New Synthetic Approach for the Preparation of 1-Aryl-3,4-dihydroisoquinolines by Liebeskind–Srogl Reaction

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Dedicated to Professor József Reiter on the occasion of his 75th birthday

Abstract: An efficient synthetic methodology has been developed to construct 1-aryl-3,4-dihydroisoquinoline derivatives. The reaction was performed under neutral conditions by a palladium-catalyzed desulfitative carbon–carbon cross-coupling protocol.

Key words: isoquinolines, cross-coupling, Liebeskind–Srogl reaction, arylation, CuTC

The isoquinolines constitute an important class of both simple and complex alkaloids.[1] They also have been used as intermediates in organic synthesis. For example, some isoquinoline derivatives are utilized as chiral ligands for catalytic asymmetric transformations[2] and as electrophosphorescent iridium complexes.[3] Moreover, isoquinolines and their saturated counterparts such as dihydroisoquinolines and tetrahydroisoquinolines possess a vast spectrum of biological and pharmaceutical activities including antibacterial,[4] antitumor,[5] antitubercular,[6] antiplasmodial,[7] anti-HIV,[8] and antifungal effects[9] and some representatives are noncompetitive AMPA receptor antagonists.[10] An important member of the tetrahydroisoquinoline family is solifenacin (Vesicare®), A competitive cholinergic receptor antagonist which is developed for treating contraction of overactive bladder.[11] Other compounds containing 1-aryl-3,4-dihydroisoquinoline units represent a potent series of c-Jun N-terminal kinase 3 (JNK3) inhibitors (Figure 1).[12]

1-Substituted-3,4-dihydroisoquinolines were also tested in vitro against the leukemia L 1210 cell line.[13] Furthermore, certain 1-aryl-3,4-dihydroisoquinolines have been used as starting materials of several alkaloid derivatives and chiral tetrahydroisoquinolines.[14]

In continuation of our efforts to synthesize new alkaloid derivatives,[15] we now describe a simple procedure for the preparation of 1-aryl-3,4-dihydroisoquinolines. In general, 3,4-dihydroisoquinolines have been constructed by Bischler–Napieralski cyclization. This ring-closure reaction traditionally requires harsh conditions, for example, treatment of the amide formed from phenylethylamine

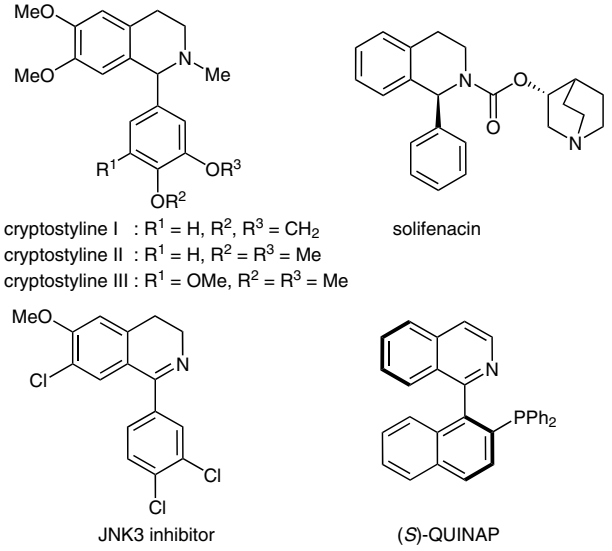
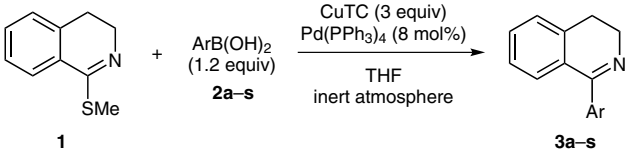


Figure 1 Structure of some important isoquinoline derivatives

with $POCl_3$, P_2O_5, or polyphosphoric acid (PPA) at high temperature and long reaction time.[16]

In the present paper, a different approach was used. 1-Aryl-3,4-dihydroisoquinoine target compounds have now been prepared by the application of the Liebeskind–Srogl protocol,[17] a palladium-catalyzed cross-coupling reaction. The starting material of the cross coupling, 1-(methylsulfanyl)-3,4-dihydroisoquinoline (**1**) was prepared according to our earlier procedure based on a microwave-assisted thionation reaction from commercially available 1,2,3,4-tetrahydroisoquinoline, followed by an S-alkylation step with methyl iodide.[18]



Scheme 1 Arylation of 1-(methylsulfanyl)-3,4-dihydroisoquinoline (**1**)

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At the beginning of our investigations, the conditions of the coupling reaction (Scheme 1) were chosen based on the similar and optimized reactions of analogous nitrogen heterocycles described by Kappe and Prokopcová.[19] 3 Equiv. of copper(I)-thiophene-2-carboxylate (CuTC) as Cu(I) cofactor and 8 mol% of $Pd(PPh_3)_4$ in refluxing tetrahydrofuran (45–60 min) was in most cases suitable for the full conversion and good yields were observed (65–89%, Table 1, entries 1–3,5,8–14). It is worth mentioning that the 3-nitrophenyl derivative (**3q**) was obtained after a short reaction time (15 min) in a yield of 89% (Table 1, entry 17). However, for several analogues (Table 1, entries 4, 6, 7, 15, 16, 18, 19) increasing the reaction time to 3–7 h was indispensable for the full conversion and provided yields between 61 and 89%. This protocol[20] was used successfully in the presence of various functional groups, such as formyl (**3d**), methoxycarbonyl (**3e**), carboxybenzyl (**3g**), benzyloxy (**3k**), methylsulfanyl (**3m**), and *tert*-butoxycarbonyl (**3p**).

As the one exception, when using 4-(dimethylamino)phenylboronic acid (**2f**) as the starting material, the product **3f** was isolated only in 32% yield (Table 1, entry 6). An inhibiting steric effect was observed by the *ortho*-substituted boronic acids that necessitated of longer reaction times (Table 1, entries 18 and 19). Moreover, there was no reaction detected in the case of 2-cyanophenyl- and 2-chlorophenylboronic acid. The increase of the amount of the boronic acid to two equivalents also did not result in any success, nor did the increase in reaction temperature by refluxing in 1,4-dioxane.

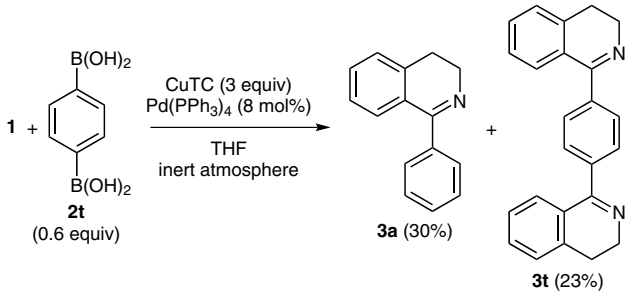
Table 1 Reaction Details for the Arylation of 1-(Methylsulfanyl)-3,4-Dihydroisoquinoline (**1**)[a]

Entry	**3**	Ar	Time (h)	Yield (%)[b]
1	**3a**	Ph	0.75	78
2	**3b**	4-MeC_6H_4	1	83
3	**3c**	4-$F_3CC_6H_4$	0.75	76
4	**3d**	4-$OHCC_6H_4$	3	89
5	**3e**	4-$MeO_2CC_6H_4$	1	85
6	**3f**	4-$Me_2NC_6H_4$	4	32
7	**3g**	4-$CbzHNC_6H_4$	4	88
8	**3h**	4-$MeOC_6H_4$	1	82
9	**3i**	3,4-$(MeO)_2C_6H_3$	1	88
10	**3j**	1,3-benzodioxol-5-yl	1	71
11	**3k**	4-$BnOC_6H_4$	1	82
12	**3l**	4-FC_6H_4	0.75	89
13	**3m**	4-$MeSC_6H_4$	1	65
14	**3n**	4-ClC_6H_4	1	85
15	**3o**	3-NCC_6H_4	3	65
16	**3p**	3-$BocHNC_6H_4$	4	76
17	**3q**	3-$O_2NC_6H_4$	0.25	89
18	**3r**	2-$MeOC_6H_4$	3	71
19	**3s**	2-FC_6H_4	7	61

[a] Reaction conditions: CuTC (3 equiv), $Pd(PPh_3)_4$ (8 mol%), boronic acid (1.2 equiv), reflux, THF.
[b] Yields are given for isolated products.

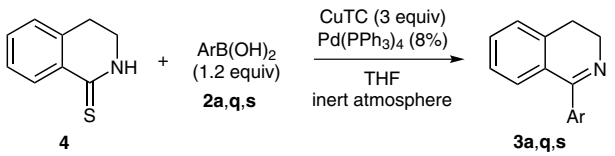
The application of phenylboronic acid pinacol ester instead of phenylboronic acid (**2a**) proved to be disadvantageous resulting in only traces of the desired 1-phenyl-3,4-dihydroisoquinoline (**3a**) as, under the same conditions, detected by HPLC–MS.

In the reaction of 1,4-benzenediboronic acid (**2t**) under the same conditions, two products were isolated: the appropriate bisisoquinoline derivative **3t** and 1-phenyl-3,4-dihydroisoquinoline (**3a**) in yields of 23% and 30%, respectively (Scheme 2). The unexpected compound **3a** may be formed by deboronation in the transmetalation step of the cross-coupling circle.[17b]



Scheme 2 The reaction of 1-(methylsulfanyl)-3,4-dihydroisoquinoline (**1**) with 1,4-benzenediboronic acid (**2t**)

As a continuation of our investigations, the precursor of **1**, the isoquinoline embedded with a thioamide fragment **4**, was examined for the Liebeskind–Srogl reaction with three boronic acids (**2a**,**q**,**s**, Scheme 3, Table 2). It was found that applying the same conditions as in the reactions of **1**, much lower yields were obtained. Even the most reactive 3-nitrophenylboronic acid (**2q**) could not approach the observed yield of the previous reaction with **1** (Table 2, entry 2) after a doubled reaction time.



Scheme 3 The arylation of 3,4-dihydroisoquinoline-1(2*H*)-thione (**4**)

Table 2 Reaction Details for the Arylation of 3,4-Dihydroisoquinoline-1(2*H*)-thione (**4**)[a]

Entry	**3**	Ar	Time (h)	Yield (%)[b]
1	**3a**	Ph	0.75	66
2	**3q**	3-$O_2NC_6H_4$	0.5	56
3	**3s**	2-FC_6H_4	7	36

[a] Reaction conditions: CuTC (3 equiv), $Pd(PPh_3)_4$ (8 mol%), boronic acid (1.2 equiv), reflux, THF.
[b] Yields are given for isolated products.

All the dihydroisoquinoline derivatives **3a**–**t** prepared were characterized by IR, ^{1}H NMR, and ^{13}C NMR spectroscopy and mass spectrometry. Products **3a**,**b**,**h**,**i**,**k**,**m**,**n**,**q**,**r** have been described and characterized previously, while compounds **3c**–**g**,**j**,**l**,**o**,**p**,**s**,**t** have not been fully characterized or are new.

In conclusion, a simple and convenient method has been developed for the synthesis of 1-aryl-3,4-dihydroisoquinoline based on the Liebeskind–Srogl reaction. The advantages of this method can be enumerated as applying a mild and neutral process, coupling a variety of boronic acids, and also enabling to substitute isoquinolines with aryl groups that are sensitive to the harsh conditions of Bischler–Napieralski reaction. Most of the arylations were completed within one hour and preceded in high yields. It was found that the 1-(methylsulfanyl)-3,4-dihydroisoquinoline (**1**) is a more reactive species than the 3,4-dihydroisoquinoline-1(2*H*)-thione (**4**).

Supporting Information for this article is available online at http://www.thieme-connect.com/products/ejournals/journal/10.1055/s-00000083.

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(19) Prokopcová, H.; Kappe, C. O. *J. Org. Chem.* **2007**, *72*, 4440.
(20) **General Procedure for the Synthesis of 1-Aryl-3,4-dihydroisoquinolines**
To the stirred solution of 1-(methylsulfanyl)-3,4-dihydroisoquinoline (**1**, 1.0 mmol, 0.18 g) in THF (10 mL) under argon atmosphere arylboronic acid (1.2 mmol), CuTC (3 equiv, 3.0 mmol, 0.57 g), and $Pd(PPh_3)_4$ (8 mol%, 0.08 mmol, 92 mg) were added. The reaction was followed by TLC and HPLC–MS. The mixture was refluxed until the starting material disappeared. After cooling, the solvent was evaporated and $CHCl_3$–MeOH (7:1) mixture (50 mL) was added. The crude reaction mixture was subsequently washed with 25% aq NH_3 (2 × 25 mL). The aqueous layer was extracted with $CHCl_3$–MeOH (7:1) mixture (2 × 25 mL). The combined organic phase was dried over Na_2SO_4 and the residue after evaporation purified by flash chromatography (silica gel 60 PF_{254}) using CH_2Cl_2–MeOH as the eluents.

1-[4-(Trifluoromethyl)phenyl]-3,4-dihydroisoquinoline (3c)
Yield 0.21 g (76%), white crystals, mp 77–78 °C. IR (KBr): 2958, 1610, 1565, 1323, 1109, 846 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.73–7.68 (m, 4 H), 7.41–7.39 (m, 1 H), 7.30–7.24 (m, 2 H), 7.19–7.18 (m, 1 H), 3.90–3.67 (m, 2 H), 2.82 (t, *J* = 7.4 Hz, 2 H) ppm; lit.:[22] ^1H NMR (400 MHz, $CDCl_3$): δ = 7.70 (m, 4 H), 7.40 (m, 1 H), 7.26 (m, 2 H), 7.20 (m, 1 H), 3.88 (m, 2 H), 2.82 (m, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 142.5, 138.7, 131.2 (q, *J* = 33.0 Hz), 131.0, 129.2, 128.3, 127.6, 127.5, 126.7, 125.1 (q, *J* = 3.8 Hz), 124.1 (q, *J* = 272.0 Hz), 47.9, 26.2 ppm. HRMS: *m/z* calcd for $C_{16}H_{13}NF_3$ $[M + H]^+$: 276.1000; found: 276.1002.

4-(3,4-Dihydroisoquinolin-1-yl)benzaldehyde (3d)
Yield 0.21 g (89%), pale yellow crystals, mp 102–104 °C. IR (KBr): 2940, 1702, 1604, 1203 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 10.09 (s, 1 H), 7.96–7.94 (m, 2 H), 7.78–7.76 (m, 2 H), 7.41–7.40 (m, 1 H), 7.30–7.28 (m, 1 H), 7.27–7.25 (m, 1 H), 7.19–7.17 (m, 1 H), 3.90 (t, *J* = 7.3 Hz, 2 H), 2.83 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 191.8, 166.4, 144.8, 138.7, 136.8, 131.0, 129.5, 129.4, 128.3, 127.6, 127.4, 126.7, 47.9, 26.1 ppm. HRMS: *m/z* calcd for $C_{16}H_{14}NO$ $[M + H]^+$: 236.1075; found: 236.1081.

Methyl 4-(3,4-Dihydroisoquinolin-1-yl)benzoate (3e)[21]
Yield 0.23 g (85%), yellow oil. IR (film): 2950, 1724, 1610, 1279, 1104 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 8.11–8.09 (m, 2 H), 7.68–7.67 (m, 2 H), 7.42–7.38 (m, 1 H), 7.29–7.24 (m, 2 H), 7.19–7.18 (m, 1 H), 3.95 (s, 3 H), 3.90–3.87 (m, 2 H), 2.82 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.8, 166.6, 143.3, 138.7, 130.9, 130.8, 129.4, 128.8, 128.4, 127.6, 127.5, 126.7, 52.2, 47.8, 26.2 ppm. HRMS: *m/z* calcd for $C_{17}H_{16}NO_2$ $[M + H]^+$: 266.1181; found: 266.1171.

4-(3,4-Dihydroisoquinolin-1-yl)-*N*,*N*-dimethylaniline (3f)
Yield 0.08 g (32%), yellow crystals, mp 102–105 °C (MeCN). IR (KBr): 3444, 2888, 1608, 1525, 1346, 1195, 823 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.55–7.53 (m, 2 H), 7.40–7.36 (m, 2 H), 7.26–7.25 (m, 1 H), 6.74–6.73 (m, 2 H), 3.78 (t, *J* = 7.1 Hz, 2 H), 3.00 (s, 3 H), 2.76 (t, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.7, 151.3 139.3, 130.2, 130.0, 129.1, 128.2, 127.2, 126.7, 126.3, 111.5, 65.5, 40.4, 26.6 ppm. HRMS: *m/z* calcd for $C_{17}H_{19}N_2$ $[M + H]^+$: 251.1548; found: 251.1562.

Benzyl [4-(3,4-Dihydroisoquinolin-1-yl)phenyl]-carbamate (3g)
Yield 0.31 g (88%), white crystals, mp 194–195 °C (MeCN). IR (KBr): 3337, 2976, 1703, 1609, 1591, 1534, 1230, 1056, 744 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.57–7.55 (m, 2 H), 7.46–7.32 (m, 8 H), 7.31–7.21 (m, 3 H), 6.96 (s, 1 H), 5.22 (s, 2 H), 3.81 (t, *J* = 7.2 Hz, 2 H), 2.78 (t, *J* = 7.1 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.6, 153.2, 138.9, 135.9, 134.0, 130.6, 129.7, 128.7, 128.6, 128.4, 127.8, 127.4, 126.5, 118.0, 67.1, 47.5, 26.3 ppm. HRMS: *m/z* calcd for $C_{23}H_{21}N_2O_2$ $[M + H]^+$: 357.1603; found: 357.1598.

1-(1,3-Benzodioxol-5-yl)-3,4-dihydroisoquinoline (3j)[22]
Yield 0.18 g (71%), yellow oil. IR (film): 2940, 1600, 1486, 1440, 1232, 1039, 936, 746 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38–7.36 (m, 1 H), 7.33–7.31 (m, 1 H), 7.28–7.24 (m, 2 H), 7.14–7.09 (m, 2 H), 6.86–6.84 (m, 1 H), 6.00 (s, 2 H), 3.82–3.78 (m, 2 H), 2.78 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.4, 148.6, 147.5, 139.0, 133.1, 130.6, 128.7, 127.9, 127.3, 126.5, 123.1, 109.3, 107.8, 101.2, 47.5, 26.3 ppm. HRMS: *m/z* calcd for $C_{16}H_{13}NO_2$ $[M+H]^+$: 251.0946; 251.0942.

1-(4-Fluorophenyl)-3,4-dihydroisoquinoline (3l)[23]
Yield 0.20 g (89%), yellow crystals, mp 37–38 °C (hexane). IR (KBr): 2941, 1604, 1506, 1152, 847 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.61–7.58 (m, 2 H), 7.41–7.37 (m, 1 H), 7.28–7.24 (m, 3 H), 7.12–7.09 (m, 2 H), 3.83 (t, *J* = 7.1 Hz, 2 H), 2.80 (t, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 166.2, 163.5 (d, *J* = 249.0 Hz), 138.9, 135.1, 130.8, 130.7 (d, *J* = 8.3 Hz), 128.6, 127.7, 127.5, 126.6, 115.1 (d, *J* = 22.0 Hz), 47.6, 26.3 ppm. HRMS: *m/z* calcd for $C_{15}H_{13}NF$ $[M + H]^+$: 226.1032; found: 226.1033.

3-(3,4-Dihydroisoquinolin-yl)benzonitrile (3o)
Yield 0.15 g (65%), pale yellow oil. IR (film): 2943, 2230, 1611, 1568, 1310, 708 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.93–7.92 (m, 1 H), 7.87–7.85 (m, 1 H), 7.74–7.72 (m, 1 H), 7.56–7.53 (m, 1 H), 7.44–7.41 (m, 1 H), 7.31–7.26 (m, 2 H), 7.17–7.15 (m, 1 H), 3.87 (t, *J* = 7.2 Hz, 2 H), 2.82 (t, *J* = 7.3 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.4, 140.2, 138.7, 133.0, 132.7, 132.4, 131.2, 129.0, 127.9, 127.7, 127.2, 126.8, 118.4, 112.5, 47.8, 26.1 ppm. HRMS: *m/z* calcd for $C_{16}H_{13}N_2$ $[M + H]^+$: 233.1079; found: 233.1069.

***tert*-Butyl [3-(3,4-Dihydroisoquinolin-1-yl)phenyl]-carbamate (3p)**
Yield 0.25 g (76%), yellow oil. IR (KBr): 3232, 2975, 1723, 1609, 1549, 1240, 1159, 777 cm^{-1}. ^1H NMR (500 MHz, DMSO-d_6): δ = 9.42 (s, 1 H), 7.74 (s, 1 H), 7.64–7.61 (m, 1 H), 7.56–7.53 (m, 1 H), 7.44 (t, *J* = 7.4 Hz, 1 H), 7.36–7.28 (m, 3 H), 7.16 (d, *J* = 7.5 Hz, 1 H), 7.10 (d, *J* = 7.5 Hz, 1 H), 3.71 (t, *J* = 7.2 Hz, 2 H), 2.73 (t, *J* = 7.2 Hz, 2 H) ppm. ^{13}C NMR (125 MHz, DMSO-d_6): δ = 165.8, 152.9, 139.5, 139.3, 138.6, 130.8, 128.9, 128.4, 127.6, 127.3, 126.8, 122.4, 119.0, 118.3, 79.2, 47.1, 28.3, 25.8 ppm. HRMS: *m/z* calcd for $C_{20}H_{23}N_2O_2$ $[M + H]^+$: 323.1760; found: 323.1743.

1-(2-Fluorophenyl)-3,4-dihydroisoquinoline (3s)[24]
Yield 0.14 g (61%), yellow crystals, mp 79–80 °C (*i*-Pr_2O). IR (KBr): 3444, 2946, 1612, 1447, 1210, 768 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.53–7.50 (m, 1 H), 7.44–7.36 (m, 2 H), 7.26–7.21 (m, 3 H), 7.13–7.07 (m, 2 H), 3.90 (br s, 2 H), 2.87 (br s, 2 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 163.9, 161.1, 160.0, 159.1, 137.2, 130.9, 130.8, 130.7, 127.4, 127.0 (d, *J* = 15.1 Hz), 124.3 (d, *J* = 3.4 Hz), 115.8 (d,

J = 22.0 Hz), 94.8, 47.8, 26.0 ppm. HRMS: *m/z* calcd for $C_{15}H_{13}NF$ $[M + H]^+$: 226.1032; found: 226.1031.

1,1′-Benzene-1,4-diyldi-3,4-dihydroisoquinoline (3t)
Yield 0.04 g (23%), white crystals, mp 198–199 °C (MeCN). IR (KBr): 3421, 2942, 1603, 1315 cm^{-1}. ^1H NMR (500 MHz, $CDCl_3$): δ = 7.66–7.62 (m, 4 H), 7.48–7.45 (m, 2 H), 7.39–7.38 (m, 2 H), 7.36–7.32 (m, 2 H), 7.25–7.24 (m, 2 H), 3.76 (br s, 4 H), 2.77 (br s, 4 H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$): δ = 165.5, 139.4, 138.7, 130.9, 128.5, 127.8, 127.2, 126.9, 47.3, 25.8 ppm. HRMS: *m/z* calcd for $C_{24}H_{21}N_2$ $[M + H]^+$: 337.1705; found: 337.1711.

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