Accepted Manuscript

Palladium–catalysed Suzuki–Miyaura Coupling Reactions of Bromhexine and Ambroxol

Muhammad Sharif , Anahit Pews–Davtyan , Jan Lukas , Susann Pohlers , Arndt Rolfs , Peter Langer , Matthias Beller

PII: S0040-4020(14)00846-1

DOI: 10.1016/j.tet.2014.05.116

Reference: TET 25665

To appear in: *Tetrahedron*

Received Date: 21 February 2014

Revised Date: 30 May 2014

Accepted Date: 31 May 2014

Please cite this article as: Sharif M, Pews–Davtyan A, Lukas J, Pohlers S, Rolfs A, Langer P, Beller M, Palladium–catalysed Suzuki–Miyaura Coupling Reactions of Bromhexine and Ambroxol, *Tetrahedron* (2014), doi: 10.1016/j.tet.2014.05.116.

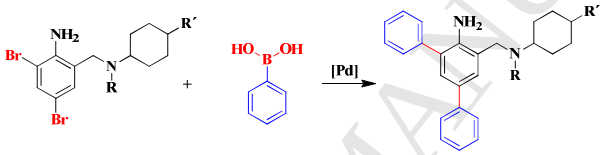
Graphical Abstract

Palladium–catalysed Suzuki–Miyaura Coupling Reactions of Bromhexine and Ambroxol

Leave this area blank for abstract info.

Muhammad Sharif,[a,c] Anahit Pews-Davtyan,[a] Jan Lukas,[b] Susann Pohlers,[b] Arndt Rolfs,*[b] Peter Langer,[a,d] and Matthias Beller*[a]

[a]*Leibniz-Institut für Katalyse an der Universität Rostock e.V. Albert-Einstein-Str. 29a, 18059 Rostock, Germany*
[b]*Albrecht Kossel-Institute for Neuroregeneration, Medical University Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany*
[c]*Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, Pakistan*
[d]*Institut für Chemie, Universität Rostock, Albert-Einstein-Str. 3a, 18059 Rostock, Germany*



The Suzuki-Miyaura coupling reaction was applied for the synthesis of biologically relevant derivatives of known mucolytic agents Bromhexine and Ambroxol. Using commercially available electron–rich and electron–poor arylboronic acids the desired products are obtained in moderate to high yields (42-81%).

Tetrahedron
journal homepage: www.elsevier.com

Palladium–catalysed Suzuki–Miyaura Coupling Reactions of Bromhexine and Ambroxol

Muhammad Sharif,[a,c] Anahit Pews–Davtyan,[a] Jan Lukas,[b] Susann Pohlers,[b] Arndt Rolfs,*[b] Peter Langer,[a,d] and Matthias Beller*[a]

[a]Leibniz–Institut für Katalyse an der Universität Rostock e.V. Albert–Einstein–Str. 29a, 18059 Rostock, Germany, Tel.

[b]*Albrecht Kossel–Institute for Neuroregeneration, Medical University Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany*
[c]*Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, Pakistan*
[d]*Institut für Chemie, Universität Rostock, Albert–Einstein–Str. 3a, 18059 Rostock, Germany*

Article history:
Received
Received in revised form
Accepted
Available online

Abstract: The Suzuki–Miyaura coupling reaction was applied for the synthesis of biologically relevant derivatives of known mucolytic agents Bromhexine and Ambroxol. Using commercially available electron–rich and electron–poor arylboronic acids the desired products are obtained in moderate to high yields (42–81%).

Keywords:
Catalysis
Palladium
Suzuki–Miyaura
Bromhexine
Ambroxol

1. Introduction

The well–known mucolytic agent Bromhexine (2,4–dibromo–6–{[cyclohexyl(methyl)amino]methyl}aniline) constitutes a synthetic benzylamine derivative of the parent molecule vasicine, an alkaloid that has been found in the plant *Adhatoda vasica*.[1] Bromhexine as well as its metabolite Ambroxol (4–{[(2–amino–3,5–dibromophenyl)methyl]amino}cyclohexan–1–ol) belong to the group of expectorants with a long history and are frequently used in the treatment of respiratory diseases, associated with increased mucus production, like acute and chronic bronchitis. Clinical studies of these drugs (as active ingredients in mucolytic drugs Bisolvon Forte, Mucosolvan, Mucoangin etc.) have shown that they significantly improve the coughing, promote mucus clearance as well as production and transport of sputum of patients.[2–4] Additionally, Ambroxol is able to enhance production of pulmonary surfactant,[5–8] which is vitally important especially for newborns.

Among other ways of action these bioactive substances decrease the viscosity of mucoid sputum by depolymerisation of the high molecular weight mucopolysaccharide protein fibers.[9]

Besides the secretolytic activity Ambroxol and Bromhexine exert a wide range of other pharmacological activities, such as anti–inflammatory, antioxidant, local anaesthetic effects through sodium channel blocking, and the recently detected effectiveness in the treatment of chronic pancreatitis, etc.[10] In addition, they inhibit or scavenge oxidative and nitrosative stress[11–13] and the risk of viral infections can be reduced by clearing the bronchial tree.[14] Interestingly, it was also demonstrated that Ambroxol can function as a chemical chaperone in Gaucher disease, a rare condition of glycosphingolipid storage (OMIM #230800) by stabilising mutant lysosomal glucocerebrosidase (beta–glucosidase, GCase, EC 3.2.1.45)[15].

In spite of the significant pharmacological importance of Bromhexine and Ambroxol and extensive exploration of their biology over decades, the synthetic chemistry of the title compounds and their catalytic transformations were scarcely investigated.

Based on our interest in Pd–catalysed coupling reactions,[16] and a joint programme for the development of biologically active compounds,[16d,17] we became interested to explore the coupling chemistry of Bromhexine and Ambroxol. In general, selective catalytic coupling reactions should allow for the preparation of a multitude of biologically interesting derivatives (Figure 1).

* Corresponding author. Tel.: +49-381-1281-113; fax: +49-381-1281-51113; e-mail: Matthias.beller@catalysis.de

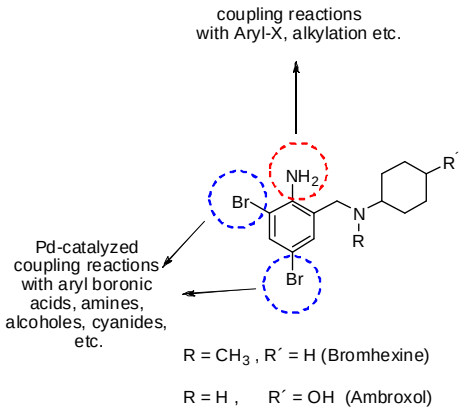


Figure 1. Different possibilities for metal-catalyzed coupling reactions of Ambroxol and Bromhexine.

To the best of our knowledge, no general study on coupling reactions of Ambroxol and Bromhexine has been reported to date, except acylations of Ambroxol and Bromhexine[18] and one example of a Sonogashira coupling product with Bromhexine.[19] Herein, we report our investigations on Suzuki–Miyaura coupling reactions of Bromhexine and Ambroxol. The new synthesized potentially bioactive products are not readily available by other methods.

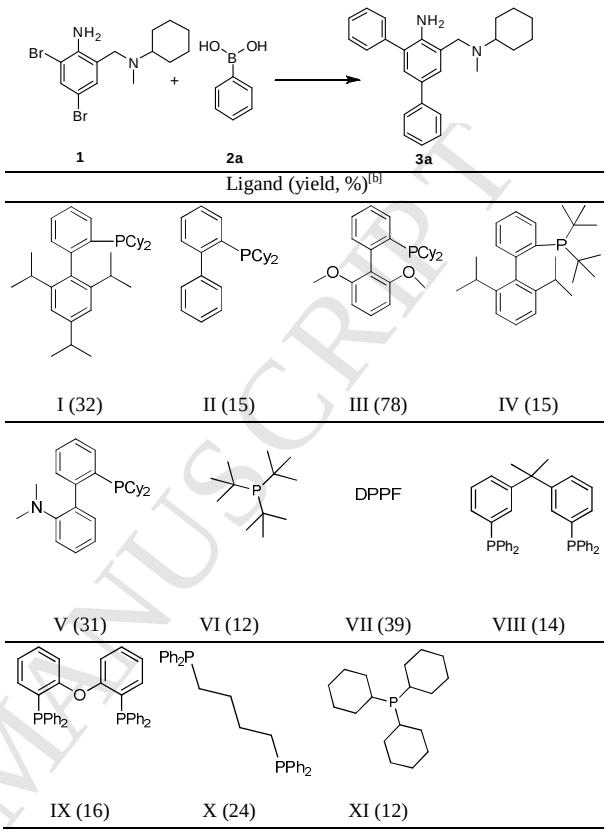
1. Results and Discussion

In recent years, numerous palladium catalysts for the cross–coupling reactions of halogenated arenes and different organoboron reagents (Suzuki–Miyaura reaction) have been developed and the methodology has found widespread application in the functionalization of different types of organic molecules.[20]

In order to identify suitable reaction conditions, in our study initially model coupling reactions between Bromhexine (**1**) and phenylboronic acid (**2a**) using different phosphine ligands and solvents were performed. Selected results are presented in Tables 1 and 2, respectively. Low yields of the desired coupling product **3a** were observed in the presence of 5 mol% of $Pd(OAc)_2$ and commercially available ligands **II**, **IV, VI, VIII, IX** and **XI** (Table 1). However, in the presence of Buchwald´s ligand **III** (S–Phos),[21] a 78% yield of the dicoupled product was obtained in 12 hours using the 1,4–dioxane as a solvent.

Next, we screened different solvents using ligand **III.** Moreover, variation of reaction temperature (60–140 °C) and monitoring of reaction time by TLC and GC analysis were performed. More specifically, the model reaction was performed at 140, 120, 100 °C. While at 120 and 140 °C the reaction is completed in 6-8 hours, at 100 °C the reaction needed 10 hours to achieve full conversion. Further lowering the temperature reaction prolonged the reaction time to 16-20 hours. Best yields (76–81%) of the coupling product were found in solvents 1,4–dioxane, 1,2–dichloroethane, NMP, and acetonitrile (Table 2, entries 1, 3, 6, and 10). Notably, the conversion was complete in 3–5 hours at 100 °C in the presence of the given solvents.

Table 1. Model coupling reaction using $Pd(OAc)_2$ and different ligands.[a]



[a] Reaction conditions: Bromhexine 1 (1.0 mmol), phenylboronic acid 2a (3.0 mmol), $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), solvent: 1,4–dioxane (3 mL), K_2CO_3 (1M, 2ml) in H_2O, 100 °C, 10–12 h, conventional heating in pressure tube. [b] GC yields.

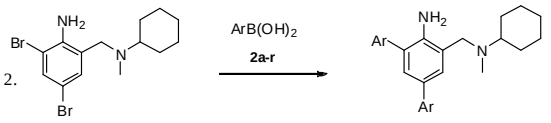
Table 2. Model coupling reaction using $Pd(OAc)_2$/S–Phos (ligand III) and different solvents.[a]

Entry	Solvent	Yield (%)[b]
1	1,4–dioxane	78
2	CCl_4	24
3	1,2–dichloroethane	76
4	1,2–dichlorobenzene	40
		30[c]
5	THF	48
		39[c]
6	NMP	77
7	DCM	47[c]
8	Toluene	69[c]

9	DMF	49[c]
10	CH_3CN	81[c]

[a] Reaction conditions: Bromhexine **1** (1.0 mmol), phenylboronic acid **2a** (3.0 mmol), $Pd(OAc)_2$ (5 mol%), S–Phos (ligand **III**, 10 mol%), K_2CO_3 (1M, 2ml) in H_2O, 100 °C, 10–12 h, conventional heating in pressure tube. [b] GC yield. [c] Isolated yield.

Table 3. Suzuki–Miyaura coupling products of Bromhexine (3a–r)[a]



1 **3a-r**

Entry	2	3	Ar	Yield of 3 (%)[b]
1	a	a	C_6H_5	81[c]
2	b	b	4–$(MeO)C_6H_4$	59
3	c	c	2,6–$(MeO)_2C_6H_3$	77
4	d	d	2–MeC_6H_4	77
5	e	e	4–EtC_6H_4	76
6	f	f	4–$VinylC_6H_4$	42
7	g	g	4–$AcetylC_6H_4$	73
8	h	h	4–FC_6H_4	74
9	i	i	Thiophen–2–yl	67
10	j	j	3,5–$(Me)_2C_6H_3$	59
11	k	k	6–(MeO)Pyridin–3–yl	78
12	l	l	2–$CF_3C_6H_4$	69
13	m	m	3–MeC_6H_4	72
14	n	n	4–$(EtO)C_6H_4$	68
15	o	o	4–(n–Bu)C_6H_4	80
16	p	p	3,5–$(MeO)_2C_6H_3$	58
17	q	q	3,5–$(CF_3)_2C_6H_3$	60
18	r	r	3,5–$F_2C_6H_3$	68

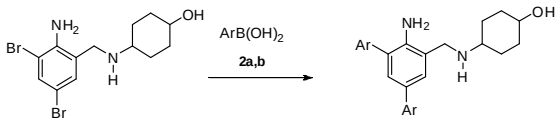
[a] Reagents and conditions: Bromhexine **1** (1.0 mmol), **2a–r** (3.0 mmol), K_2CO_3 (1M, 2mL) in H_2O, $Pd(OAc)_2$ (5 mol%), S–Phos (ligand III, 10 mol%), 1,4–dioxane, 100 °C, 3–4 h. [b] Isolated yields. [c] Solvent–acetonitrile.

The optimized reaction conditions were used to demonstrate the scope and limitations of this protocol. In fact, Suzuki–Miyaura coupling reactions of Bromhexine (**1)** and Ambroxol (**4)** with arylboronic acids afforded products **3a–r** (Table 3) and **5a–b** (Table 4) in moderate to high yields. To our delight, no protection of the inherent reactive functional groups (amino and hydroxyl function) is necessary. In addition to the basic starting materials, also the corresponding hydrochlorides (commercially available form of **1** and **4**) can be used in the respective coupling reactions, but typically the salt free ones give slightly higher yields.

As shown in Table 3, a variety of mono– and disubstituted electron–poor or electron–rich arylboronic acids gave the desired arylated derivatives of Bromhexine. Apart from substituted benzene compounds also heteroarylboronic acids led to the desired coupling products (Table 3, entries 9, and 11). All the new compounds could be easily isolated by standard column chromatography and were fully characterized. The tolerance of functional groups and the generality of the procedure were also demonstrated in the coupling reactions of unprotected Ambroxol (**4**) with two boronic acids (Table 4). Both coupling products were obtained without any complication using our standard procedure in high yields.

For the initial evaluation of potential biological activity of the prepared compounds an inhibition test with recombinant wild type GCase (active agent: Imiglucerase) was performed. As shown in Figure 2, all compounds tested showed significant inhibitory effects on the enzyme). Noteworthy, compared to the parent molecule (closed circles), compounds **3i** and **3j** even showed more potent inhibition. These initial biological tests of the compounds suggest a putative medical application for patients with Gaucher disease. In a somewhat counterintuitive approach, enzyme inhibitors have been revealed to elevate activity in the cellular context by stabilising the proteins' mutant, hence abolished, structure. Ambroxol functions as a potent inhibitor for the GCase and mainly compounds **3i** and **3j** display strong inhibitory effect towards the enzyme *in vitro* which makes these substances likely candidates for pharmacological chaperone testing in Gaucher disease.[22]

Table 4: Suzuki–Miyaura coupling products of Ambroxol (5a–b)[a]



4 **5a-b**

Entry	2	4	Ar	Yield of 5 (%)[b]
1	a	a	C_6H_5	70
2	b	b	4–$(MeO)C_6H_4$	73

[a] Reagents and conditions: Ambroxol **4** (1.0 mmol), **2a,b** (3.0 mmol), K_2CO_3 (1M, 2ml) in H_2O, $Pd(OAc)_2$ (5 mol%), S–Phos (ligand **III**, 10 mol%), 1,4–dioxane, 120 °C, 4–6 h. [b] Isolated yields.

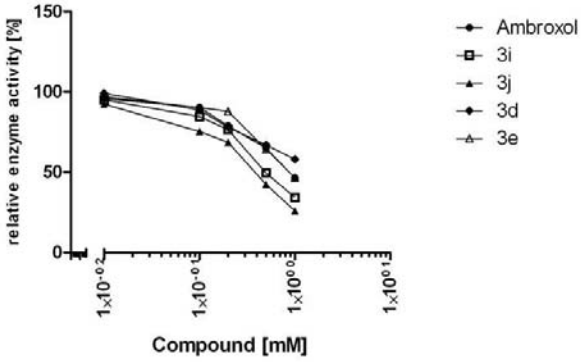


Figure 2. Inhibition of recombinant GCase (Imiglucerase, Genzyme Corporation, Cambridge, MA, USA) by Ambroxol and chosen compounds. The inhibitory curve for Ambroxol at pH 6.7 showed diminishment of activity. Total reduction at 1 mM was 53.7%. Compounds 3d and 3e showed inhibition only at concentrations ≥100 μM. Compounds 3i and 3j were more efficient at the tested concentrations than the lead substance Ambroxol.

3. Conclusion

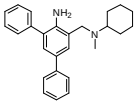
In conclusion, palladium–catalysed Suzuki–Miyaura coupling reactions of Bromhexine and Ambroxol with various aryl– and heteroarylboronic acids are conveniently carried out using a commercially available palladium catalyst system. Twenty potentially bioactive derivatives have been smoothly prepared in moderate to high yields. Electronic and steric factors in the arylboronic acid do not show a significant effect on the reactivity. This synthetic procedure allows for a straightforward access to the target compounds. Most of obtained products can be also considered as functionalized *meta*–terphenyl derivatives, which are of interest for other applications, too.[23]

4. Experimental Section

All reactions were carried out under argon atmosphere. Reactions were monitored by TLC analysis (pre–coated silica gel plates with fluorescent indicator UV_{254}, 0.2 mm) and visualized with 254 nm UV light or iodine. Chemicals were purchased from Aldrich, Fluka, Acros, AlfaAsar, Strem and unless otherwise noted were used without further purification. All compounds were characterized by ^{1}H NMR, ^{13}C NMR, GC–MS, HRMS and IR spectroscopy. ^{1}H spectra were recorded on Bruker AV 300 and AV 400 spectrometers. ^{13}C NMR spectra were recorded at 282 MHz. IR spectra were recorded on FT–IR ALPHA (Bruker) with Platinum–ATR (Bruker). EI (70 eV) mass spectra were recorded on MAT 95XP (Thermo ELECTRON CORPORATION). GC was performed on Agilent 6890 chromatograph with a 30 m HP5 column. HRMS was performed on MAT 95XP (EI) and Agilent 6210 Time–of–Flight LC/MS (ESI). GC–MS was performed on Agilent 5973 chromatograph Mass Selective Detector. All yields reported refer to isolated yields.

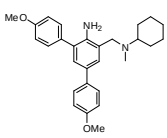
4.1. General procedure of Suzuki couplings reactions (3a–r, 5a–b): The reaction was carried out in an Ace–pressure tube. To a dioxane suspension (3 mL) of 1 (200 mg, 0.53 mmol), arylboronic acids (1.60 mmol), K_2CO_3 (1M in water, 2 ml), $Pd(OAc)_2$ (5 mol%) and ligand III (S–Phos, 10 mol%) were added under argon atmosphere. The pressure tube was fitted with a Teflon cap and heated at 100 °C (TLC control). The mixture was cooled to room temperature and diluted with ethyl acetate. The organic layer was washed with water. After removal of the solvent in vacuum, the coupling products were isolated by column chromatography in hexane/ethyl acetate.

*4.1.1. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–diphenylaniline (**3a**)*



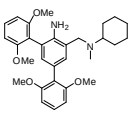
Yield: 145 mg (81%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.50 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.04–1.54 (m, 6H), 1.73 (t, 4H, *J* = 13.7 Hz), 2.09 (s, 3H), 2.04 (t, 1H, *J* = 10.3 Hz), 3.68 (s, 2H), 5.07 (s, 2H, NH_2), 7.12–7.18 (m, 2H), 7.22–7.50 (m, 10H); ^{13}C NMR ($CDCl_3$): δ = 25.9 ($2CH_2$), 26.3 (CH_2), 28.2 ($2CH_2$), 36.3 (CH_3), 58.3 (CH_2), 61.9 (CH), 124.1 (C), 126.0 (CH), 126.2 (2CH), 127.7 (C), 128.2 (CH), 128.6 (2CH), 128.7 (2CH), 129.3 (2CH), 139.8, 141.7, 143.9 (C); GC–MS (EI, 70 eV): *m/z* (%) 370 (100) [M^+]; HRMS (EI): Calc for $C_{26}H_{30}N_2$: 370.24035; found: 370.240754; FTIR (ATR, cm^{-1}): 2955, 2921, 2851, 1616, 1467, 1377, 1226, 1072, 1032, 966, 885, 835, 776, 741, 720, 698, 647, 600, 575, 561, 501.

*4.1.2. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(4–methoxyphenyl)aniline (**3b**)*



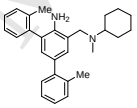
Yield: 108 mg (59%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.25 (solvent ethyl acetate/hexane/TEA 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.01–1.42 (m, 5H), 1.65 (d, 1H, *J* = 12.3 Hz), 2.21 (s, 3H), 3.79 (s, 2H), 3.84 (s, 3H), 3.88 (s, 3H), 5.09 (s, 2H, NH_2), 6.96 (dt, 2H, *J* = 8.90, 4.39 Hz), 7.01 (dt, 2H, *J* = 8.90, 4.40 Hz), 7.22 (d, 1H, *J* = 2.41 Hz), 7.30 (d, 2H, *J* = 2.41 Hz), 7.45 (dt, 2H, *J* = 8.92, 4.41 Hz), 7.51 (dt, 2H, *J* = 8.92, 4.41 Hz); ^{13}C NMR ($CDCl_3$): δ = 25.9 ($2CH_2$), 26.2 (CH_2), 28.1 ($2CH_2$), 36.3 (CH_3), 55.2 ($2OCH_3$), 58.2 (CH_2), 61.9 (CH), 114.0 (2CH), 114.1 (2CH), 127.2 (2CH), 127.6 (2CH), 129.7 (C), 134.4 (2CH), 131.9, 133.9, 143.4, 158.2, 158.6 (C); GC–MS (EI, 70 eV): *m/z* (%) 432 (100) [M^+]; HRMS (ESI): Calc for $C_{28}H_{34}N_2O_2$: 431.2693; found: 431.2692 (M+H); FTIR (ATR, cm^{-1}): 3426, 3256, 2926, 2851, 1736, 1608, 1573, 1510, 1466, 1360, 1281, 1240, 1174, 1107, 1073, 1029, 965, 890, 826, 794, 726, 683, 636, 590, 545, 527, 464, 412.

*4.1.3. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(2,6–dimethoxyphenyl)aniline (**3c**)*



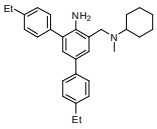
Yield: 183 mg (77%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.51 (solvent ethyl acetate); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.85–1.34 (m, 7H), 1.48–1.55 (m, 2H), 1.72 (t, 1H, *J* = 13.0 Hz), 1.96 (s, 1H), 2.21 (s, 3H), 2.44 (t, 1H, *J* = 11.0 Hz), 3.61 (s, 6H), 3.63 (s, 6H), 3.98 (t, 3H, *J* = 6.74), 6.54 (dd, 4H, *J* = 10.2, 8.41 Hz), 6.96 (q, 2H, *J* = 4.20 Hz), 7.08 (t, 1H, *J* = 8.41 Hz), 7.18 (t, 1H, *J* = 8.31 Hz); ^{13}C NMR ($CDCl_3$): δ = 25.9 ($2CH_2$), 26.3 (CH_2), 28.0 ($2CH_2$), 30.6 (CH), 36.3 (CH_3), 55.9 ($2OCH_3$), 56.0 ($2CH_3$), 60.9 (CH), 64.2 (CH), 104.8 (CH), 104.9 (CH), 116.9, 119.2, 120.4, 121.3 (C), 127.3 (CH), 128.6 (CH), 132.3 (CH), 133.2 (CH), 144.2, 157.8, 158.4 (C); GC–MS (EI, 70 eV): *m/z* (%) 490 (12) [M^+], 407 (100); HRMS (EI): Calc for $C_{30}H_{38}N_2O_4$: 490.2826; found: 490.2822 (M+H); FTIR (ATR, cm^{-1}): 3433, 3263, 2926, 2851, 1736, 1616, 1583, 1467, 1430, 1280, 1243, 1170, 1102, 1030, 966, 882, 779, 725, 607, 557.

*4.1.4. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(2–methylphenyl)aniline (**3d**)*



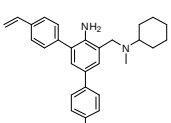
Yield: 148 mg (77%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.50 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.98–1.53 (m, 6H), 1.72 (t, 4H, *J* = 13.8 Hz), 2.09 (s, 3H), 2.29 (s, 3H), 2.31 (s, 3H), 2.40 (t, 1H, *J* = 11.7 Hz), 3.67 (s, 2H), 5.06 (s, 2H, NH_2), 6.97 (d, 1H, *J* = 7.59 Hz), 7.06 (d, 1H, *J* = 6.70 Hz), 7.15–7.29 (m, 8H); ^{13}C NMR ($CDCl_3$): δ = 21.4 (CH_3), 21.5 (CH_3), 25.9 ($2CH_2$), 26.3 (CH_2), 28.2 ($2CH_2$), 36.3 (CH_3), 58.3 (CH_2), 61.9 (CH), 123.4 (CH), 123.9 (C), 126.3 (2CH), 126.8 (CH), 127.1 (CH), 127.8 (CH), 128.1 (CH), 128.5 (CH), 128.6 (CH), 130.0 (CH), 138.1, 138.3, 139.6, 141.2, 143.8 (C); HRMS (ESI): Calc for $C_{28}H_{35}N_2$: 399.27948; found: 399.28053 (M+H); HRMS (EI): Calc for $C_{28}H_{34}N_2$: 398.2716; found: 398.2721; FTIR (ATR, cm^{-1}): 3430, 3255, 3026, 2924, 2851, 2787, 1665, 1604, 1468, 1448, 1378, 1338, 1293, 1260, 1203, 1159, 1093, 1033, 966, 878, 835, 780, 727, 701, 650, 630, 609, 589, 523, 466, 436.

*4.1.5. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(4–ethylphenyl)aniline (**3e**)*



Yield: 173 mg (76%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.50 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.02–1.28 (m, 11H), 1.53 (d, 1H, *J* = 12.8 Hz), 1.73 (t, 4H, *J* = 14.3 Hz), 2.09 (s, 3H), 2.41 (t, 1H, *J* = 11.1 Hz), 2.53–2.65 (m, 4H), 3.67 (s, 2H), 5.05 (s, 2H, NH_2), 7.11–7.18 (m, 4H), 7.21 (s, 1H), 7.24 (d, 1H, *J* = 2.27 Hz), 7.33 (dt, 2H, *J* = 8.31, 4.13 Hz), 7.40 (dt, 2H, *J* = 8.31, 4.15 Hz); ^{13}C NMR ($CDCl_3$): δ = 15.5 (CH_3), 15.6 (CH_3), 25.9 (CH_2), 26.3 (CH_2), 28.2 (CH_2), 28.4 (CH_2), 28.6 (CH_2), 36.3 (CH_3), 58.3 (CH_2), 61.9 (CH), 115.1, 123.8 (C), 126.2 (2CH), 127.7 (CH), 128.0 (CH), 128.2 (2CH), 128.2 (2CH), 129.3 (2CH), 137.0, 138.7 (C), 142.1 (2C), 143.1 (2C), 143.8 (2C); GC–MS (EI, 70 eV): *m/z* (%) 426 (100) [M^+], 407 (100); HRMS (ESI): Calc for $C_{30}H_{39}N_2$: 427.3108; found: 427.3112 (M+H); FTIR (ATR, cm^{-1}): 3431, 3257, 3021, 2961, 2925, 2851, 1662, 1612, 1510, 1468, 1450, 1409, 1375, 1336, 1293, 1257, 1203, 1182, 1158, 1114, 1048, 1020, 965, 891, 826, 785, 683, 590, 545, 517, 422.

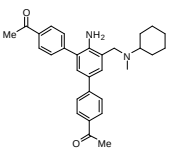
*4.1.6. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(4–ethenylphenyl)aniline (**3f**)*



Yield: 96 mg (42%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.60 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99–1.43 (m, 6H), 1.65 (d, 1H, *J* = 12.7 Hz), 1.84 (t, 4H, *J* = 12.7 Hz), 2.20 (s, 3H), 2.51 (t, 1H, *J* = 11.7 Hz), 3.78 (s, 2H), 5.01–5.44 (m, 4H), 5.79 (t, 2H, *J* = 16.4 Hz), 6.73 (t, 1H, *J* = 11.1 Hz), 6.80 (t, 1H, *J* = 11.1 Hz), 7.28 (d, 1H, *J* = 2.15 Hz), 7.36 (d, 1H, *J* = 2.15 Hz), 7.42–7.58 (m, 8H); ^{13}C NMR ($CDCl_3$): δ = 26.0 (CH_2), 26.4 (CH_2), 28.3 (CH_2), 36.4 (CH_3), 58.4 (CH_2), 62.1 (CH), 113.2 (CH_2), 114.0 (CH_2), 126.3 (2CH), 126.6 (2CH),

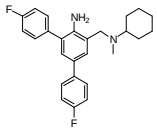
126.7 (2CH), 127.6 (CH), 128.1 (CH), 129.5 (2CH), 135.5 (2C), 136.5 136.6 (C), 139.2, 140.6 (C), 144.1 (2C); HRMS (ESI): Calc for $C_{30}H_{35}N_2$: 423.2794; found: 423.2806 $[M+H]^+$; FTIR (ATR, cm^{-1}): 3430, 3254, 3021, 2925, 2851, 1665, 1607, 1509, 1468, 1450, 1409, 1390, 1337, 1292, 1234, 1204, 1158, 1113, 1054, 1032, 987, 965, 892, 832, 786, 683, 610, 5422.

*4.1.7. 1–{4–[5–(4–Acetylphenyl)–2–amino–3–{[cyclohexyl(methyl)amino]methyl}phenyl]phenyl}ethan–1–one (**3g**)*



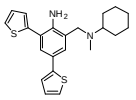
Yield: 143 mg (73%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.33 (solvent ethyl acetate/hexane3:7); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.08–1.45 (m, 7H), 1.55–1.75 (m, 2H), 1.76–1.96 (m, 4H), 2.11–2.32 (m, 3H), 2.62 (s, 3H), 2.66 (s, 3H), 3.81 (s, 2H), 7.34 (d, 1H, *J* = 3.00 Hz), 7.38 (s, 1H), 7.63 (t, 4H, *J* = 8.50 Hz), 7.98 (dt, 2H, *J* = 8.75, 3.38 Hz), 8.06 (dt, 2H, *J* = 8.75, 3.38 Hz); ^{13}C NMR ($CDCl_3$):δ = 25.9 ($2CH_2$), 26.2 (CH_2), 26.6 (CH_3), 26.7 (CH_3), 28.1 (CH_2), 28.2 (CH_2), 29.6 (CH_2), 29.7 (CH_2), 36.4 (CH_3), 62.1 (CH), 126.1 (2CH), 129.0 (CH), 129.2 (C), 129.5 (CH), 134.5, 134.9, 135.9, 136.4, 145.0, 145.5 (C), 197.7 (CO); HRMS (ESI): calc for $C_{30}H_{35}N_2O_2$ $[M+H]^+$: 455.2693; found: 455.2704. IR (ATR): $\tilde{\nu}$ = 3432, 3191, 2925, 2851, 2789, 1674, 1596, 1559, 1510, 1469, 1402, 1390, 1355, 1264, 1182, 1113, 1078, 1014, 955, 893, 830, 766, 731, 684, 589, 471, 397.

*4.1.8. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(4–fluorophenyl)aniline (**3h**)*



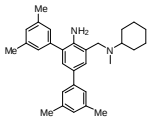
Yield: 160 mg (74%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.40 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.00–1.32 (m, 5H), 1.54 (d,1H, *J* = 11.4 Hz), 1.74 (t, 4H, *J* = 12.5 Hz), 2.10 (s, 3H), 2.15 (t, 1H, *J* = 11.4 Hz), 3.67 (s, 2H), 5.02 (s, 2H, NH_2), 6.94–7.16 (m, 6H), 7.34–7.45 (m, 4H); ^{13}C NMR ($CDCl_3$):δ = 25.9 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 36.4 (CH_3), 58.3 (CH_2), 62.1 (CH), 115.6 (CH), 124.2, 127.0 (C), 127.7 (2CH), 127.8 (2CH), 128.2 (2CH), 129.1 (C), 130.9 (2CH), 131.1 (2CH), 135.4, 137.2, 143.9 (C), 161.9 (dd, CF, *J* = 244.7, 18.0 Hz); GC–MS (EI, 70 eV): *m/z* (%) 406 (17) $[M^+]$, 323 (100); HRMS (ESI): calc for $C_{26}H_{29}F_2N_2$ $[M+H]^+$: 407.2293; found: 407.2301; FTIR (ATR, cm^{-1}): 3433, 3254, 2926, 2852, 1614, 1508, 1468, 1403, 1381, 1293, 1218, 1156, 1125, 1094, 1073, 1032, 965, 891, 829, 812, 801, 767, 720, 683, 609, 585, 556, 527.

*4.1.9. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(thiophen–2–yl)aniline (**3i**)*



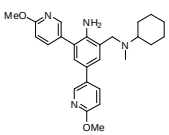
Yield: 135 mg (67%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.64 (solvent ethyl acetate/hexane 0.5:9.5); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99–1.29 (m, 5H), 1.54 (d,1H, *J* = 13.1 Hz), 1.73 (t, 4H, *J* = 13.7 Hz), 2.09 (s, 3H), 2.39 (t, 1H, *J* = 11.1 Hz), 3.64 (s, 2H), 5.41 (s, 2H, NH_2), 6.93 (d, 1H, *J* = 3.60 Hz), 7.02–7.08 (m, 3H), 7.10–716 (m, 2H); ^{13}C NMR ($CDCl_3$):δ = 25.8 ($2CH_2$), 26.3 (CH_2), 28.2 ($2CH_2$), 36.3 (CH_3), 58.1 (CH_2), 61.9 (CH), 120.0 (C), 121.2 (CH), 123.0 (CH), 123.5 (2C), 124.1 (C), 125.3 (CH), 126.1 (CH), 127.5 (2CH), 127.8 (CH), 127.9 (CH), 140.7, 144.8 (C); GC–MS (EI, 70 eV): *m/z* (%) 382 (33) $[M^+]$, 299 (100); HRMS (ESI): calc for $C_{22}H_{27}S_2N_2$ $[M+H]^+$: 383.1610; found: 383.1621; FTIR (ATR, cm^{-1}): 3423, 3218, 2924, 2850, 1735, 1613, 1472, 1449, 1427, 1345, 1321, 1298, 1229, 1180, 1124, 1080, 1026, 964, 883, 841, 816, 785, 686, 599, 565, 541, 489.

*4.1.10. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(3,5–dimethylphenyl)aniline (**3j**)*



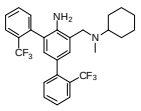
Yield: 133 mg (59%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.22 (solvent ethyl acetate/hexane 1:9); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04–1.31 (m, 6H), 1.56 (d,1H, *J* = 12.4 Hz), 1.75 (t, 4H, *J* = 13.5 Hz), 2.10 (s, 3H), 2.27 (s, 6H), 2.29 (s, 6H), 2.41 (s, 1H), 3.67 (s, 2H), 5.04 (s, 1H), 6.82 (s, 1H), 6.91 (s, 1H), 7.04 (s, 2H), 7.11 (s, 2H), 7.15 (d, 1H, *J* = 2.20 Hz), 7.23 (s, 1H); ^{13}C NMR ($CDCl_3$):δ = 21.4 ($2CH_3$), 21.5 ($2CH_3$), 26.0 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 36.4 (CH_3), 58.4 (CH_2), 62.1 (CH), 124.3 (2CH), 125.1 (2CH), 127.1 (2CH), 127.8 (CH), 128.1 (CH), 128.3, 130.1 (C), 138.1 (2C), 138.3 (2C), 139.6, 141.5, 143.8, 151.9 (C); GC–MS (EI, 70 eV): *m/z* (%) 426 (19) $[M^+]$, 343 (100); HRMS (ESI): calc for $C_{30}H_{39}N_2$ $[M+H]^+$: 427.3107; found: 427.3116; FTIR (ATR, cm^{-1}): 3427, 3018, 2923, 1600, 1449, 1376, 1346, 1297, 1261, 1159, 1073, 1034, 965, 891, 844, 785, 756, 731, 702, 665, 634, 600, 536, 463, 432, 415, 397, 381.

*4.1.11. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(6–methoxypyridin–3–yl)aniline (**3k**)*



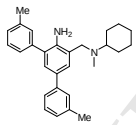
Yield: 133 mg (78%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.55 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04–1.78 (m, 6H), 1.56 (d, 1H, *J* = 11.4 Hz), 1.74 (t, 4H, *J* = 12.1 Hz), 2.11 (s, 3H), 2.40 (t, 1H, *J* = 11.4 Hz), 3.67 (s, 2H), 3.88 (s, 3H), 3.92 (s, 3H), 6.69 (d, 1H, *J* = 8.58 Hz), 6.76 (d, 1H, J = 8.58), 7.10 (s, 2H), 7.62–7.69(m, 2H); ^{13}C NMR ($CDCl_3$):δ = 25.9 ($2CH_2$), 26.3 (CH_2), 28.2 ($2CH_2$), 36.4 (CH_3), 53.5 (OCH_3), 53.6 (OCH_3), 58.3 (CH_2), 61.9 (CH), 110.6 (CH), 110.9 (CH), 124.4 (C), 127.5 (CH), 128.1 (CH), 130.1 (CH), 136.9 (CH), 139.7 (CH), 144.2 (CH), 144.5 (C), 147.1 (CH), 162.9, 163.4 (C); HRMS (ESI): calc for $C_{26}H_{33}N_4O_2$ $[M+H]^+$: 433.2598; found: 433.2597; FTIR (ATR, cm^{-1}): 3427, 3257, 3012, 2926, 2851, 2789, 1601, 1562, 1492, 1464, 1423, 1358, 1278, 1174, 1124, 1076, 1022, 965, 885, 827, 756, 734, 690, 647, 626, 598, 566, 539, 476, 420.

*4.1.12. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(2–(trifluoromethyl)phenyl)aniline (**3l**)*



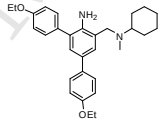
Yield: 184 mg (69%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.62 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.09–1.40 (m, 6H), 1.57–1.65 (m, 1H), 1.75–1.83 (m, 4H), 2.19 (s, 3H), 2.38–2.48 (m, 1H), 3.63 (d, 1H, *J* = 14.1 Hz), 3.84 (d, 1H, *J* = 14.1 Hz), 4.62 (s, 1H), 6.94 (s, 1H), 7.03 (s, 1H), 7.36–7.62 (m, 6H), 7.71 (d, 1H, *J* = 7.92 Hz), 7.80 (d, 1H, *J* = 7.92 Hz); ^{13}C NMR ($CDCl_3$):δ = 25.9, 26.0, 27.1, 29.1, 30.8 (d, *J* = 13.4 Hz), 36.3, 57.9, 61.0, 64.4, 122.4 (d, *J* = 31.0 Hz), 122.7, 124.3, 126.0 (d, *J* = 5.20 Hz), 126.6, 127.8, 128.1, 128.7 (d, *J* = 29.6 Hz), 129.4, 129.9 (d, *J* = 29.6 Hz), 130.7 (d, *J* = 2.92 Hz), 131.1, 131.9, 132.4, 132.8, 139.6 (d, *J* = 271.9 Hz), 144.3; GC–MS (EI, 70 eV): *m/z* (%) 506 (7) $[M^+]$, 423 (100); HRMS (EI): calc for $C_{28}H_{28}N_2F_6$: 506.2151; found: 506.2156; FTIR (ATR, cm^{-1}): 3444, 3258, 3063, 3034, 2928, 2853, 2793, 2669, 1738, 1715, 1617, 1604, 1588, 1575, 1493, 1469, 1446, 1421, 1380, 1361, 1347, 1335, 1311, 1260, 1225, 1204, 1160, 1125, 1106, 1078, 1051, 1033, 988, 969, 957, 892, 860, 854, 835, 766, 756, 736, 691, 663, 653, 693, 611, 597, 567, 555, 543.

*4.1.13. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(3–methylphenyl)aniline (**3m**)*



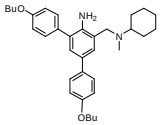
Yield: 151 mg (72%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.60 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.99–1.33 (m, 6H), 1.55 (d, 1H, *J* = 11.6 Hz), 1.74 (t, 4H, *J* = 13.5 Hz), 2.10 (s, 3H), 2.31 (s, 6H), 2.33 (s, 3H), 2.37–2.45 (m, 1H), 3.68 (s, 2H), 5.04 (s, 2H), 6.97–7.30 (m, 10H); ^{13}C NMR ($CDCl_3$):δ = 21.4 (CH_3), 21.5 (CH_3), 25.9 ($2CH_2$), 26.3 (CH_2), 28.2 ($2CH_2$), 36.3 (CH_3), 58.3 (CH_2), 61.9 (CH), 123.4 (CH), 123.9 (C), 126.3 (CH), 127.1 (CH), 127.7 (CH), 128.5 (CH), 128.6 (CH), 129.9 (CH), 130.0, 138.1, 138.3, 139.6, 141.2, 143.7 (C); GC–MS (EI, 70 eV): *m/z* (%) 398 (16) $[M^+]$, 315 (100); HRMS (ESI): calc for $C_{28}H_{35}N_2$ $[M+H]^+$: 399.2794; found: 399.2797; FTIR (ATR, cm^{-1}): 3433, 3255, 3025, 2924, 2851, 2787, 1604, 1508, 1468, 1449, 1378, 1292, 1260, 1203, 1159, 1125, 1094, 1057, 1033, 966, 907, 879, 835, 812, 780, 727, 701, 648, 630, 609, 585, 556.

*4.1.14. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(4–ethoxyphenyl)aniline (**3n**)*



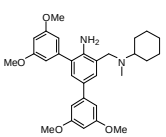
Yield: 165 mg (68%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.40 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.04–1.37 (m, 6H), 1.44 (q, 6H, *J* = 14.1 Hz), 1.64 (d, 1H, *J* = 13.8 Hz), 1.83 (t, 4H, *J* = 13.5 Hz), 2.19 (s, 3H), 2.44–2.53 (m, 1H), 3.75 (s, 2H), 4.03–4.28 (m, 5H), 6.82-6.93 (m, 4H), 7.12 (d, 1H, *J* = 2.29 Hz), 7.20 (d, 1H, *J* = 2.29 Hz), 7.31-7.43 (m, 4H); ^{13}C NMR ($CDCl_3$):δ = 14.9 ($2CH_3$), 26.0 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 36.4 (CH_3), 58.4 (CH_2), 62.0 (CH), 63.5 ($2CH_2$), 114.7 , 114.8, 115.4, 124.0, 127.3, 127.6, 127.6 (CH), 127.9 (2C), 128.9 (CH), 129.8 (2C), 130.5 (CH), 130.9 (CH), 133.8, 143.4, 157.7, 158.1 (C); HRMS (ESI): calc for $C_{30}H_{39}N_2O_2$ $[M+H]^+$: 459.3006; found: 459.3012; FTIR (ATR, cm^{-1}): 3427, 3253, 3033, 2976, 2925, 2851, 1679, 1606, 1509, 1466, 1390, 1357, 1277, 1237, 1173, 1114, 1073, 1043, 964, 921, 890, 824, 802, 726, 686, 637, 611, 591, 561, 527, 411, 378.

*4.1.15. 2–4–Bis(4–butoxyphenyl)–6–{[cyclohexyl(methyl)amino]methyl}–aniline (**3o**)*



Yield: 218 mg (80%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.30 (solvent ethyl acetate/hexane 1:4); ^1H NMR (300 MHz, $CDCl_3$): δ = 0.90 (t, 3H, *J* = 7.35 Hz), 0.92 (t, 3H, *J* = 7.35 Hz), 0.99–1.31 (m, 5H), 1.43 (hept, 4H), 1.55 (d, *J* = 12.2 Hz), 1.64–1.79 (m, 8H), 2.10 (s, 3H), 2.42 (t, 1H, *J* = 10.7 Hz), 3.67 (s, 2H), 3.91 (q, 4H, *J* = 6.60 Hz), 4.32 (s, 2H), 6.80- 6.90 (m, 4H), 7.10 (d, 1H, *J* = 2.23 Hz), 7.19 (d, 1H, *J* = 2.23 Hz), 7.29-7.40 (m, 4H); ^{13}C NMR ($CDCl_3$):δ = 13.9 ($2CH_3$), 19.9 ($2CH_2$), 25.9 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 31.4 ($2CH_2$), 36.4 (CH_3), 58.2 (CH_2), 62.0 (CH), 67.8 ($2CH_2$), 114.7 (2CH), 114.8 (2CH), 123.8 (C), 127.3 (2CH), 127.6 (CH), 127.7 (CH), 127.9, 129.8 (C), 130.4 (2CH), 131.8, 133.8, 143.5, 157.9, 158.3 (C); GC–MS (EI, 70 eV): *m/z* (%) 514 (24) $[M^+]$, 403 (100); HRMS (ESI): calc for $C_{34}H_{47}N_2O_2$ $[M+H]^+$: 515.3632; found: 515.3636; FTIR (ATR, cm^{-1}): 3429, 3260, 3033, 2926, 2853, 1608, 1572, 1509, 1464, 1380, 1345, 1278, 1240, 1173, 1110, 1070, 1026, 1009, 968, 890, 826, 726, 685, 624, 594, 562, 528, 414.

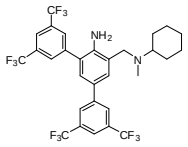
*4.1.16. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(3,5–dimethoxyphenyl)aniline (**3p**)*



Yield: 283 mg (58%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.61 (solvent ethyl acetate/Hexane 1:9); ^1H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.33 (m, 5H), 1.45–1.58 (m, 1H), 1.72 (t, 4H, *J* = 13.0 Hz), 2.10 (s, 3H), 2.40 (t, 1H, *J* = 10.7 Hz), 3.67 (s, 2H), 3.73 (s, 6H), 3.74 (s, 6H), 6.30 (t, 1H, *J* = 2.36 Hz), 6.38 (t, 1H, *J* = 2.36 Hz), 6.56 (d, 2H, *J* = 2.25 Hz), 6.62 (d,

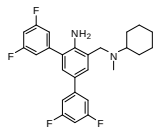
2H, *J* = 2.25 Hz), 7.16 (d, 1H, *J* = 2.58 Hz), 7.26 (d, 1H, *J* = 2.58 Hz); ^{13}C NMR ($CDCl_3$): δ = 26.0 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 36.4 (CH), (CH_3), 55.4 ($2OCH_3$), 55.5 ($2CH_3$), 58.4 (CH), 98.3 (CH), 99.6 (CH), 104.6 (2CH), 107.2 (2CH), 123.9 (C), 127.5 (C), 127.7 (C), 128.4 (2CH), 129.7 (2C), 141.7 (C), 143.5 (C), 144.3 (C), 161.1 (d, C, *J* = 4.75 Hz); HRMS (ESI): Calc for $C_{30}H_{39}N_2O_4$: 491.2904; found: 491.2902 $(M+H)^+$; FTIR (ATR, cm^{-1}): 3430, 3264, 2927, 2851, 1735, 1589, 1452, 1418, 1393, 1364, 1336, 1295, 1257, 1202, 1150, 1084, 1061, 991, 949, 892, 830, 755, 735, 695, 648, 537, 469, 421.

*4.1.17. 2,4–Bis[3,5–bis(trifluoromethyl)phenyl]–6–{[cyclohexyl(methyl)amino]methyl}–aniline (**3q**)*



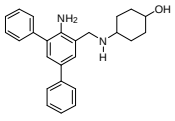
Yield: 389 mg (60%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.26 (solvent ethyl acetate/Hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.13–1.45 (m, 5H), 1.67 (d, 1H, *J* = 12.9 Hz), 1.88 (t, 4H, *J* = 13.3 Hz), 2.24 (s, 3H), 2.54 (t, 1H, *J* = 12.1 Hz), 3.86 (s, 3H), 5.36 (s, 2H), 7.34 (q, 2H, *J* = 12.6 Hz), 7.79 (s, 1H), 7.94 (s, 1H), 8.00 (d, 4H, *J* = 7.39 Hz); ^{13}C NMR ($CDCl_3$): δ = 25.9 ($2CH_2$), 26.3 (CH_2), 28.3 ($2CH_2$), 36.4 (CH_3), 58.2 (CH_2), 62.3 (CH), 119.7–119.9 (m, CH), 121.3–121.5 (m, CH), 123.3 (d, *J* = 272.6 Hz, $2CF_3$), 123.5 (d, *J* = 272.6 Hz, $2CF_3$), 126.2 (d, *J* = 3.72 Hz, 2CH), 127.3 (CH), 127.8 (CH), 128.9 (d, *J* = 16.7 Hz, C), 129.3 (CH), 129.7 (d, *J* = 3.72 Hz, 2CH); GC–MS (EI, 70 eV): *m/z* (%) 642 (8) $[M^+]$, 571 (48), 560 (25), 559 (100), 530 (35), 112 (29); HRMS (EI): Calc for $C_{30}H_{36}N_2F_{12}$: 642.1898; found: 642.1893 (M+H); FTIR (ATR, cm^{-1}): 3456, 3271, 2934, 2859, 1492, 1453, 1366, 1272, 1224, 1126, 1070, 1048, 990, 965, 942, 900, 877, 844, 783, 755, 729, 709, 699, 681, 663, 605, 558, 541, 519, 472, 411, 393.

*4.1.18. 2–{[Cyclohexyl(methyl)amino]methyl}–4,6–bis(3,5–difluorophenyl)aniline (**3r**)*



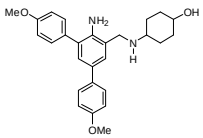
Yield: 300 mg (68%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.51 (solvent ethyl acetate/Hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.99–1.27 (m, 5H), 1.54 (d, 1H, *J* = 12.3 Hz), 1.73 (t, 4H, *J* = 12.3 Hz), 2.16 (s, 3H), 2.37 (t, 1H, *J* = 12.3 Hz), 3.65 (s, 2H), 5.26 (s, 2H), 6.53–6.61 (m, 1H), 6.66–6.74 (m, 1H), 6.68–6.99 (m, 4H), 7.13 (t, 4H, *J* = 2.30 Hz); ^{13}C NMR ($CDCl_3$): δ = 25.9 ($2CH_2$), 26.4 (CH_2), 28.3 ($2CH_2$), 36.4 (CH_3), 58.3 (CH_2), 62.1 (CH), 101.3 (t, *J* = 25.5 Hz, CH), 102.8 (t, *J* = 25.5 Hz, CH), 108.8 (d, *J* = 25.4 Hz, CH), 108.9 (d, *J* = 9.90 Hz, CH), 112.2 (d, *J* = 25.5 Hz, CH), 112.3 (d, *J* = 9.90 Hz, CH), 124.4 (CH), 124.5 (C), 127.4 (t, *J* = 2.65, C), 128.7 (CH), 142.7 (d, *J* = 9.49 Hz, C), 144.3 (t, *J* = 9.49 Hz, C), 144.9 (2C), 163.3 (dd, *J* = 249.5, 6.18 Hz, 2CF), 163.4 (dd, *J* = 249.5, 6.18 Hz, 2CF), GC–MS (EI, 70 eV): *m/z* (%) 442 (13) $[M^+]$, 371 (41), 359 (100), 330 (58), 315 (40), 112 (28); HRMS (EI): Calc for $C_{26}H_{26}N_2F_4$: 442.2026; found: 442.2022 (M+H); FTIR (ATR, cm^{-1}): 3441, 3255, 2928, 2853, 1618, 1590, 1491, 1452, 1428, 1396, 1365, 1325, 1240, 1170, 1140, 1078, 1034, 986, 949, 893, 849, 783, 757, 702, 709, 640, 614, 568, 527, 509, 484.

*4.1.19. 4–{[(2–Amino–3,5–diphenyl)methyl]amino}cyclohexan–1–ol (**5a**)*



Yield: 131 mg (70%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.39 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.09–1.31 (m, 5H), 1.86–2.00 (m, 3H), 2.01 (s, 1H), 2.44–2.55 (m, 1H), 3.49–3.64 (s, 2H), 3.87 (s, 2H), 4.90 (s, 2H), 7.19–7.34 (m, 6H), 7.37–7.43 (m, 4H), 7.46–7.51 (m, 2H); ^{13}C NMR ($CDCl_3$):δ = 30.9 (CH_2), 33.8 ($2CH_2$), 50.8 ($2CH_2$), 55.7 (CH), 70.3 (CH), 126.2 (CH), 126.3 (2CH), 127.2 (CH), 127.8 (CH), 128.2 (CH), 128.6 (2CH), 128.8 (2CH), 129.2 (2CH), 130.3, 139.4, 140.9 (C), 143.5 (C), 145.0 (C); GC–MS (EI, 70 eV): *m/z* (%) 372 (21) $[M^+]$, 273 (100); HRMS (ESI): calc for $C_{25}H_{29}N_2O$ $[M+H]^+$: 373.2591; found: 373.2597; FTIR (ATR, cm^{-1}): 3337, 3055, 3028, 2926, 2853, 1733, 1598, 1463, 1439, 1370, 1241, 1070, 964, 884, 807, 759, 696, 647, 606, 496.

*4.1.20. 4–{[(2–Amino–3,5–bis(4–methoxyphenyl)phenyl]methyl}amino)cyclohexan–1–ol (**5b**)*



Yield: 158 mg (73%); yellow viscous oil; (from ethyl acetate/hexane); R_f = 0.30 (solvent ethyl acetate/hexane 1:4); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 0.77–0.99 (m, 1H), 1.07–1.32 (m, 6H), 1.87–2.01 (m, 4H), 2.46–2.56 (m, 1H), 3.49–3.59 (m, 1H), 3.75 (s, 3H), 3.79 (s, 3H), 3.85 (s, 2H), 4.77 (s, 2H), 6.83–6.94 (m, 4H), 7.19–7.21 (m, 2H), 7.29–7.43 (m, 4H); ^{13}C NMR ($CDCl_3$):δ = 30.1 ($2CH_2$), 33.7 ($2CH_2$), 55.4 (OCH_3), 55.8 (CH), 70.5 (CH), 114.2 (2CH), 114.3 (2CH), 127.4 (2CH), 127.9 (C), 128.4 (CH), 128.9 (CH), 130.4 (2CH), 130.5, 131.6, 133.5, 143.1, 158.5, 158.9 (C); HRMS (ESI): calc for $C_{27}H_{33}N_2O_3$ $[M+H]^+$: 433.2485; found: 433.4958; FTIR (ATR, cm^{-1}): 3331, 2922, 2852, 1608, 1512, 1460, 1400, 1282, 1244, 1177, 1109, 1077, 1031, 964, 901, 830, 795, 722, 592, 549, 527, 485.

Glucocerebrosidase inhibition assay

Forty units of recombinant Glucocerebrosidase (Cerezyme, Genzyme Corporation, Cambridge, MA, USA) were dissolved in citrate phosphate puffer (pH 6.7) and mixed with increasing compound concentrations. Reactions were started by the addition of 4MU–b–Glc (Sigma, 1 mM final concentration) and the mixture was incubated for 15 minutes in a 37°C water bath under slight agitation. The reaction was stopped using glycine NaOH buffer (pH 10.5) and recorded with a fluorescent plate reader (Tecan, Männedorf, Switzerland) at a wave length of 466 nm.

Acknowledgements

We thank the State of Mecklenburg–Western Pomerania, the BMBF (Bundesministerium für Bildung und Forschung), the Deutsche Forschungsgemeinschaft (Graduiertenkolleg 1213 and Leibniz prize) and the Fonds der Chemischen Industrie for financial support. We thank our analytical department for their excellent technical and analytical support.

References and notes

1. Gent, M.; Knowlson, P.A.; Prime, F. J. *Lancet* **1969**, *294*, 1094–1096.
2. (a) Latli, B.; Hrapchak, M.; Switeck, H–K.; Retz, D. M.; Krishnamurthy, D.; Senanayake, C. H. *J. Label Compd. Radiopharm.* **2010**, *53*, 15–23; (b) Lapenna, D.; Ciafani, G.; Pierdomenico, S. D.; Neri, M.; Giamberardino, M. D.; Cuccurullo, F. *Bio. Pharm.* **2007**, *74*, 265–272.
3. (a) Kopitar, Z.; Jauch, R.; Hankwitz, R.; Pelzer, H. *Eur. J. Pharm.* **1973**, *21*, 6–10; (b) Schraven, E.; Koss, F. W.; Keck, J.; Beisenherz, G. *Eur. J. Pharmacol.* **1967**, *1*, 445–451.
4. Maegawa, G. H. B.; Tropak, M. B.; Buttner, J. D.; Rigat, B. A.; Fuller, M.; Pandit, D.; Tang, L.; G. Kornhaber, J.; Hamuro, Y.; Clarke, J. T. R.; Mahuran, D. J. *J. Bio. Chem.* **2009,** *284*, 23502–23516.
5. Gremmel, J.–F. *J. Vet. Pharmacol. Therap.* **2010**, *27*, 219–225.
6. Nobata, N.; Fujimura, M.; Ishiura, Y.; Nakao, S. *J. Clin. Exp. Med.* **2006**, *6*, 79–83.
7. Meijer, L. A.; Verstegen, J. C. M.; Bull, S.; Fink–Gremmels, J. *J. Vet. Pharmacol. Ther*. **2004**, *27*, 219–225.
8. (a) Gibbs, B. F.; Schmutzler, W.; Vollrath, I. B.; Brosthardt, P.; Braam, U.; Wolff, H. H.; Klarwasser, G. Z. *Inflamm. Res*. **1999**, *48*, 86–93; (b) Heath, M. F.; Jacobson, W. *Lungs* **1985**, *163*, 337–344.
9. Langlands, J. H. M.; *Lancet* **1970**, *295*, 448–450.
10. For reviews see: (a) Malerba, M.; Ragnoli, B. *Expert Opinion on Drug Metabolism & Toxicology* **2008**, *4*, 1119–1129; (b) Beeh, K. M.; Beier, J.; Esperaster, A.; Paul, L. D. *Eur. J. Med. Res*. **2008**, *13*, 557–562; (c) Tsujimoto, T.; Kawaratani, H.; Yoshiji, H.; Uemura, M.; Fukui, H. *Current Drug Abuse Reviews* **2008**, *1*, 197–202; (d) Weiser, T.; *CNS Neuroscience & Therapeutics* **2008**, *14*, 17–24.
11. (a) Ulas, M. M.; Hizarci, M.; Kunt, A.; Ergun, K.; Kocabeyoglu, S. S.; Korkmaz, K.; Lafci, G.; Gedik, S.; Cagli, K. *J. Cardiovasc. Pharmacol*. **2008**, *52*, 518–523; (b) Gaida, W.; Klinder, K.; Arndt, K.; Weiser, T. *Neuropharm*. **2005**, *49*, 1220–1227.
12. Felix, K.; Pairet, M.; Zimmermann, R. *Life Sci.* **1996**, *59*, 1141–1147.
13. Pfeifer, S.; Zissel, G.; Kienast, K. *Eur. J. Med. Res*. **1997,** *2*, 129–132.
14. Meijer, L. A.; Verstegen, J. C. M.; Bull, S.; Gremmel, J. F. *J. Vet. Pharmacol. Therap.* **2010**, *27*, 219–225.
15. Maegawa, G. H. B.; Tropak, M. B.; Buttner, J. D.; Rigat, B. A.; Fuller, M.; Pandit, D.; Tang, L.; Kornhaber, G. J.; Hamuro, Y.; Clarke, J. T. R.; Mahuran, D. J. *J. Biol. Chem.* **2009,** *284*, 23502–23516.
16. (a) Wu, X.–F.; Neumann, H.; Beller, M. *Chem. Soc. Rev*. **2011**, *40*, 4986–5009; (b) Wu, X.–F.; Neumann, H.; Beller, *Angew. Chem. Int. Ed*. **2010**, *49*, 5284–5288; *Angew. Chem.* **2010**, *122*, 5412–5416; (c) Mangu, N.; Spannenberg, A.; Beller, M.; Tse, M.–K. *Synlett* **2010**, *2*, 211–214; (d) Pews–Davtyan, A.; Tillack, A.; Ortinau, S.; Rolfs, A.; Beller, M. *Org. Biomol. Chem*. **2008**, *6*, 992–997; (e) Schwarz, N.; Pews–Davtyan, A.; Alex, K.; Tillack, A.; Beller, M. *Synthesis* **2007**, *23*, 3722–3730; (f) Zapf, A.; Beller, M. *Chem. Commun.* **2005**, 431–440; (g) Zapf, A.; Jackstell, R.; Rataboul, F.; Riermeier, T.; Monsees, A.; Fuhrmann, C.; Shaikh, N.; Dingerdissen, U.; Beller, M. *Chem. Commun.* **2004**, 38–39; (h) Reimann, S.; Sharif, M.; Hein, M.; Villinger, A.; Wittler, K.; Ludwig, R.; Langer, P. *Eur. J. Org. Chem*. **2012**, 604; (i) Sharif, M.; Zeeshan, M.; Reimann, S.;Villinger, A.; Langer, P. *Tetrahedron Lett.* **2010**, *51*, 2810; (j) Sharif, M.; Reimann, S.; Villinger, A.; Langer, P. *Synlett* **2010**, 913; (k) Munawar Hussain,

Dhafer Saber Zinad, Ghazwan Ali Salman, Muhammad Sharif, Alexander Villinger, Peter Langer*, *Synlett.* **2010**, 276; (l), Muhammad Sharif, Sebastian Reimann, Kai Wittler, Leif R. Knöpke, Annette-E. Surkus, Christian Roth, Alexander Villinger, Ralf Ludwig,* Peter Langer*, *Eur. J. Org. Chem.* **2011**, 5261; (m) Muhammad Sharif, Aneela Maalik, Sebastian Reimann, Jamshed Iqbal, Tamás Patonay, Alexander Villinger, Peter Langer*, *J. Fluorine Chem.* **2013**, 146, 19; (n) Shahzad Ahmed, Muhammad Sharif***,** Khurram Shoaib, Sebastian Reimann, Jamshed Iqbal, Anke Spannenberg, Peter Langer*, *Tetrahedron Lett.* **2013**, 54, 1669; (o) Muhammad Sharif, Anahit Pews–Davtyan, Jan Lukas, Johannes Schrank, Peter Langer, Arndt Rolfs* and Matthias Beller* *Eur. J. Org. Chem.* **2013**, 2783; (p) Sebastian Reimann, Kai Wittler, Stella Schmode, Muhammad Sharif, Anke Spannenberg, Ralf Ludwig, and Peter Langer. *Eur. J. Org. Chem.* **2013**, 8115; (q) Muhammad Sharif, Aneela Maalik, Sebastian Reimann, Jamshed Iqbal, Tamás Patonay, Alexander Villinger, Anke Spannenberg, and Peter Langer*, *Tetrahedron* **2013**, *69*, 174.

17. (a) Pews–Davtyan, A.; Tillack, A.; Schmöle, A.–C.; Ortinau, S.; Frech, M. J.; Rolfs, A.; Beller, M. *Org. Biomol. Chem.* **2010**, *8*, 1149–1153; (b) Schmöle, A.–C.; Brennführer, A.; Karapetyan, G.; Jaster, R.; Pews–Davtyan, A.; Hübner, R.; Ortinau, S.; Beller, M.; Rolfs, A.; Frech, M. J. *Bioorg. Med. Chem.* **2010**, *18*, 6785–6795.
18. (a) Yamada, T.; Takemura, Y.; Niisato, N.; Mitsuyama, E.; Iwasaki, Y.; Marunaka, Y. *Biochem. Biophys. Research Commun.* **2009**, *380*, 586–590; (b) Goeber, B.; Liskowski, H.; Franke, P. *Pharmazie* **1988,** *43*, 23–26.
19 Duplais, Ch.; Forman, A. J.; B. Baker, A.; Lipshutz, B. H. *Chem. Eur. J.* **2010**, *16*, 3366–3371.
20. For selected reviews in this area see: (a) Fortman, G. C.; Nolan, S. P. *Chem. Soc. Rev.* **2011**, *40*, 5151–5169; (b) Balanta, A.; Godard, C.; Claver**,** C. *Chem. Soc. Rev***.** **2011**, *40*, 4973–4985; (c) Fihri, A.; Bouhrara, M.; Nekoueishahraki, B.; Basset, J–M.; Polshettiwar, V. *Chem. Soc. Rev.* **2011**, *40*, 5181–5203; (d) Mehtaa, V. P.; Van der Eycken, E. V. *Chem. Soc. Rev.* **2011**, *40*, 4925–4936; (e) Doucet, H. *Eur. J. Org. Chem.* **2008**, 2013–2030; (f) Littke, A. F.; Fu, G. C. *Angew. Chem, Int. Ed.* **2002**, *41*, 4176–4212; *Angew. Chem.* **2002**, *114*, 4350–4386.
21. (a) Barder, T. E.; Walker, S. D.; Martinelli, J. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2005**, *127*, 4685–4696; (b) Walker, S. D.; Barder, T. E.; Martinelli, J. R.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2004**, *43*, 1871–1876; *Angew. Chem.* **2004**, *116*, 1907–1912.
22. Asano, N.; Ishii, S.; Kizu, H.; Ikeda, K.; Yasuda, K.; Kato, A.; Martin, O.R.; Fan, J.–Q. *Eur. J. Biochem.* **2000**, *267*, 4179–4186.
23. (a) Gasowska, J. S.; Cowling, S. J.; Cockett, M. C. R.; Hird, M.; Lewis, R. A.; Raynes, E. P.; Goodby, J. W. *J. Mater. Chem.* **2010**, *20*, 299–307; (b) Bahadir, M.; Pieper, A.; Vogt, R.; Wichmann, H.; Grunenberg, J.; Hopf, H.; *Chemosphere* **2003,** *50*, 1151–1156.

Supplementary Material

Scans of NMR spectra for all compounds are provided.

SUPPORTING INFORMATION

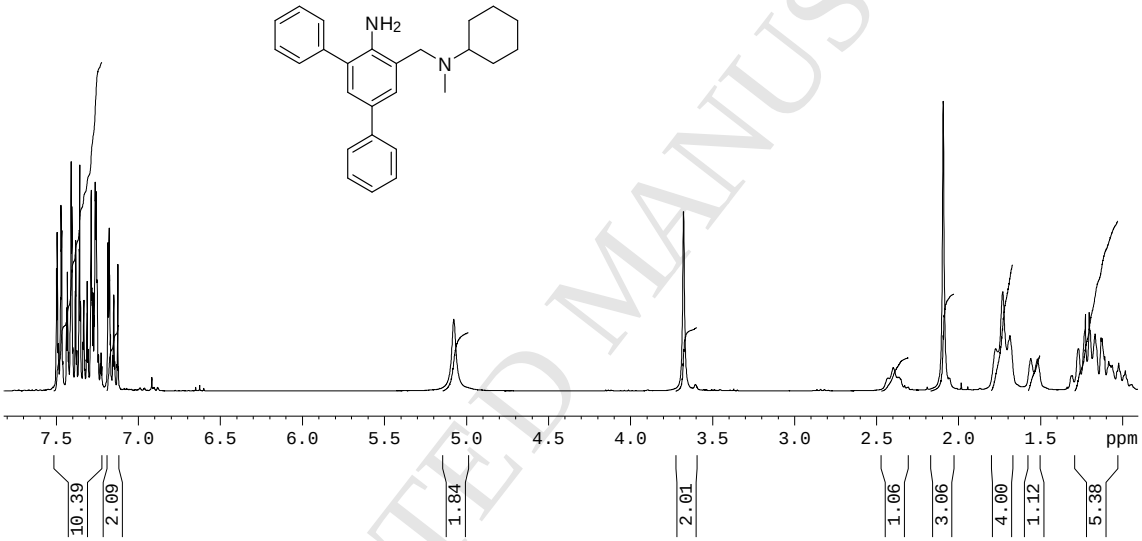
Palladium–catalysed Suzuki–Miyaura Coupling Reactions of Bromhexine and Ambroxol

Muhammad Sharif,[a,c] Anahit Pews-Davtyan,[a] Jan Lukas,[b] Susann Pohlers,[b] Arndt Rolfs,*[b] Peter Langer,[a,d] and Matthias Beller*[a]

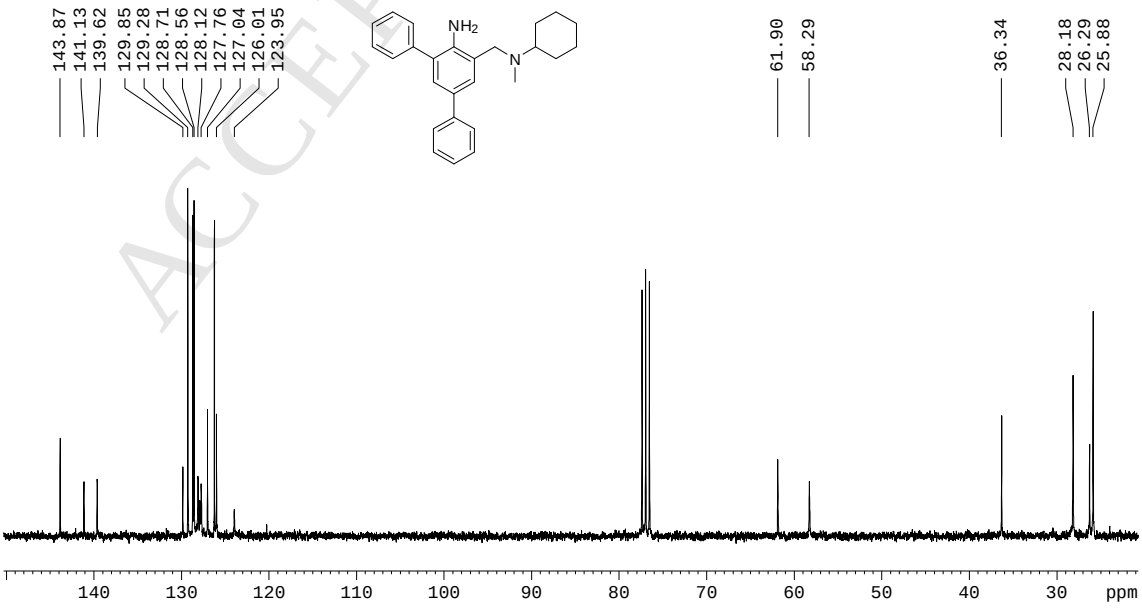
[a]*Leibniz–Institut für Katalyse an der Universität Rostock e.V. Albert–Einstein–Str. 29a, 18059 Rostock, Germany*
[b]*Albrecht Kossel–Institute for Neuroregeneration, Medical University Rostock, Gehlsheimer Str. 20, 18147 Rostock, Germany*
[c]*Department of Chemistry, COMSATS Institute of Information Technology, Abbottabad, Pakistan*
[d]*Institut für Chemie, Universität Rostock, Albert–Einstein–Str. 3a, 18059 Rostock, Germany*

2-{[Cyclohexyl(methyl)amino]methyl}-4,6-diphenylaniline (3a):

^{1}H NMR

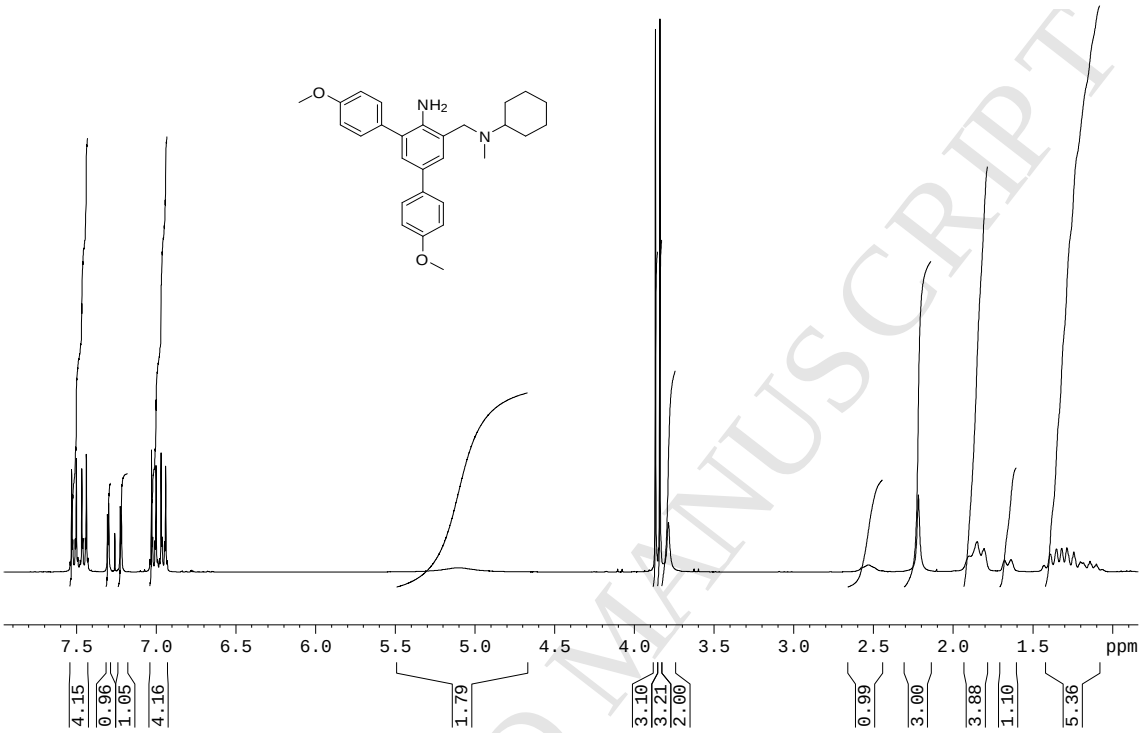


^{13}C NMR

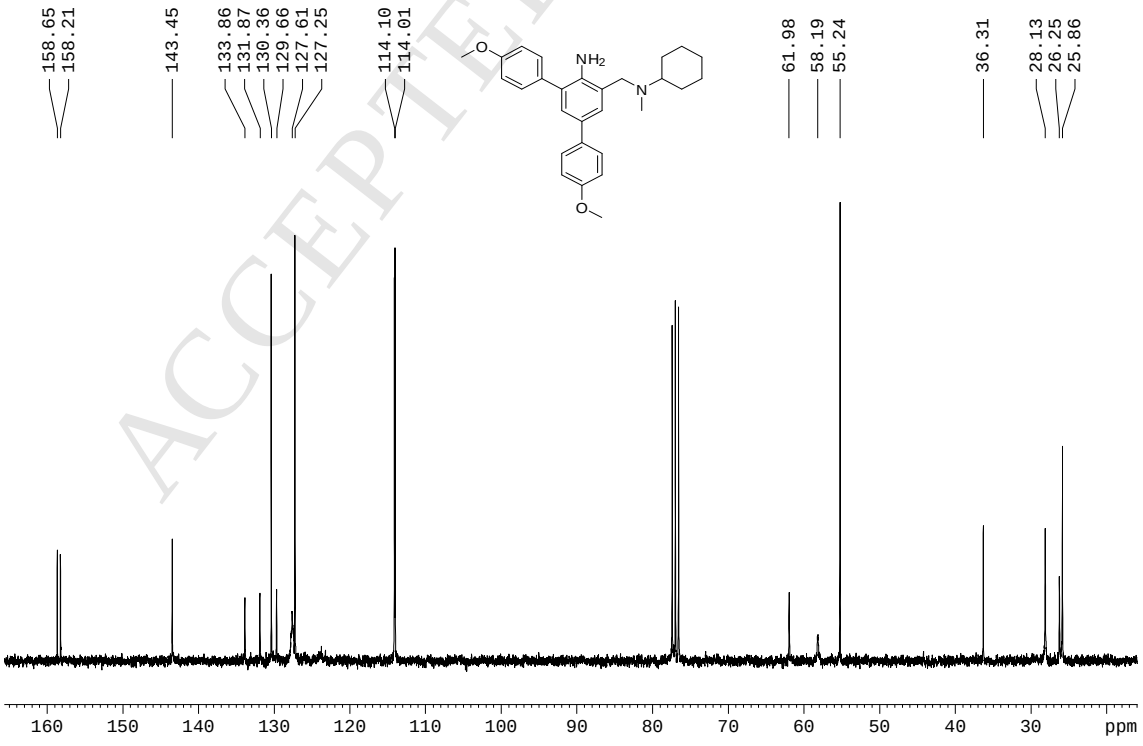


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(4-methoxyphenyl)aniline (3b):

^{1}H NMR

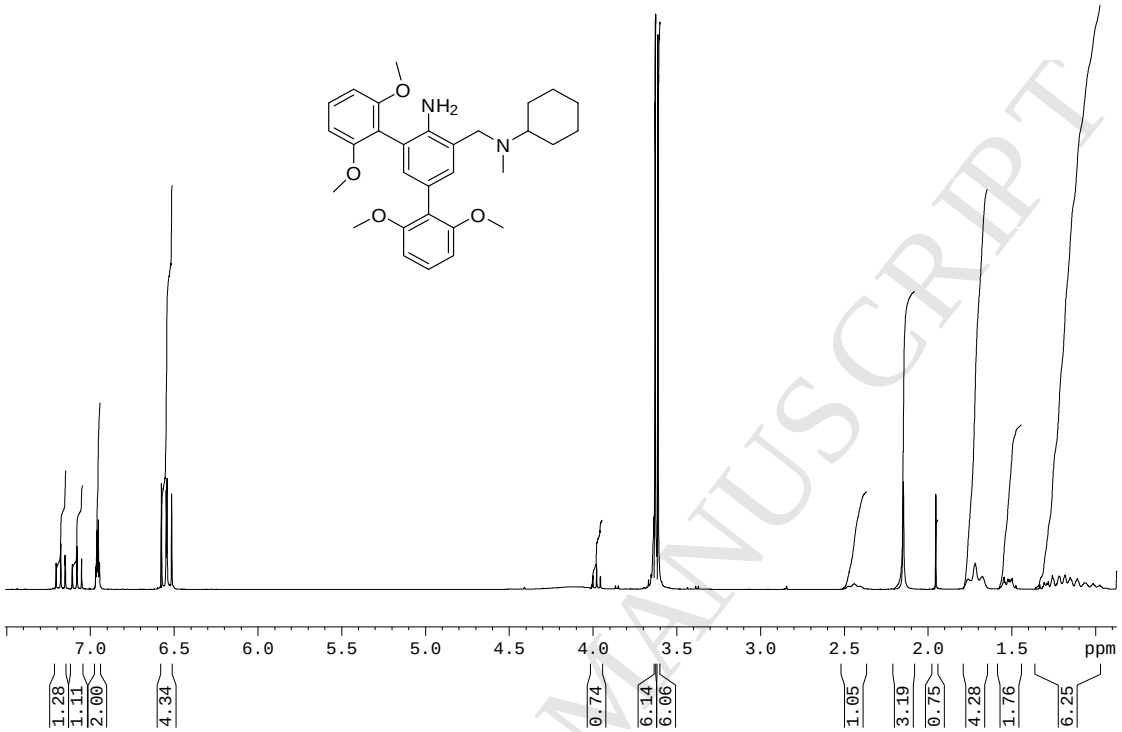


^{13}C NMR

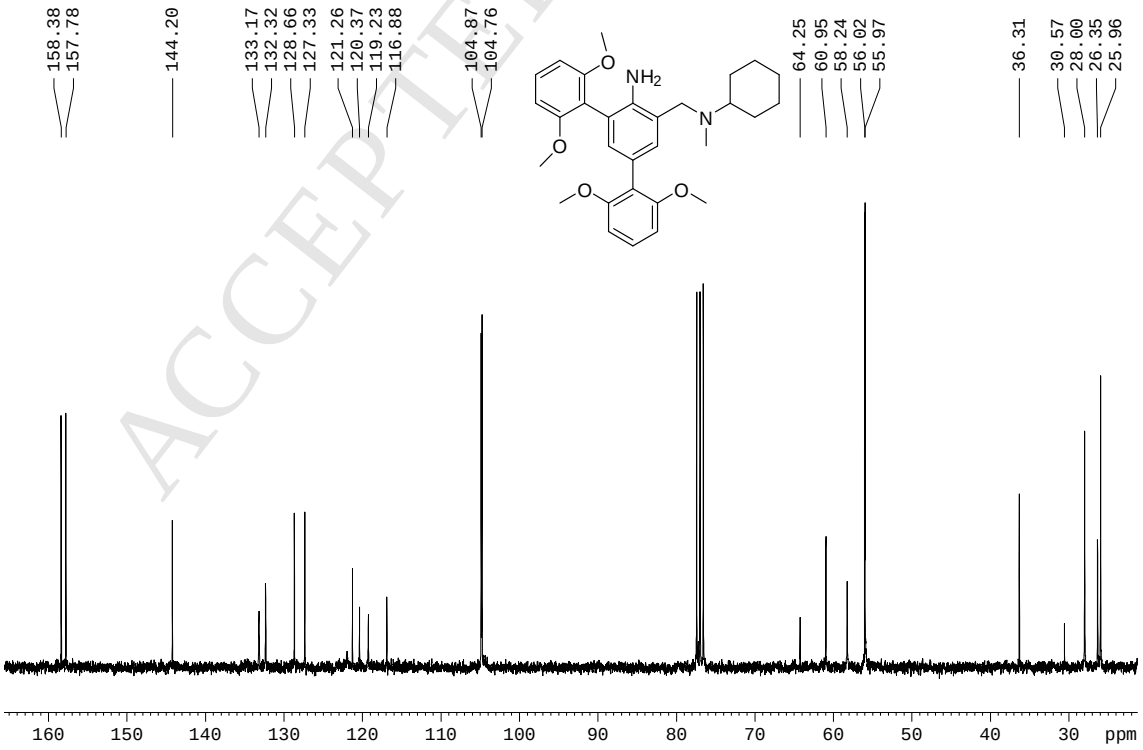


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(2,6-dimethoxyphenyl)aniline (3c):

^{1}H NMR

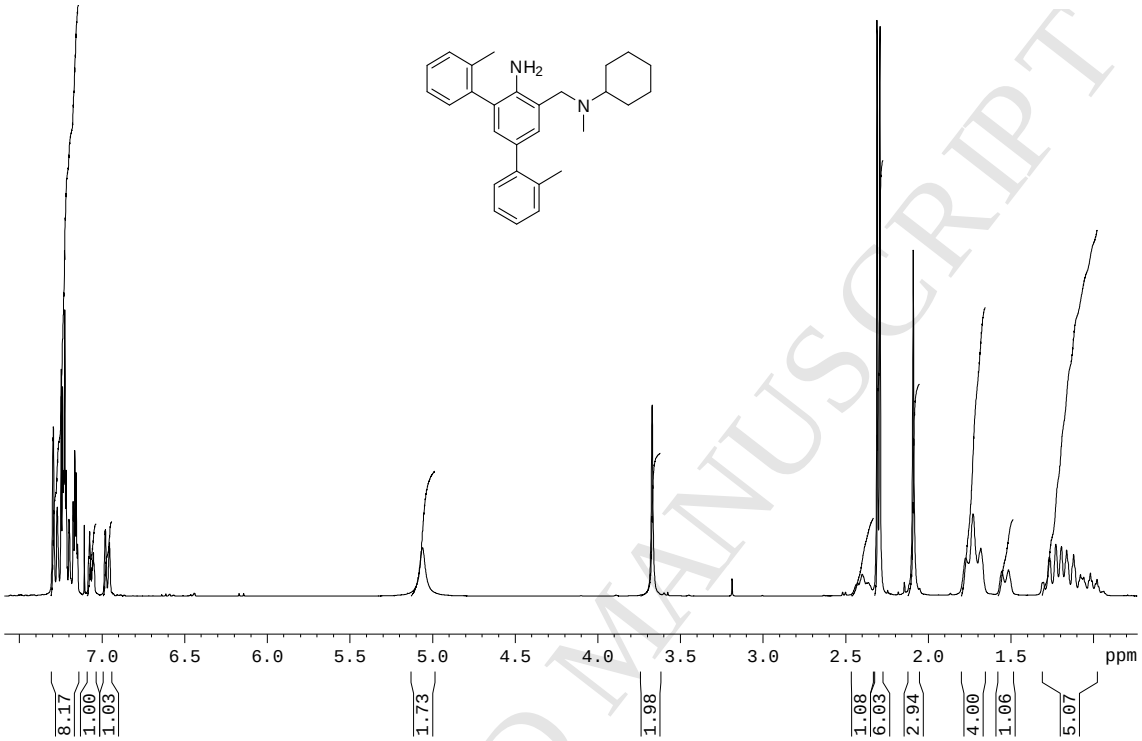


^{13}C NMR

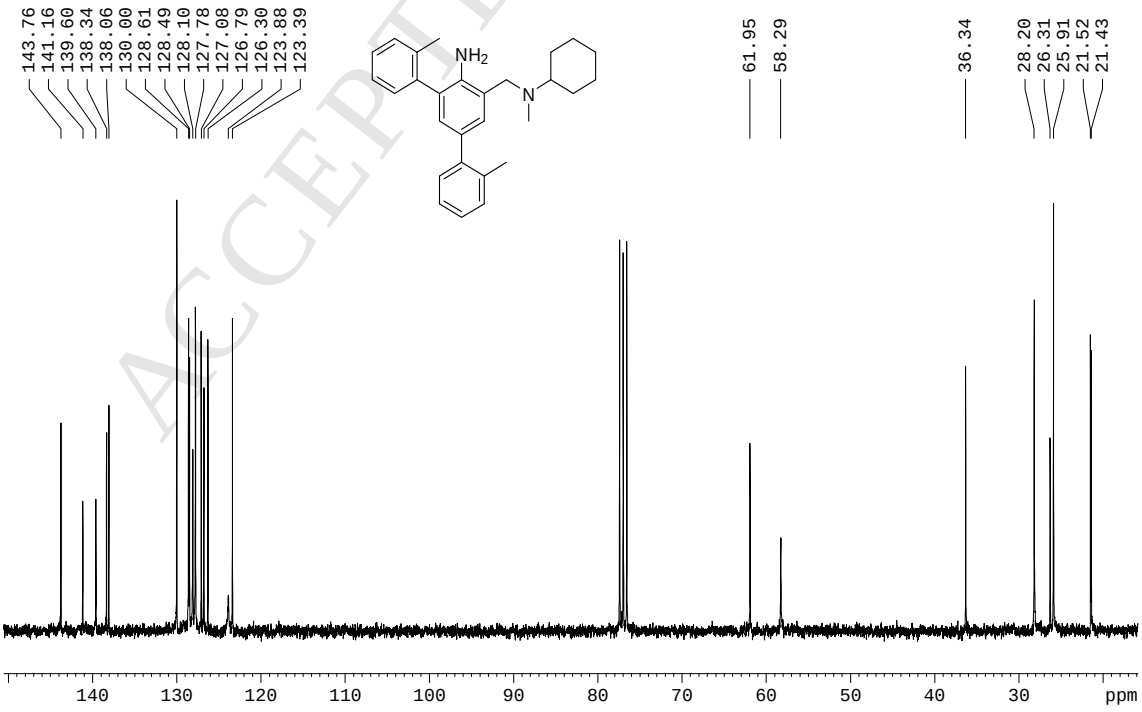


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(2-methylphenyl)aniline (3d):

^{1}H NMR

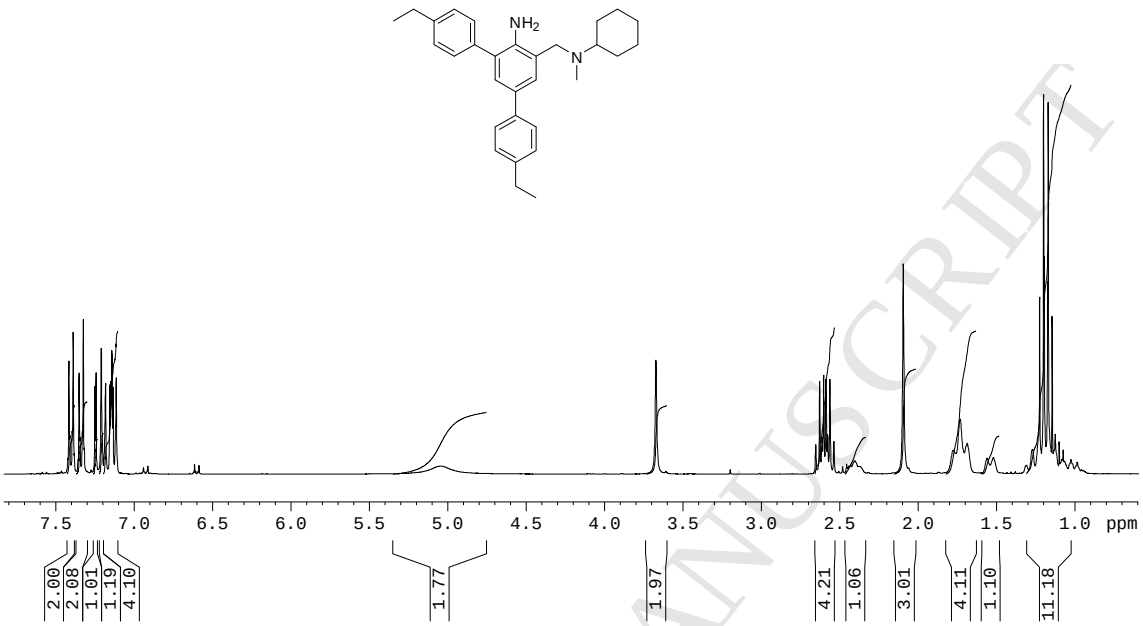


^{13}C NMR

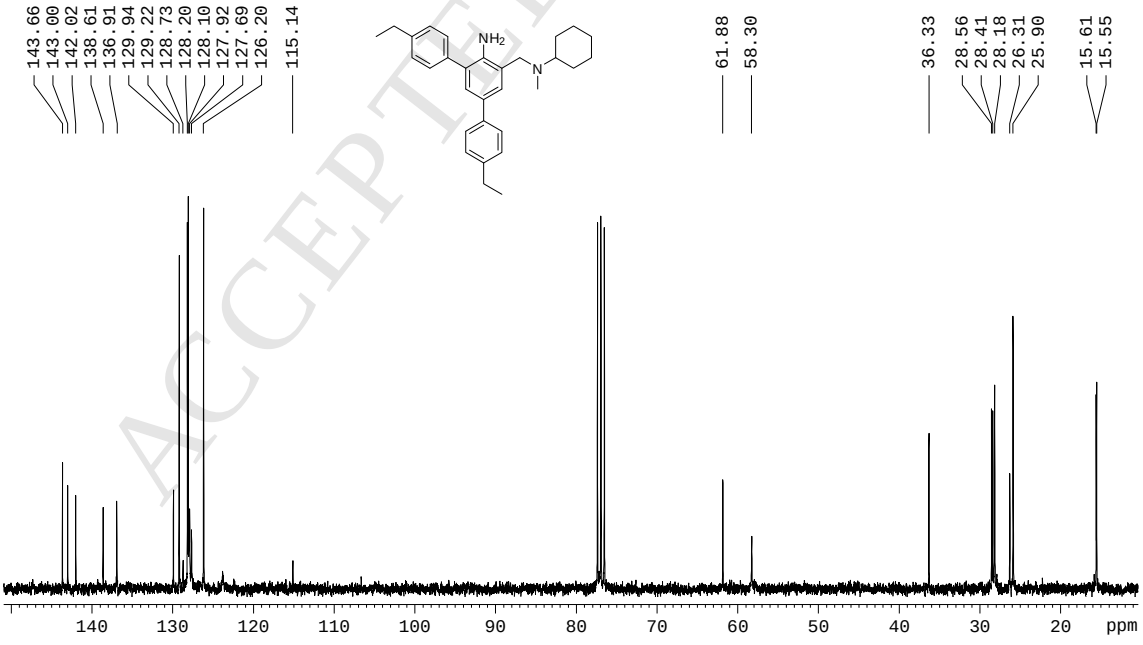


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(4-ethylphenyl)aniline (3e):

^{1}H NMR

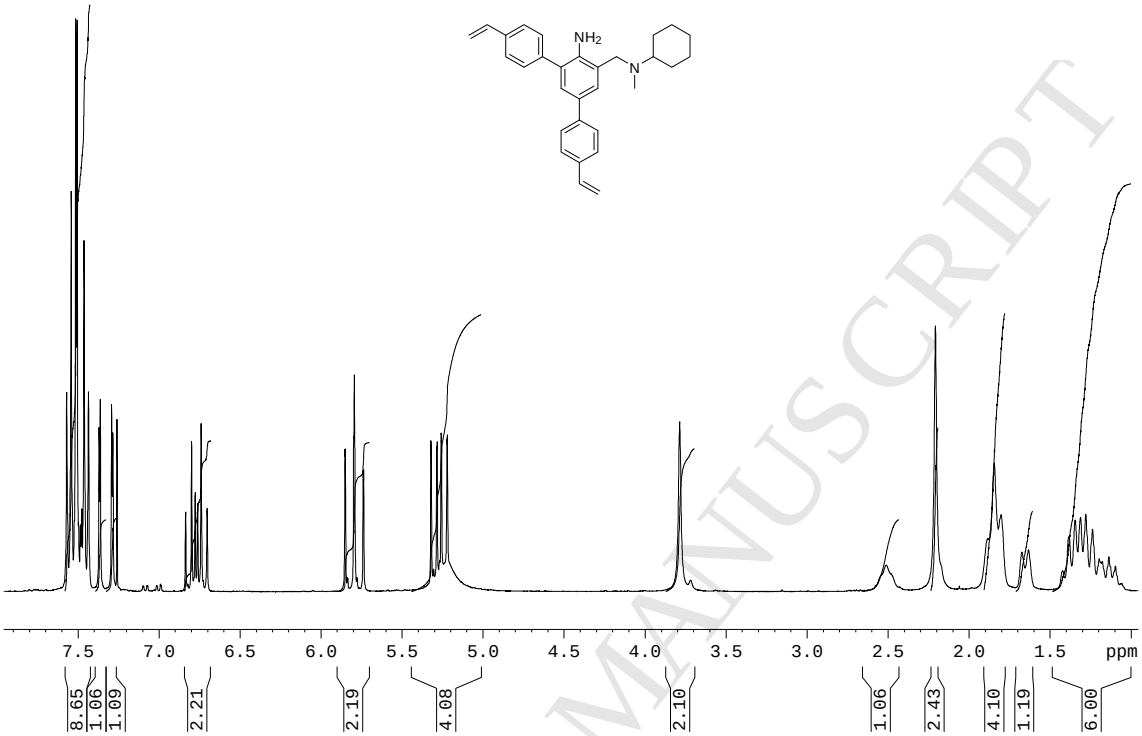


^{13}C NMR

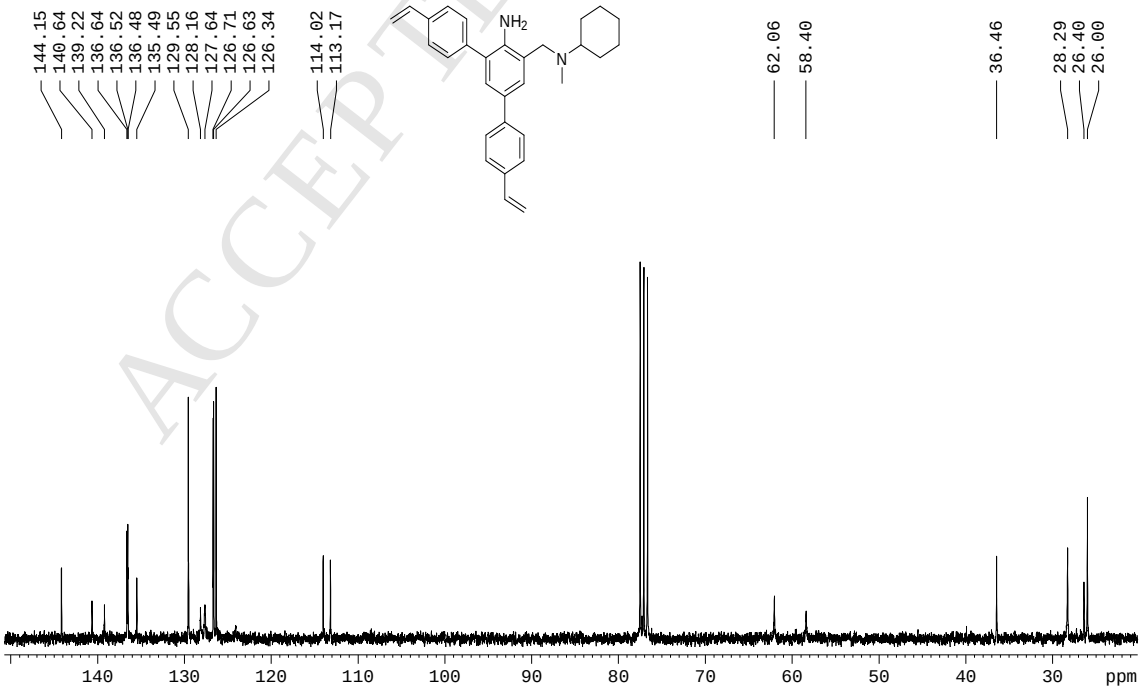


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(4-ethenylphenyl)aniline (3f):

^{1}HNMR

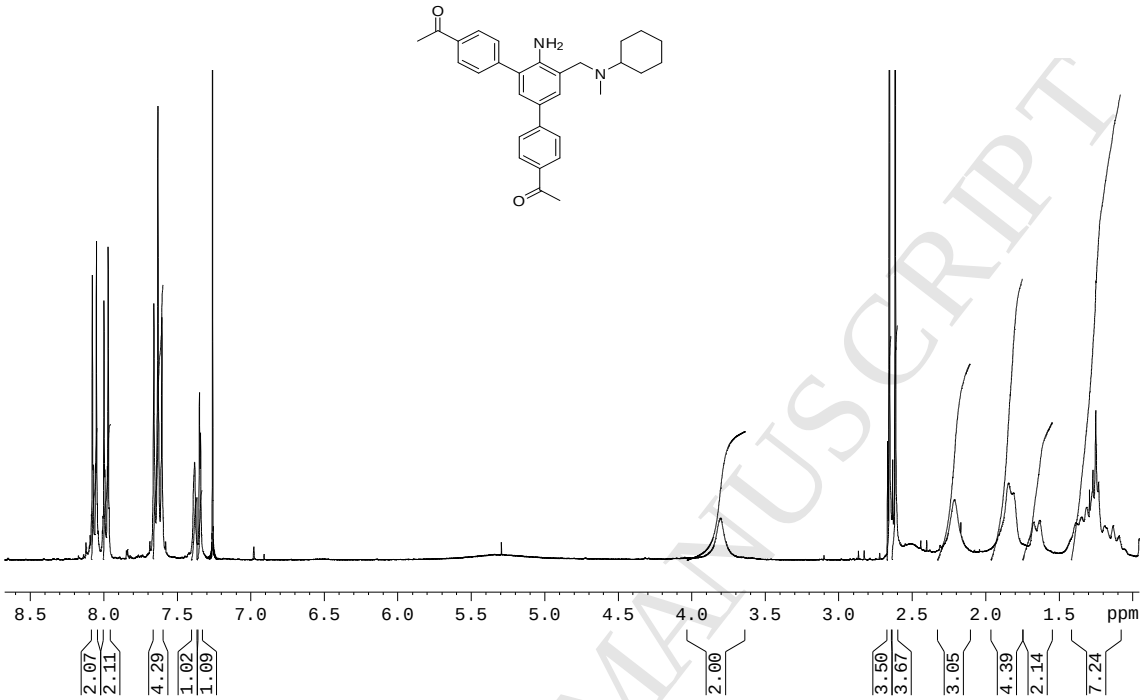


^{13}C NMR

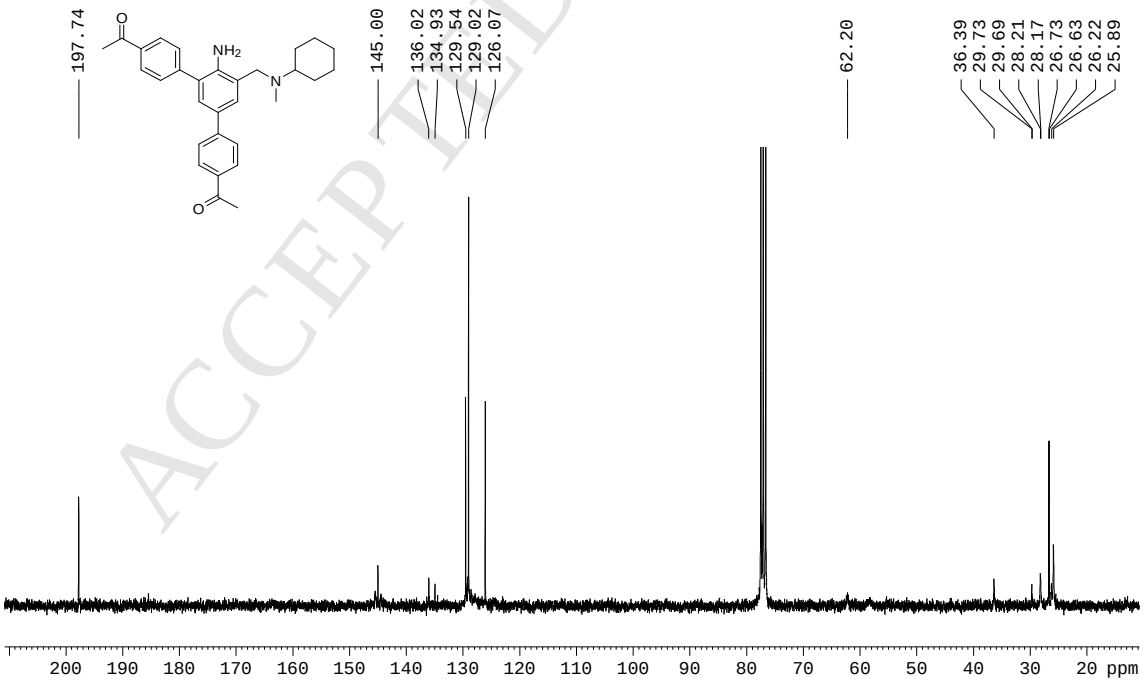


1-{4-[5-(4-Acetylphenyl)-2-amino-3-{[cyclohexyl(methyl)amino]methyl}phenyl]phenyl}ethan-1-one (3g):

^{1}H NMR

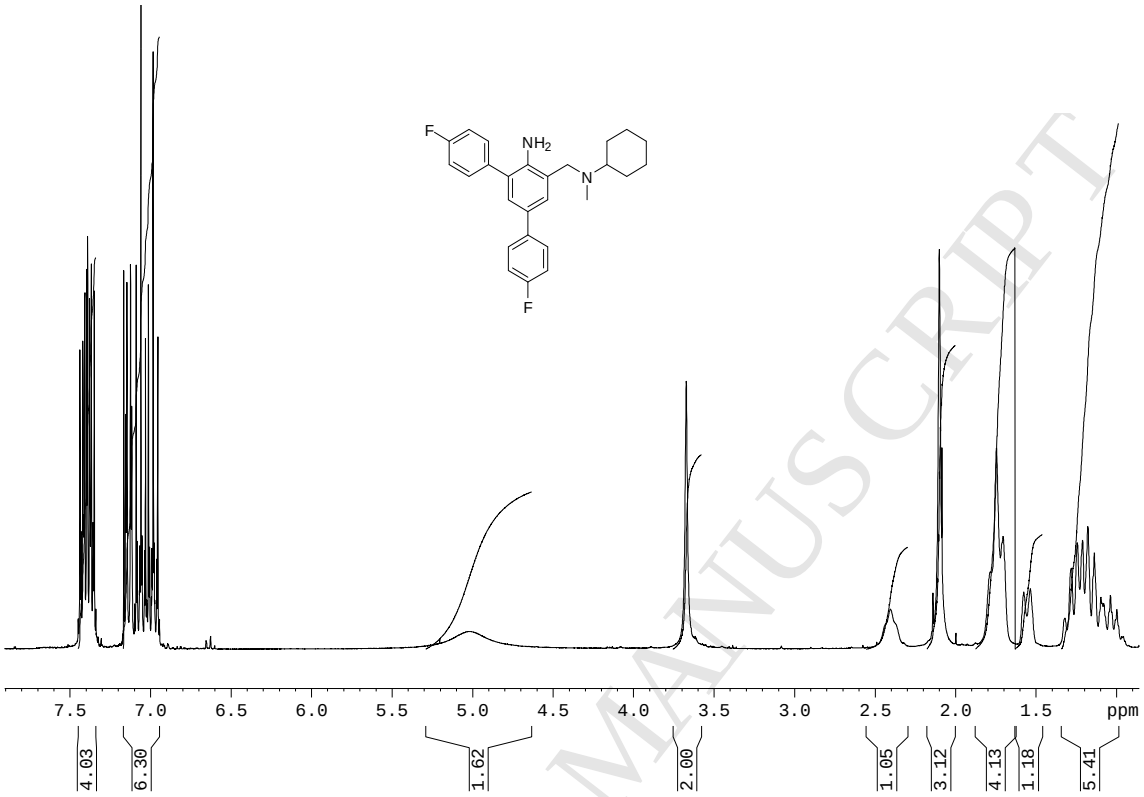


^{13}C NMR

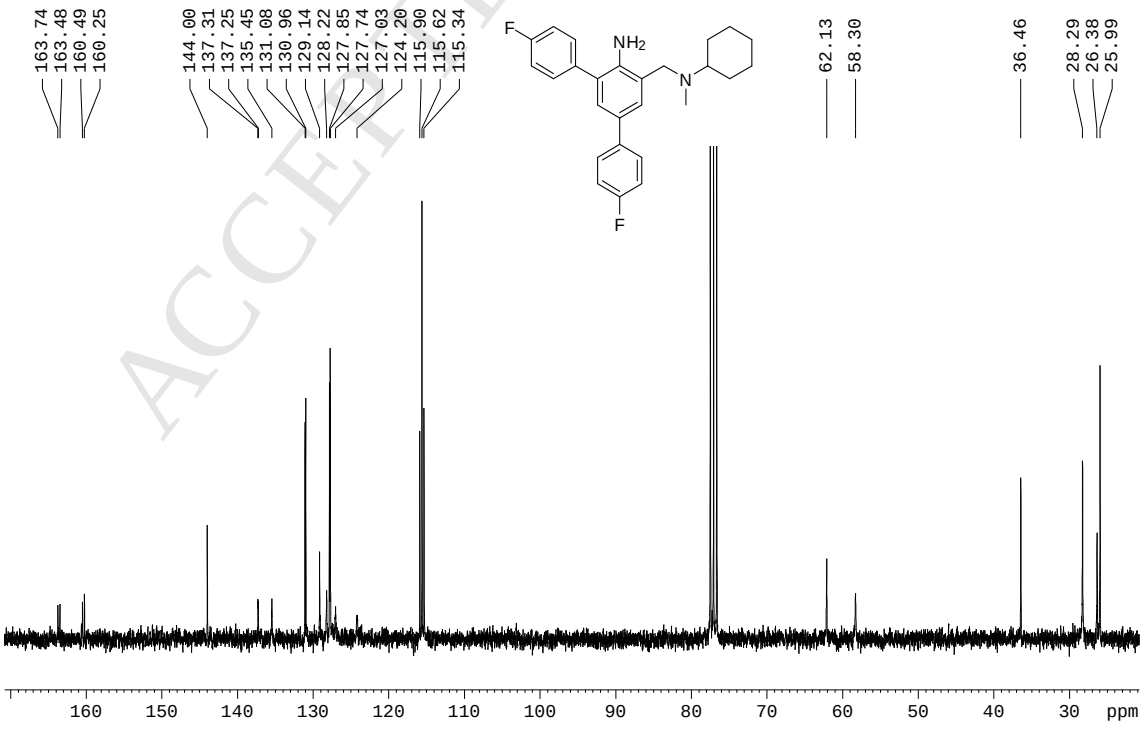


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(4-fluorophenyl)aniline (3h):

^{1}H NMR

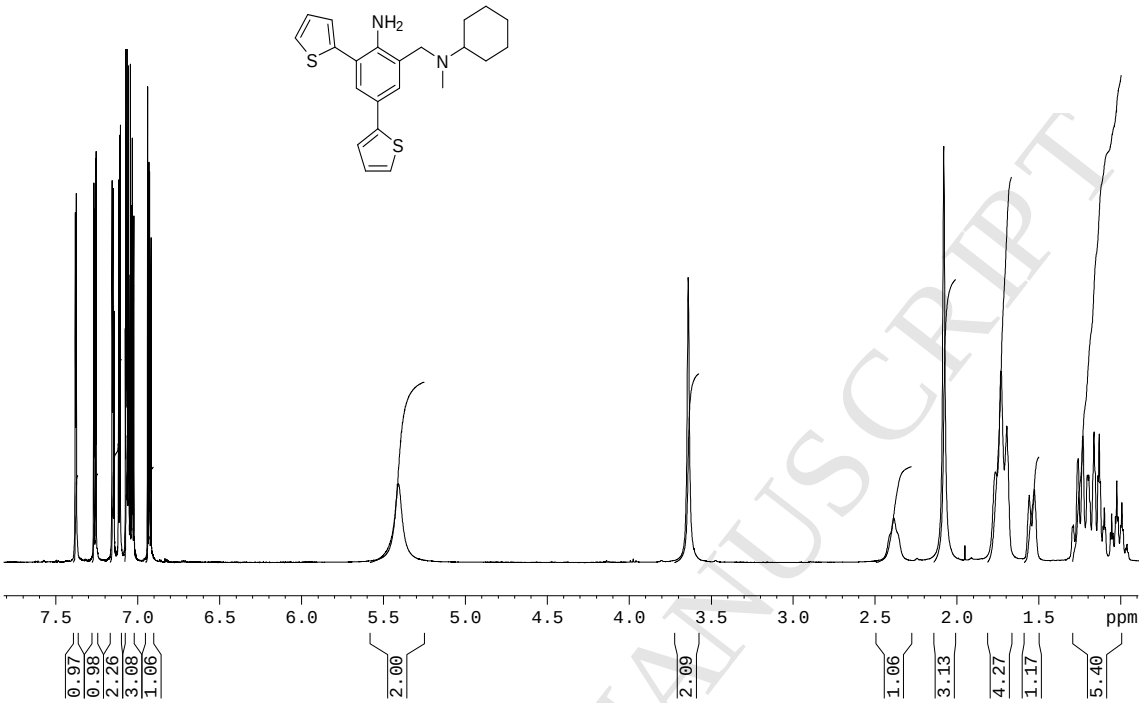


^{13}C NMR

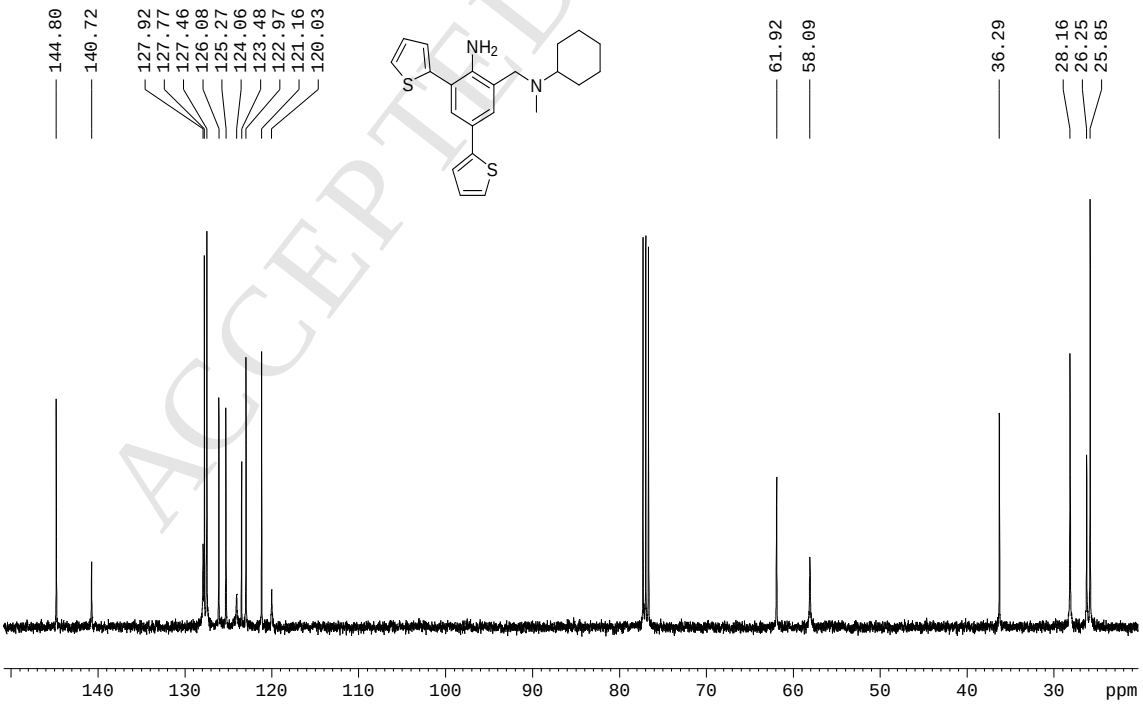


2-((Cyclohexyl(methyl)amino)methyl)-4,6-di(thiophen-2-yl)aniline) (3i):

^{1}H NMR

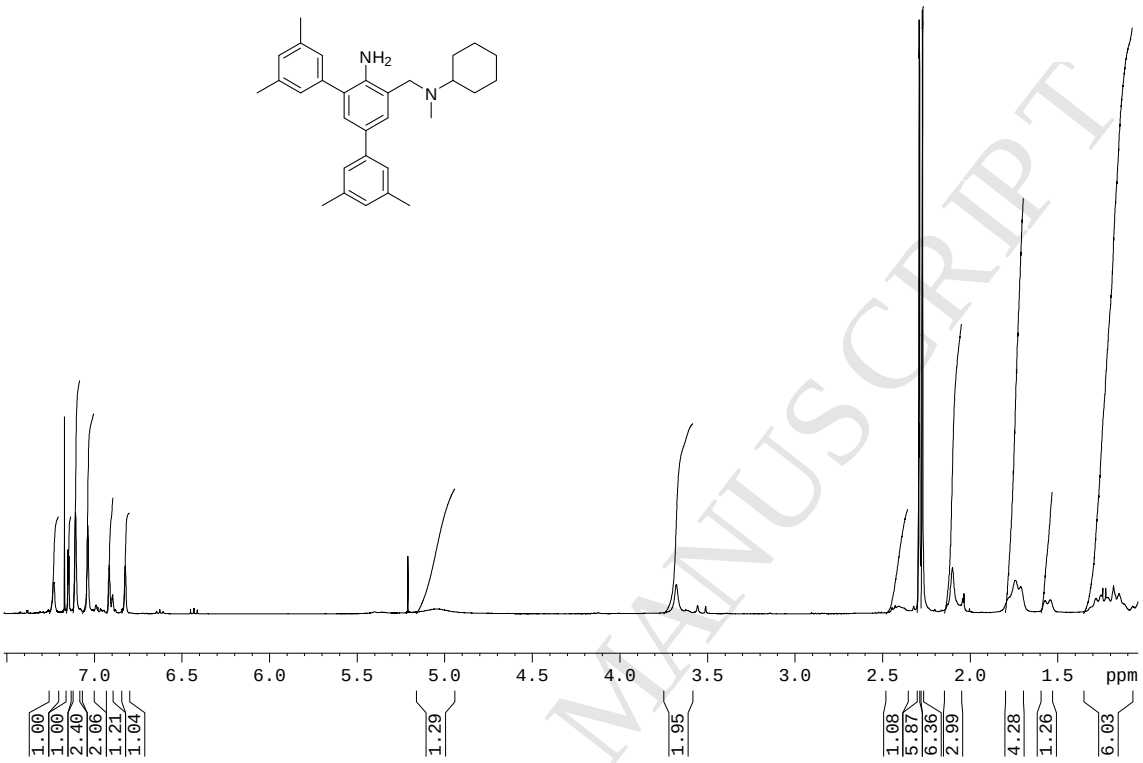


^{13}C NMR

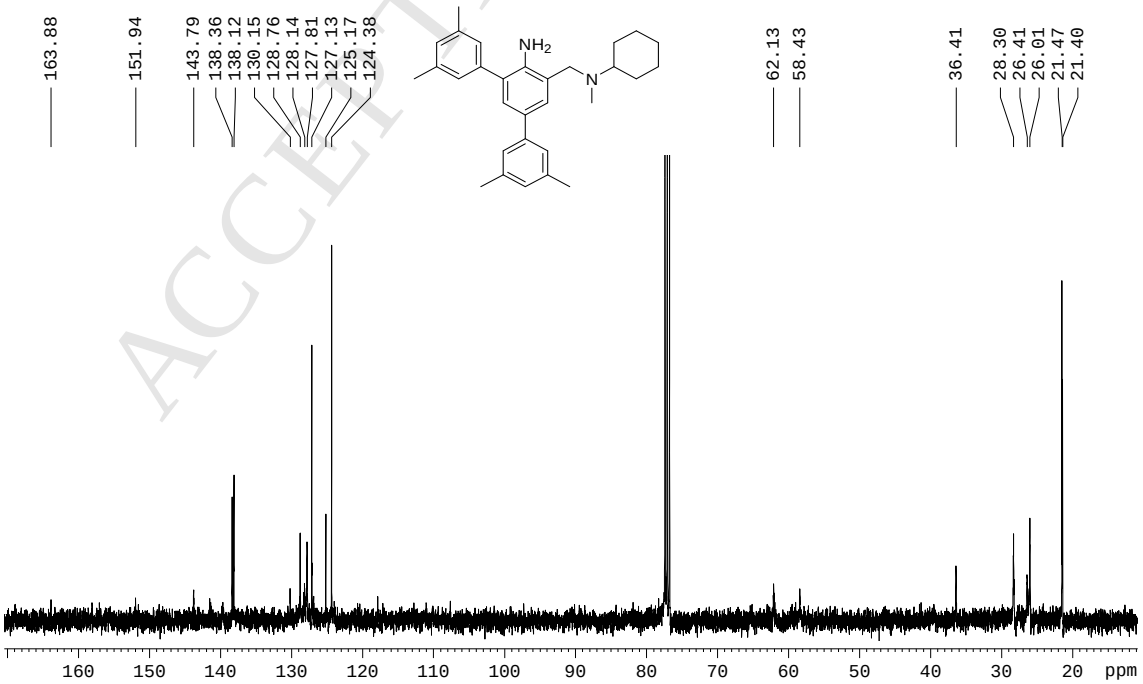


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(3,5-dimethylphenyl)aniline (3j):

^{1}H NMR

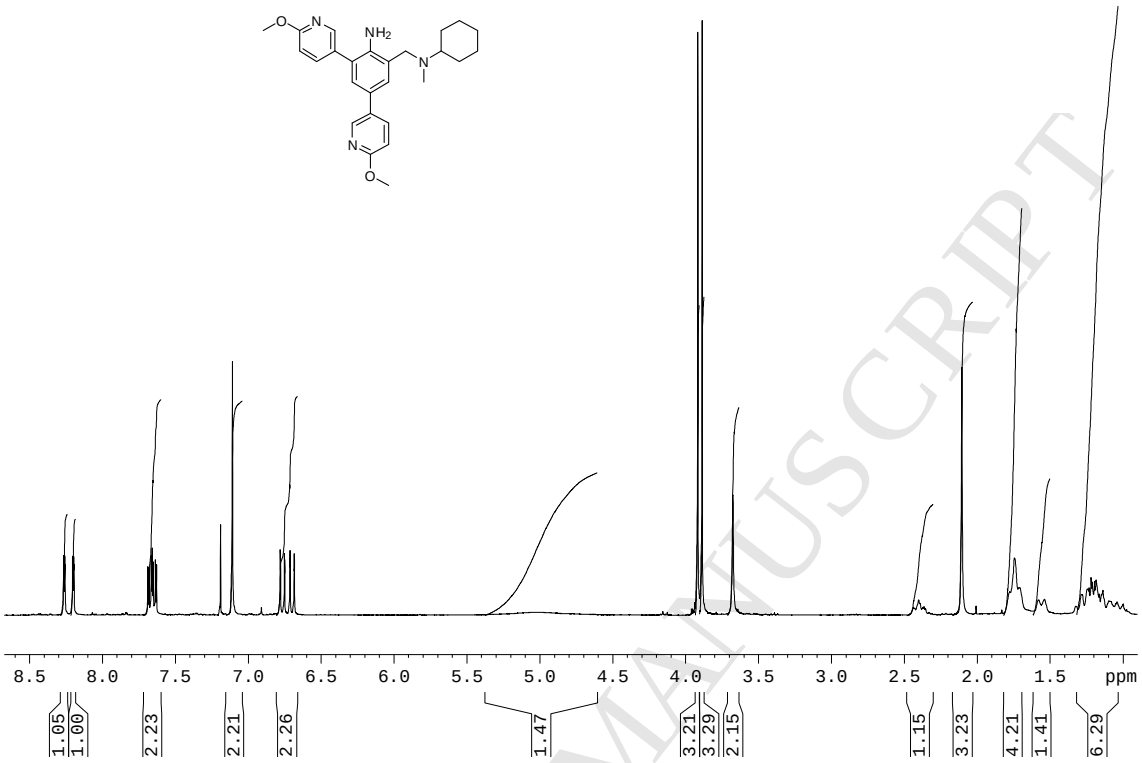


^{13}C NMR

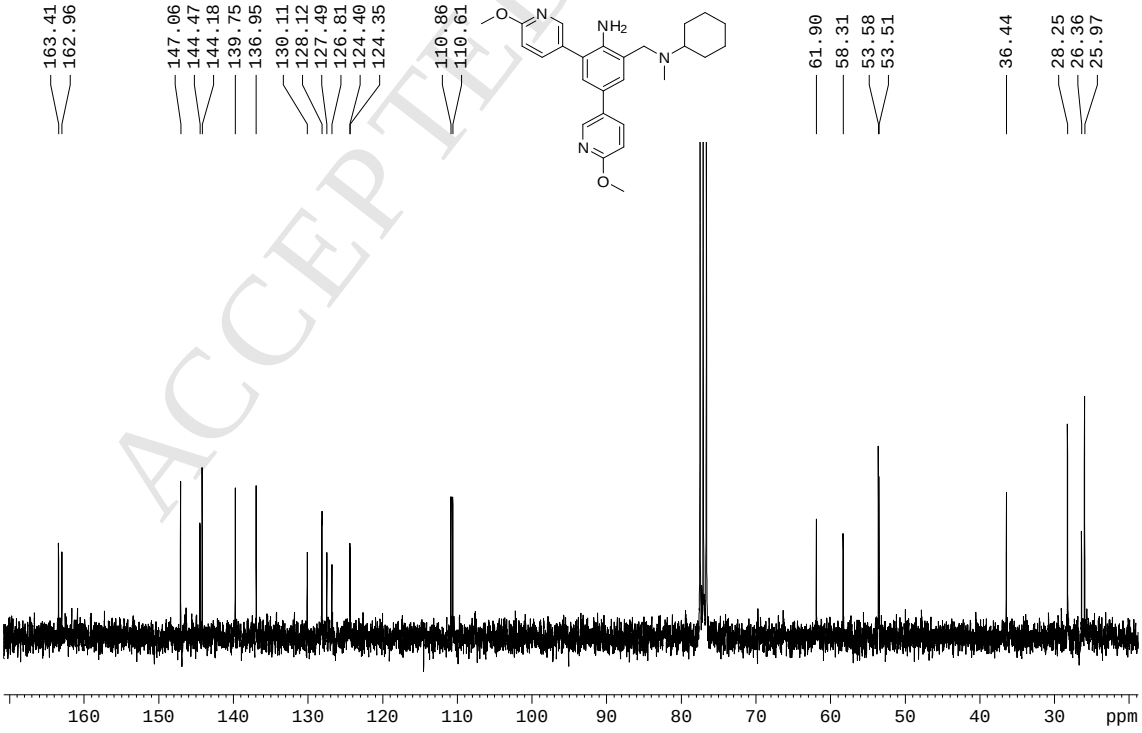


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(6-methoxypyridin-3-yl)aniline (3k):

^{1}H NMR

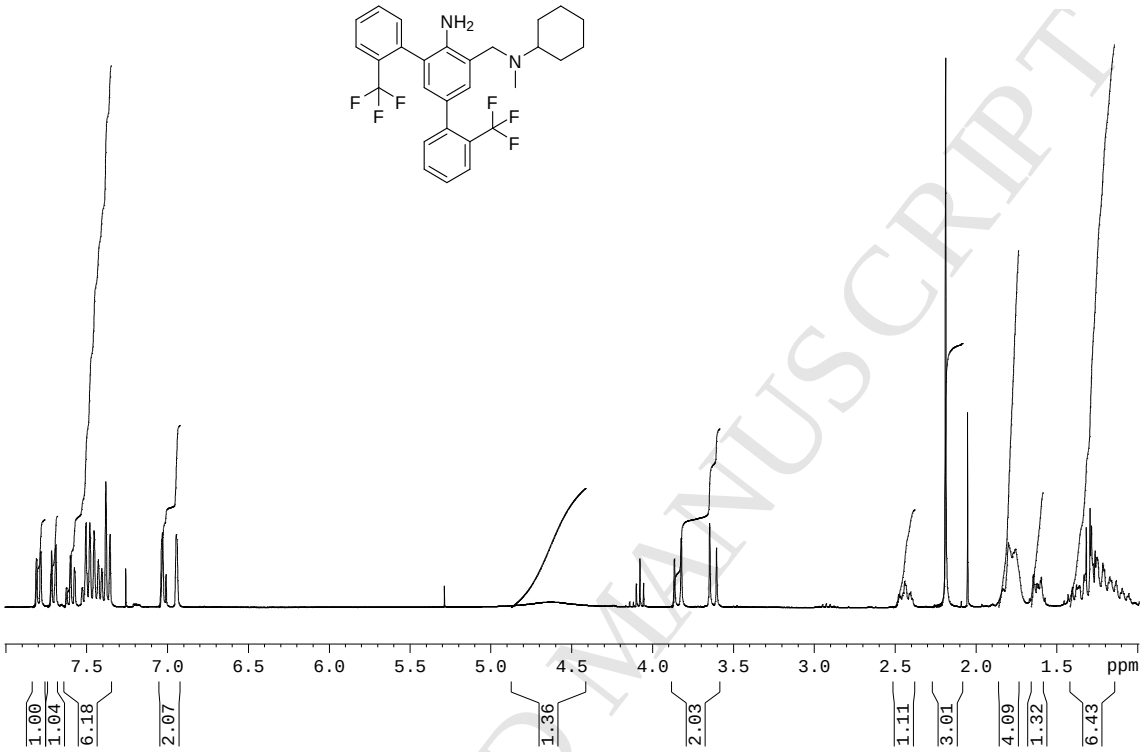


^{13}C NMR

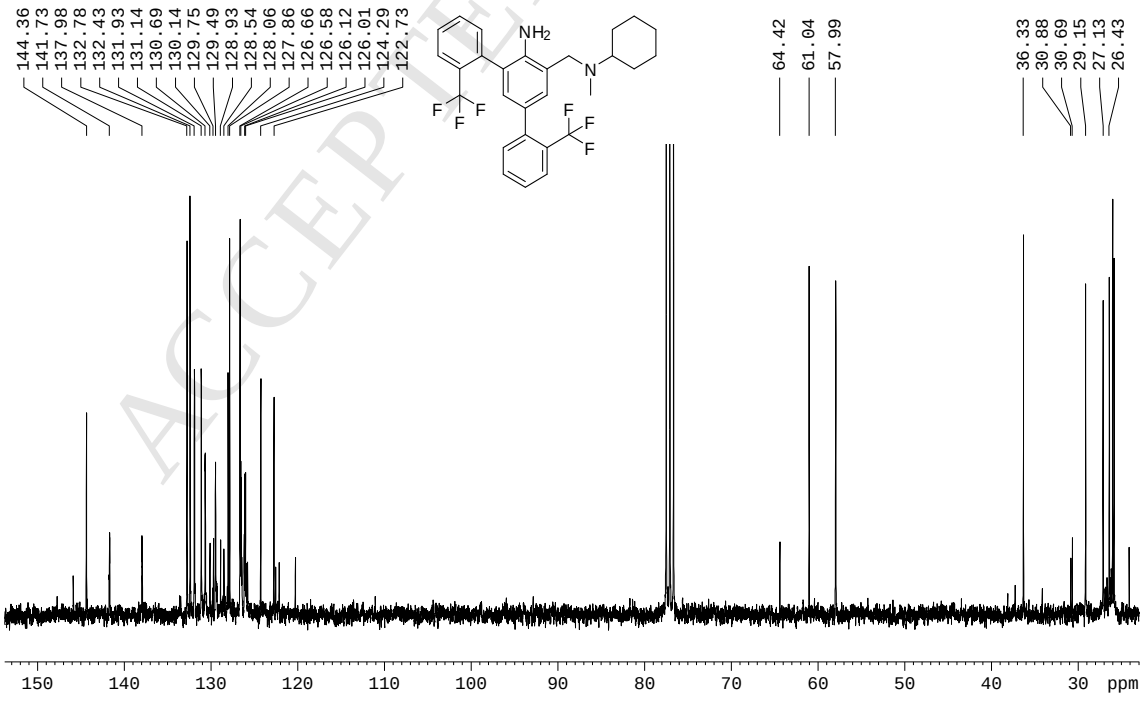


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(2-(trifluoromethyl)phenyl)aniline (3l):

^{1}H NMR

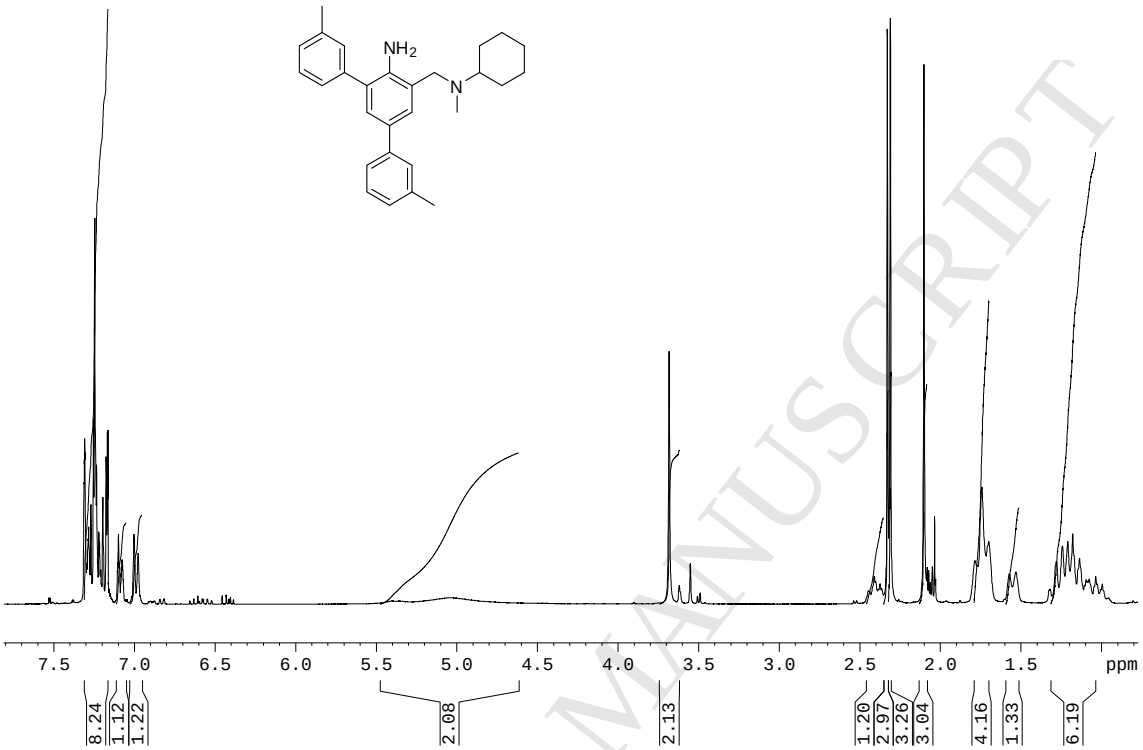


^{13}C NMR

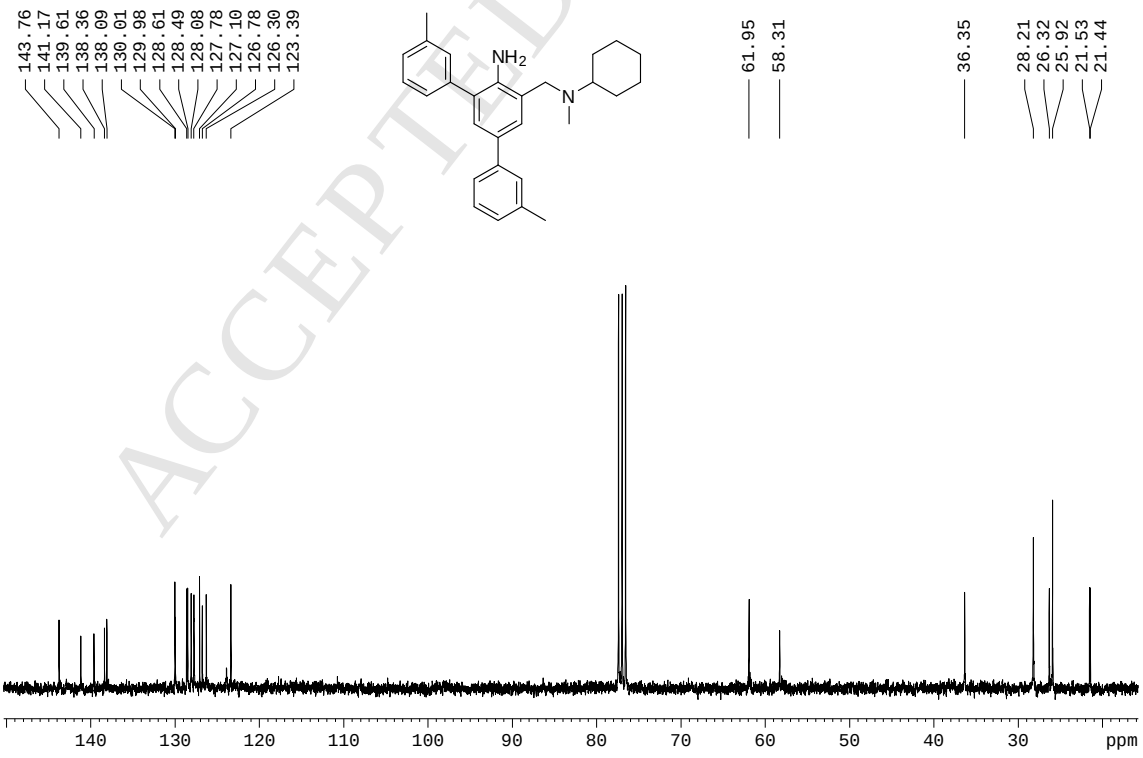


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(3-methylphenyl)aniline (3m):

^{1}H NMR

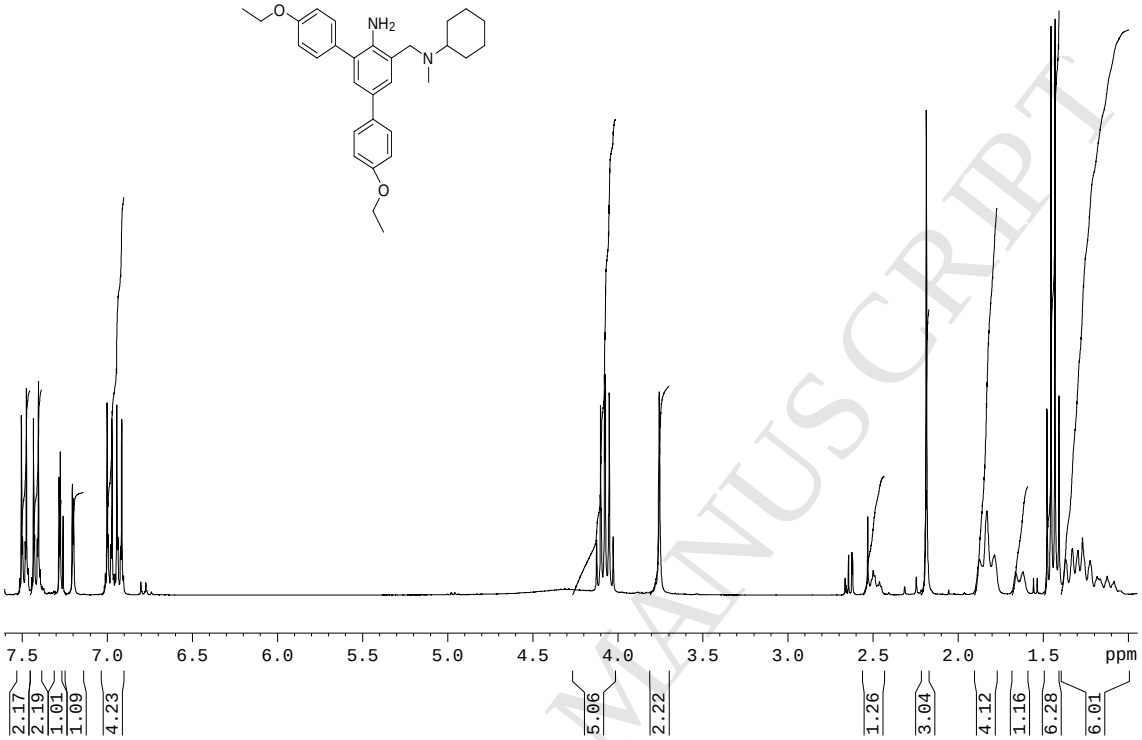


^{13}C NMR

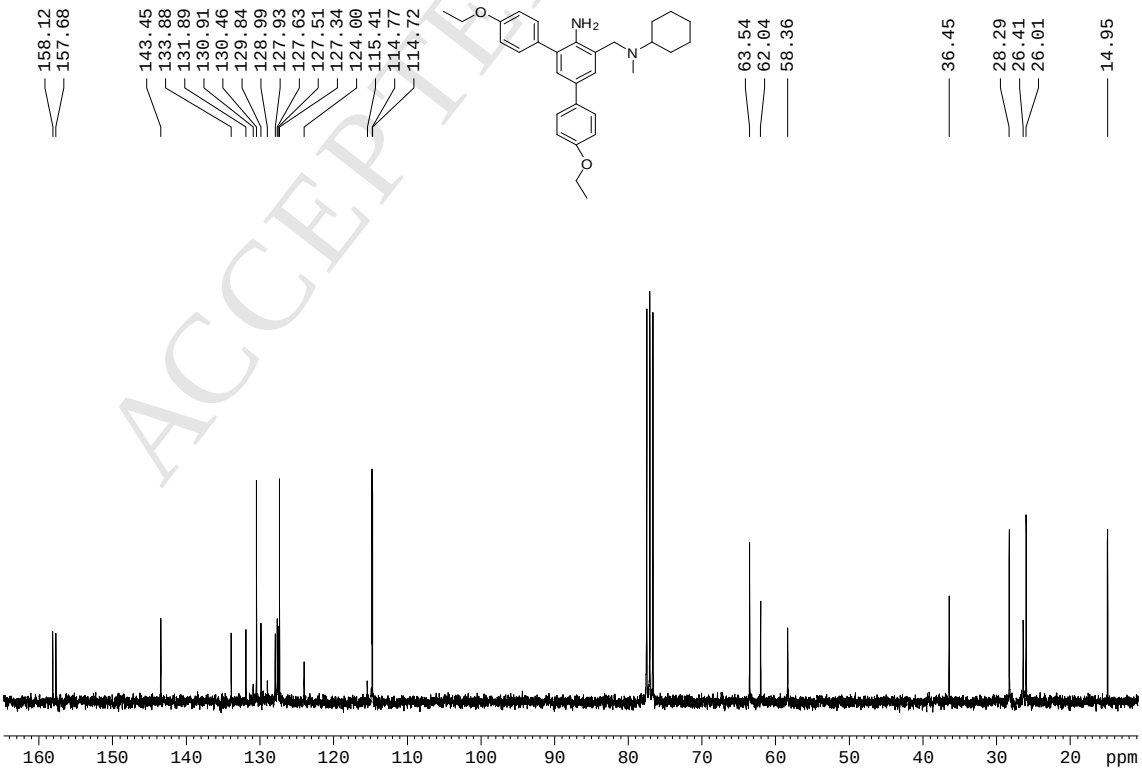


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(4-ethoxyphenyl)aniline (3n):

^{1}H NMR

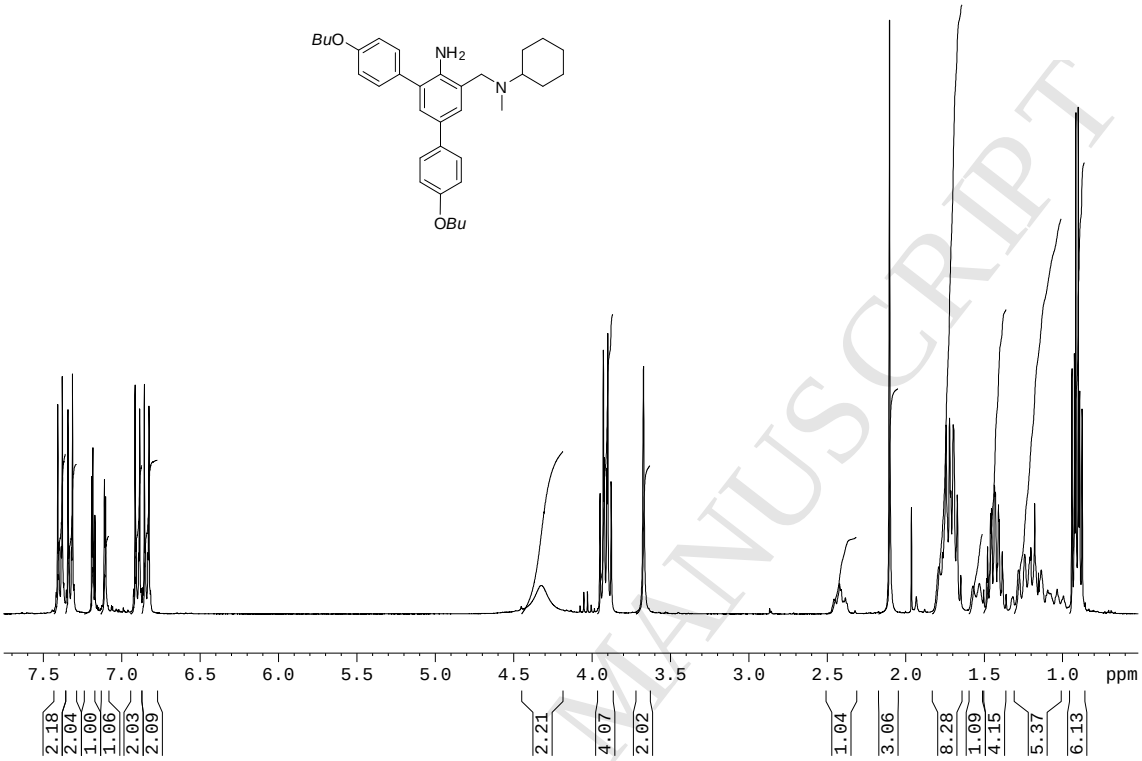


^{13}C NMR

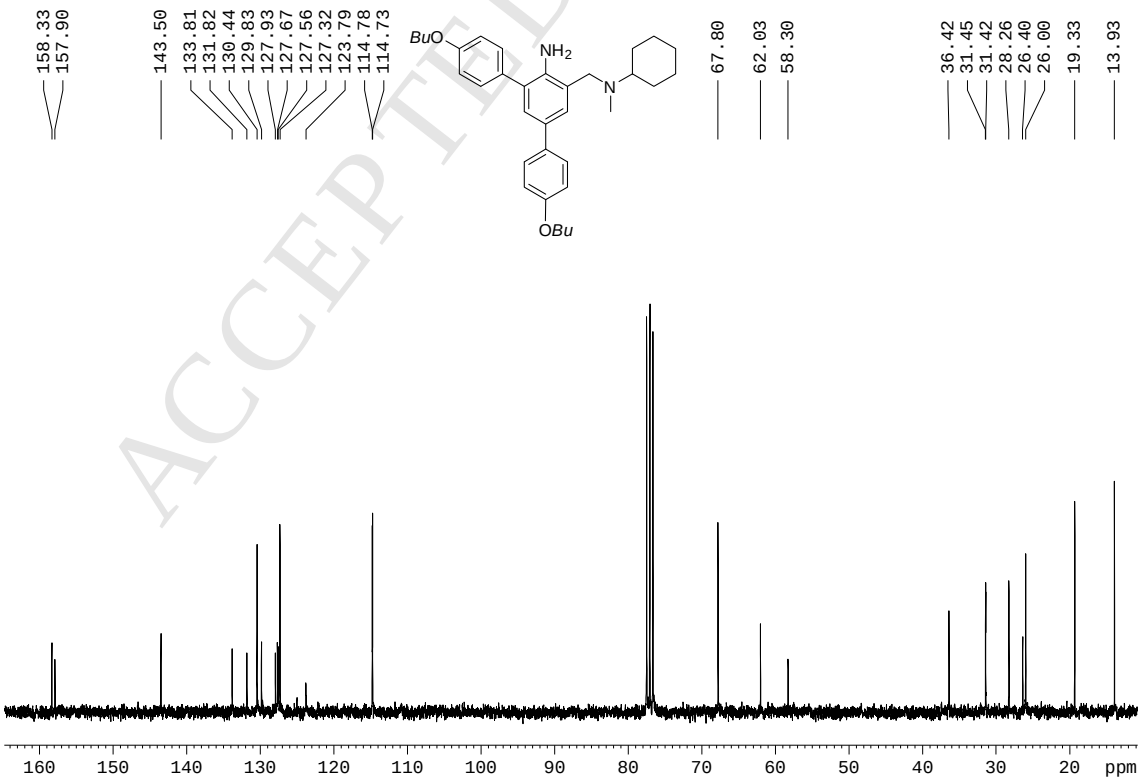


2-4-Bis(4-butoxyphenyl)-6-{[cyclohexyl(methyl)amino]methyl}-aniline (3o):

^{1}H NMR

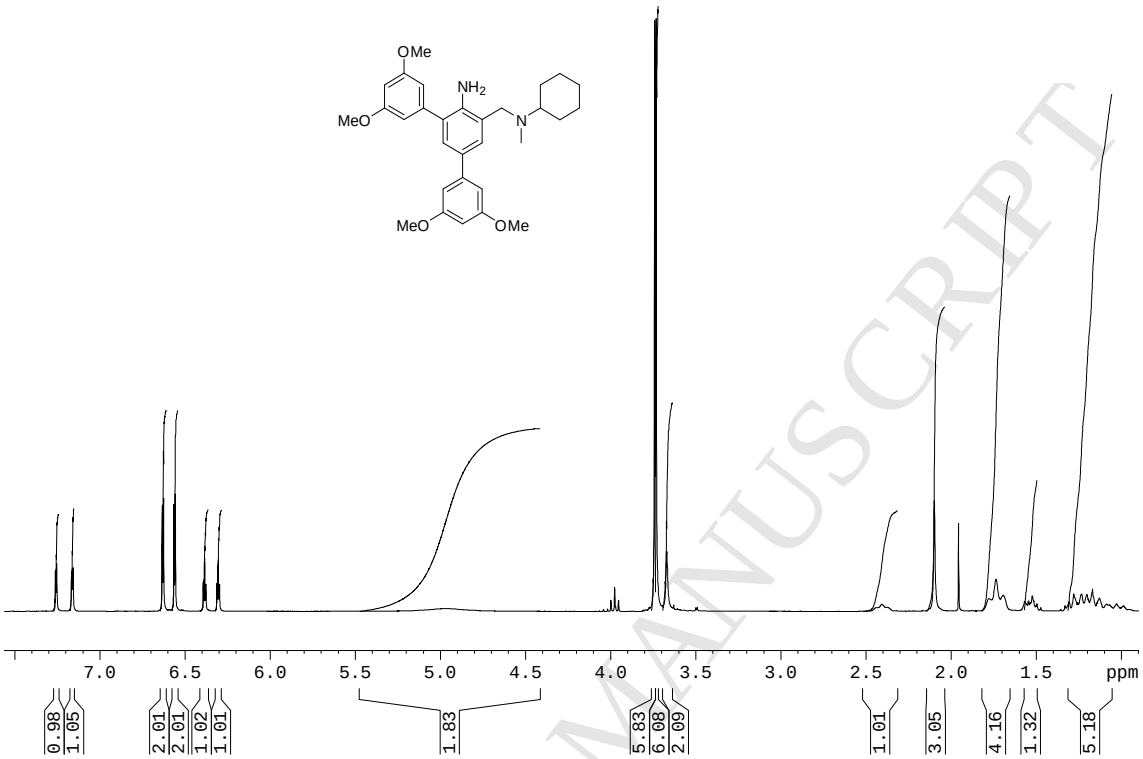


^{13}C NMR

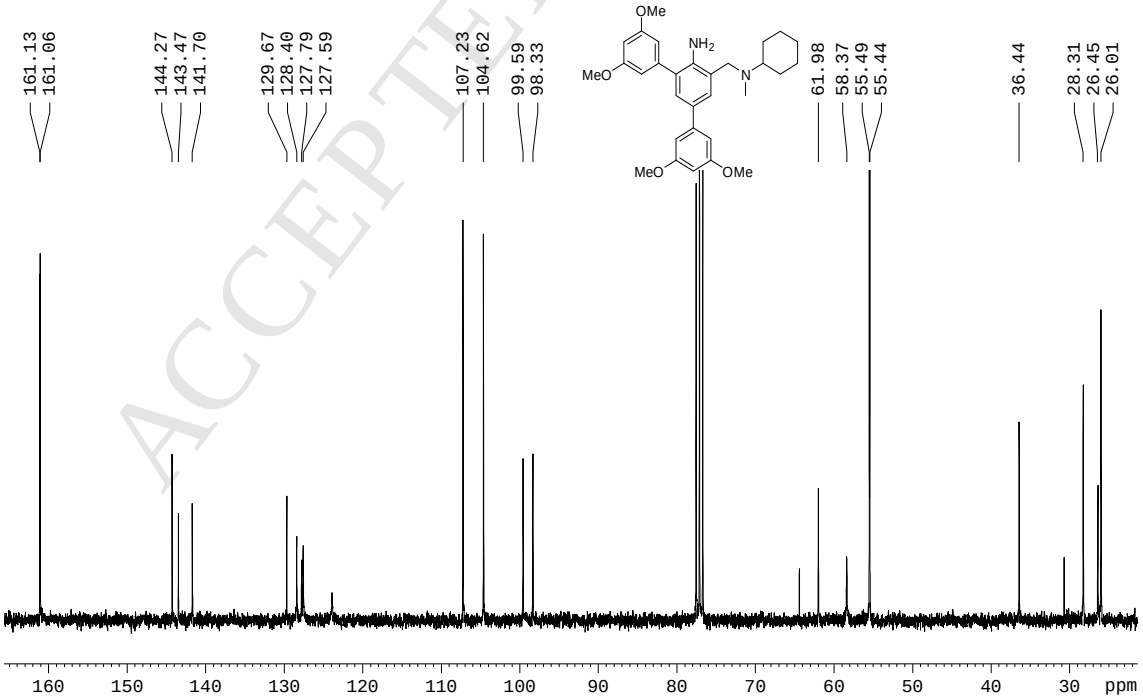


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(3,5-dimethoxyphenyl)aniline (3p):

^{1}H NMR

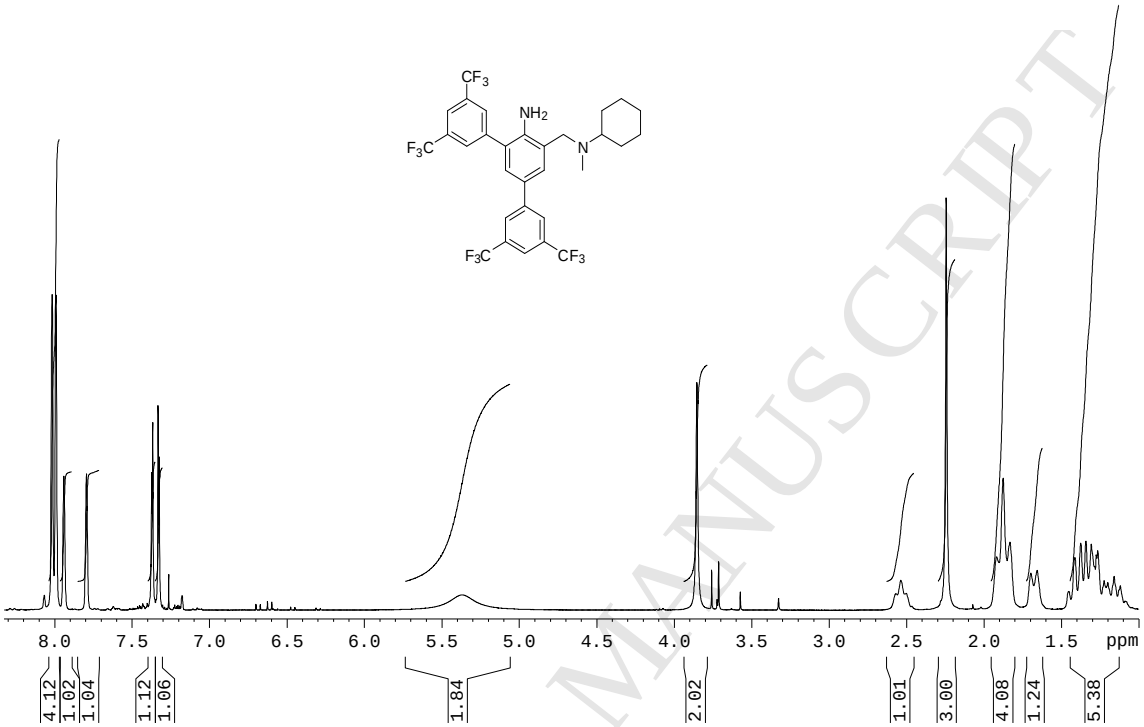


^{13}C NMR

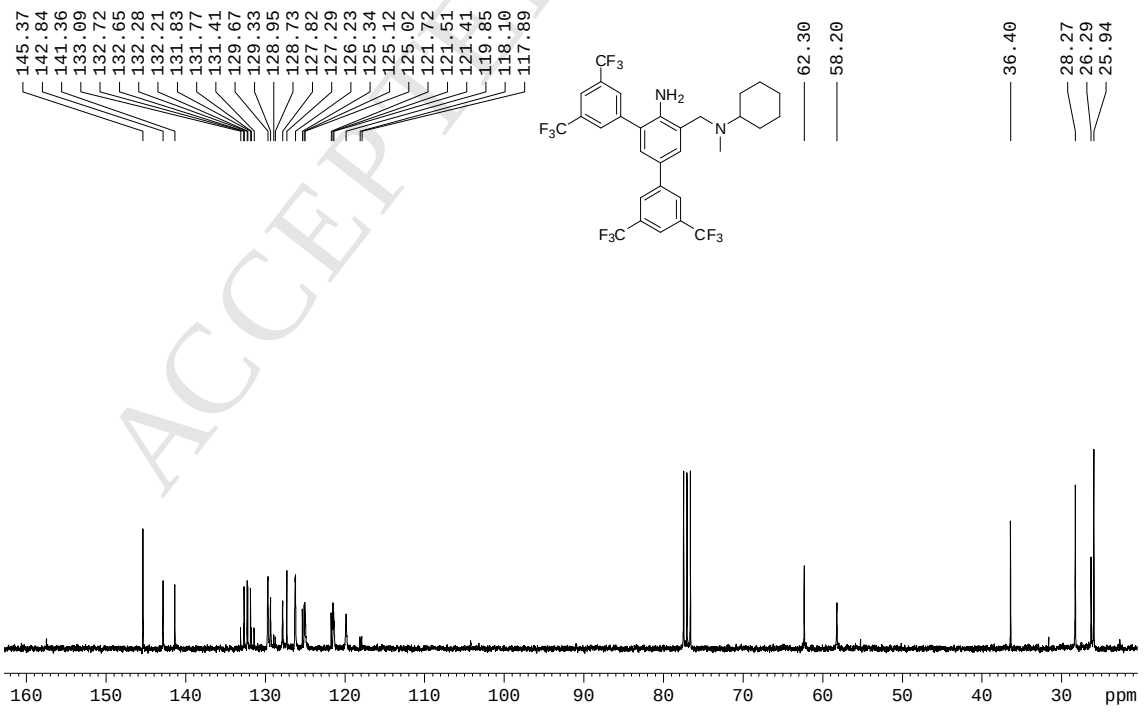


2,4-Bis[3,5-bis(trifluoromethyl)phenyl]-6-{[cyclohexyl(methyl)amino]methyl}aniline (3q):

^{1}H NMR

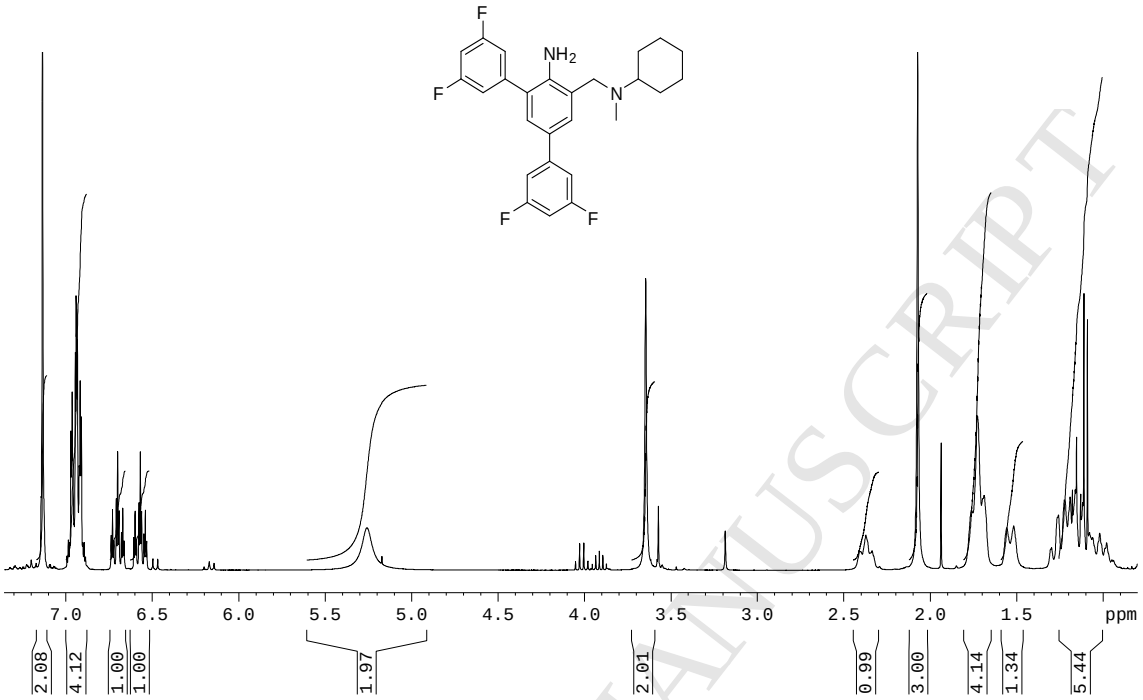


^{13}C NMR

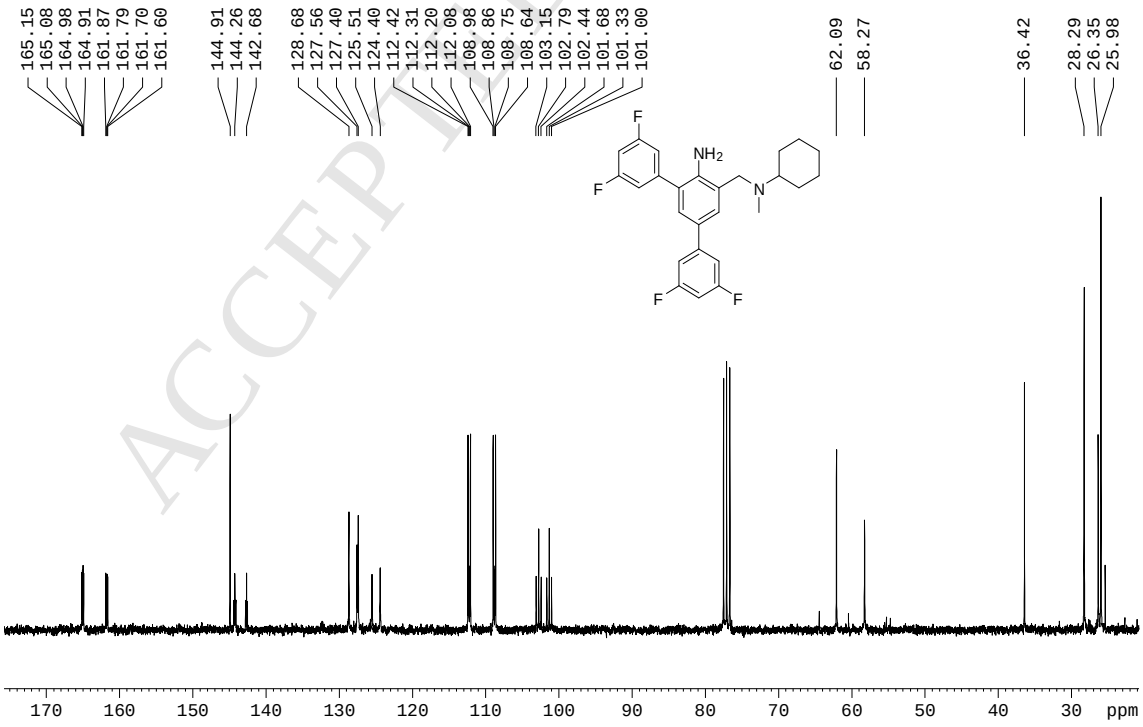


2-{[Cyclohexyl(methyl)amino]methyl}-4,6-bis(3,5-difluorophenyl)aniline (3r):

^{1}H NMR

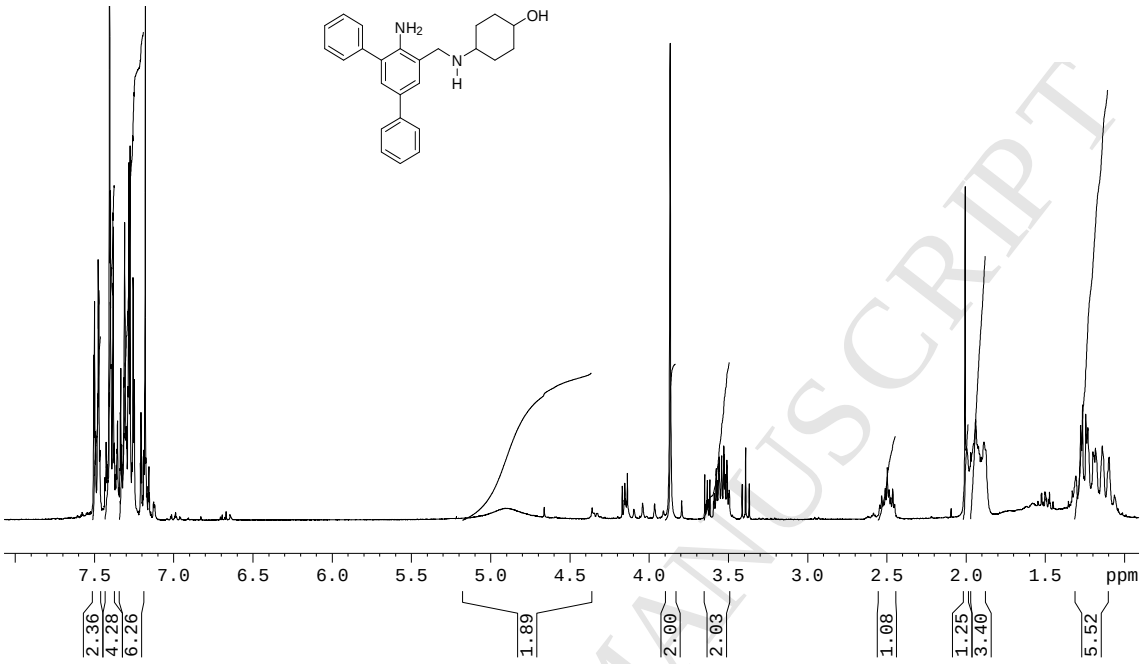


^{13}C NMR

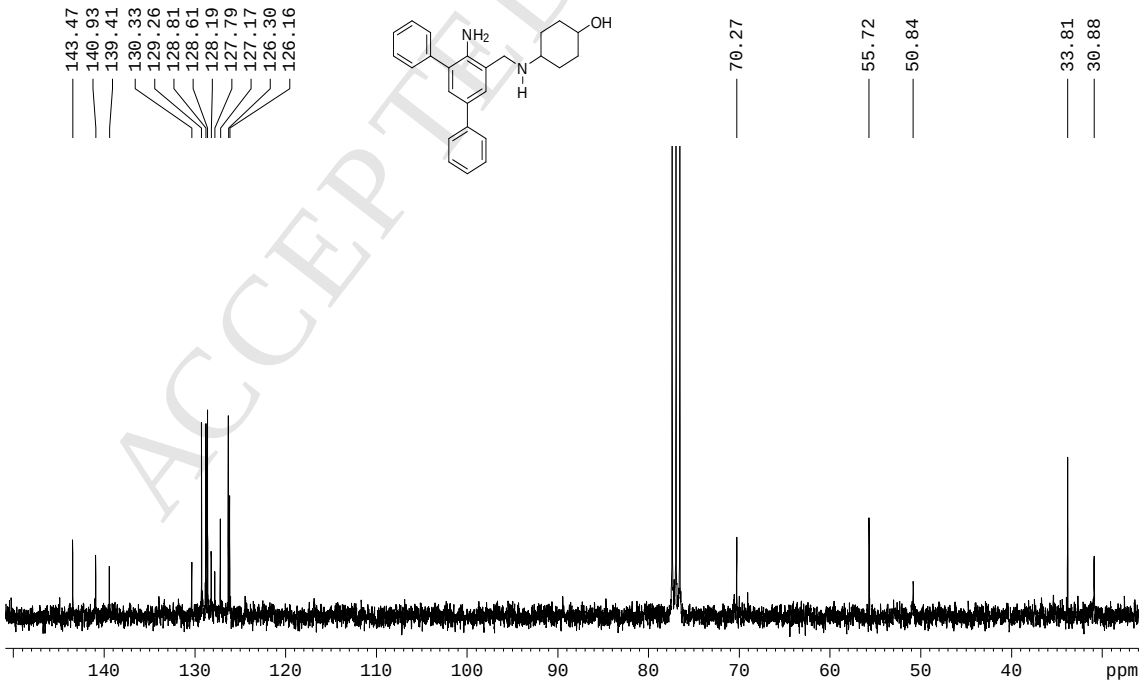


4-{[(2-Amino-3,5-diphenyl)methyl]amino}cyclohexan-1-ol (5a):

^{1}H NMR

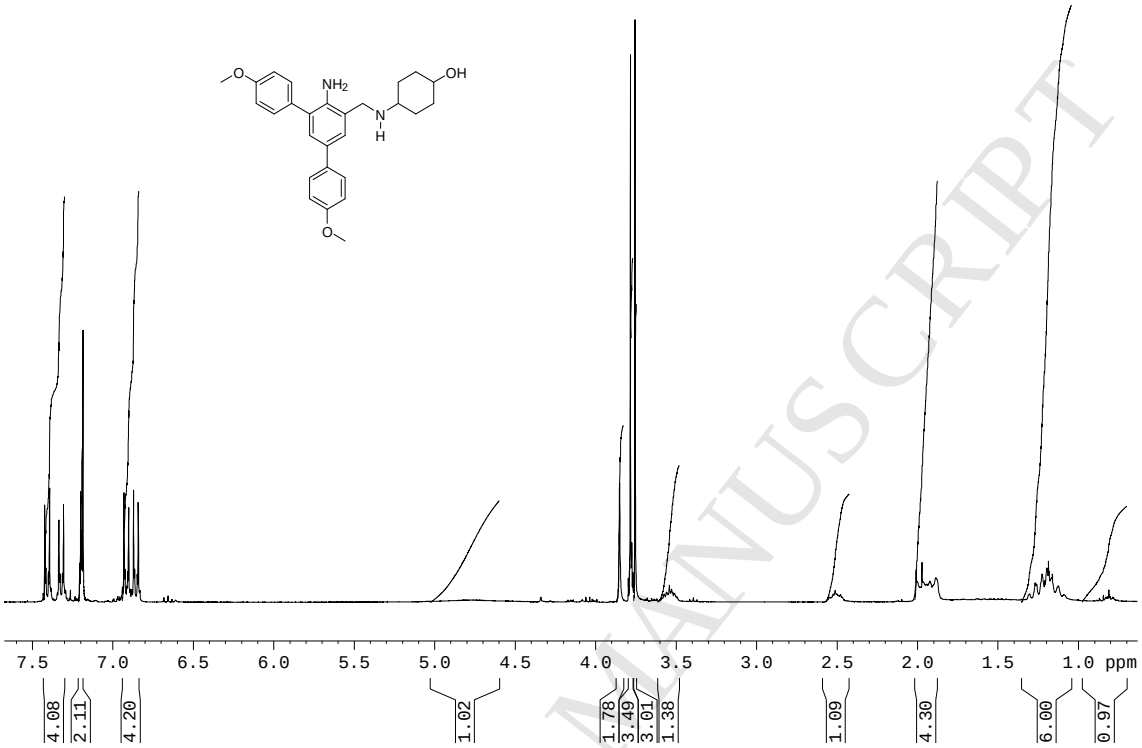


^{13}C NMR



4-{[(2-Amino-3,5-bis(4-methoxyphenyl)phenyl]methyl}amino)cyclohexan-1-ol (5b):

^{1}H NMR



^{13}C NMR