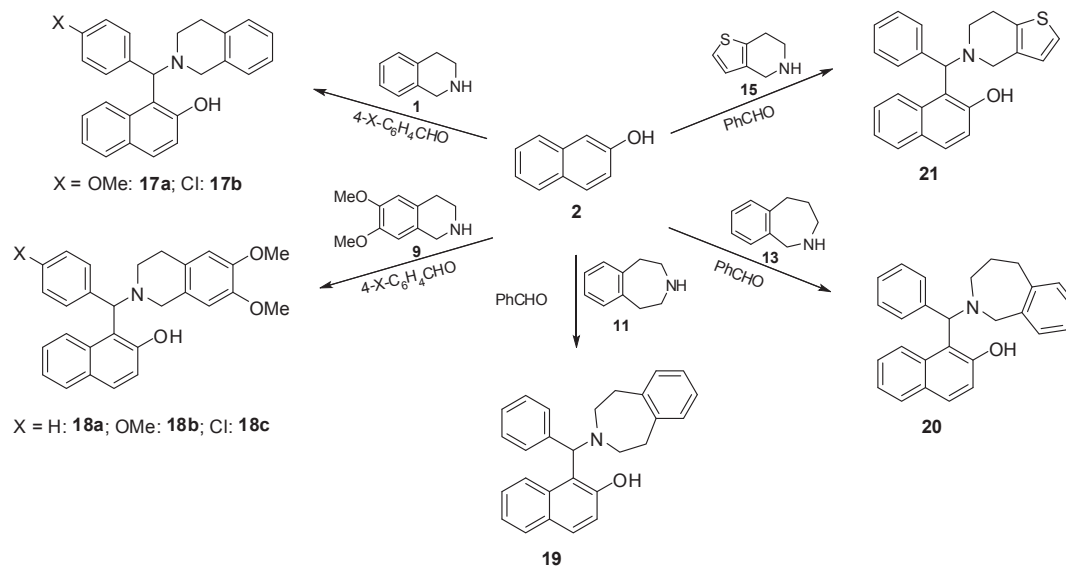
tetrahydroisoquinoline (**9**), the aldehyde substrates were benzaldehyde, 4-methoxybenzaldehyde and 4-chlorobenzaldehyde. The structures of the tertiary aminonaphthol products **17a–b**, **18a–c** and **19–21** are shown in Scheme 4.

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 *i*Pr₂O:MeOH (4:1).

^b Recrystallized from MeOH.

^c Recrystallized from *i*Pr₂O:MeOH (1:1).

^d Recrystallized from *i*Pr₂O: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 ¹H and ¹³C NMR spectra were recorded in DMSO solutions in 5 mm tubes, at room temperature, on a Bruker spectrometer at 400 (¹H) and 100.6 (¹³C) 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 60F₂₅₄ 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-1*H*-isoquinolin-2-yl)phenylmethyl]naphthalen-1-ol (6**).** Mp: 138–140 °C. ¹H 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). ¹³C 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 C₂₆H₂₃NO: 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-1*H*-isoquinolin-2-yl)-(4-methoxyphenyl)methyl]naphthalen-1-ol (8a**).** Mp: 178–179 °C. ¹H 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). ¹³C 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 C₂₇H₂₅NO₂: 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-1*H*-isoquinolin-2-yl)methyl]naphthalen-1-ol (8b**).** Mp: 180–182 °C. ¹H 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 $\text{C}_{26}\text{H}_{22}\text{ClNO}$: 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. ^1H 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 $\text{C}_{28}\text{H}_{27}\text{NO}_3$: 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. ^1H 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 $\text{C}_{29}\text{H}_{29}\text{NO}_4$: 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. ^1H 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 $\text{C}_{28}\text{H}_{26}\text{ClNO}_3$: 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. ^1H 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 $\text{C}_{27}\text{H}_{25}\text{NO}$: 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. ^1H 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 $\text{C}_{27}\text{H}_{25}\text{NO}$: 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. ^1H 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 $\text{C}_{24}\text{H}_{21}\text{NOS}$: 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. ^1H 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 $\text{C}_{26}\text{H}_{23}\text{NO}$: 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. ^1H 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 $\text{C}_{27}\text{H}_{25}\text{NO}_2$: 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. ^1H 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 $\text{C}_{26}\text{H}_{22}\text{ClNO}$: 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. ^1H 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 $\text{C}_{28}\text{H}_{27}\text{NO}_3$: 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. ^1H 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 $\text{C}_{29}\text{H}_{29}\text{NO}_4$: 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. ^1H 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 $\text{C}_{28}\text{H}_{26}\text{ClNO}_3$: 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. ^1H 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 $\text{C}_{27}\text{H}_{25}\text{NO}$: 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. ^1H 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 $\text{C}_{27}\text{H}_{25}\text{NO}$: 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. ^1H 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 $\text{C}_{24}\text{H}_{21}\text{NOS}$: 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-ol²⁵ (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 $i\text{Pr}_2\text{O}$ and recrystallized from n -hexane:EtOAc (10 mL:1 mL).

Yield: 57 mg (85%), Mp: 148–149 °C. ^1H 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 $\text{C}_{26}\text{H}_{23}\text{NO}$: C, 85.45, H, 6.34, N, 3.83. Found: C, 85.47, H, 6.32, N, 3.81.

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