Supporting Information

Biphenyl scaffold for the design of NMDA-receptor negative modulators: molecular modeling, synthesis, and biological activity

Dmitry S. Karlov[a], Nadezhda S. Temnyakova[b], Dmitry A. Vasilenko[b], Oleg I. Barygin[c], Mikhail Y. Dron[c], Arseniy S. Zhigulin[c], Elena B. Averina[b,d], Yuri K. Grishin[b], Vladimir V. Grigoriev[d], Alexey V. Gabrel'yan[d], Viktor A. Aniol[e], Natalia V. Gulyaeva[e], Sergey V. Osipenko[a], Yury I. Kostyukevich[a], Vladimir A. Palyulin[b,d], Petr A. Popov[a], Maxim V. Fedorov[a,f]

[a] Skolkovo Institute of Science and Technology, Skolkovo Innovation Center, 143026 Moscow, Russian Federation
[b] Department of Chemistry, Lomonosov Moscow State University, 119991 Moscow, Russian Federation
[c] I. M. Sechenov Institute of Evolutionary Physiology and Biochemistry, Russian Academy of Sciences, 194223 St. Petersburg, Russian Federation
[d] Institute of Physiologically Active Compounds, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation
[e] Institute of Higher Nervous Activity and Neurophysiology, Russian Academy of Sciences, 117485 Moscow, Russian Federation
[f] University of Strathclyde, Physics John Anderson Building, 107 Rottenrow East Glasgow, UK G4 0NG

Contents

1. Molecular modeling details S1
2. *In vitro* assays S2
3. Animal testing S3
4. Synthesis S4
5. Spectra S12
6. LC-MS results S40
7. References S45

Molecular modeling details

Docking and structure preparation

The docking study was performed using Autodock Vina[1] with the exhaustiveness value equal to 5000 for the compound 10i and 500 for all other cases. Only automatically recognised rotatable torsions were allowed to rotate during docking study. The structure of the receptor was taken from Protein Data Bank (PDB code: 6e7r[2]) was prepared with MGL Tools[3]. The receptor was kept rigid during docking and the scoring function was not modified.

Ligand and protein parameters were assigned with GAFF[4] and Amber ff14SB force field[5], respectively. Charges for the docked ligands were calculated with AM1-BCC method[6]. The resulting structures were solvated precisely utilizing 3D-RISM and Placevent[7] approaches. The resulting complex neutralization

was performed by the addition of sodium ions and solvated (TIP3P water model) obtaining the octahedral boxes containing about 100,000 atoms.

Molecular dynamics simulations

All simulations were carried out in Amber18 package[8]. First, the energy minimization step included 1000 steps of steepest descent and 1000 steps of conjugate gradients minimization were performed. Second, the optimized structures were introduced to a heating phase with restrained Cartesian coordinates (force constant 2.0 kcal/(mol × Å2)) of protein Cα and all ligand atoms during the NVT simulation (50 ps) using Berendsen thermostat with the default temperature coupling constant and integration step value set to 1 fs. Third, the NPT simulation (500 ps) with restraints applied identically to the heating phase was conducted for the obtained structures using Langevin thermostat (collision frequency γ set to 2.0 ps−1). The application of SHAKE algorithm allowed us to use an integration step of 2 fs. After the system density became stable, 10 ns trajectory was recorded for each prepared system. Binding energy calculation was performed using MM-PBSA and MM-GBSA[9] approaches implemented in AmberTools18 with one trajectory approach. MM-GBSA approach was applied using Generalized Born solvation model developed by Onufriev and Case[10]. MM-PBSA approaches were utilized with variable internal dielectric constant: 2, 4, 8. RMSD and number of hydrogen bonds were computed using CPPTRAJ11 program

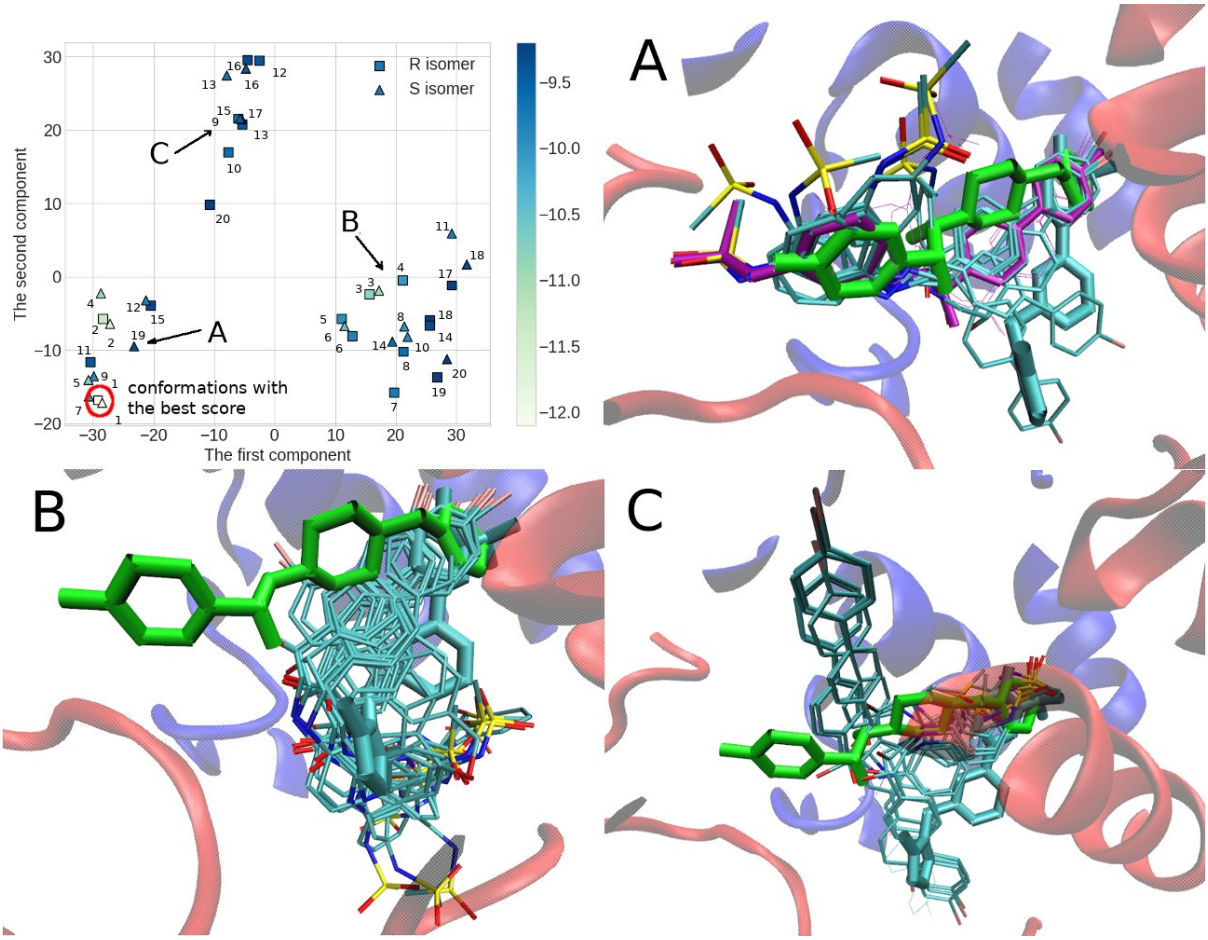


Figure 1S. The results of docking thorough docking study performed for compounds 10i (R and S isomers). Upper left panel shows the Principle Component Analysis (PCA) application results for ligands' coordinates obtained by docking procedure. The docking score is labeled by the color of a point. The color of the best pose is white while darker color corresponds to a docking pose with higher

value of the scoring function. 20 best conformations for both R and S isomers are shown. Conformations which correspond to three resulting clusters are visualized on subplots A, B, and C. Red circle denotes the best docking pose which corresponds to cluster A and is shown in magenta. Each point is labeled by a number which is a number of the current conformation in a sorted list of docking solutions (Table 1S).

Table 1S. The results of MD trajectory analysis for top 20 docking solutions for R and S enantiomers of the compound **10i**.

Number of conformation in the sorted list of docking solutions	R/S	Vina docking score, kcal/mol	MM-GBSA binding energy ± std, kcal/mol	Mean RMSD of the ligand ± std, Å	Mean number of hydrogen bonds with protein during the simulation
1	R	-11.7	**-60.7 ± 3.4**	1.67 ± 0.07	1.93
	S	-12.1	**-59.1 ± 3.0**	1.72 ± 0.13	2.04
2	R	-11.0	-27.6 ± 4.5	1.82 ± 0.11	1.65
	S	-11.7	**-52.5 ± 3.6**	1.95 ± 0.12	1.53
3	R	-10.5	-32.7 ± 3.2	2.89 ± 0.14	1.63
	S	-11.0	-45.4 ± 3.7	0.75 ± 0.16	2.17
4	R	-9.8	-38.1 ± 3.3	2.50 ± 0.16	1.98
	S	-10.9	-44.5 ± 3.3	2.85 ± 0.22	1.08
5	R	-9.7	-36.2 ± 5.2	1.62 ± 0.20	0.63
	S	-10.7	-43.8 ± 2.6	2.12 ± 0.06	0.06
6	R	-9.6	-36.1 ± 3.5	2.27 ± 0.24	1.04
	S	-10.5	-36.7 ± 5.1	1.50 ± 0.16	0.81
7	R	-9.5	-27.7 ± 4.4	1.32 ± 0.23	0.37
	S	-10.1	**-53.1 ± 2.9**	0.67 ±	2.58

				0.11	
8	R	-9.4	-33.9 ± 3.4	2.03 ± 0.17	0.83
	S	-10.0	-31.8 ± 4.5	0.99 ± 0.16	0.71
9	R	-9.4	-34.3 ± 4.2	2.30 ± 0.23	1.49
	S	-9.9	-41.9 ± 3.2	1.58 ± 0.09	1.49
10	R	-9.4	-35.7 ± 5.0	2.81 ± 0.24	0.75
	S	-9.9	-38.1 ± 2.5	2.20 ± 0.11	0.92
11	R	-9.2	-46.7 ± 3.0	1.05 ± 0.16	1.65
	S	-9.8	-40.5 ± 3.6	1.80 ± 0.21	1.23
12	R	-9.2	-34.7 ± 4.5	1.79 ± 0.17	1.04
	S	-9.8	-43.3 ± 3.2	1.33 ± 0.10	1.40
13	R	-9.2	-33.4 ± 3.3	1.68 ± 0.11	0.78
	S	-9.7	-23.1 ± 2.5	1.88 ± 0.26	0.76
14	R	-9.1	-33.6 ± 4.3	1.43 ± 0.17	0.45
	S	-9.6	-24.4 ± 2.5	2.26 ± 0.20	0.96
15	R	-9.1	-39.8 ± 4.0	1.09 ± 0.16	1.83
	S	-9.5	-40.6 ± 3.2	0.93 ± 0.22	0.30
16	R	-9.1	-28.3 ± 3.3	2.27 ± 0.10	0.77
	S	-9.4	-37.2 ± 2.9	1.92 ± 0.09	0.49

17	R	-9.0	-23.0 ± 3.2	1.61 ± 0.24	1.35
	S	-9.3	-42.8 ± 3.1	2.13 ± 0.15	0.83
18	R	-9.0	-36.3 ± 3.8	0.76 ± 0.14	1.23
	S	-9.3	-26.4 ± 2.7	0.85 ± 0.17	1.60
19	R	-9.0	-31.2 ± 2.8	1.94 ± 0.14	0.93
	S	-9.3	-40.1 ± 3.1	2.83 ± 0.15	1.00
20	R	-9.0	-31.2 ± 2.8	1.84 ± 0.17	1.16
	S	-9.2	-28.6 ± 3.4	1.73 ± 0.42	0.71

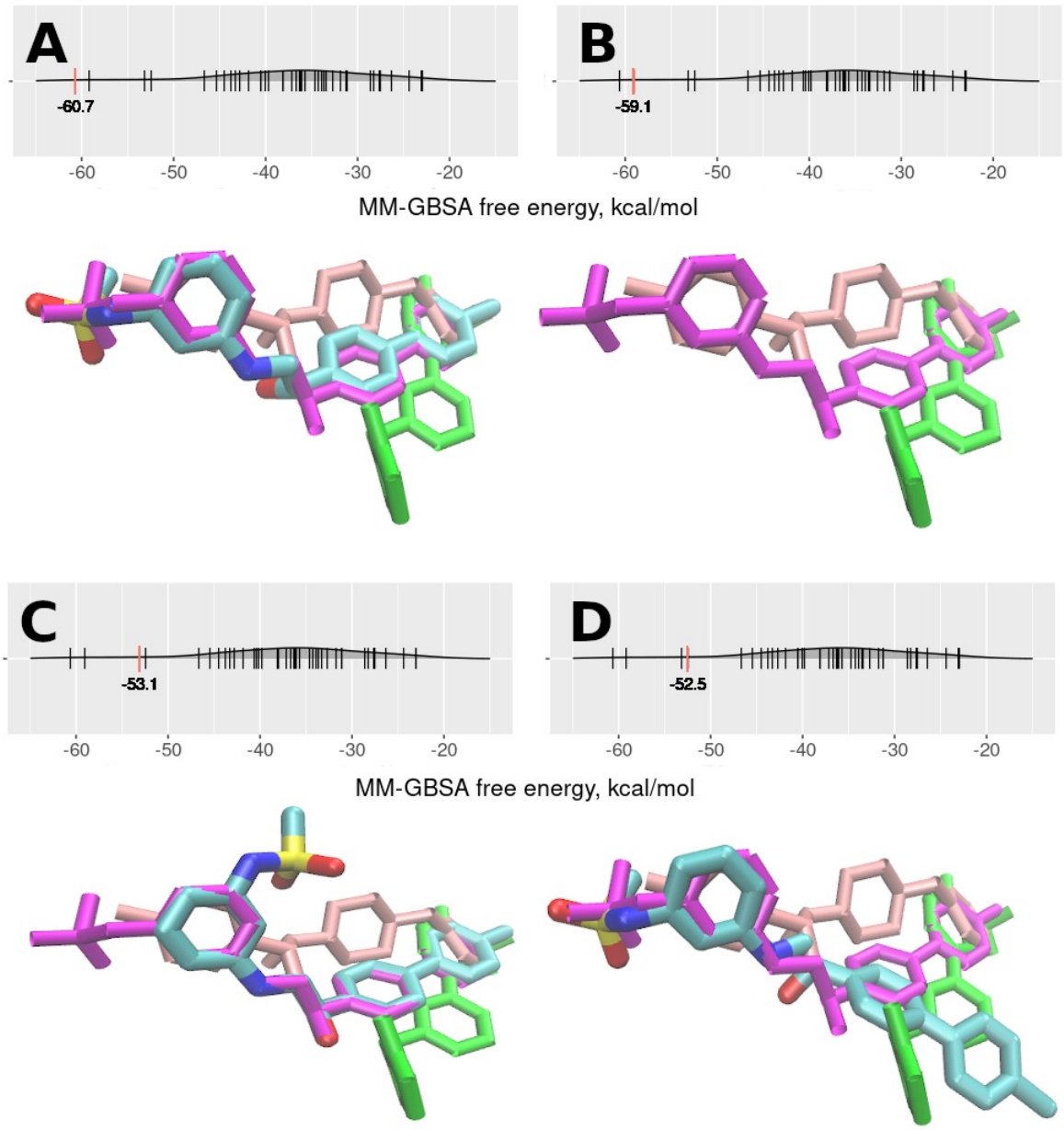


Figure 2S. The binding modes of four top ranked docking poses in terms of MM-GBSA binding free energy. (A) - conformation 1R, (B) - conformation 1S, (C) - conformation 2S, (D) - conformation 7S. The notation corresponds to Table 1S. The X-ray coordinates of ifenprodil (pink), EVT-101 (green), and the best conformation of compound 10i (S-enantiomer) - conformation labeled as 1S in Table 1S were taken as reference.

In vitro assays

Electrophysiological study

All experimental procedures were approved by Animal Care and Use Committee of the Sechenov Institute of Evolutionary Physiology and Biochemistry of the Russian Academy of Sciences. Outbred male Wistar rats of 13–18 d old and 25–35 g were obtained from the local (IEPHB) facility. Maximum efforts were made to minimize the number of animals used and to minimize discomfort. Rats were anesthetized with urethane and then decapitated. Brains were removed quickly and cooled to 2–4 °C. Transverse hippocampal slices were prepared using a vibratome (Campden Instr.) and single neurons

were freed from slices by vibrodissociation[12]. All experiments were performed at room temperature. The whole-cell patch-clamp technique was used for recording membrane currents in response to applications of an agonist. The series resistance of about 20 MΩ was compensated by 70–80 % and monitored during experiments. Currents were recorded using an EPC-8 amplifier (HEKA Electronics, Lambrecht, Germany), filtered at 5 kHz, sampled and stored on a personal computer. Drugs were applied using RSC-200 (BioLogic) perfusion system under computer control. The extracellular solution contained (in mM): NaCl 143, KCl 5, $CaCl_2$ 2.5, D-glucose 18, HEPES 10 (pH was adjusted to 7.4 with NaOH). The pipette solution contained (in mM): CsF 100, CsCl 40, NaCl 5, $CaCl_2$ 0.5, EGTA 5, HEPES 10 (pH was adjusted to 7.2 with CsOH). Experiments were conducted on hippocampal pyramidal neurons (CA1 area). NMDA receptors were activated by 100 μM NMDA plus 10 μM glycine. The percentage of blockage of the steady-state current by investigated compound concentrations was measured at –80 mV holding potential and IC_{50} values were obtained from fits by the Hill equation of concentration-inhibition relationships. All data are presented as means ± SD estimated from at least four experiments.

Radioligand experiments

The preparation of rat brain membranes is described previously[13]. The hippocampal tissue was homogenized with a Potter homogenizer (teflon pestle and glass vessel), using a tissue grinder at half-maximal setting, in 20 vol of buffer No. 1 (5 mM HEPES / 4.5 mM Tris buffer, pH 7.6, sucrose 0.32 M). The homogenate is diluted with a buffer for study No. 2 (5 mM HEPES / 4.5 mM Tris buffer, pH 7.6) in a ratio of 1:50, then it was centrifuged at 1000g for 10 min. The supernatant was collected and then centrifuged at 25000g for 20 min. The precipitate is homogenized in buffer No. 2 at a ratio of 1:50 and centrifuged for 20 minutes at 8000 g. The precipitate is suspended in buffer No. 3 (5 mM HEPES / 4.5 mM Tris buffer, (pH 7.6), 5 mM Na_4EDTA), and the suspension is centrifuged again. This washing procedure is performed four times, and at the last wash, Na_4EDTA is excluded from the buffer composition. The final precipitate is resuspended in 5 vol of buffer No. 2 and stored in liquid nitrogen. On the day of use the membrane fraction is thawed. The working solution (final volume 0.5 ml) contains 200 μl of buffer No. 2, 50 μl of [H^3]-ifenprodil (40 nM) with specific activity 179 Ci/mM and 250 μl of the membrane suspension. Non-specific binding is determined in the presence of 50 μL of unlabeled ifenprodil (10 μM). The mixture is incubated at room temperature for 2 hours. At the end of the incubation, the samples are filtered through GF/B glass fiber filters (Whatman), pre-moistened in 0.3% polyethyleneimine for 2 hours at 4 °C. Each tube is washed once with cold buffer No. 2, then the filters are washed three times with the same buffer volume. Filters are air-dried until completely dry and transferred to scintillation vials, into which 5 ml of scintillation fluid containing 4 g of diphenyloxazole (PPO), 0.2 g of diphenyloxazoylbenzene (POPOP) and 1 l of toluene are added. Radioactivity is determined on a TriCarb2800 TR scintillation counter (PerkinElmer, Packard, USA) with a counting efficiency of about 65%. The study of the effect of the investigated compounds on the binding of [H^3]-ifenprodil with rat hippocampal membranes is carried out with the addition of 50 μl of the solution of the studied compounds to the incubation medium in the concentration range 10^{-8} - 10^{-3} M. Each concentration was measured 3 times and the average value is reported.

Animal testing

In the present study we analyzed the antidepressant activity of compound 10h using the forced swimming test (FST), which is a commonly used test in preclinical studies of new antidepressant drugs[16-19]. Forty adult male ICR (CD-1) mice weighing 20–25 g were used in behavioral experiment. Mice were housed under standard vivarium conditions (7-8 mice in cage) with free access to food and water and artificial light-dark cycle (light phase 8:00-20:00). Animals were handled prior to experiment,

marked and randomly assigned for four groups (n=10 in each): negative control group (intraperitoneal injection of isotonic NaCl solution with 5% DMSO), positive control group (oral administration of fluoxetine, 160 mg/kg), and two groups injected intraperitoneally with 1 mg/kg or 5 mg/kg of compound **10h** dissolved in isotonic NaCl with 5% DMSO. All solutions were prepared on the day of experiment and administered one hour before the FST.

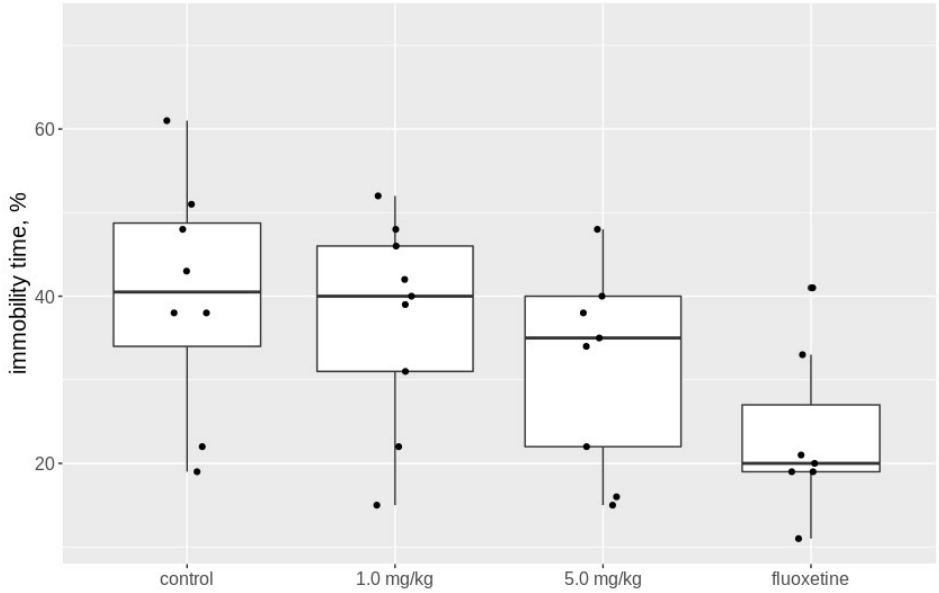


Figure 3S. The results of Porsolt Forced Swimming Test for compound **10h**.

The assessment of antidepressant activity of compound **10h** was performed in the FST in one-day paradigm. Mice were placed into plexiglas cylinders filled with at least 20 cm of water (24–26°C) for 5 minutes. The water in the cylinders was replaced and its temperature checked for each animal. Behavior of mice was videotaped for later analysis. We measured the total time of immobility, defined as passive floating with only single movements allowed, necessary to keep the head above the water surface. The values of total immobility time were compared with respective values of control group using non-parametric Mann-Whitney U-test.

Synthesis

NMR spectra were recorded on spectrometers Agilent 400-MR (400.0 MHz for ^{1}H; 100.6 MHz for ^{13}C) and Bruker Avance 400 (400.1 MHz for ^{1}H; 100.6 MHz for ^{13}C) at room temperature; the chemical shifts δ were measured in ppm with respect to the solvent (^{1}H: $CDCl_3$, δ = 7.26 ppm, CD_3OD, δ = 3.31 ppm, DMSO-d_6, δ = 2.50 ppm,; ^{13}C: $CDCl_3$, δ = 77.16 ppm, CD_3OD, δ = 49.0 ppm, DMSO-d_6, δ = 39.5 ppm,). Chemical shifts (δ) are given in ppm; *J* values are given in Hz. When necessary, assignments of signals in NMR spectra were made using 2D techniques. Accurate mass measurements (HRMS) were performed on a Bruker micrOTOF II instrument using electrospray ionization (ESI). The measurements were done in a positive ion mode (interface capillary voltage 4500 V) or in a negative ion mode (3200 V). Melting points (mp) are uncorrected. Analytical thin layer chromatography was carried out with Silufol silica gel plates (supported on aluminum); the detection was done by UV lamp (254 and 365 nm) and chemical staining (5% aqueous solution of $KMnO_4$). Column chromatography was performed on silica gel (230–400 mesh, Merck). Purity was determined by LC-MS analysis on Ultimate 3000 RSLC coupled with Q Exactive mass-spectrometer LC-MS system (both Thermo Scientific). Separation was performed on Acclaim PepMap C18 RCLS nano column (25 cm×0.075 mm, 2 μ) in the

following gradient: 0-5 min 40%B, 5-25 min 40-95%B, 25-35 min 95%B, 35-40 min 95-40%B, 40-50 min 40%B. Mobile phase consisted of 0.1% formic acid (A) and 0.1% formic acid in acetonitrile (B). Injection volume was set at 0.25 μL. Compounds were detected in ESI-positive full-scan mode.

α-Bromketone **7b** was synthesized from commercially available 1-(4'-bromobiphenyl-4-yl)ethanone by known procedure[20]. All other starting materials were commercially available.

All reagents except commercial products of satisfactory quality were purified by literature procedures prior to use.

1.1. Synthesis of 3-aminophenyl tert-butyl carbonate 8e

To a suspension of NaH (440 mg of a 60% suspension NaH in mineral oil, 10.48 mmol) in THF (10 ml) was added a solution of 3-aminophenol (1.0 g, 9.52 mmol) in THF (10 ml) at 0°C in argon atmosphere and then the mixture was stirred at room temperature for 30 min. A solution of Boc_2O (2.08 g, 9.52 mmol) in THF (7 ml) was added and the resulting mixture was stirred at room temperature for 24 h. Then the reaction mixture was cooled to 0°C and quenched with 20 ml water. The aqueous phase was extracted with diethyl ether (3x20 ml), the combined organic layers were washed with water (3x15ml), saturated aqueous NaCl (2x15ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, the residue was used without further purification.

Yield 1.76 g (90 %); colorless oil; δ_H (400 MHz, $CDCl_3$): 1.54 (s, 9H, $3CH_3$), 3.72 (br.s, 2H, NH_2), 6.43-6.47 (m, 1H, CH(Ar)), 6.47-6.55 (m, 2H, 2CH(Ar)), 7.06-7.14 (m, 1H, CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 27.7 ($3CH_3$), 83.3 (C), 107.9 (CH), 110.9 (CH), 112.5 (CH), 129.9 (CH), 147.8 (C), 151.98 (C), 152.00 (C); HRMS $[M + H]^+$: calcd. for $C_{11}H_{16}NO_3$ 210.1125, found 210.1124.

1.2. Synthesis of compounds 9a-i

General Procedure 1 for preparation of compounds **9a-c**.

The mixture of corresponding phenol **8** (1 mmol) and K_2CO_3 (0.28 g, 2 mmol) in anhydrous MeCN (8 mL) was stirred at r.t. for 30 min, then α-bromketone **7a** (0.28 g, 1 mmol) in anhydrous MeCN (4 mL) was added in one portion. The resulting mixture was stirred at r.t. for 12 h (TLC monitoring), and then was poured into cold water (15 ml) and extracted with CH_2Cl_2 (3x15 ml). The combined organic layers were washed with water (3x15ml), saturated aqueous NaCl (2x15ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, the residue was purified by column chromatography (SiO_2, petroleum /ethyl acetate, 4/1, compound **9a,c**) or recryctallization from acetone (compound **9b**).

3-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate 9a[21]:

The compound **9a** was prepared from phenol **8a**. Yield 0.21 g (62 %); light yellow solid, mp 107-110 °C; R_f = 0.48 (petroleum/ethylacetate, 8/1); δ_H (400 MHz, $CDCl_3$): 2.28 (s, 3H, CH_3), 5.27 (s, 2H, CH_2), 6.71-6.77 (m, 2H, 2CH(Ar)), 6.82-6.87 (m, 1H, CH(Ar)), 7.24-7.31 (m, 1H, CH(Ar)), 7.38-7.45 (m, 1H, CH(Ar)), 7.45-7.52 (m, 2H, 2CH(Ar)), 7.60-7.66 (m, 2H, 2CH(Ar)), 7.68-7.74 (m, 2H, 2CH(Ar)), 8.03-8.10 (m, 2H, 2CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 21.3 (CH_3), 71.1 (CH_2), 108.8 (CH(Ar)), 112.6 (CH(Ar)), 115.0 (CH(Ar)), 127.4 (2CH(Ar)), 127.6 (2CH(Ar)), 128.6 (CH(Ar)), 128.9 (2CH(Ar)), 129.2 (2CH(Ar)), 130.1 (CH(Ar)), 133.2 (C(Ar)), 139.8 (C(Ar)), 146.8 (C(Ar)), 151.7 (C(Ar)), 159.0 (C(Ar)), 169.5 (C=O), 193.9 (C=O). HRMS $[M + H]^+$: calcd. for $C_{22}H_{19}O_4$ 347.1278, found 347.1274.

1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanone 9b[22]:

The compound **9b** was prepared from phenol **8b**. Yield 0.22 g (76 %); colorless solid, mp 92-93°C; δ_H (400 MHz, $CDCl_3$): 5.30 (s, 2H, CH_2), 6.95-7.04 (m, 3H, 3CH(Ar)), 7.28-7.34 (m, 2H, 2CH(Ar)), 7.39-7.45 (m, 1H, CH(Ar)), 7.46-7.52 (m, 2H, 2CH(Ar)), 7.61-7.67 (m, 2H, 2CH(Ar)), 7.70-7.75 (m, 2H, 2CH(Ar)), 8.06-8.13 (m, 2H, 2CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 70.9 (CH_2), 114.9 (2CH(Ar)), 121.8 (CH(Ar)), 127.4 (2CH(Ar)), 127.5 (2CH(Ar)), 128.5 (CH(Ar)), 128.9 (2CH(Ar)), 129.1 (2CH(Ar)), 129.7 (2CH(Ar)), 133.3 (C(Ar)), 139.7 (C(Ar)), 146.6 (C(Ar)), 158.1 (C(Ar)), 194.3 (C=O). HRMS $[M + H]^+$:calcd. for $C_{20}H_{17}O_2$ 289.1223, found 289.1222.

4-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate 9c:

The compound **9c** was prepared from phenol **8c**. Yield 0.34 g (99 %); light yellow solid, mp 130-131°C; R_f = 0.24 (petroleum/ethylacetate, 4/1); δ_H (400 MHz, $CDCl_3$): 2.28 (s, 3H, CH_3), 5.28 (s, 2H, CH_2), 6.93-6.99 (m, 2H, 2CH(Ar)), 6.99-7.04 (m, 2H, 2CH(Ar)), 7.39-7.45 (m, 1H, CH(Ar)), 7.46-7.52 (m, 2H, 2CH(Ar)), 7.61-7.67 (m, 2H, 2CH(Ar)), 7.70-7.75 (m, 2H, 2CH(Ar)), 8.05-8.11 (m, 2H, 2CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 21.2 (CH_3), 71.4 (CH_2), 115.7 (2CH(Ar)), 122.6 (2CH(Ar)), 127.4 (2CH(Ar)), 127.6 (2CH(Ar)), 128.6 (CH(Ar)), 128.9 (2CH(Ar)), 129.1 (2CH(Ar)), 133.2 (C(Ar)), 139.7 (C(Ar)), 145.0 (C(Ar)), 146.8 (C(Ar)), 155.8 (C(Ar)), 170.0 (C=O), 194.1 (C=O). HRMS $[M + H]^+$:calcd. for $C_{22}H_{19}O_4$ 347.1278, found 347.1275.

General Procedure 2 for preparation of compounds **9d-i**.

The mixture of corresponding aniline **8** (1 mmol) and α-bromketone **7** (1 mmol) in MeOH (4 ml) was stirred at r.t. for 24 h (TLC monitoring), and then the reaction mixture was refluxed for 30 min. After cooling the precipitate was filtered and purified by column chromatography or recrystallization from acetone.

1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanone 9d[23]:

The compound **9d** was prepared from aniline **8d** and α-bromketone **7a**. Yield 0.18 g (62 %); light yellow solid, mp 160-162°C; R_f= 0.92 (CH_2Cl_2/CH_3OH, 20/1); δ_H (400 MHz, $CDCl_3$): 4.66 (s, 2H, CH_2), 4.97 (br.s, 1H, NH), 6.71-6.81 (m, 3H, 3CH(Ar)), 7.21-7.29 (m, 2H, 2CH(Ar)), 7.39-7.46 (m, 1H, CH(Ar)), 7.46-7.54 (m, 2H, 2CH(Ar)), 7.62-7.68 (m, 2H, 2CH(Ar)), 7.72-7.77 (m, 2H, 2CH(Ar)), 8.07-8.14 (m, 2H, 2CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 50.5 (CH_2), 113.2 (2CH(Ar)), 117.9 (CH(Ar)), 127.4 (2CH(Ar)), 127.6 (2CH(Ar)), 128.5 (2CH(Ar)), 128.6 (CH(Ar)), 129.2 (2CH(Ar)), 129.5 (2CH(Ar)), 133.7 (C(Ar)), 139.8 (C(Ar)), 146.7 (C(Ar)), 147.3 (C(Ar)), 194.8 (C=O). HRMS $[M + H]^+$:calcd. for $C_{20}H_{18}NO$ 288.1383, found 288.1381.

3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl tert-butyl carbonate 9e:

The compound **9e** was prepared from aniline **8e** and α-bromketone **7a**. Yield 0.22 g (55 %); colorless solid, mp 188-189 °C with decomp.; δ_H (400 MHz, DMSO-d_6): 1.47 (s, 9H, $3CH_3$), 3.40 (br.s 1H, NH), 4.73 (s, 2H,CH_2), 6.32-6.40 (m, 1H, CH(Ar)), 6.51-6.57 (m, 1H, CH(Ar)), 6.58-6.66 (m, 1H, CH(Ar)), 7.04-7.14 (m, 1H, CH(Ar)), 7.41-7.48 (m, 1H, CH(Ar)), 7.48-7.57 (m, 2H, 2CH(Ar)), 7.73 -7.82 (m, 2H, 2CH(Ar)), 7.83-7.91 (m, 2H, 2CH(Ar)), 8.13-8.22 (m, 2H, 2CH(Ar)); δ_C (100.6 MHz, DMSO-d_6): 27.3 ($3CH_3$), 49.9 (CH_2), 82.7 ($\underline{C}(CH_3)_3$), 105.3 (CH(Ar)), 108.8 (CH(Ar)), 110.2 (CH(Ar)), 127.0 (2CH(Ar)), 127.1 (2CH(Ar)), 128.5 (CH(Ar)), 128.7 (2CH(Ar)), 129.1 (2CH(Ar)), 129.5 (CH(Ar)),

133.9 (C(Ar)), 138.9 (C(Ar)), 145.0 (C(Ar)), 149.5 (C(Ar)), 151.4 (C(Ar)), 151.7 (C=O), 196.0 (C=O). HRMS $[M + H]^+$:calcd. for $C_{25}H_{26}NO_4$ 404.1856, found 404.1848.

N-(3-((2-([1,1'-biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)acetamide 9g:

The compound **9g** was prepared from aniline **8g** and α-bromketone **7a**. Yield 0.22 g (64 %); light yellow solid, mp 124-127 °C; R_f= 0.32 (CH_2Cl_2/CH_3OH, 20/1); δ_H (400 MHz, DMSO-d_6): 1.99 (s, 3H, CH_3), 4.66 (br.d, *J* = 5.5 Hz, 2H, CH_2), 5.94 (br.t, *J* = 5.5 Hz, 1H, NH), 6.32-6.39 (m, 1H, 1CH(Ar)), 6.78-6.84 (m, 1H, CH(Ar)), 6.88-6.93 (m, 1H, CH(Ar)), 6.94-7.01 (m, 1H, CH(Ar)), 7.41-7.48 (m, 1H, CH(Ar)), 7.49-7.56 (m, 2H, 2CH(Ar)), 7.74 -7.80 (m, 2H, 2CH(Ar)), 7.83-7.90 (m, 2H, 2CH(Ar)), 8.11-8.17 (m, 2H, 2CH(Ar)), 9.66 (s, 1H, NH); δ_C (100.6 MHz, DMSO-d_6): 24.1 (CH_3), 49.9 (CH_2), 103.3 (CH(Ar)), 107.6 (2CH(Ar)), 127.00 (2CH(Ar)), 127.04 (2CH(Ar)), 128.5 (CH(Ar)), 128.6 (2CH(Ar)), 128.9 (CH(Ar)), 129.1 (2CH(Ar)), 134.0 (C(Ar)), 138.9 (C(Ar)), 140.0 (C(Ar)), 144.9 (C(Ar)), 148.5 (C(Ar)), 168.0 (C=O), 196.4 (C=O). HRMS $[M + K]^+$:calcd. for $C_{22}H_{20}N_2O_2K$ 383.1156, found 383.1158.

***N*-(3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide 9h:**

The compound **9h** was prepared from aniline **8h** and α-bromketone **7a**. Yield 0.21g (55 %); light yellow solid, mp 196-198°C; R_f=0.73 (CH_2Cl_2/CH_3OH, 20/1); δ_H (400 MHz, DMSO-d_6): 2.95 (s, 3H, CH_3), 4.67 (d, *J*= 5.5 Hz, 2H, CH_2), 6.09 (t, *J*= 5.5 Hz, 1H, NH), 6.38-6.46 (m, 2H, 2CH(Ar)), 6.51-6.55 (m, 1H, CH(Ar)), 6.99-7.05 (m, 1H, CH(Ar)), 7.41-7.48 (m, 1H, CH(Ar)), 7.49-7.56 (m, 2H, 2CH(Ar)), 7.73-7.81 (m, 2H, 2CH(Ar)), 7.84 -7.90 (m, 2H, 2CH(Ar)), 8.11-8.17 (m, 2H, 2CH(Ar)), 9.44 (s, 1H, NH); δ_C (100.6 MHz, DMSO-d_6): 39.0 (CH_3), 49.8 (CH_2), 104.0 (CH(Ar)), 107.8 (CH(Ar)), 108.1 (CH(Ar)), 127.0 (2CH(Ar)), 127.1 (2CH(Ar)), 128.5 (CH(Ar)), 128.6 (2CH(Ar)), 129.2 (2CH(Ar)), 129.6 (CH(Ar)), 134.0 (C(Ar)), 138.9 (C(Ar)), 139.1 (C(Ar)), 144.9 (C(Ar)), 149.1 (C(Ar)), 196.3 (C=O). HRMS $[M + K]^+$: calcd. for $C_{21}H_{20}N_2O_3SK$ 419.0826, found 419.0822.

N-(3-((2-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide 9i:

The compound **9i** was prepared from aniline **8h** and α-bromketone **7b**. Yield 0.23g (50 %); light yellow solid, mp 156-158 °C; R_f= 0.81 (CH_2Cl_2/CH_3OH, 20/1); δ_H (400 MHz, DMSO-d_6): 2.95 (s, 3H, CH_3), 4.67 (d, *J*= 5.5 Hz, 2H, CH_2), 6.08 (t, *J*= 5.5 Hz, 1H, NH), 6.39-6.47 (m, 2H, 2CH(Ar)), 6.52-6.55 (m, 1H, CH(Ar)), 6.99-7.05 (m, 1H, CH(Ar)), 7.67-7.76 (m, 4H, 4CH(Ar)),7.83-7.90 (m, 2H, 2CH(Ar)), 8.10-8.17 (m, 2H, 2CH(Ar)), 9.43 (s, 1H, NH); δ_C(100.6 MHz, DMSO-d_6): 39.0 (CH_3), 49.9 (CH_2), 104.0 (CH(Ar)), 107.8 (CH(Ar)), 108.1 (CH(Ar)), 122.1 (C(Ar)), 126.9 (2CH(Ar)), 128.7 (2CH(Ar)), 129.1 (2CH(Ar)), 129.6 (CH(Ar)), 132.0 (2CH(Ar)), 134.3 (C(Ar)), 138.0 (C(Ar)), 139.1 (C(Ar)), 143.5 (C(Ar)), 149.0 (C(Ar)), 196.3 (C=O). HRMS $[M + K]^+$:calcd. for $C_{21}H_{19}BrN_2O_3SK$ 498.9933, found 498.9927.

Synthesis of 1-([1,1'-biphenyl]-4-yl)-2-((3-hydroxyphenyl)amino)ethanone 9e':

A solution of trifluoroacetic acid (1.50 g, 1.00 mL, 13 mmol) in dichloromethane (1 ml) was slowly added to a solution of Boc-protected compounds **9e** (0.40 g, 1 mmol) in dichloromethane (2 ml) at 0^0C. The reaction was stirred at 0^0C for 1 hour and then at room temperature for 24 hours. Dichloromethane and the excess of trifluoroacetic acid were removed under reduced pressure. To the residue benzene (10 mL) was added and then it was removed in vacuo. This procedure was repeated three times. The residue was dissolved in water (10 mL) and washed with sat. aq $NaHCO_3$ (25 mL). The aqueous phase was extracted with ethyl acetate (3 × 15 mL) and the combined organic layers were dried over $MgSO_4$. The solvent was evaporated in vacuo. The obtained product **9e'** required no additional purification. Yield

0.25g (77 %); light yellow solid, mp 188-190°C; δ_H(400 MHz, DMSO-d_6): 4.63 (d, *J* = 5.4 Hz, 2H,CH_2), 5.78 (br.t, *J*= 5.4 Hz, 1H, NH), 5.98-6.03 (m, 1H, CH(Ar)), 6.06-6.10 (m, 1H, CH(Ar)), 6.11-6.17 (m, 1H, CH(Ar)), 6.82-6.88 (m, 1H, CH(Ar)), 7.41-7.47 (m, 1H, CH(Ar)), 7.49-7.55 (m, 2H, 2CH(Ar)), 7.74-7.79 (m, 2H, 2CH(Ar)), 7.83-7.88 (m, 2H, 2CH(Ar)), 8.12-8.17 (m, 2H, 2CH(Ar)), 8.94 (s, 1H, OH). δ_C (100.6 MHz, DMSO-d_6): 50.0 (CH_2), 99.5 (CH(Ar)), 103.8 (CH(Ar)), 104.1 (CH(Ar)), 126.97 (2CH(Ar)), 127.03 (2CH(Ar)), 128.5 (CH(Ar)), 128.6 (2CH(Ar)), 129.1 (2CH(Ar)), 129.5 (CH(Ar)), 134.0 (C(Ar)), 138.9 (C(Ar)), 144.9 (C(Ar)), 149.4 (C(Ar)), 158.2 (C(Ar)), 196.5 (C=O). HRMS $[M + H]^+$: calcd. for $C_{20}H_{18}NO_2$ 304.1332, found 304.1329.

1.3. Synthesis of compounds 10a-i

General Procedure 3 for preparation of compounds **10a,c**

To a suspension of $LiAlH_4$ (0.04 g, 1.16 mmol) in THF (9 ml) was added a solution of corresponding ketone **9** (0.58 mmol) in THF (11 ml) at 0°C in atmosphere of Ar and then the mixture was stirred at reflux for 3 h. The resulting mixture was cooled to 0°C and quenched with 20 ml water, then 10% H_2SO_4 (up to pH = 3). The aqueous phase was extracted with ethyl acetate (3x15 ml), the combined organic layers were washed with water (3x15ml), saturated aqueous NaCl (2x15ml) and dried over anhydrous $MgSO_4$. The solvent was evaporated in vacuo, the residue was purified by column chromatography on silica gel (petroleum /ethyl acetate, 3/1).

3-(2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethoxy)phenol 10a:

The compound **10a** was prepared from ketone **9a**. Yield 0.14 g (79%); colorless solid, mp 138-139 °C; R_f = 0.19 (CH_2Cl_2/CH_3OH, 20/1); LC-MS: 24.47 min, purity 93.32%; δ_H (400 MHz, CD_3OD + $CDCl_3$): 3.99 (dd, 1H, CH_2, *J* 9.8, 8.3 Hz), 4.05 (dd, 1H, CH_2, *J* 9.8, 3.7 Hz), 5.06 (dd, 1H, CH, *J* 8.3, 3.7 Hz), 6.37-6.43 (m, 3H, 3CH(Ar)), 7.01-7.08 (m, 1H, CH(Ar)), 7.27-7.33 (m, 1H, CH(Ar)), 7.36-7.42 (m, 2H, 2CH(Ar)), 7.42-7.49 (m, 2H, 2CH(Ar)), 7.52-7.59 (m, 4H, 4CH(Ar)); δ_C(100.6 MHz, CD_3OD): 73.2 (CH), 74.1 (CH_2), 103.1 (CH(Ar)), 106.8 (CH(Ar)), 109.1 (CH(Ar)), 127.90 (2CH(Ar)), 127.93 (2CH(Ar)), 127.96 (2CH(Ar)), 128.3 (CH(Ar)), 129.8 (2CH(Ar)), 130.9 (CH(Ar)), 141.6 (C(Ar)), 141.9 (C(Ar)), 142.0 (C(Ar)), 159.6 (C(Ar)), 161.4 (C(Ar)). HRMS $[M + K]^+$: calcd. for $C_{20}H_{18}O_3K$ 345.0888, found 345.0894.

4-(2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethoxy)phenol 10c:

The compound **10c** was prepared from ketone **9c**. Yield 0.13 g (72%); colorless solid, mp 123-124°C; R_f = 0.19 (petroleum /ethyl acetate, 2/1); LC-MS: rt 22.08 min, purity 90.72%; δ_H (400 MHz, CD_3OD): 4.00 (ps.d, 2H, CH_2, *J* = 5.9 Hz), 5.02 (ps.t, *J*=5.9 Hz, 1H, CH), 6.68-6.74 (m, 2H, 2CH(Ar)), 6.76-6.82 (m, 2H, 2CH(Ar)), 7.27-7.33 (m, 1H, CH(Ar)), 7.36-7.43 (m, 2H, 2CH(Ar)), 7.47-7.52 (m, 2H, 2CH(Ar)), 7.55-7.62 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, CD_3OD): 73.3 (CH), 75.1 (CH_2), 116.8 (2CH(Ar)), 116.9 (2CH(Ar)), 127.87 (2CH(Ar)), 127.89 (2CH(Ar), 128.0 (2CH(Ar)), 128.3 (CH(Ar)), 129.8 (2CH(Ar)), 141.6(C(Ar)), 141.8 (C(Ar)), 142.0 (C(Ar)), 152.5 (C(Ar)), 153.5 (C(Ar)). HRMS $[M + Na]^+$: calcd. for $C_{20}H_{18}O_3Na$ 329.1148, found 329.1148.

General Procedure 4 for preparation of compounds **10b,d,e,h,i**.

To the solution of corresponding ketone **9** (1 mmol) in the mixture of tetrahydrofuran (8 ml) and water (2 ml), $NaBH_4$ (40 mg, 1 mmol) was added in portions to maintain a gentle evolution of gas over 3 min. The resulting mixture was stirred for 3 h at room temperature, then was quenched with saturated

aqueous NH_4Cl (15 ml) and water (15 ml). The aqueous phase was extracted with ethyl acetate (3x15 ml). The combined organic layers were washed water (3x15ml), saturated aqueous NaCl (2x15ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum /ethyl acetate).

1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanol 10b:

The compound **10b** was prepared from ketone **9b**. Yield 0.23 g (80 %); colorless solid, mp 88-90°C; R_f = 0.85 (petroleum /ethyl acetate, 1/1); LC-MS: rt 28.93 min, purity: 95.08%; δ_H (400 MHz, $CDCl_3$): 2.98 (br.s, 1H, OH), 4.09 (dd, *J*=8.7 Hz, *J*= 9.6 Hz, 1H, CH_2), 4.18 (dd, *J*=3.2 Hz, *J*=9.6 Hz, 1H, CH_2), 5.20 (dd, *J*=3.2 Hz, *J*=8.7 Hz, 1H, CH), 6.94-6.99 (m, 2H, 2CH(Ar)), 6.99-7.05 (m, 1H, CH(Ar)), 7.29-7.36 (m, 2H, 2CH(Ar)), 7.36-7.43 (m, 1H, CH(Ar)), 7.45-7.52 (m, 2H, 2CH(Ar)), 7.53-7.59 (m, 2H, 2CH(Ar)), 7.61-7.68 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 72.5 (CH), 73.3 (CH_2), 114.8 (2CH(Ar)), 121.4 (CH(Ar)), 126.9 (2CH(Ar)), 127.2 (2CH(Ar)), 127.4 (2CH(Ar)), 127.5 (CH(Ar)), 128.9 (2CH(Ar)), 129.7 (2CH(Ar)), 138.8 (C(Ar)), 140.8 (C(Ar)), 141.2 (C(Ar)), 158.5 (C(Ar)). HRMS $[M + Na]^+$: calcd. for $C_{20}H_{18}O_2Na$ 313.1199, found 313.1200.

1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanol 10d[24]:

The compound **10d** was prepared from ketone **9d**. Yield 0.24g (82 %); colorless solid, mp 116-117 °C; R_f= 0.79 (petroleum /ethyl acetate, 1/1); LC-MS: rt 27.39 min, purity 98.99%; δ_H (400 MHz, $CDCl_3$): 2.76 (br.s, 1H, OH), 3.36 (dd, *J*=8.6 Hz, *J*=13.1 Hz, 1H, CH_2), 3.48 (dd, *J*=3.9 Hz, *J*=13.1 Hz, 1H, CH_2), 3.99 (br.s, 1H, NH), 4.98 (dd, *J*=3.9 Hz, *J*=8.6 Hz, 1H, CH), 6.69-6.75 (m, 2H, 2CH(Ar)), 6.77-6.84 (m, 1H, CH(Ar)), 7.20-7.28 (m, 2H, 2CH(Ar)), 7.36-7.43 (m, 1H, CH(Ar)), 7.45-7.54 (m, 4H, 4CH(Ar)), 7.59-7.68 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 51.8 (CH_2), 72.3 (CH), 113.6 (2CH(Ar)), 118.3 (CH(Ar)), 126.5 (2CH(Ar)), 127.2 (2CH(Ar)), 127.46 (2CH(Ar)), 127.52 (CH(Ar)), 128.9 (2CH(Ar)), 129.5 (2CH(Ar)), 140.8 (C(Ar)), 141.0 (C(Ar)), 141.1 (C(Ar)), 147.9 (C(Ar)). HRMS $[M + H]^+$:calcd. for $C_{20}H_{20}NO$ 290.1539, found 290.1540.

3-((2-([1,1'-biphenyl]-4-yl)-2-hydroxyethyl)amino)phenol 10e:

The compound **10e** was prepared from ketone **9e'**. Yield 0.19 g (63%); light yellow solid, mp 153-155°C; R_f= 0.24 (petroleum /ethyl acetate, 3/2); LC-MS: rt 20.26 min, purity 99.31%; δ_H (400 MHz, DMSO-d_6): 3.09 (ddd, *J* = 12.7 Hz, *J* = 7.7 Hz, *J* = 4.9 Hz, 1H, CH_2), 3.19 (ddd, *J* = 12.7 Hz, *J* = 7.0 Hz, *J* = 4.8 Hz, 1H, CH_2), 4.77 (ddd, *J* = 7.7 Hz, *J* = 4.8 Hz, *J* = 4.4 Hz, 1H, CH), 5.45 (dd, *J* = 4.9 Hz, *J* = 7.0 Hz, 1H, NH), 5.48 (d, *J* = 4.4 Hz, 1H, OH), 5.96-6.01 (m, 1H, CH(Ar)), 6.05-6.12 (m, 2H, CH(Ar)), 6.82-6.87 (m,1H, CH(Ar)), 7.32-7.39 (m, 1H, CH(Ar)), 7.43-7.51 (m, 4H, 4CH(Ar)), 7.61-7.69 (m, 4H, 4CH(Ar)), 8.92 (s, 1H, OH); δ_C(100.6 MHz, CD_3OD): 52.8 (CH_2), 72.8 (CH), 101.1 (CH(Ar)), 105.6 (CH(Ar)), 106.5 (CH(Ar)), 127.6 (2CH(Ar)), 127.91 (2CH(Ar)), 127.94 (2CH(Ar)), 128.3 (CH(Ar)), 129.8 (2CH(Ar)), 130.9 (CH(Ar)), 141.7 (C(Ar)), 142.2 (C(Ar)), 143.5 (C(Ar)), 151.2 (C(Ar)), 159.3 (C(Ar)). HRMS $[M + Na]^+$: calcd. for $C_{20}H_{19}NO_2Na$ 328.1308, found 328.1309.

***N*-(3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide 10h:**

The compound **10h** was prepared from ketone **9h**. Yield 0.31 g (80 %); colorless solid, mp 144-145 °C; R_f=0.32 (petroleum /ethyl acetate, 1/1); LC-MS: rt 23.38 min, purity: 99.53%; δ_H (400 MHz, $CDCl_3$-CD_3OD): 2.93 (s, 3H, CH_3), 3.28 (dd, *J*=8.5 Hz, *J*=13.1 Hz, 1H, CH_2), 3.38 (dd, *J*=4.0 Hz, *J*= 13.1 Hz, 1H, CH_2), 4.90 (dd, *J*= 4.0 Hz, *J*=8.5 Hz, 1H, CH), 6.41-6.46 (m, 1H, CH(Ar)), 6.49-6.54 (m, 1H,

CH(Ar)), 6.55-6.59 (m, 1H, CH(Ar)), 7.05-7.12 (m, 1H, CH(Ar)), 7.29-7.36 (m, 1H, CH(Ar)), 7.38-7.47 (m, 4H, 4CH(Ar)), 7.53-7.59 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, $CDCl_3$-CD_3OD): 38.9 (CH_3), 51.4 (CH_2), 71.8 (CH), 105.1 (CH(Ar)), 109.5 (CH(Ar)), 110.0 (CH(Ar)), 126.4 (2CH(Ar)), 127.1 (2CH(Ar)), 127.3 (2CH(Ar)), 127.4 (CH(Ar)), 128.9 (2CH(Ar)), 130.4(CH(Ar)), 138.3(C(Ar)), 140.7 (C(Ar)), 140.8 (C(Ar)), 141.2 (C(Ar)), 149.2 (C(Ar)). HRMS $[M + H]^+$:calcd. for $C_{21}H_{23}N_2O_3S$ 383.1424, found 383.1426.

***N*-(3-((2-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide 10i:**

The compound **10i** was prepared from ketone **9i**. Yield 0.38 g (83 %); colorless solid, mp 177-179°C; R_f = 0.19 (petroleum /ethyl acetate, 1/1); LC-MS: rt 27.38 min, purity 85.91%; δ_H (400 MHz, CD_3OD-$CDCl_3$): 2.92 (s, 3H, CH_3), 3.25 (dd, *J*=8.4 Hz, *J*=13.1 Hz, 1H, CH_2), 3.36 (dd, *J*=4.1 Hz, *J*= 13.1 Hz, 1H, CH_2), 4.88 (dd, *J*= 4.1 Hz, *J*=8.4 Hz, 1H, CH), 6.40-6.45 (m, 1H, CH(Ar)), 6.47-6.53 (m, 1H, CH(Ar)), 6.55-6.59 (m, 1H, CH(Ar)), 7.04-7.10 (m, 1H, CH(Ar)), 7.40-7.47 (m, 4H, 4CH(Ar)), 7.49-7.55 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, CD_3OD-$CDCl_3$): 38.8 (CH_3), 51.7 (CH_2), 71.8 (CH), 105.2 (CH(Ar)), 109.6 (CH(Ar)), 110.1 (CH(Ar)), 121.7 (CH(Ar)), 126.8 (2CH(Ar)), 127.2 (2CH(Ar)), 128.9 (2CH(Ar)), 130.5 (C(Ar)), 132.1 (2CH(Ar)), 138.9 (C(Ar)), 139.6 (C(Ar)), 140.0 (C(Ar)), 142.3(C(Ar)), 149.5 (C(Ar)). HRMS $[M + K]^+$: calcd. for $C_{21}H_{21}BrN_2O_3SK$ 499.0088, found 499.0075.

Synthesis of 1-([1,1'-biphenyl]-4-yl)-2-((3-(ethylamino)phenyl)amino)ethanol 10g:

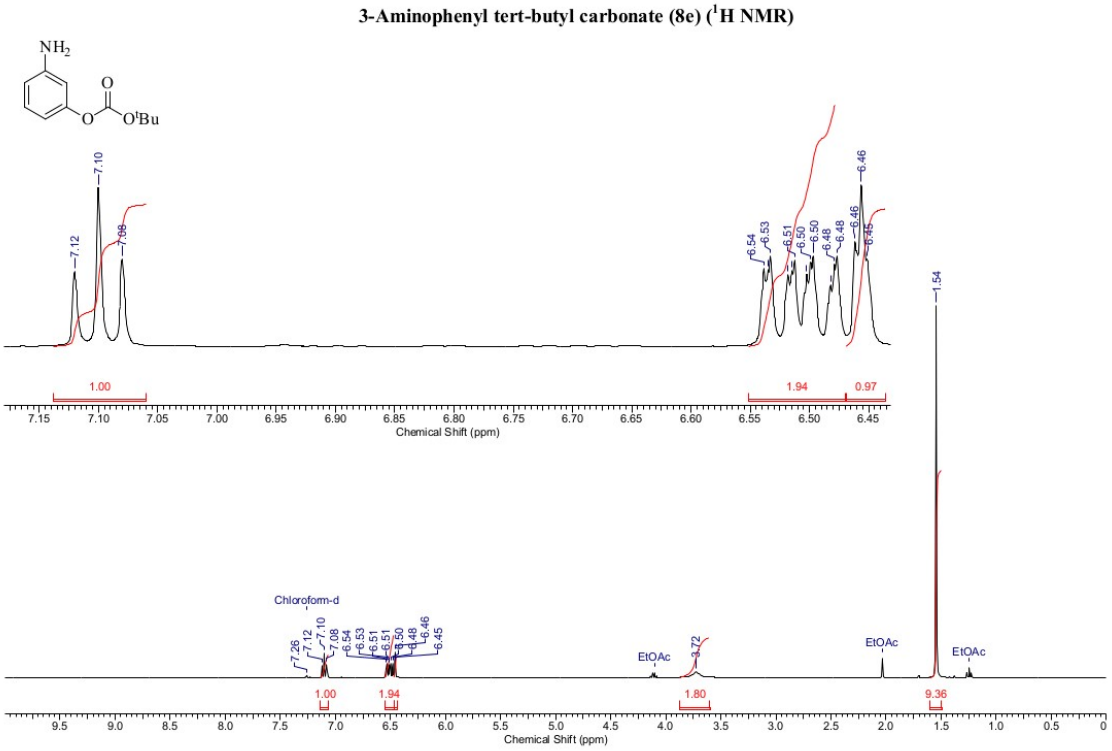
To the solution of compound **9g** (0.20 g, 0.58 mmol) and $NaBH_4$ (0.10 g, 2.67 mmol) in dry THF (3 ml) iodine (0.30 g, 1.16 mmol) in dry THF (2.5 ml) was added in portions under argon atmosphere at 0°C for 50 minutes. The resulting mixture was refluxed (70°C) for 3 h, then was cooled to 0°C and was quenched with 3N HCl (1 ml). After the gas evolution ceased, 3N NaOH (1.5 ml) was added. The organic layer was separated and the aqueous layer was extracted with ether (2x10 ml). The combined organic layers were washed with water (3x15ml), saturated aqueous NaCl (2x15ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum:ethylacetate/2:1). Yield 0.13 g (67 %); brown-yellow solid, mp 44 °C; R_f = 0.24 (petroleum /ethyl acetate, 2/1); LC-MS: rt 10.85 min, purity: 90.08%; δ_H (400 MHz, $CDCl_3$): 1.25 (t, *J*= 7.2 Hz, 3H, CH_3), 3.13 (q, *J*=7.2 Hz, 2H, CH_2), 3.31 (dd, *J*=8.6 Hz, *J*=13.2 Hz, 1H, CH_2), 3.39 (br.s, 3H, 2NH+OH), 3.45 (dd, *J*=3.9 Hz, *J*= 13.2 Hz, 1H, CH_2), 4.96 (dd, *J*=3.9 Hz, *J*=8.6 Hz, 1H, CH), 5.94-5.98 (m, 1H, CH(Ar)), 6.05-6.13 (m, 2H, 2CH(Ar)), 6.99-7.06 (m, 1H, CH(Ar)), 7.34-7.41 (m, 1H, CH(Ar)), 7.43-7.51 (m, 4H, 4CH(Ar)), 7.58-7.65 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, $CDCl_3$): 15.0 (CH_3), 38.6 (CH_2), 52.0 (CH_2), 72.3 (CH), 98.0 (CH(Ar)), 103.4 (CH(Ar)), 103.8 (CH(Ar)), 126.5 (2CH(Ar)), 127.2 (2CH(Ar)), 127.4 (2CH(Ar)), 127.5 (CH(Ar)), 128.9 (2CH(Ar)), 130.2 (CH(Ar)), 140.8 (C(Ar)), 140.9 (C(Ar)), 141.3 (C(Ar)), 149.1 (C(Ar)), 149.8 (C(Ar)). HRMS $[M + H]^+$: calcd. for $C_{22}H_{25}N_2O$ 333.1961, found 333.1953.

Synthesis of 3-(2-([1,1'-biphenyl]-4-yl)-2-aminoethoxy)phenol 10j:

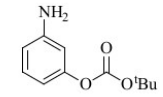
To the solution of ketone **9a** (0.17 g, 0.58 mmol) in a mixture of MeOH and H_2O (8:1, 60 ml) NH_2OH*HCl (80 mg, 1.16 mmol) and pyridine (0.10 ml, 0.1 g 1.27 mmol) were added. The resulting mixture was stirred at room temperature for 6 h, the completion of the reaction was monitored by TLC (CH_2Cl_2/MeOH, 20/1). Then the reaction mixture was concentrated and ice water (30 ml) was added. After stirring for 5 minutes the mixture was left in the refrigerator for 3 hours, the obtained precipitate of 3-{[(2-biphenyl-4-yl-2-(hydroxyimino)ethyl]oxy}phenyl acetate was filtered and dried, yield 0.17 (81 %); colorless solid; R_f = 0.43 (CH_2Cl_2/MeOH, 20/1); δ_H (400 MHz, $CDCl_3$, CD_3OD): 2.16 (s, 3H, CH_3), 5.25 (s, 2H, CH_2), 6.39-6.51 (m, 3H, 3CH(Ar)), 7.03-7.10 (m, 1H, CH(Ar)), 7.30-7.38 (m, 1H,

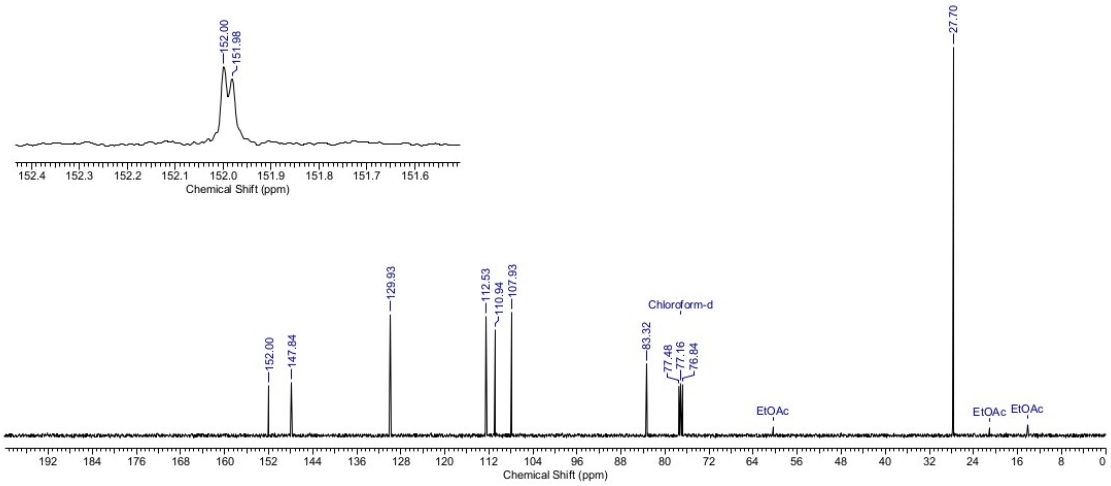
CH(Ar)), 7.39-7.46 (m, 2H, 2CH(Ar)), 7.54-7.61 (m, 4H, 4CH(Ar)), 7.69-7.74 (m, 2H, 2CH(Ar)). To a solution of 3-{[(2-biphenyl-4-yl-2-(hydroxyimino)ethyl]oxy}phenyl acetate (0.17 g, 0.525 mmol) in dry THF (3 ml) $NaBH_4$ (90 mg, 2.42 mmol) was added, then a solution of iodine (0.28 g, 1.052 mmol) in dry THF (2.5 ml) was added in portions under argon atmosphere at 0°C for 50 minutes. The reaction mixture was refluxed (70°C) for 3 h, then was cooled to 0°C and was quenched with 3N HCl (1 ml). After the gas evolution finished, 3N NaOH (1.5 ml) was added. The organic layer was separated and the aqueous phase was extracted with ether (2x10 ml). The combined organic layers were washed with water (3x15ml), saturated aqueous NaCl (2x15ml), dried over anhydrous $MgSO_4$, filtered, and concentrated in vacuo. The residue was purified by column chromatography on silica gel (petroleum:ethylacetate/2:1). **y**ield 0.10 g (65%); colorless solid, mp 162-165 °C; R_f= 0.11 (petroleum/ethyl acetate, 2/1); LC-MS: rt 9.49 min, purity 95.84 %; δ_H (400 MHz, CD_3OD): 4.09-4.20 (m, 2H, CH_2), 4.40 (dd, *J*=5.3, 7.4 Hz, 1H, CH), 6.37-6.44 (m, 3H, 3CH(Ar)), 7.02-7.08 (m, 1H, CH(Ar)), 7.27-7.34 (m, 1H, CH(Ar)), 7.37-7.43 (m, 2H, 2CH(Ar)), 7.49-7.54 (m, 2H, 2CH(Ar)), 7.55-7.61 (m, 4H, 4CH(Ar)); δ_C (100.6 MHz, CD_3OD): 66.7 (CH), 70.0 (CH_2), 103.1 (CH(Ar)), 106.8 (CH(Ar)), 109.3 (CH(Ar)), 127.9 (2CH(Ar)), 128.0 (2CH(Ar)), 128.3 (CH(Ar)), 129.7 (2CH(Ar)), 129.9 (2CH(Ar)), 131.0 (CH(Ar)), 139.2 (C(Ar)), 142.0 (C(Ar)), 142.2 (C(Ar)), 159.7 (C(Ar)), 161.3 (C(Ar)). HRMS $[(M - NH_3)+H]^+$: calcd. for $C_{20}H_{17}O_2$ 289.1223, found 289.1208.

NMR spectra

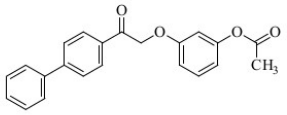


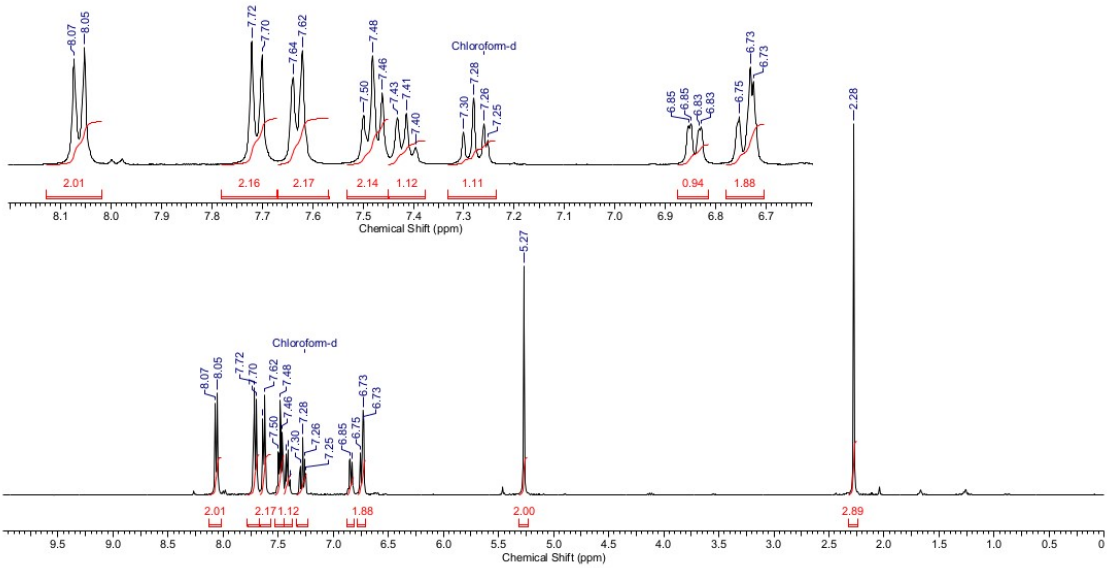
3-Aminophenyl tert-butyl carbonate (8e) (^{13}C NMR)



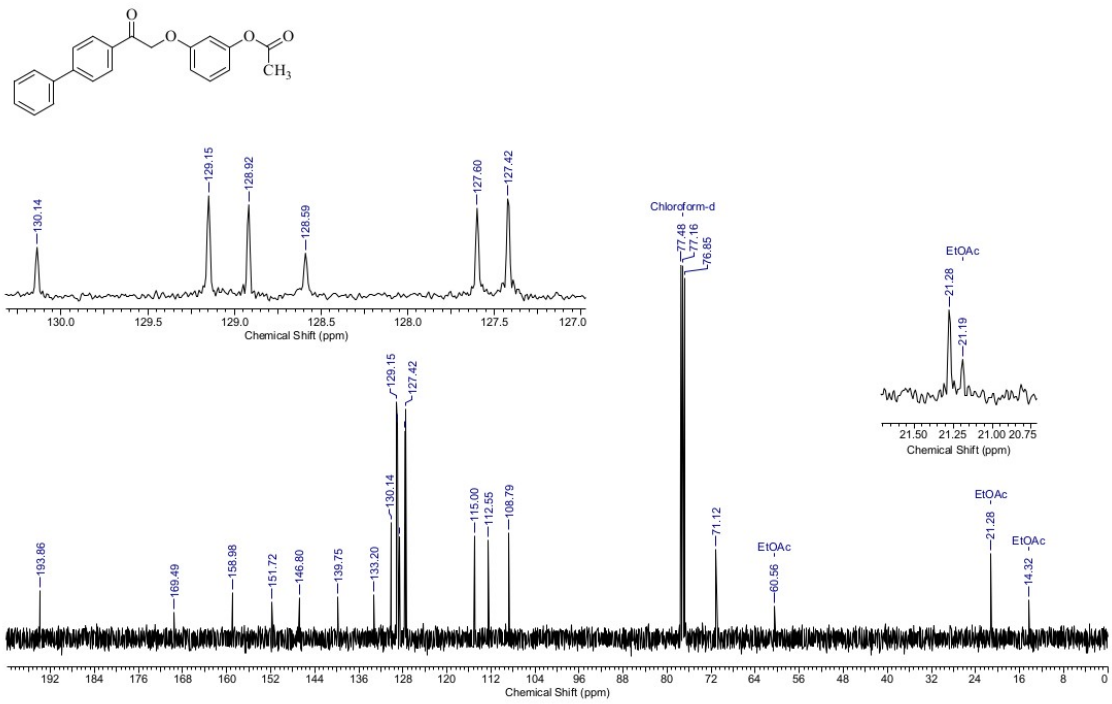


3-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate (9a) (^{1}H NMR)

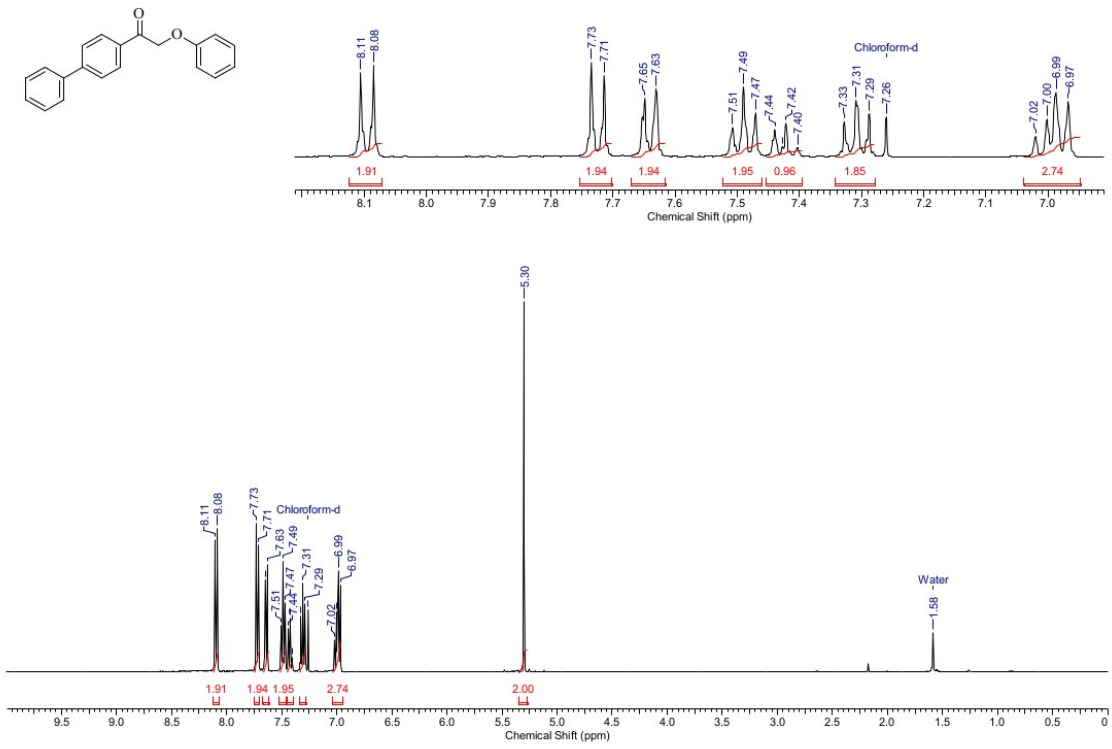




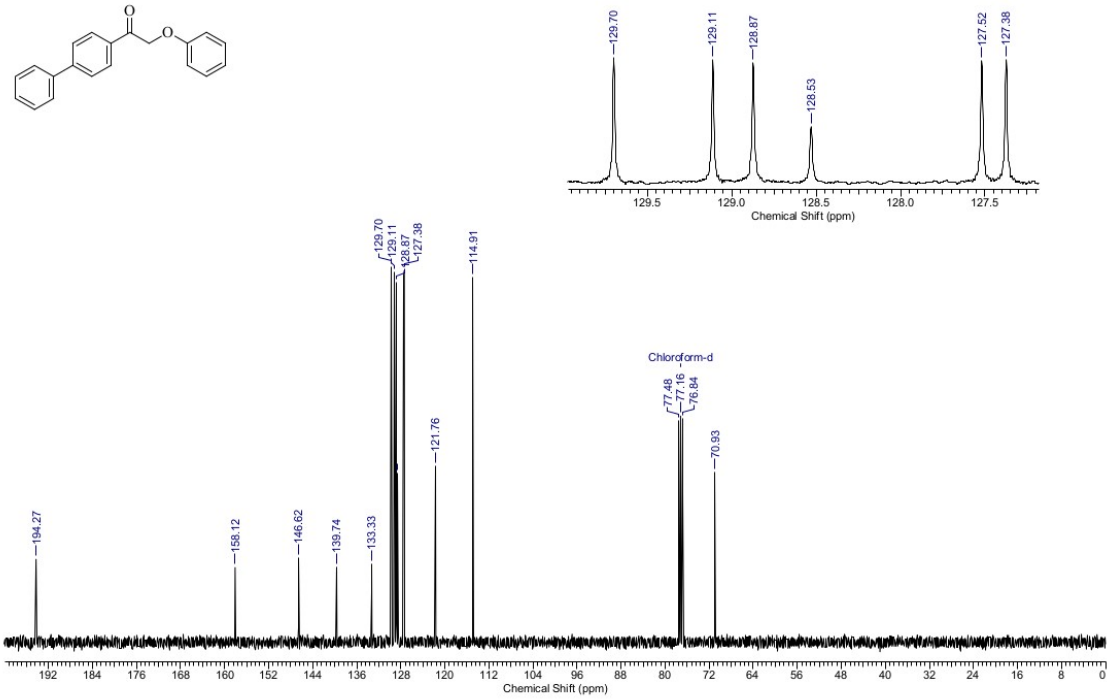
3-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate (9a) (^{13}C NMR)



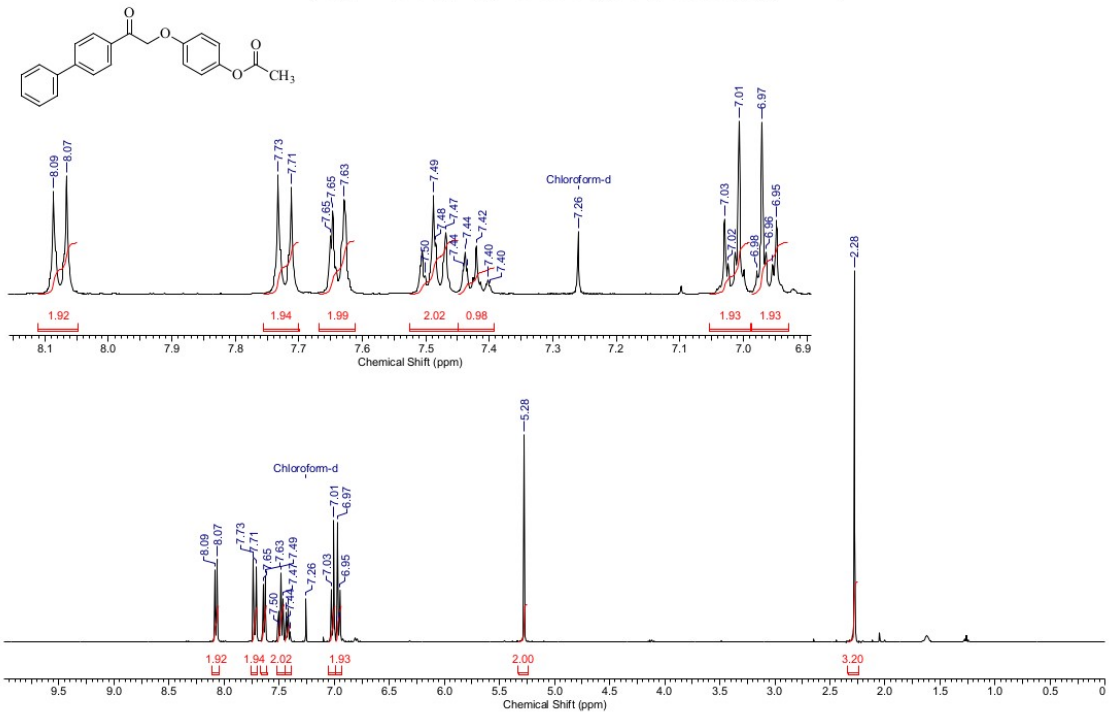
1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanone (9b) (^{1}H NMR)



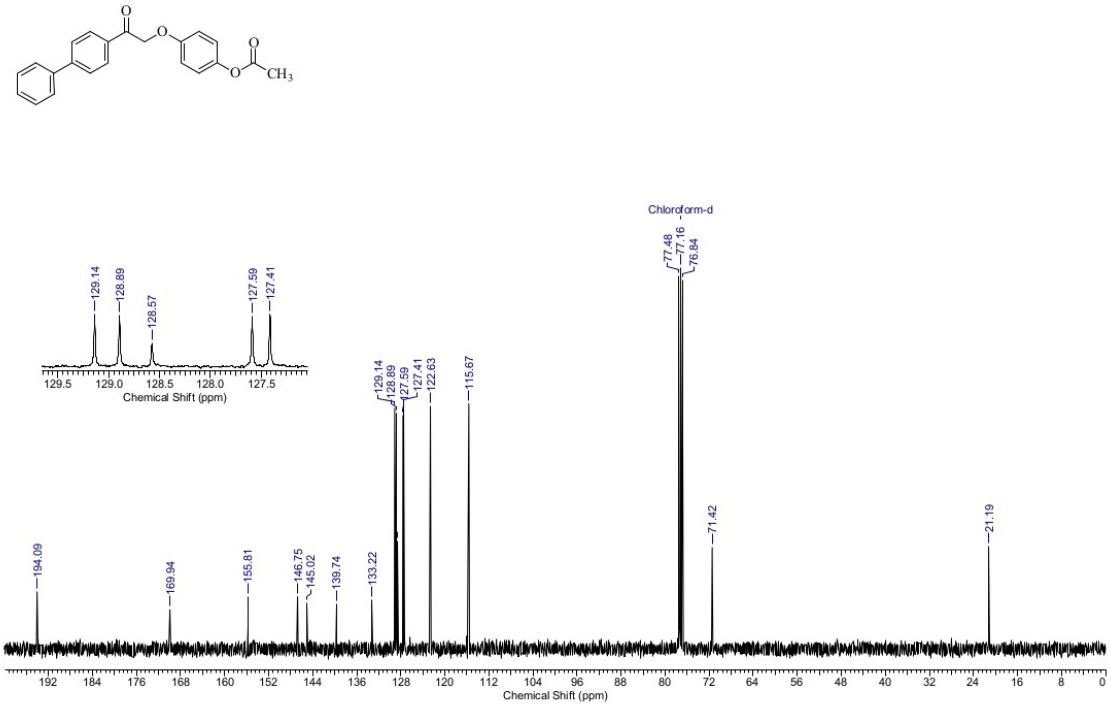
1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanone (9b) (^{13}C NMR)



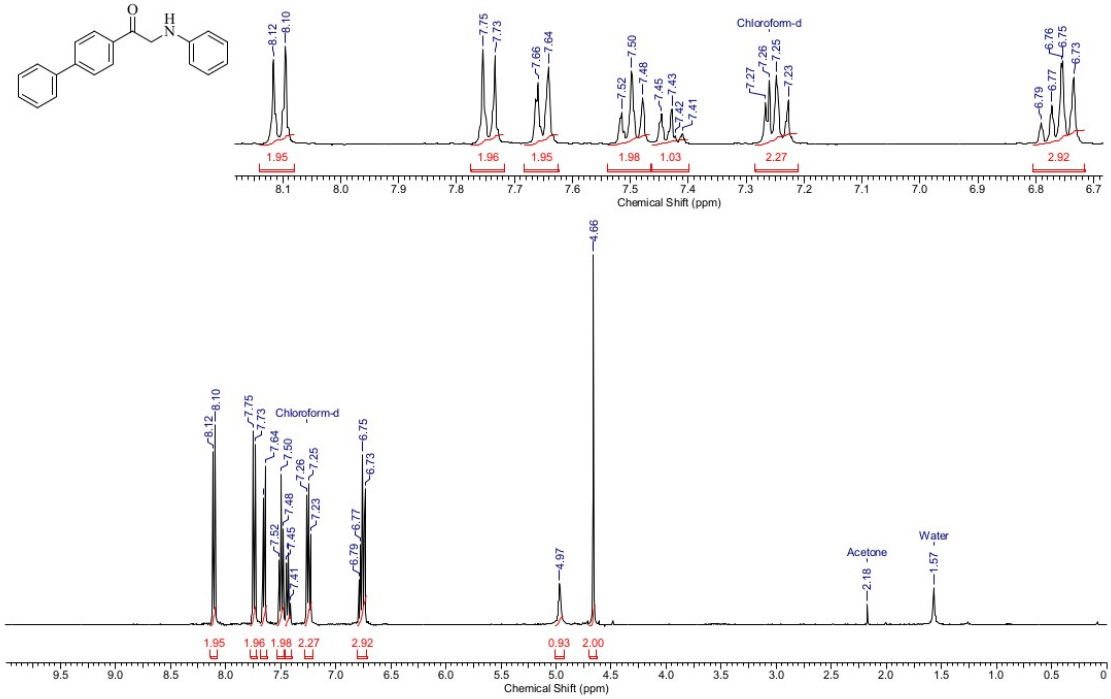
4-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate (9c) (^{1}H NMR)



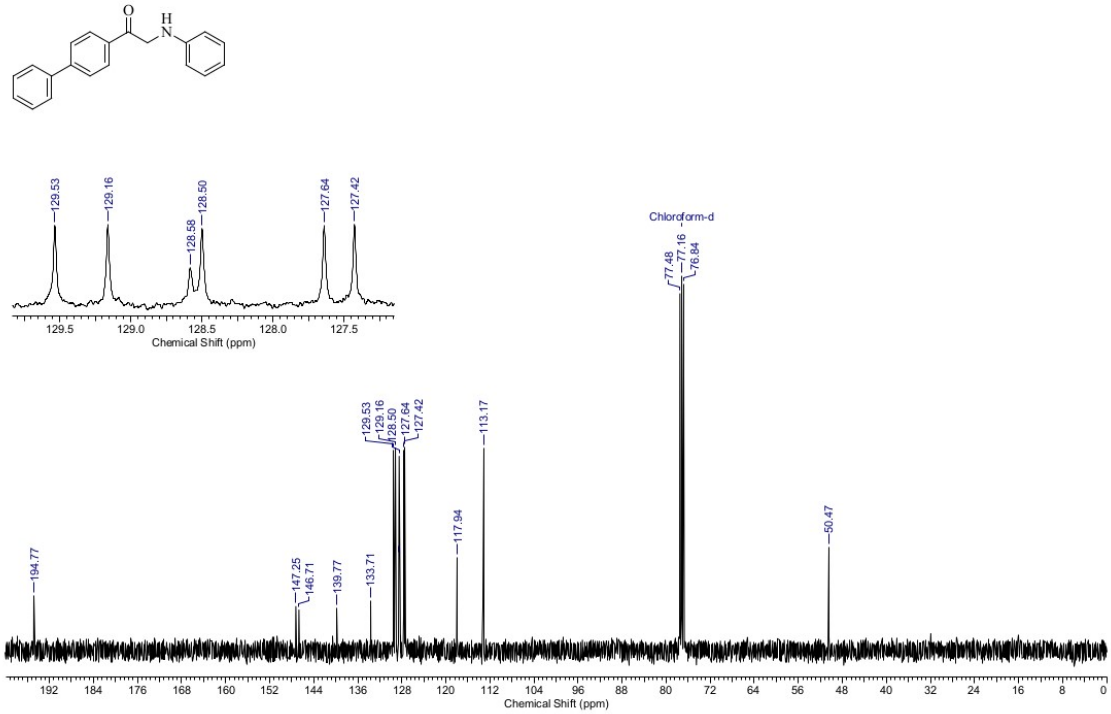
4-(2-([1,1'-Biphenyl]-4-yl)-2-oxoethoxy)phenyl acetate (9c) (^{13}C NMR)



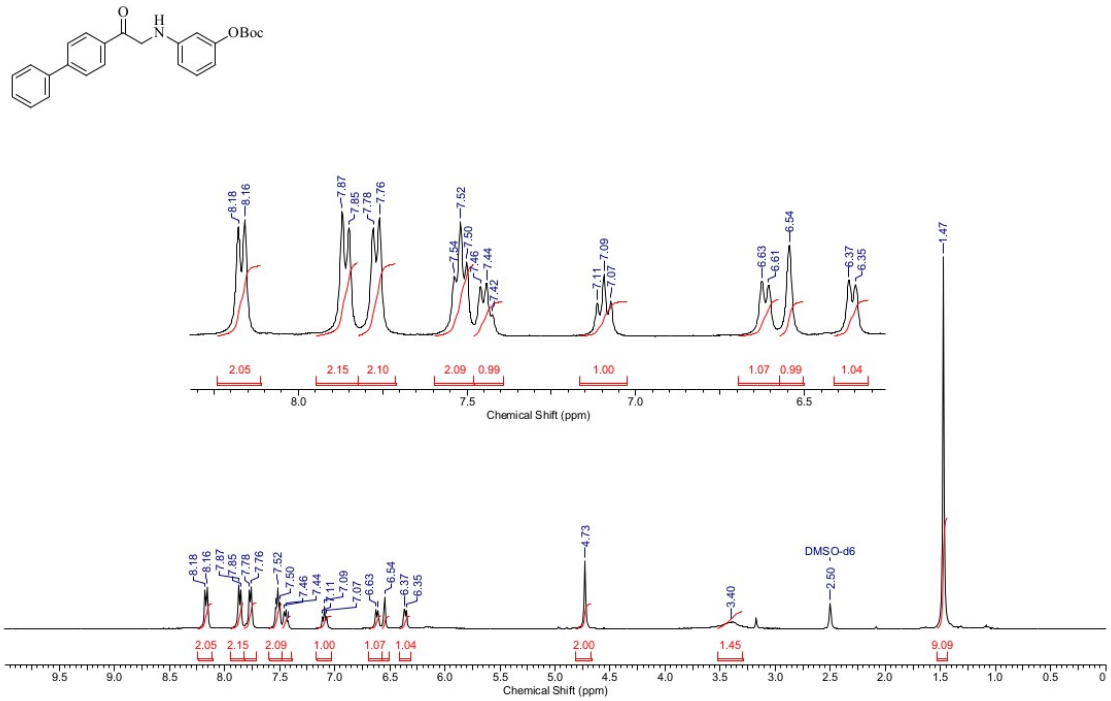
1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanone (9d) (^{1}H NMR)



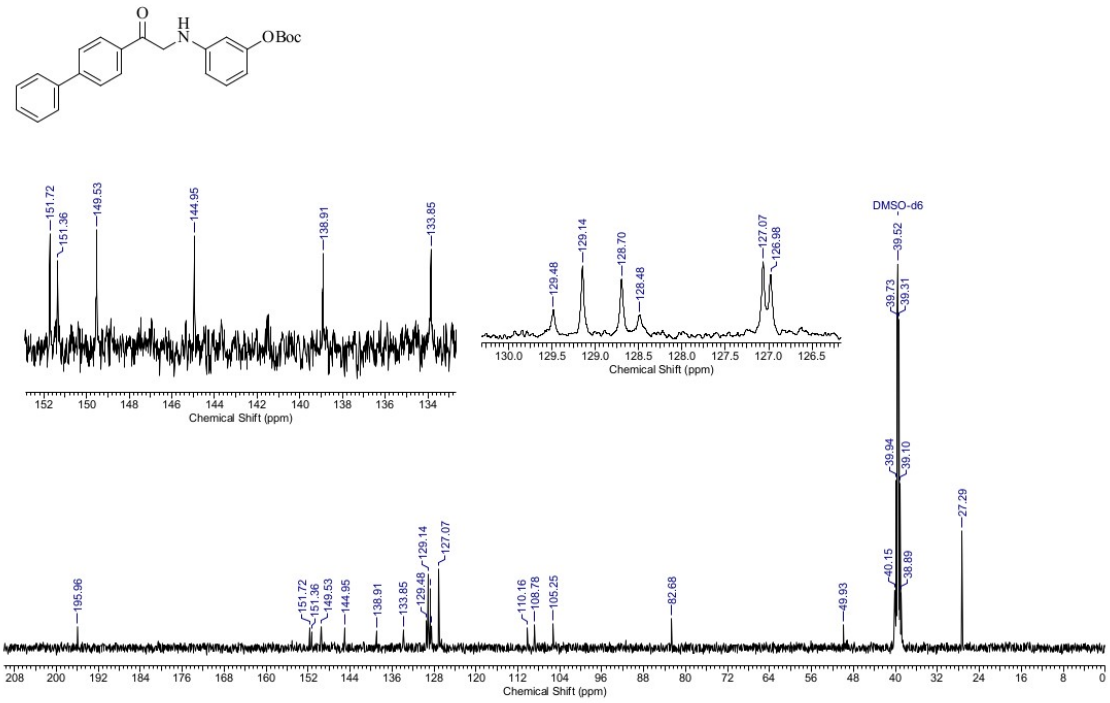
1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanone (9d) (^{13}C NMR)



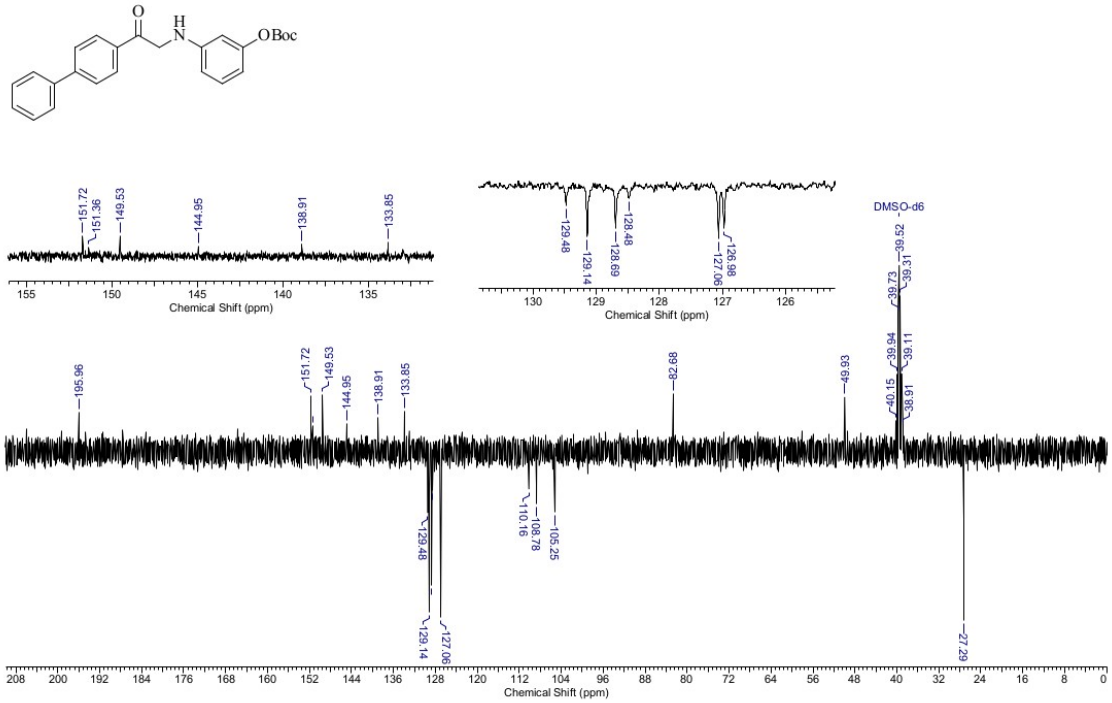
3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl tert-butyl carbonate (9e) (^{1}H NMR)



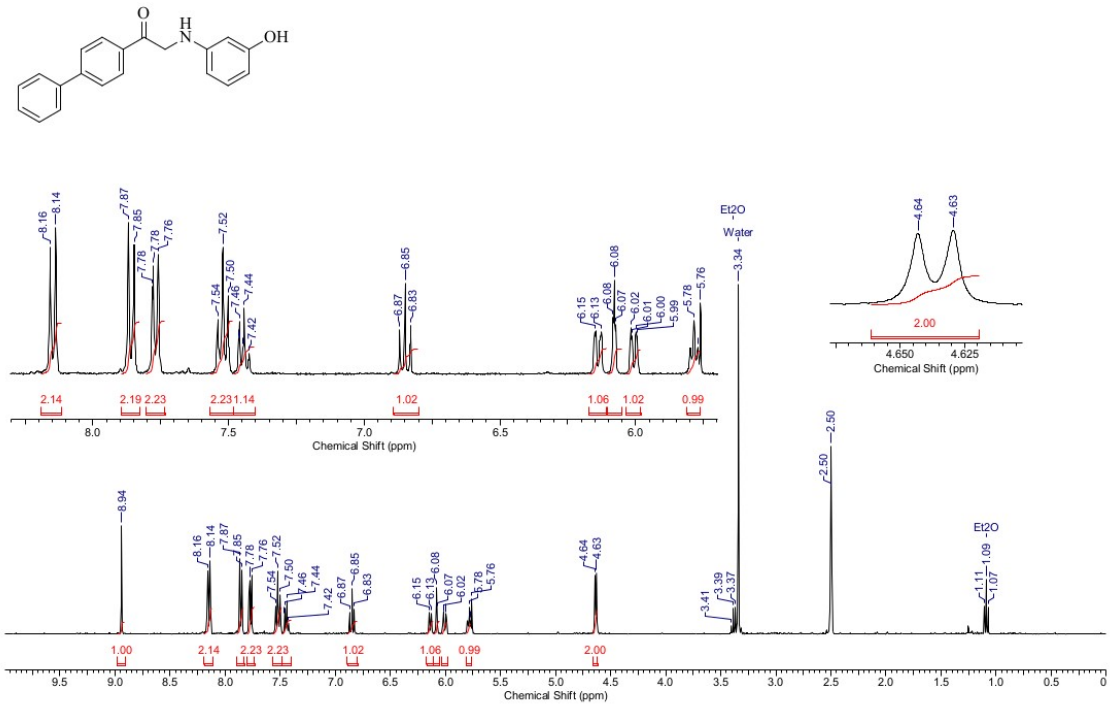
3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl tert-butyl carbonate (9e) (^{13}C NMR)



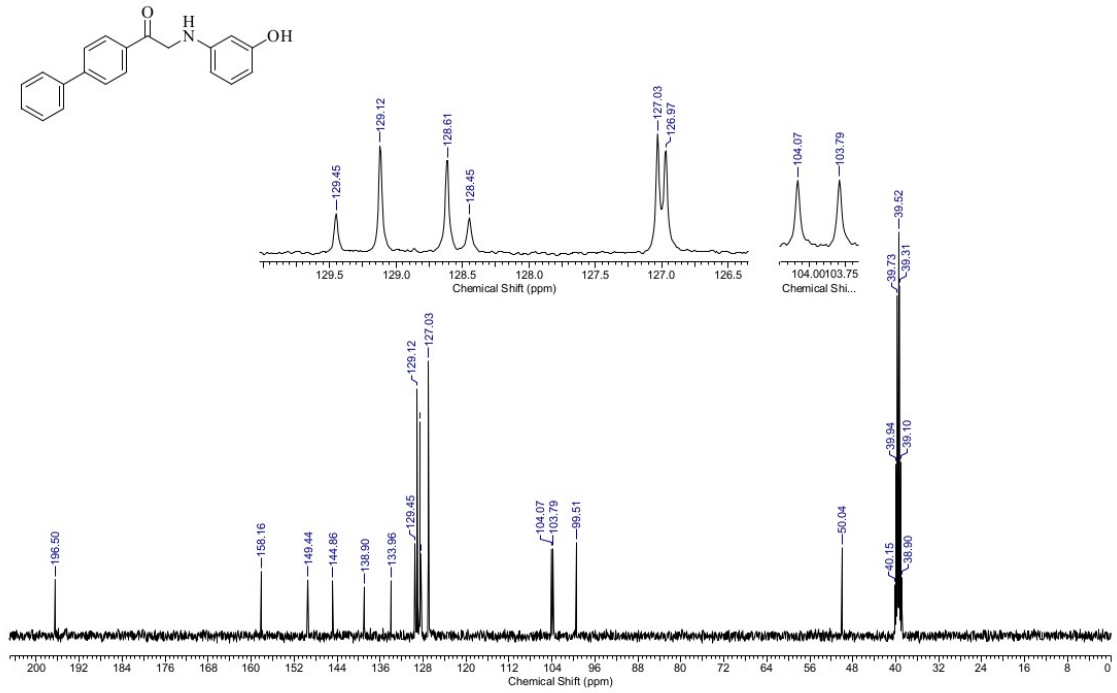
3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl tert-butyl carbonate (9e) (APT NMR)



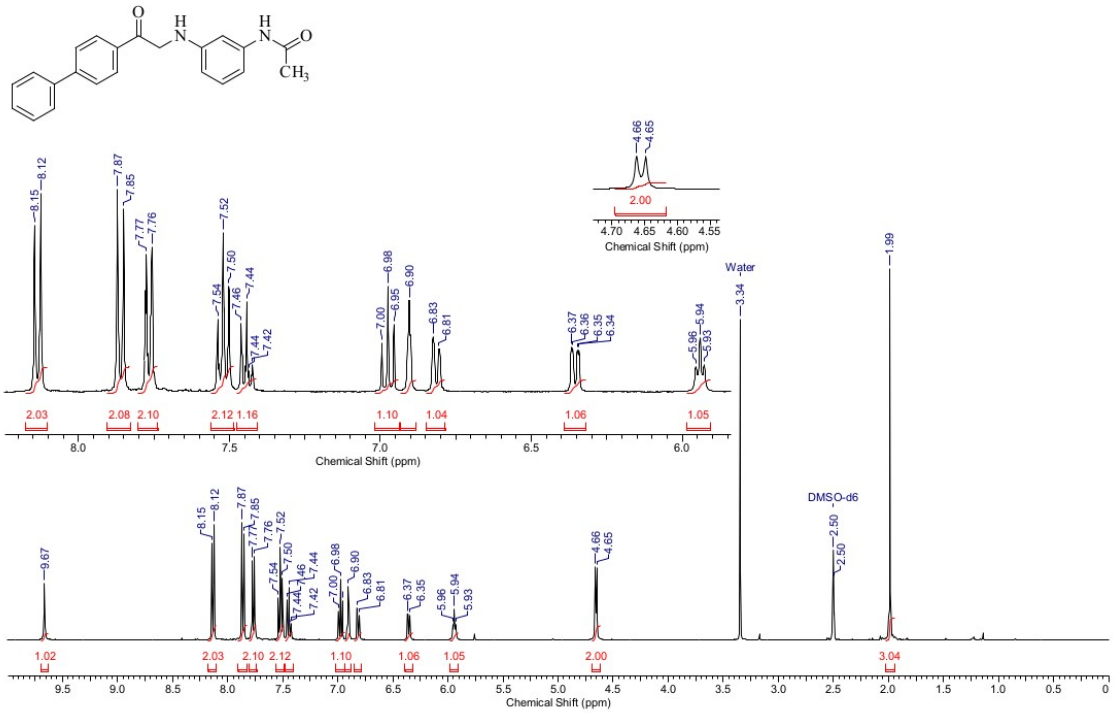
1-([1,1'-Biphenyl]-4-yl)-2-((3-hydroxyphenyl)amino)ethanone (9e') (^{1}H NMR)



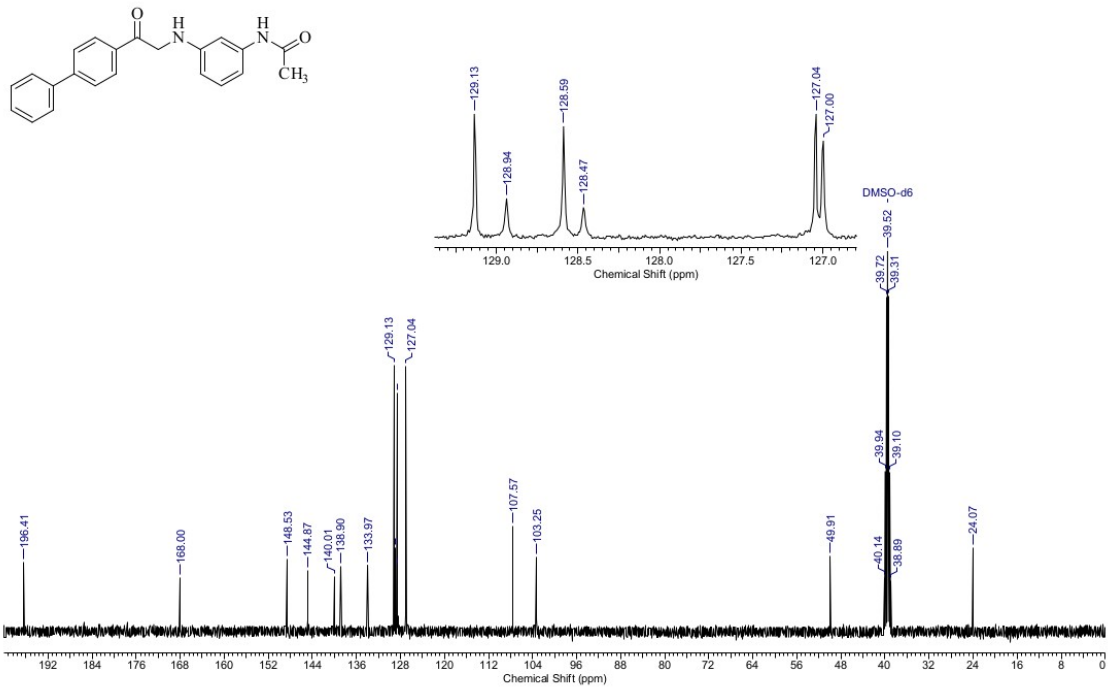
1-([1,1'-Biphenyl]-4-yl)-2-((3-hydroxyphenyl)amino)ethanone (9e') (^{13}C NMR)



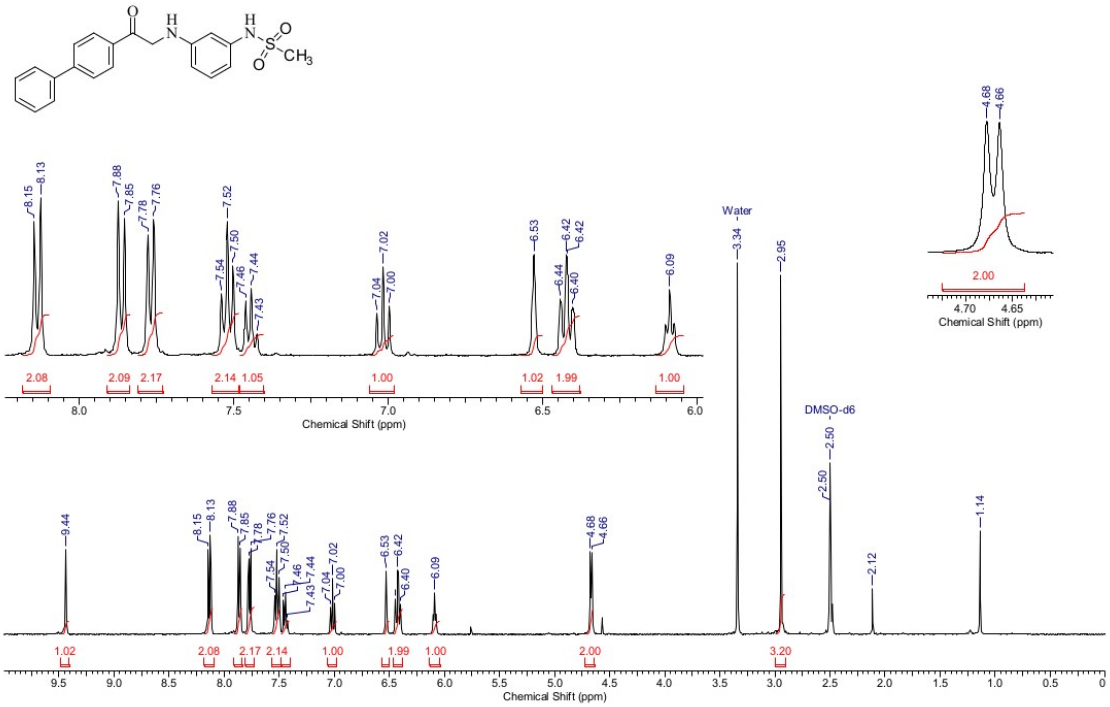
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)acetamide (9g) (^{1}H NMR)



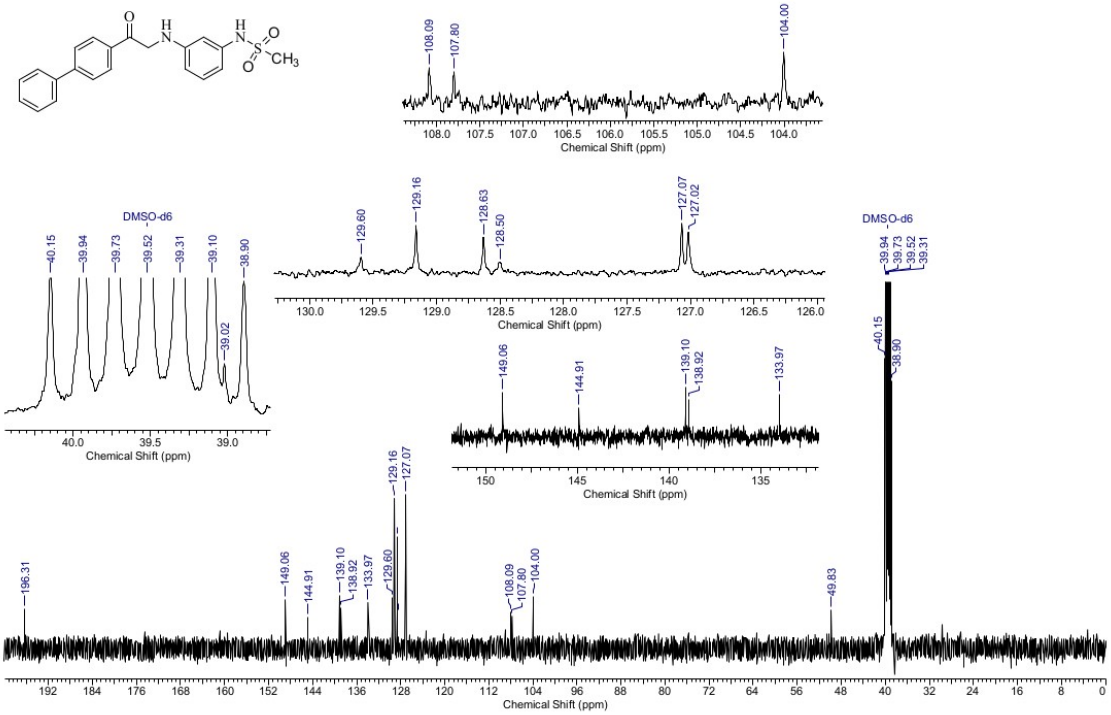
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)acetamide (9g) (^{13}C NMR)



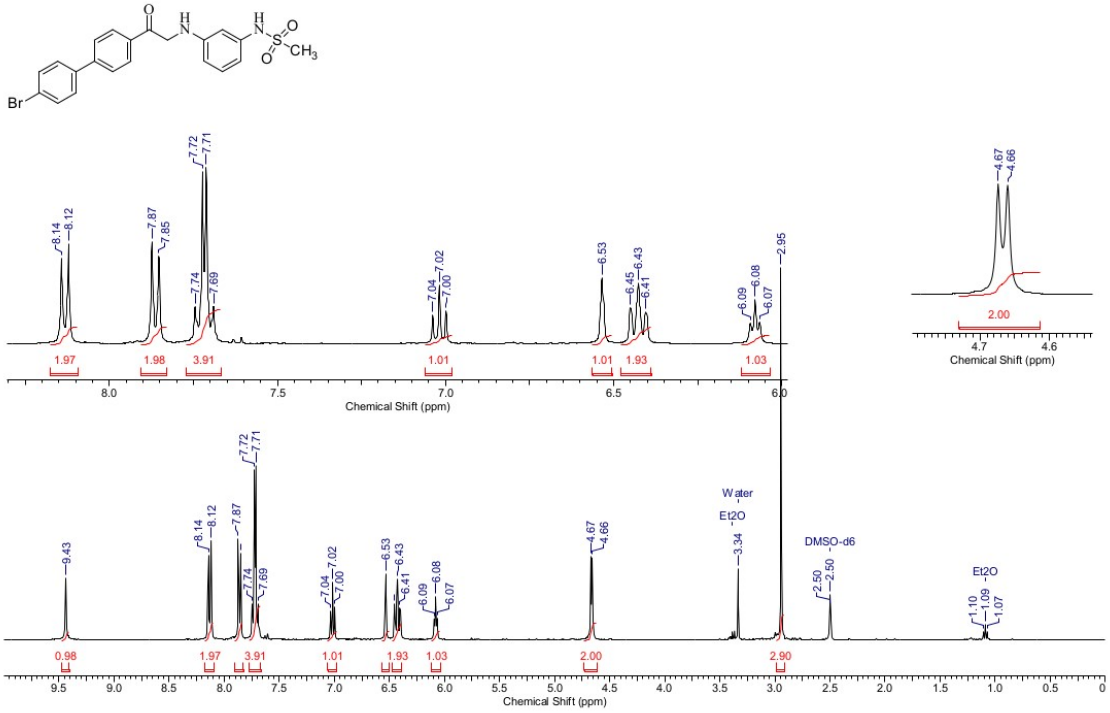
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide (9h) (^{1}H NMR)



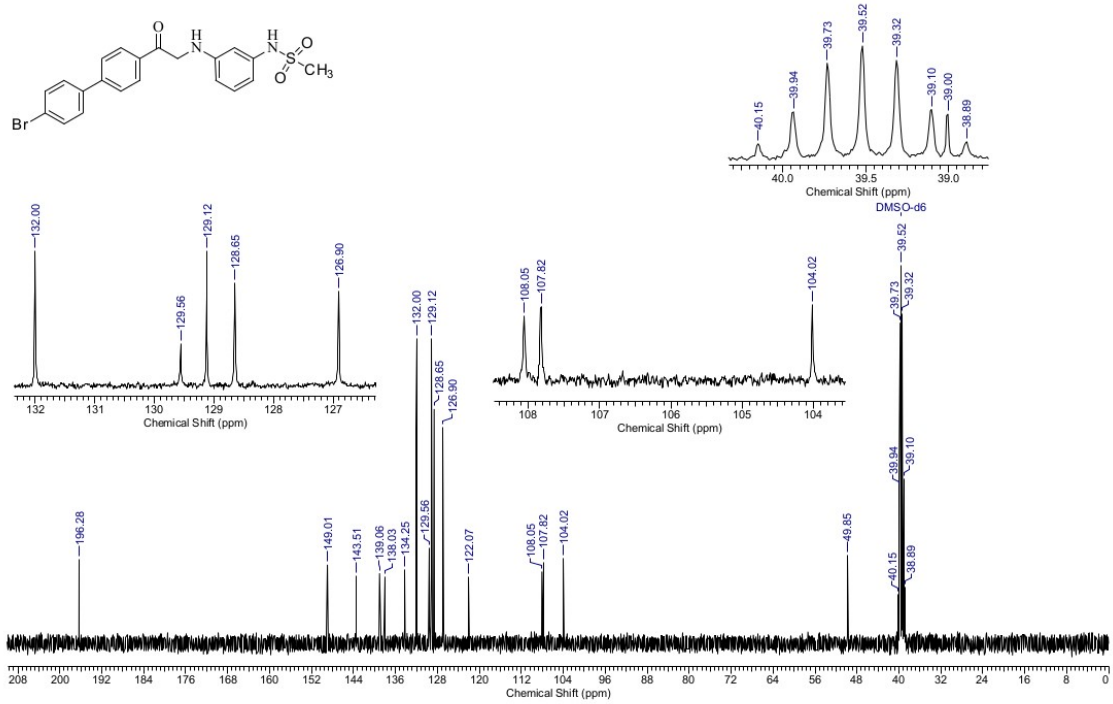
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide (9h) (^{13}C NMR)



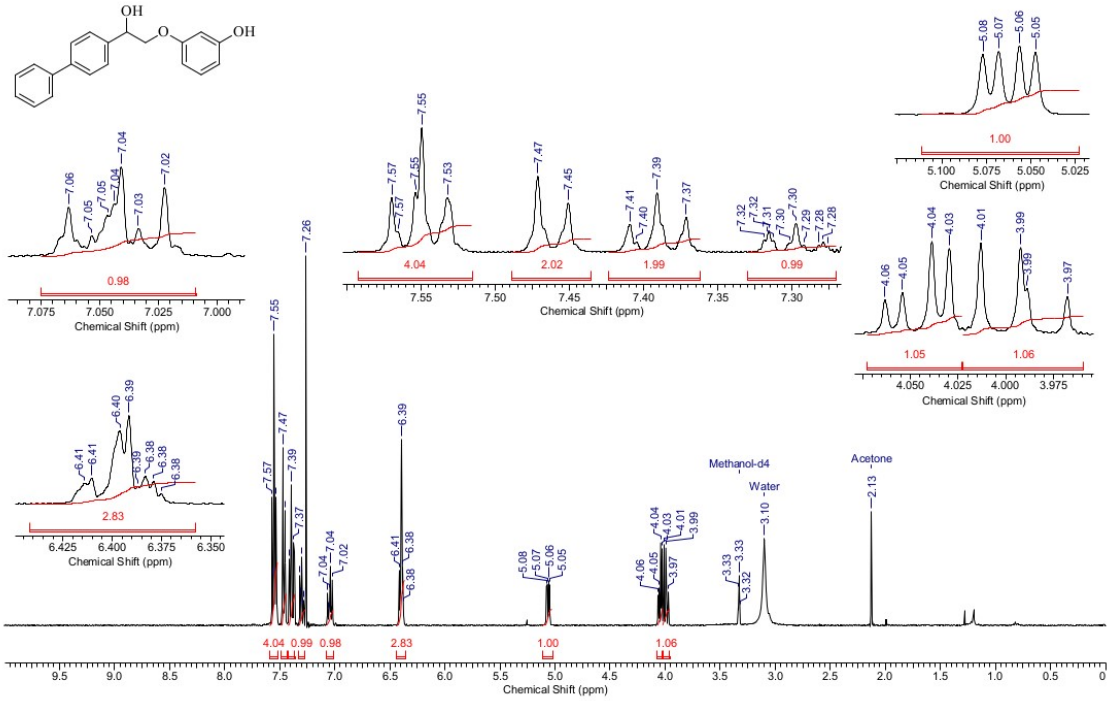
N-(3-((2-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide (9i) (^{1}H NMR)



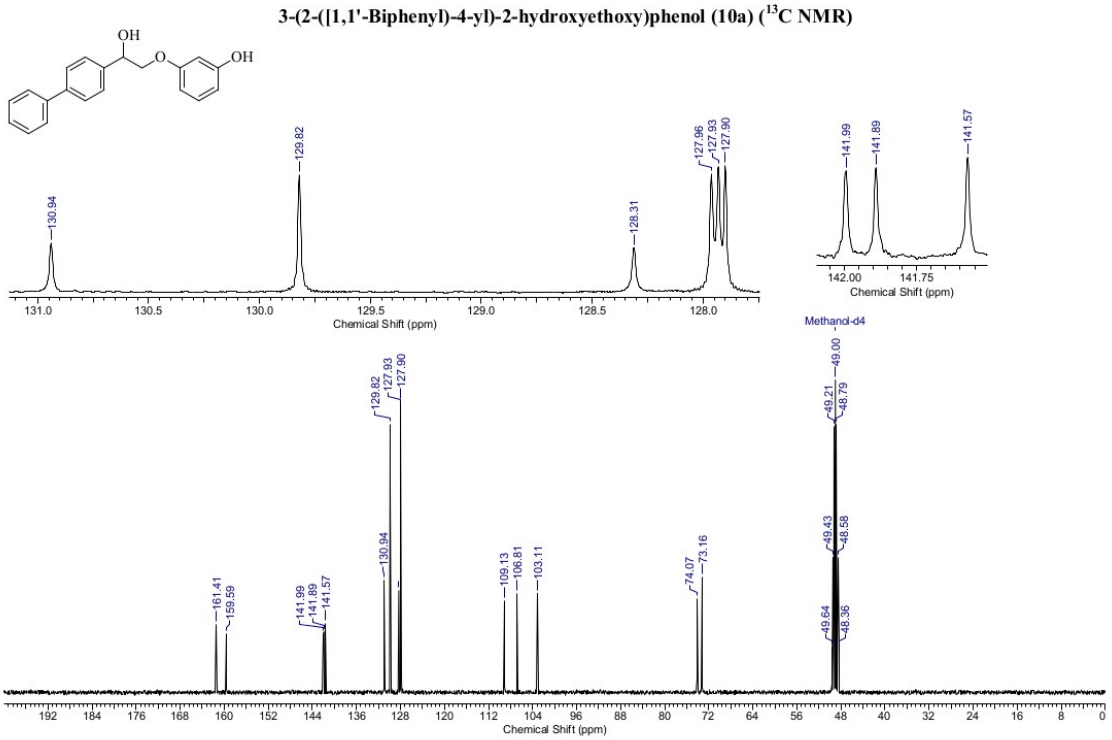
N-(3-((2-(4'-bromo-[1,1'-biphenyl]-4-yl)-2-oxoethyl)amino)phenyl)methanesulfonamide (9i) (^{13}C NMR)



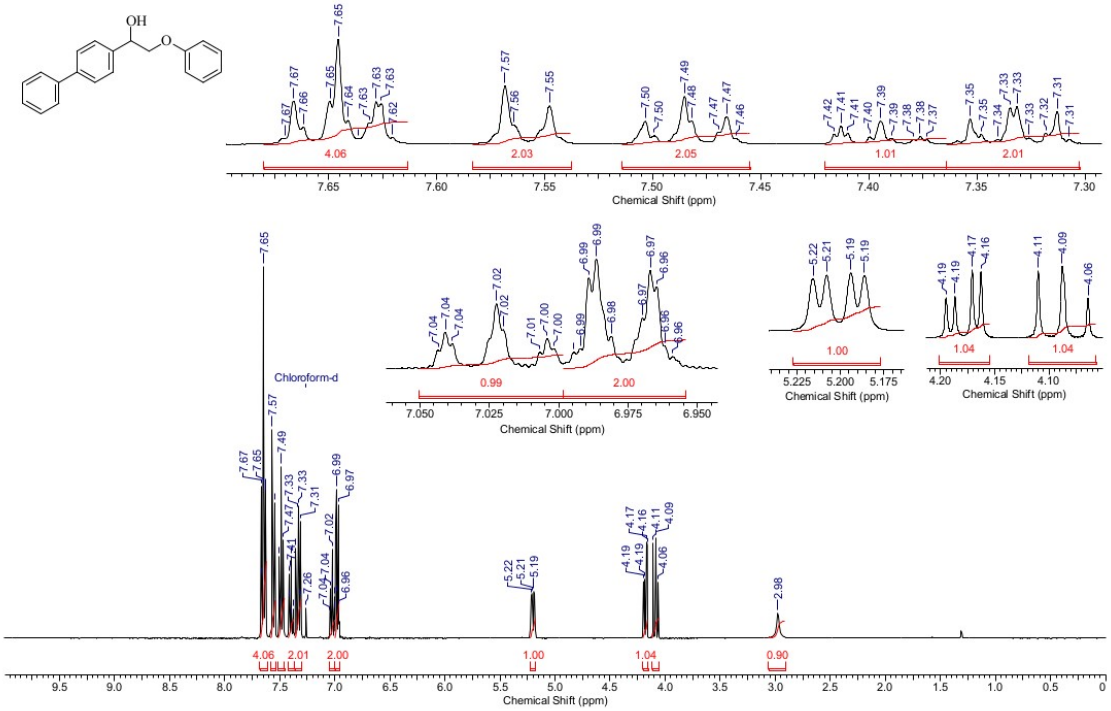
3-(2-([1,1'-Biphenyl)-4-yl)-2-hydroxyethoxy)phenol (10a) (^{1}H NMR)



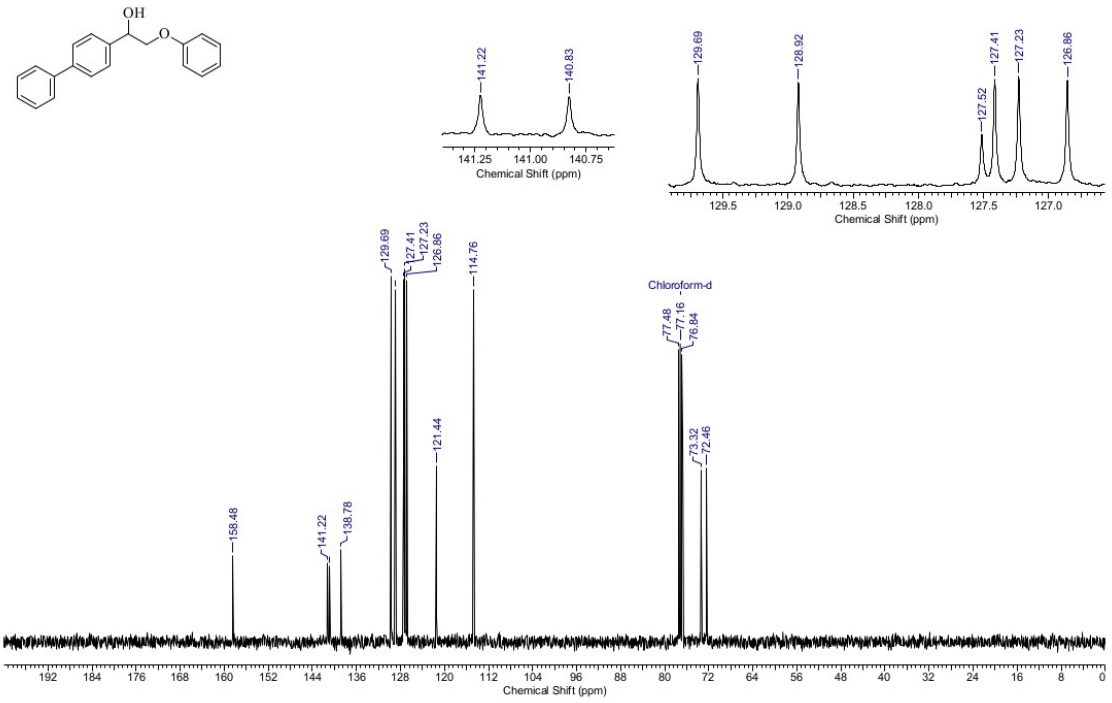
3-(2-([1,1'-Biphenyl)-4-yl)-2-hydroxyethoxy)phenol (10a) (^{13}C NMR)



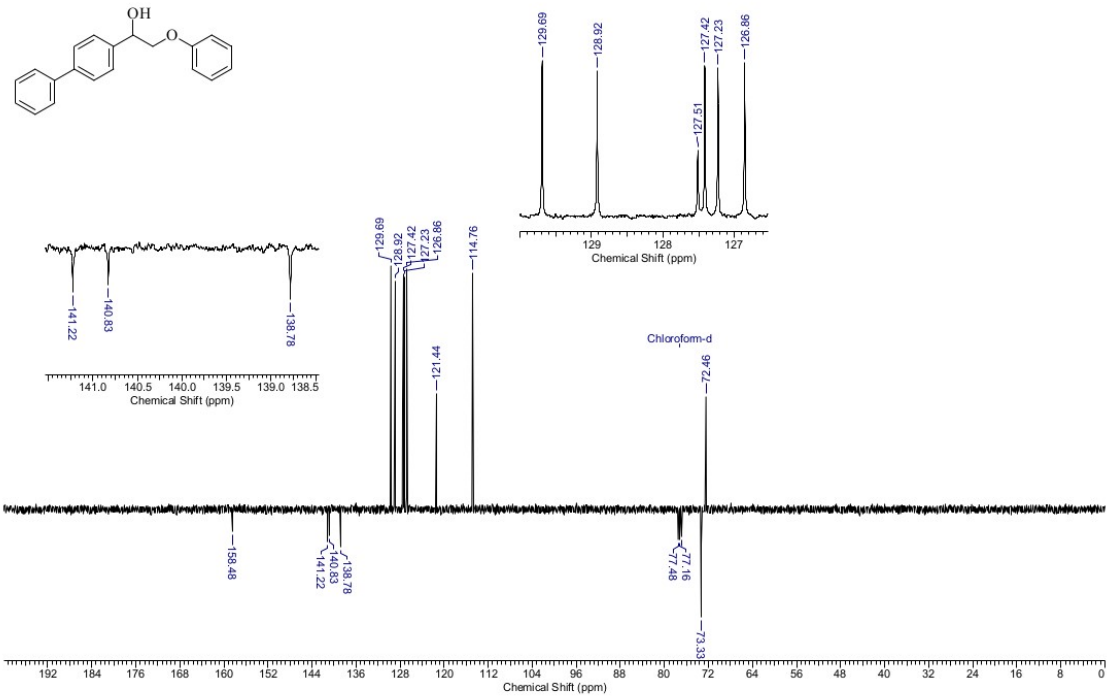
1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanol (10b) (^{1}H NMR)



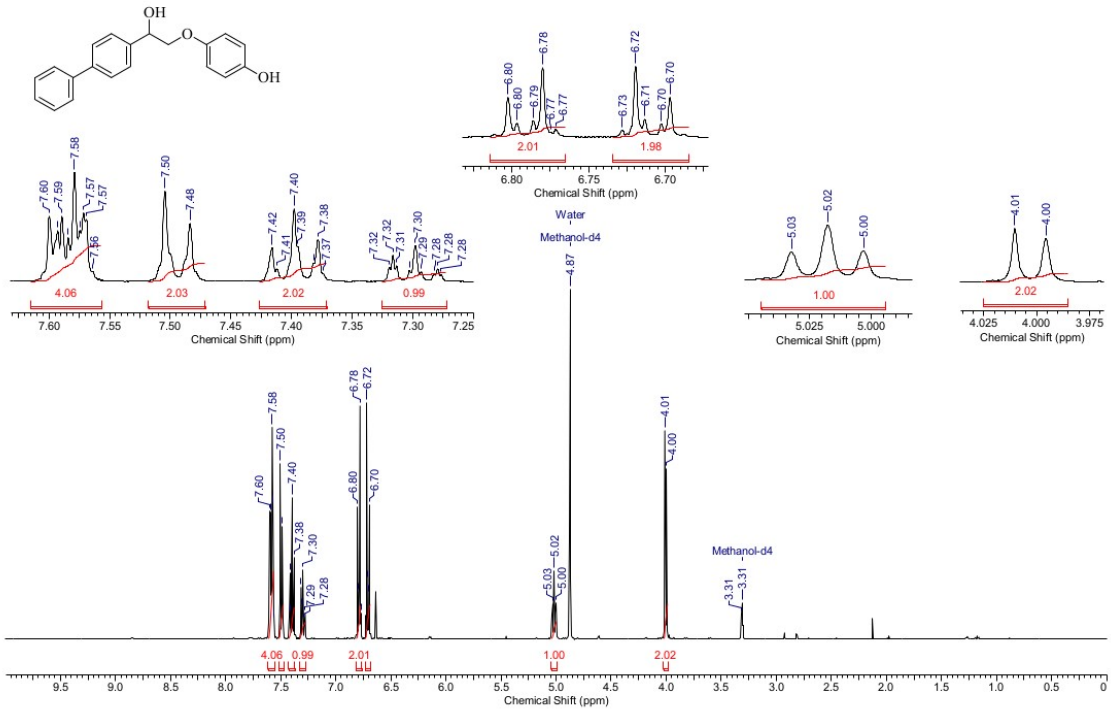
1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanol (10b) (^{13}C NMR)



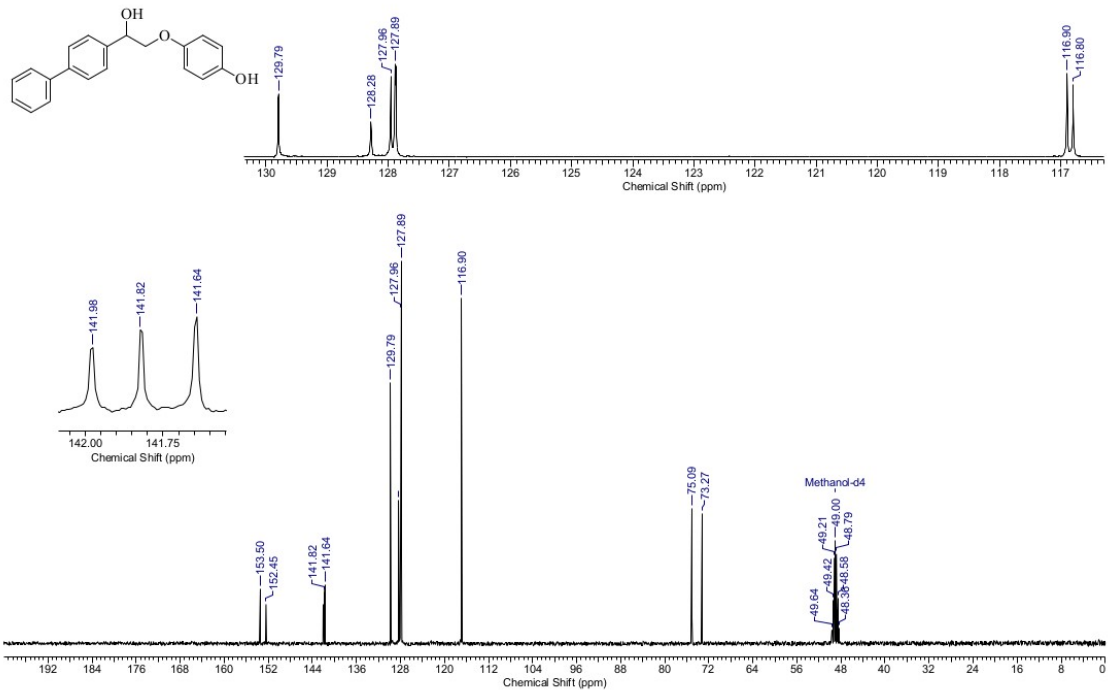
1-([1,1'-Biphenyl]-4-yl)-2-phenoxyethanol (10b) (APT NMR)



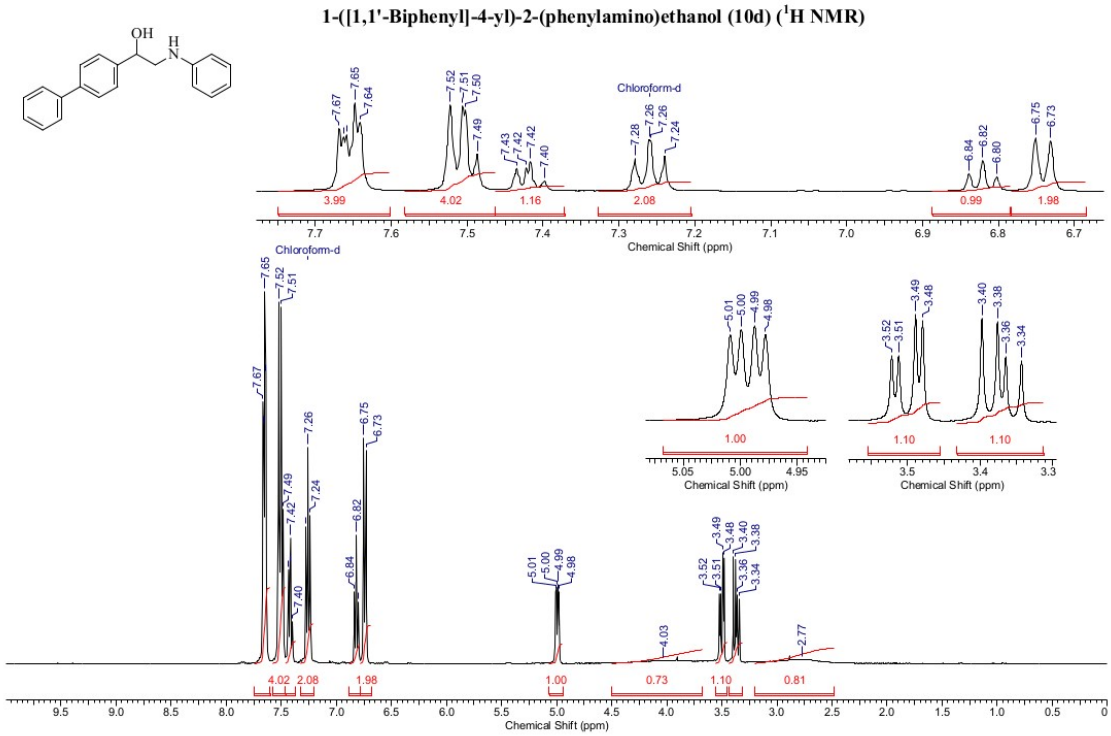
4-(2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethoxy)phenol (10c) (^{1}H NMR)



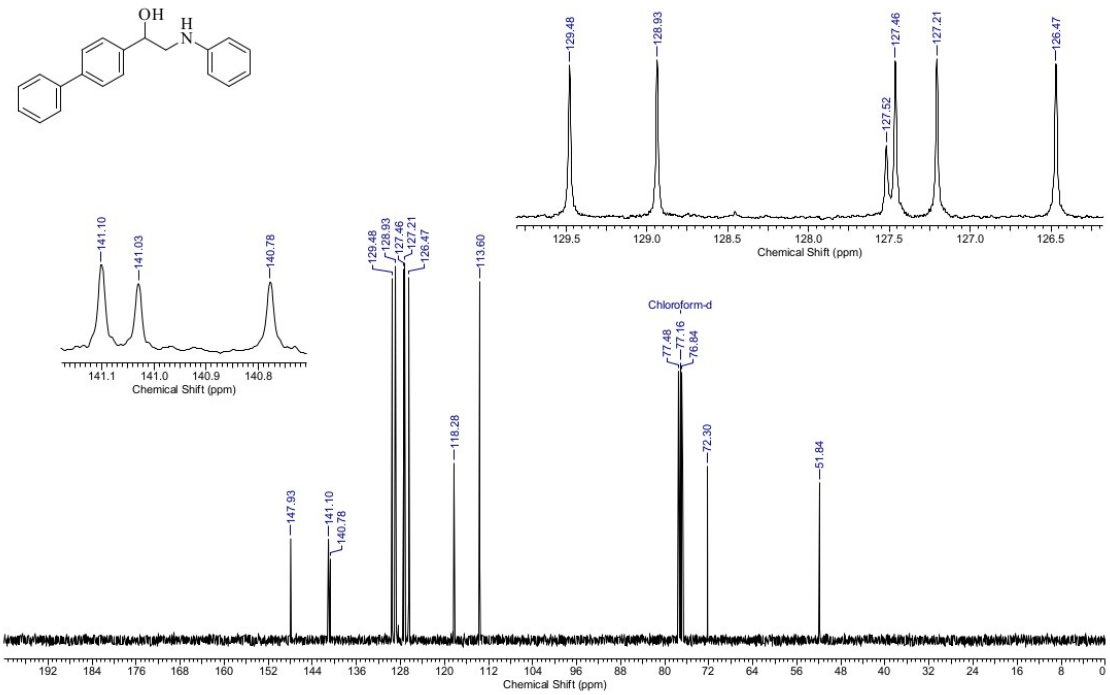
4-(2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethoxy)phenol (10c) (^{13}C NMR)



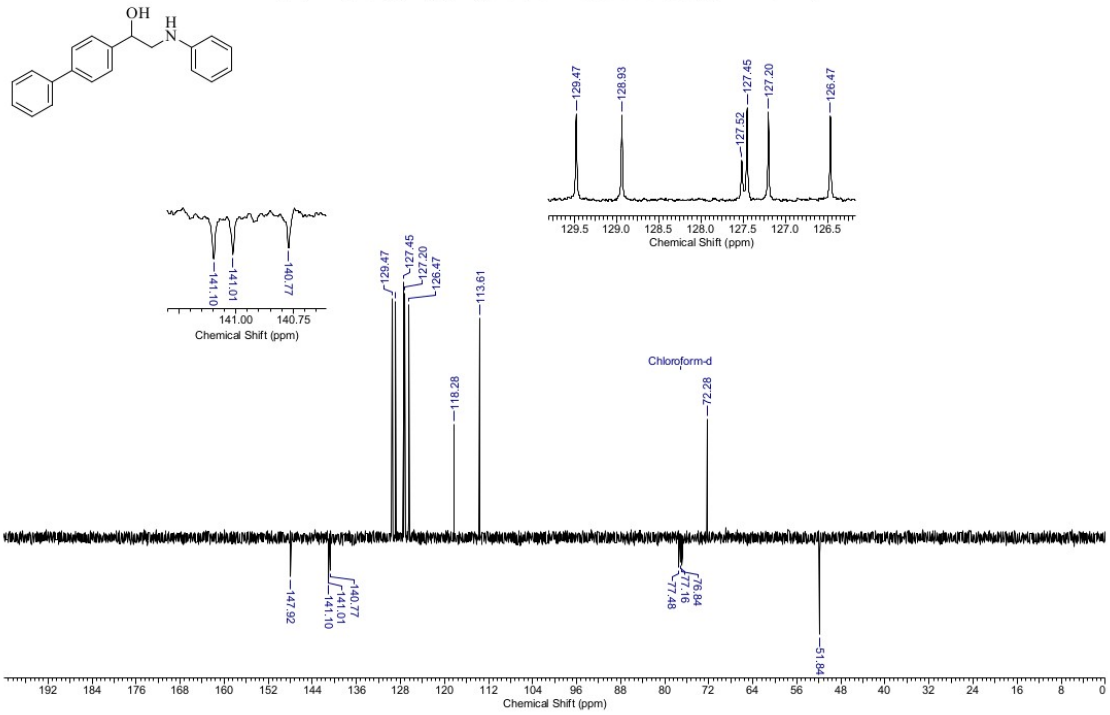
1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanol (10d) (^{1}H NMR)



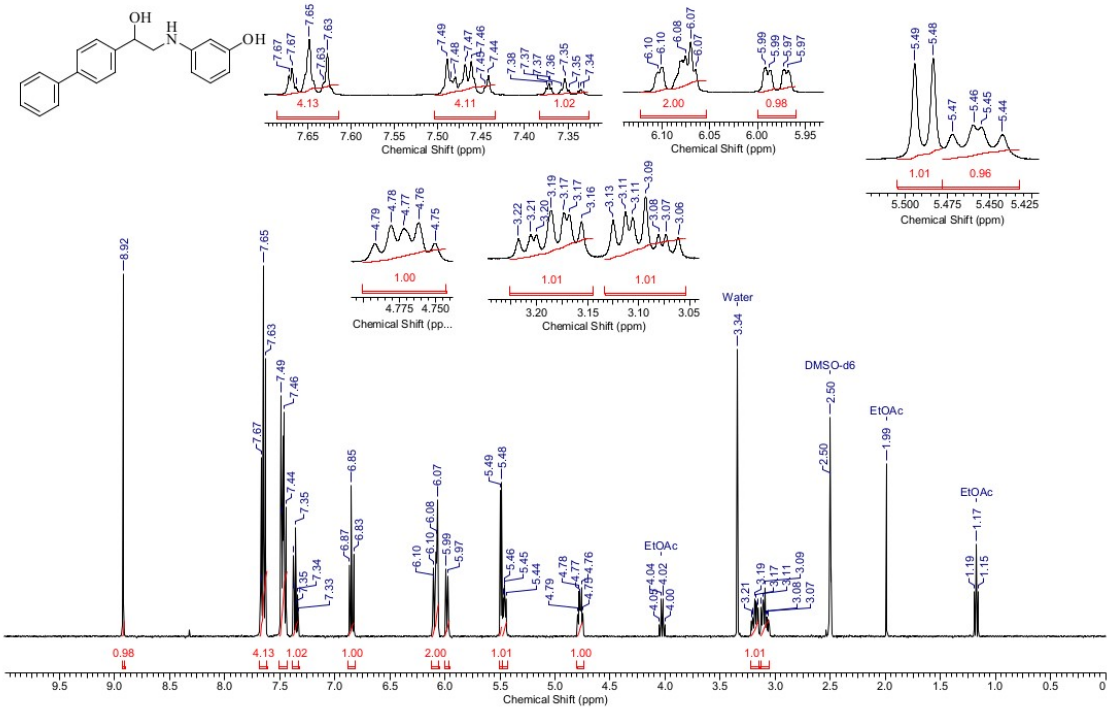
1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanol (10d) (^{13}C NMR)



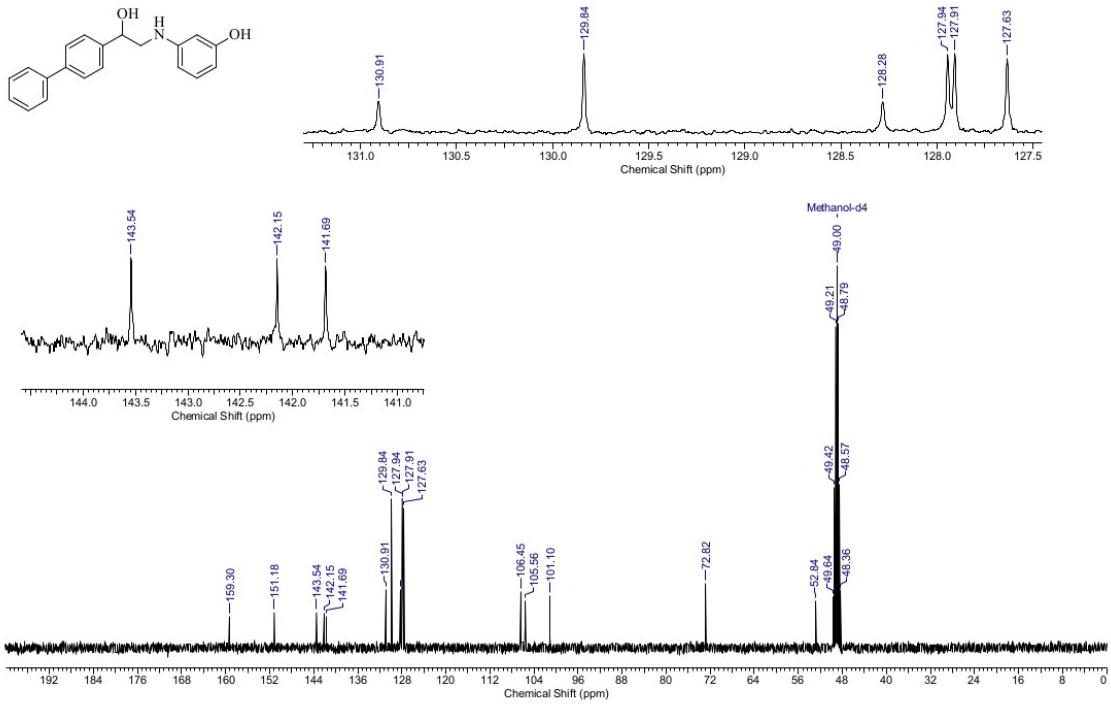
1-([1,1'-Biphenyl]-4-yl)-2-(phenylamino)ethanol (10d) (APT NMR)



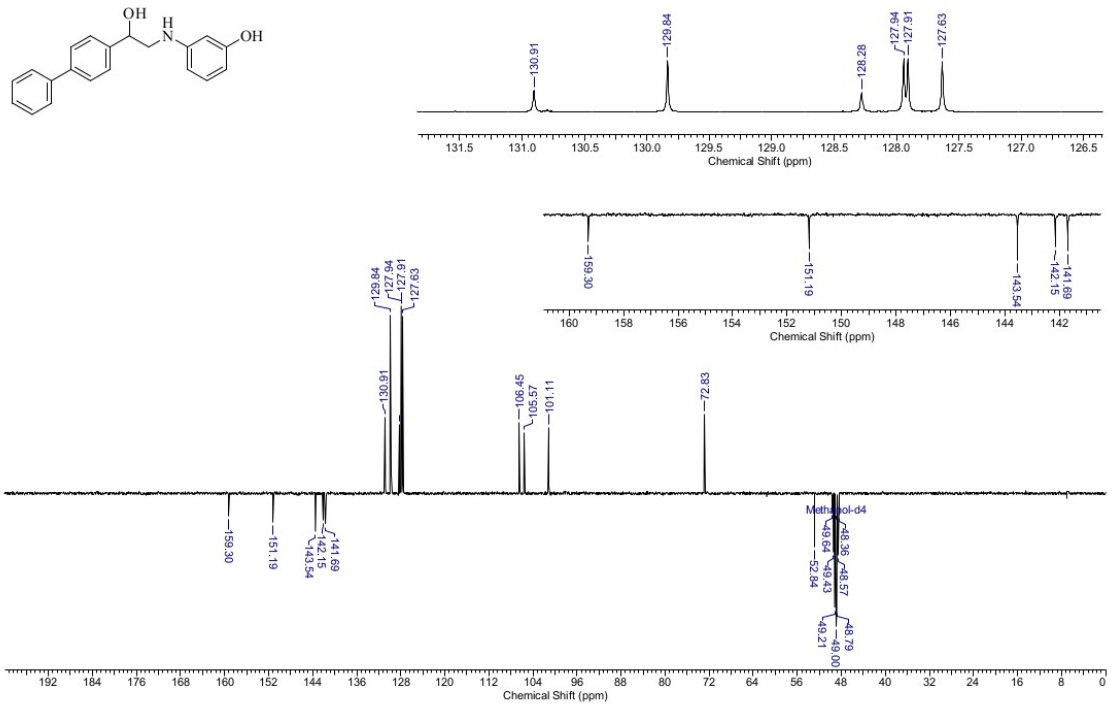
3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenol (10e) (^{1}H NMR)



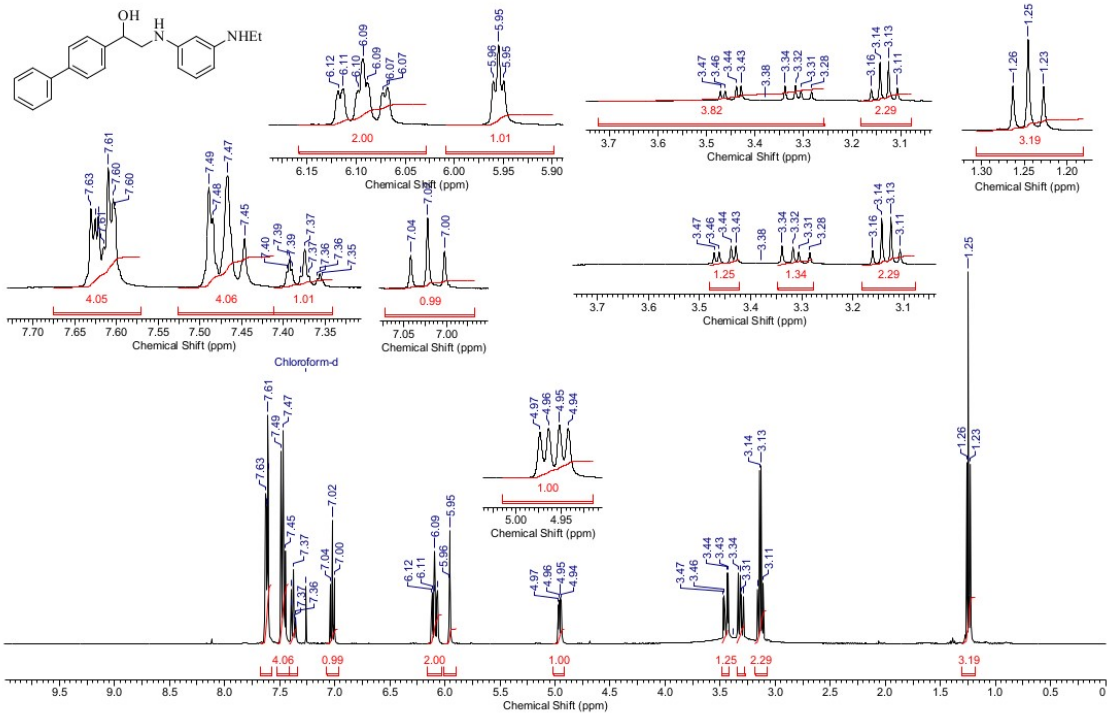
3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenol (10e) (^{13}C NMR)



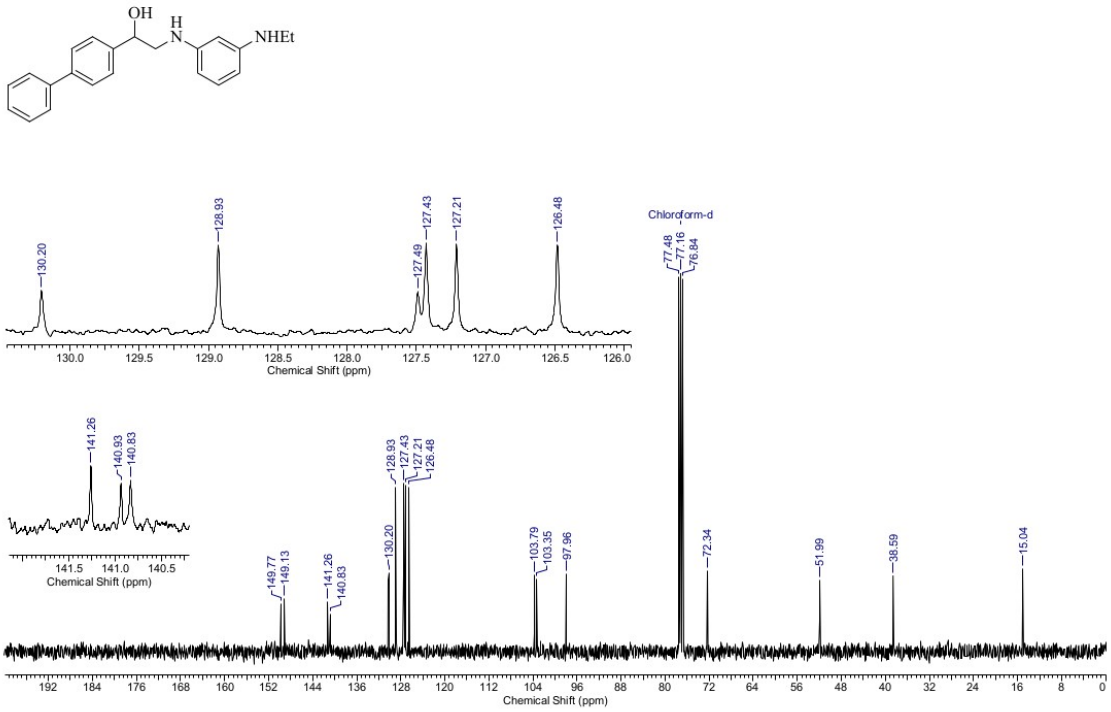
3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenol (10e) (APT NMR)



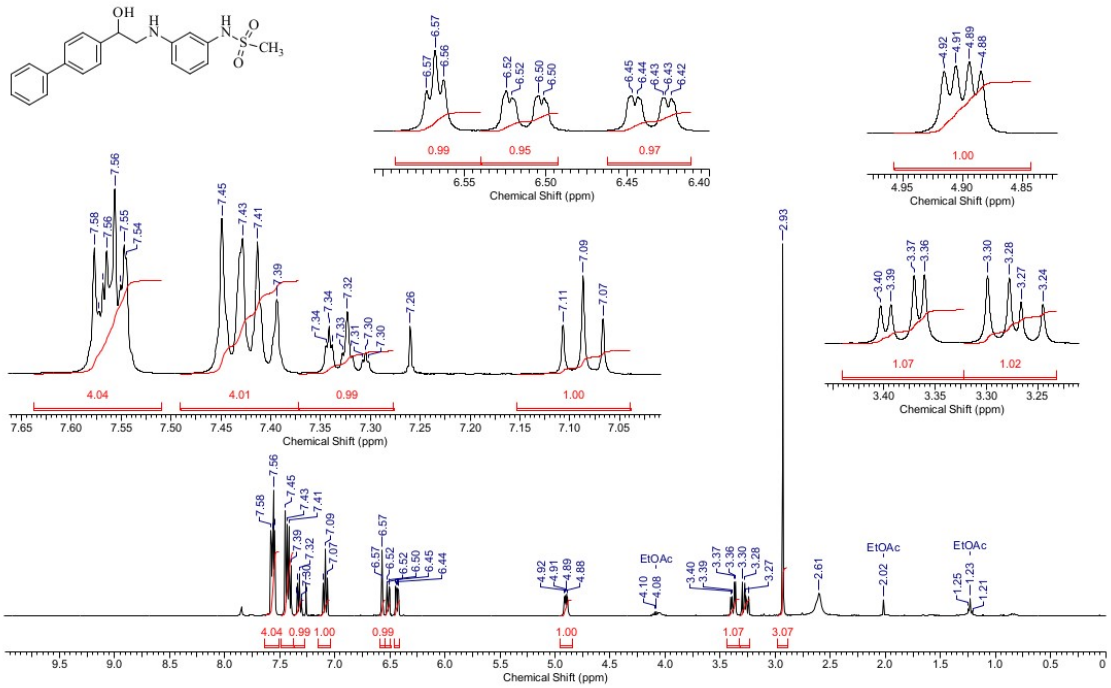
1-([1,1'-Biphenyl]-4-yl)-2-((3-(ethylamino)phenyl)amino)ethanol (10g) (^{1}H NMR)



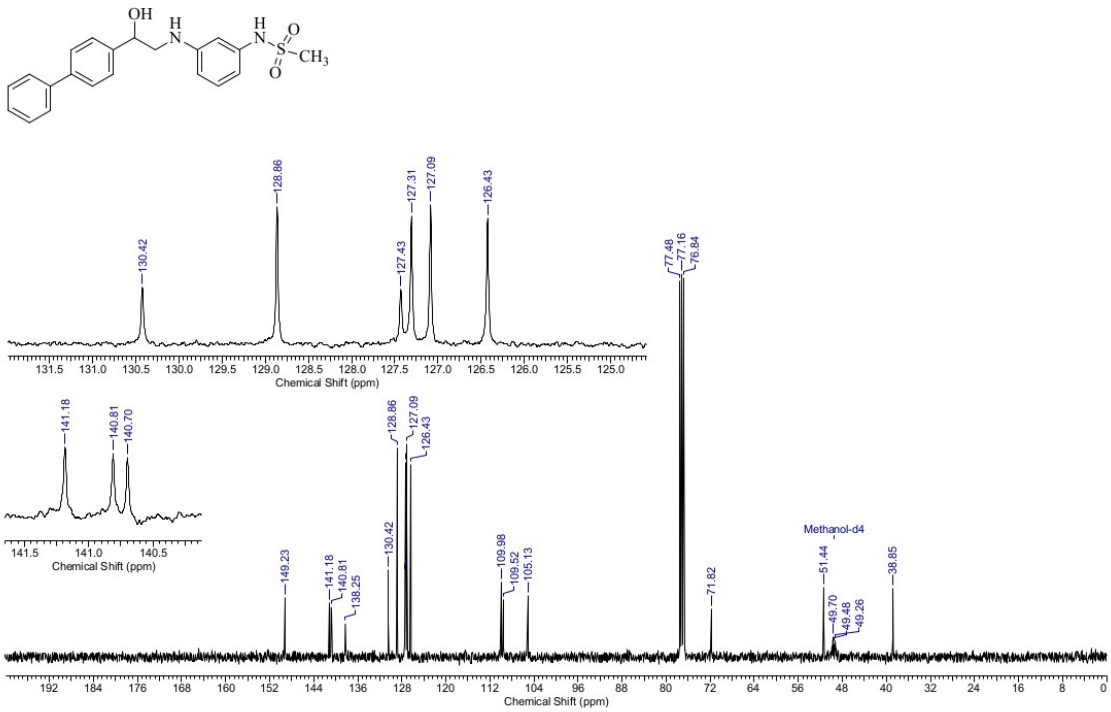
1-([1,1'-Biphenyl]-4-yl)-2-((3-(ethylamino)phenyl)amino)ethanol (10g) (^{13}C NMR)



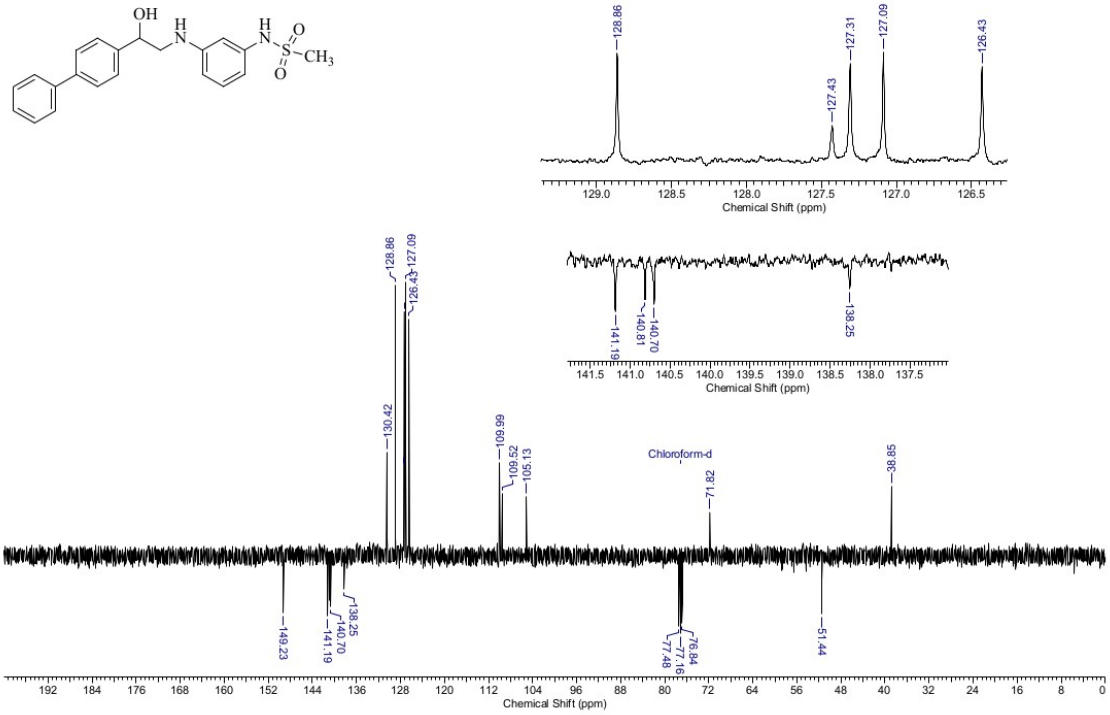
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10h) (^{1}H NMR)



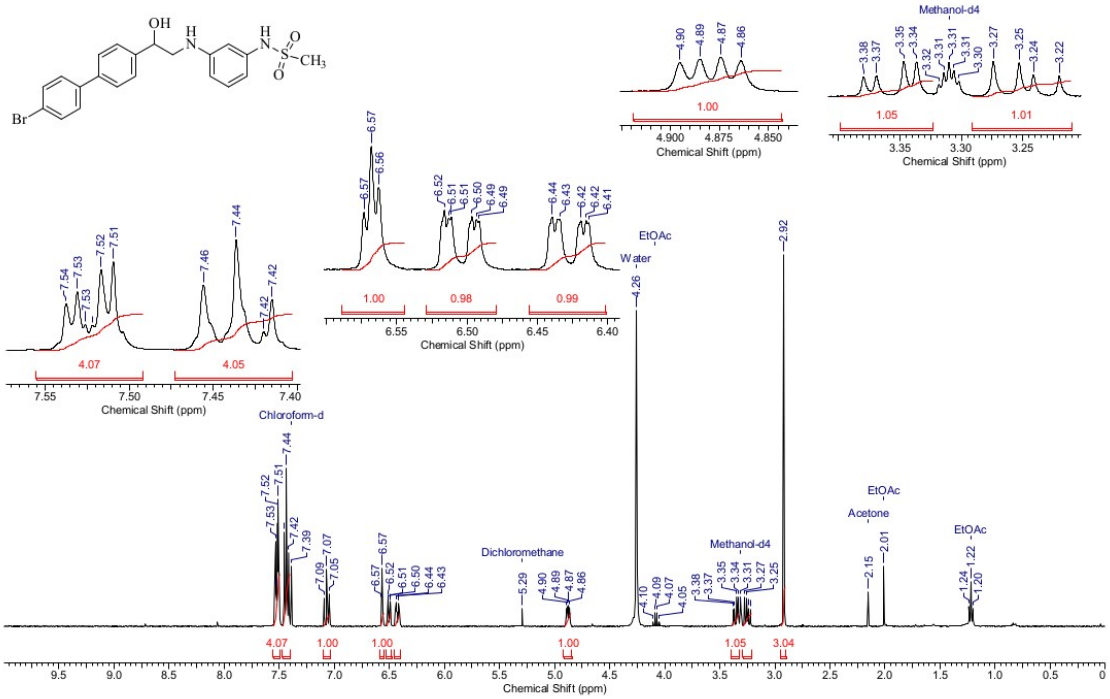
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10h) (^{13}C NMR)



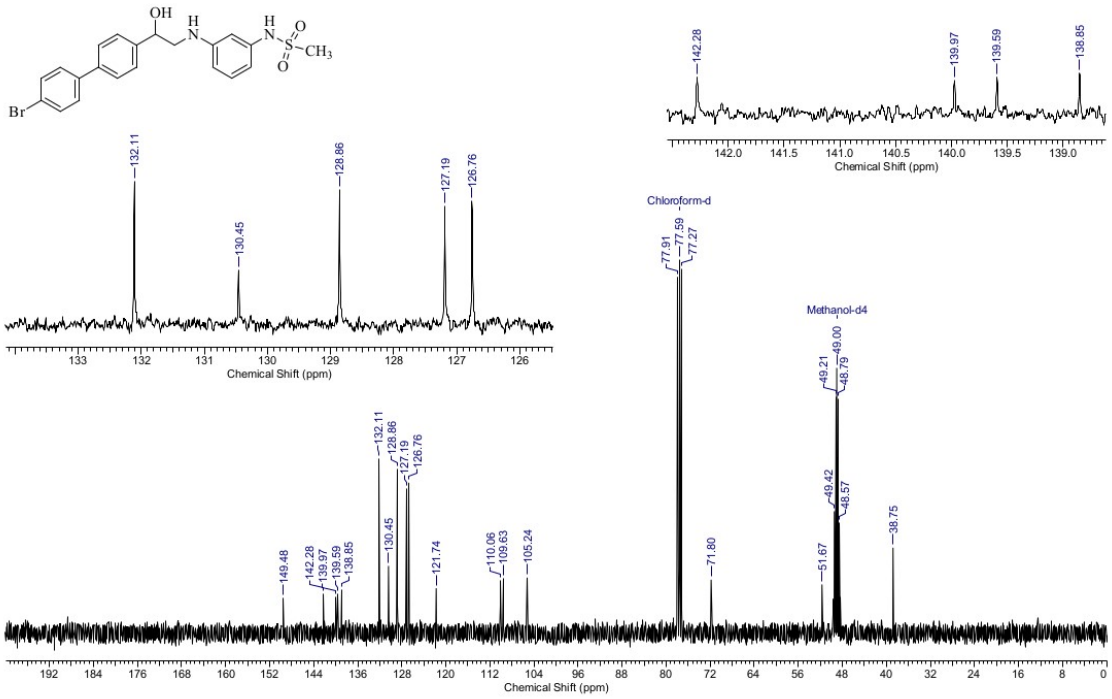
N-(3-((2-([1,1'-Biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10h) (APT NMR)



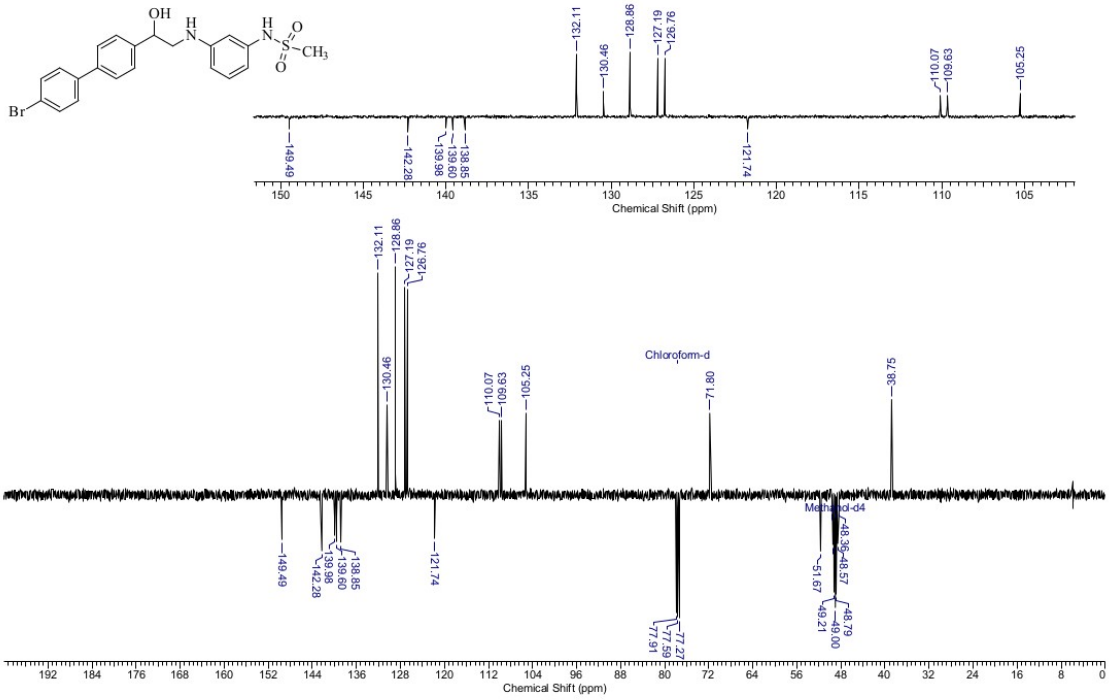
N-(3-((2-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10i) (^{1}H NMR)



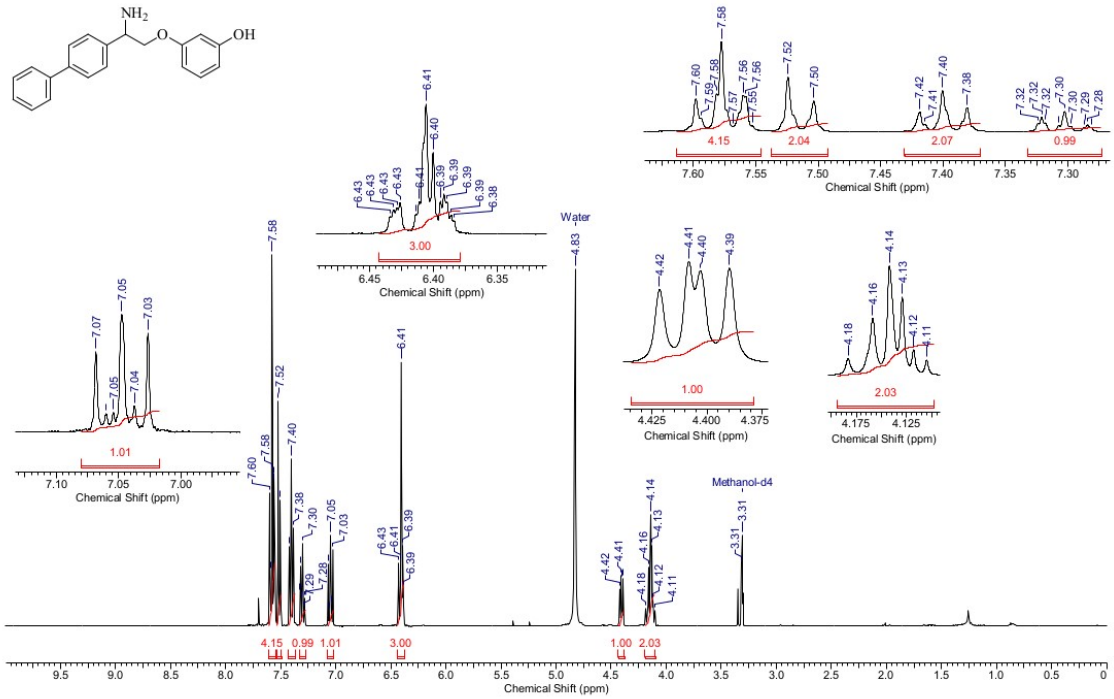
N-(3-((2-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10i) (^{13}C NMR)



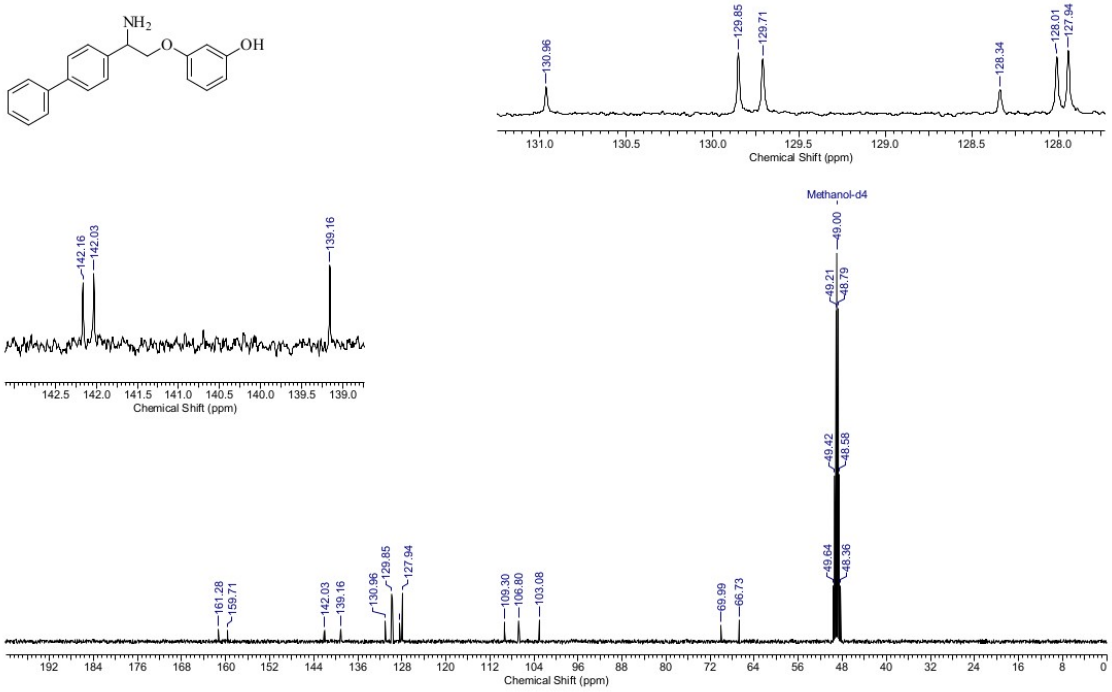
N-(3-((2-(4'-Bromo-[1,1'-biphenyl]-4-yl)-2-hydroxyethyl)amino)phenyl)methanesulfonamide (10i) (APT NMR)

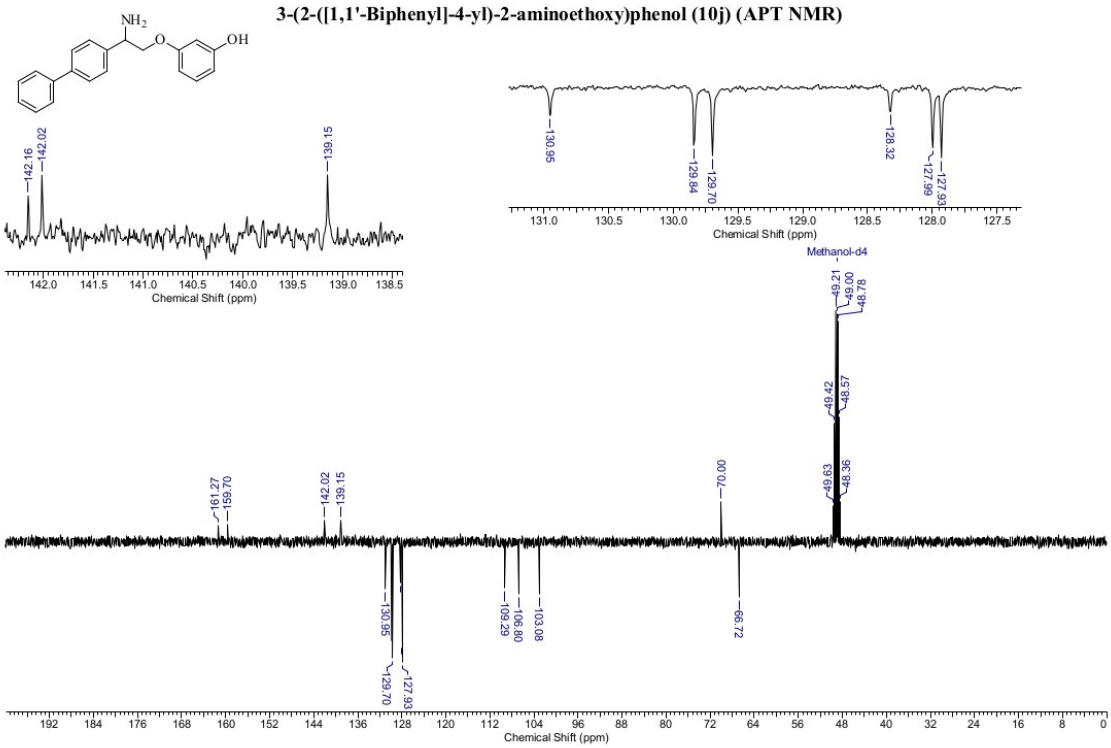


3-(2-([1,1'-Biphenyl]-4-yl)-2-aminoethoxy)phenol (10j) (^{1}H NMR)



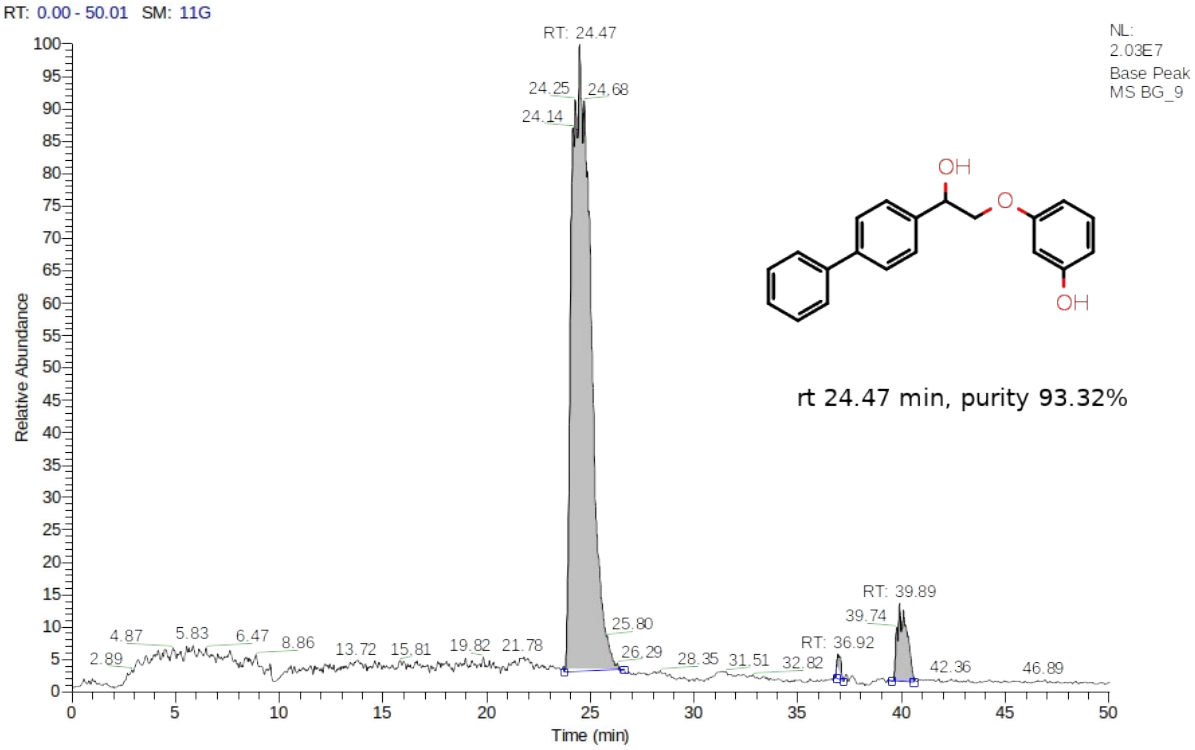
3-(2-([1,1'-Biphenyl]-4-yl)-2-aminoethoxy)phenol (10j) (^{13}C NMR)



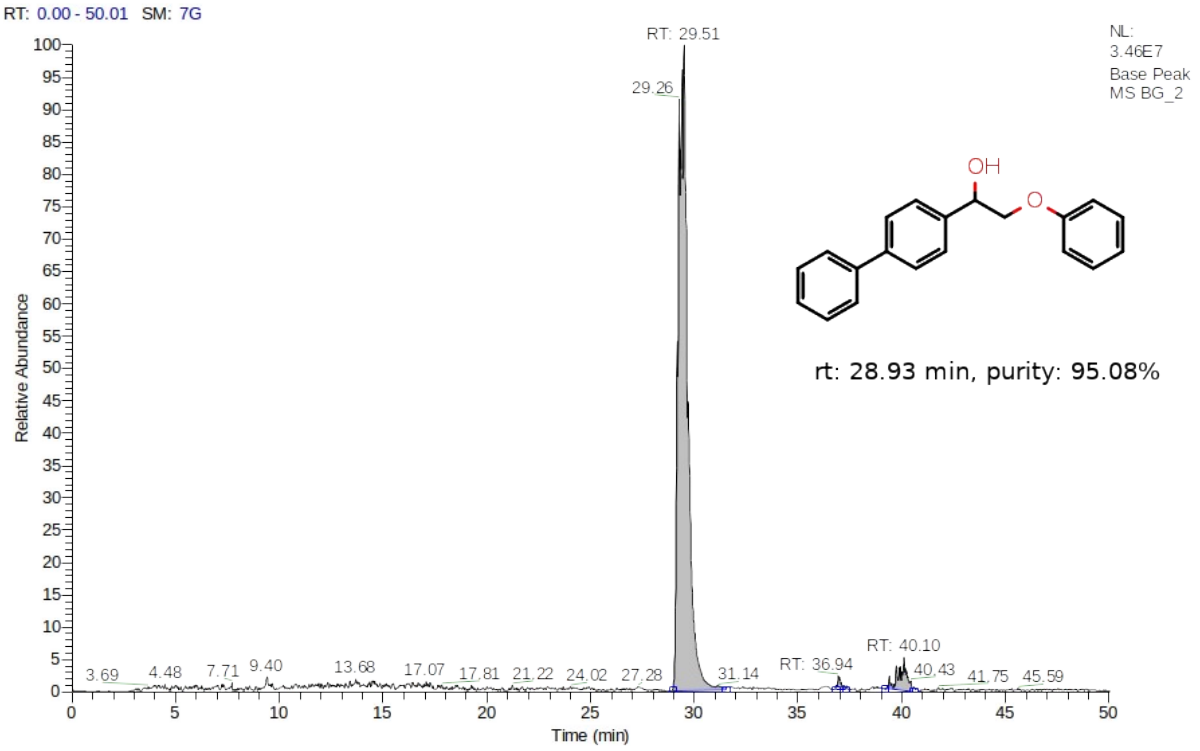


LC-MS results

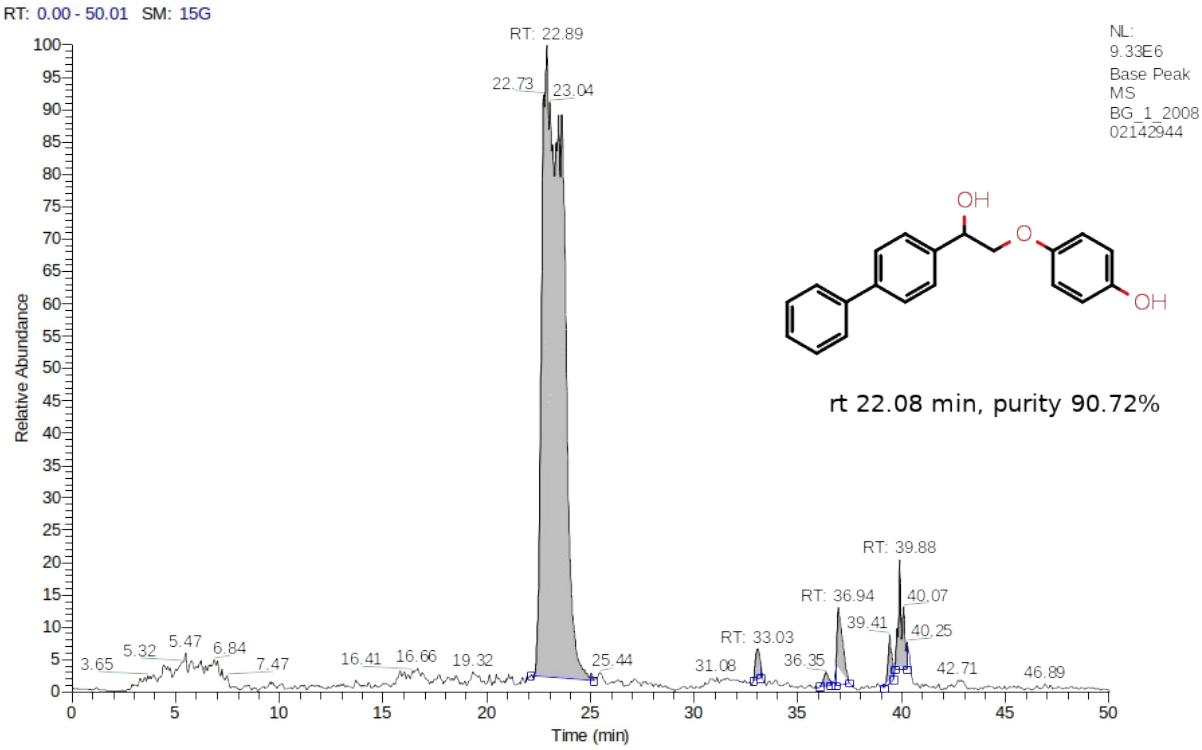
10a:



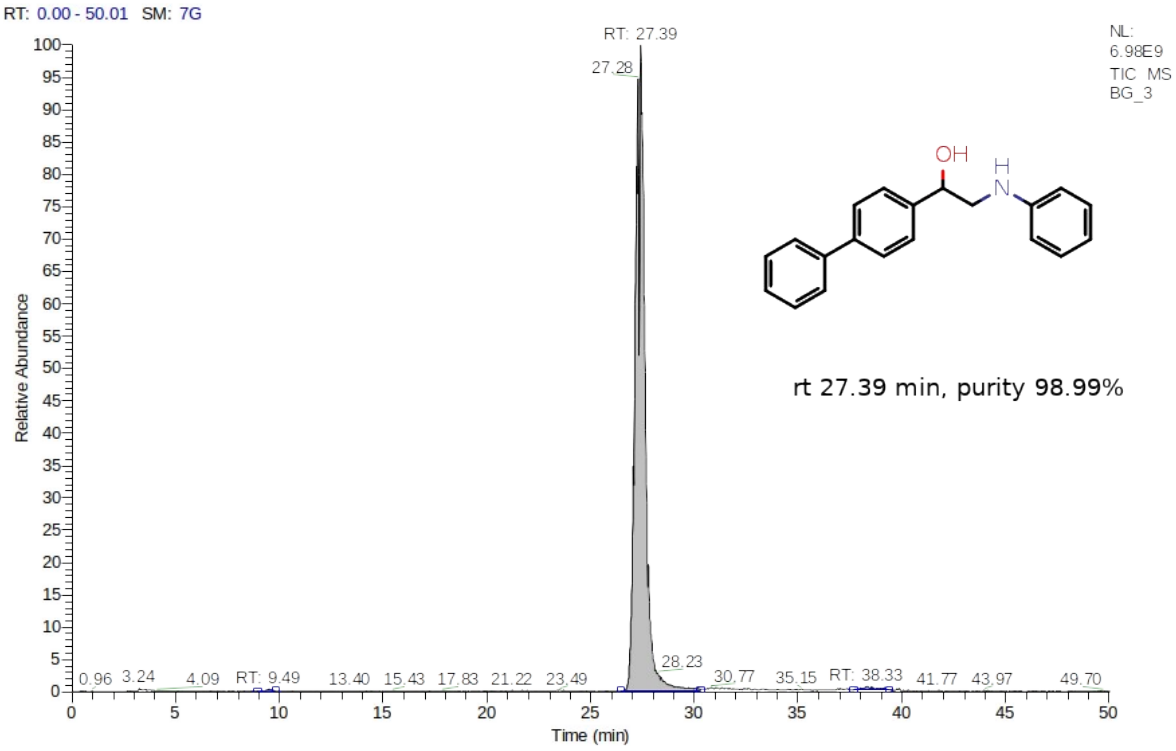
10b:


RT: 0.00 - 50.01 SM: 7G
RT: 29.51
29.26
NL:
3.46E7
Base Peak
MS BG_2
OH
O
rt: 28.93 min, purity: 95.08%
Relative Abundance
Time (min)
3.69
4.48
7.71
9.40
13.68
17.07
17.81
21.22
24.02
27.28
31.14
RT: 36.94
RT: 40.10
40.43
41.75
45.59

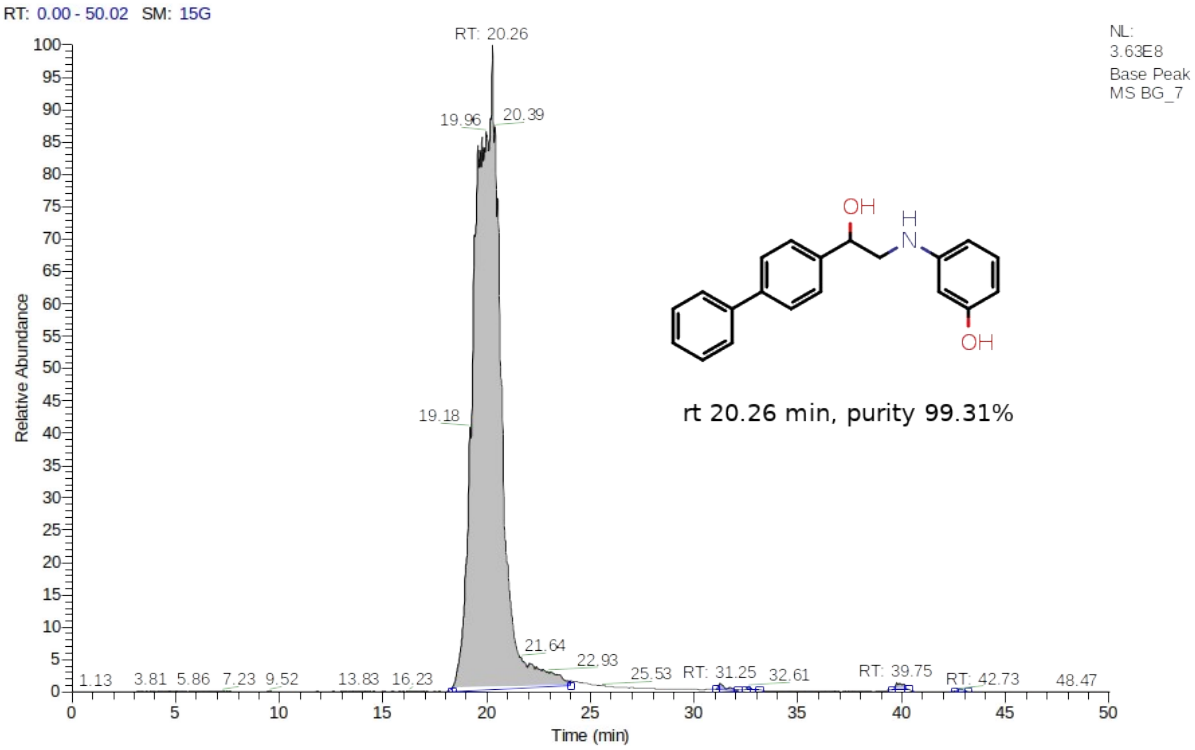
10c:


RT: 0.00 - 50.01 SM: 15G
RT: 22.89
22.73
23.04
NL:
9.33E6
Base Peak
MS
BG_1_2008
02142944
OH
O
OH
rt 22.08 min, purity 90.72%
Relative Abundance
Time (min)
3.65
5.32
5.47
6.84
7.47
16.41
16.66
19.32
25.44
31.08
RT: 33.03
36.35
RT: 36.94
RT: 39.88
40.07
39.41
40.25
42.71
46.89

10d:

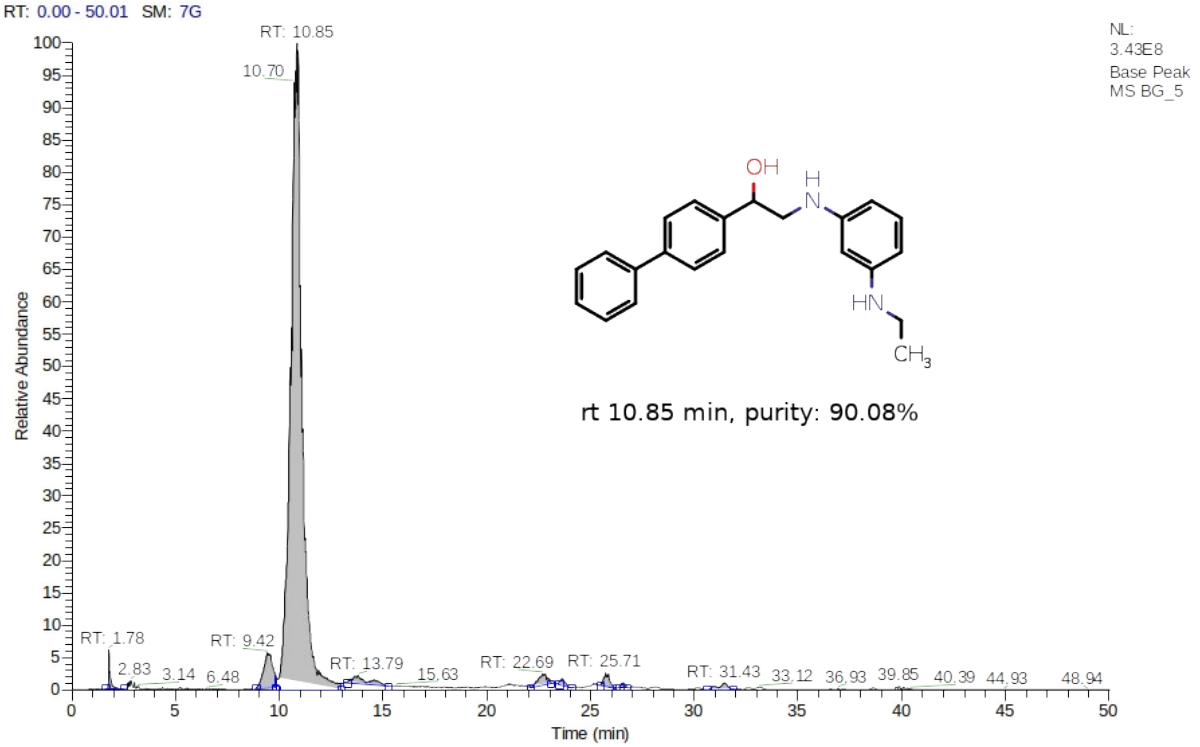

RT: 0.00 - 50.01 SM: 7G
RT: 27.39
27.28
NL:
6.98E9
TIC MS
BG_3
OH
H
N
rt 27.39 min, purity 98.99%
Relative Abundance
Time (min)
0.96 3.24 4.09 RT: 9.49 13.40 15.43 17.83 21.22 23.49 28.23 30.77 35.15 RT: 38.33 41.77 43.97 49.70

10e:

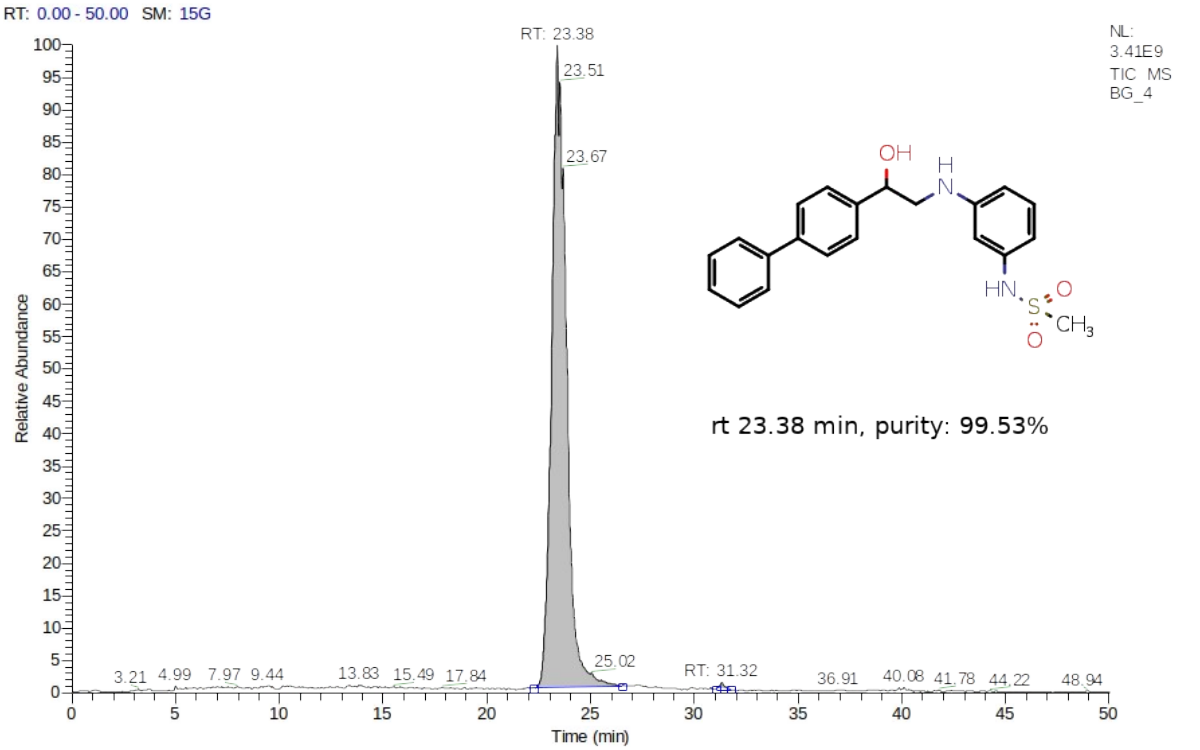

RT: 0.00 - 50.02 SM: 15G
RT: 20.26
19.96
20.39
NL:
3.63E8
Base Peak
MS BG_7
OH
H
N
OH
rt 20.26 min, purity 99.31%
Relative Abundance
Time (min)
19.18
1.13 3.81 5.86 7.23 9.52 13.83 16.23 21.64 22.93 25.53 RT: 31.25 32.61 RT: 39.75 RT: 42.73 48.47

10f:

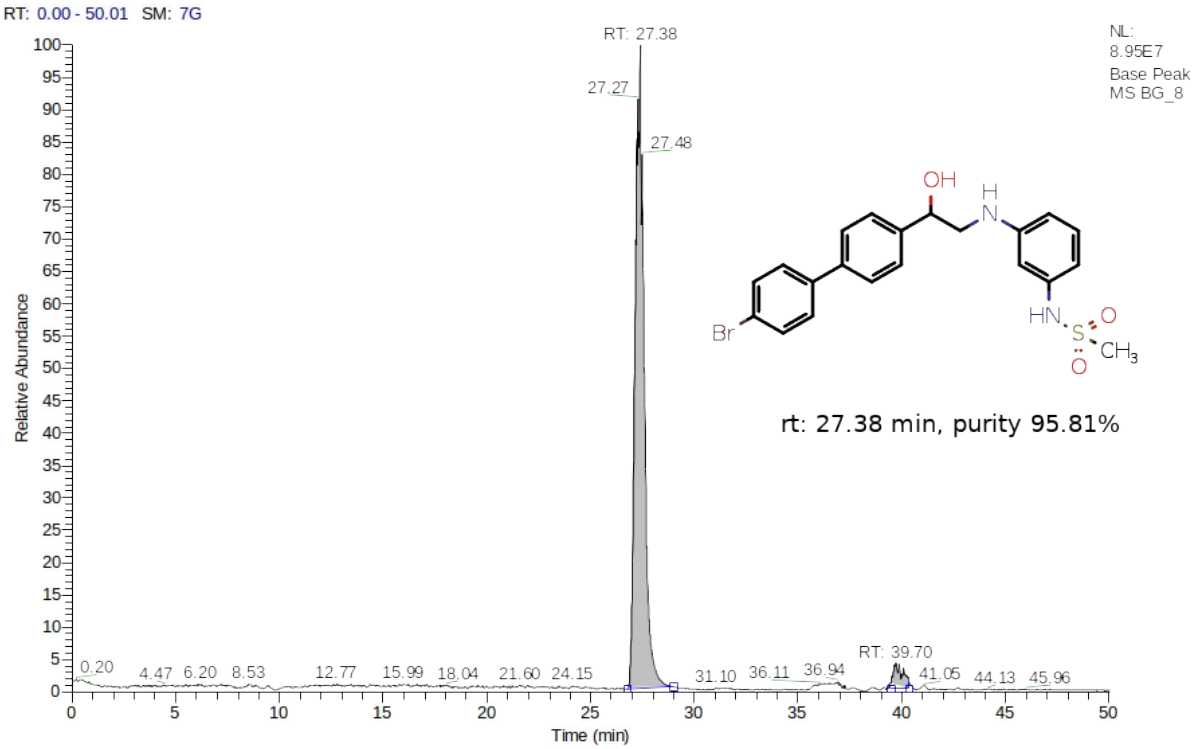
10g:


RT: 0.00 - 50.01 SM: 7G
NL:
3.43E8
Base Peak
MS BG_5
RT: 10.85
10.70
RT: 1.78
RT: 9.42
RT: 13.79
RT: 22.69
RT: 25.71
RT: 31.43
2.83
3.14
6.48
15.63
33.12
36.93
39.85
40.39
44.93
48.94
Relative Abundance
Time (min)
OH
H
N
HN
CH3
rt 10.85 min, purity: 90.08%

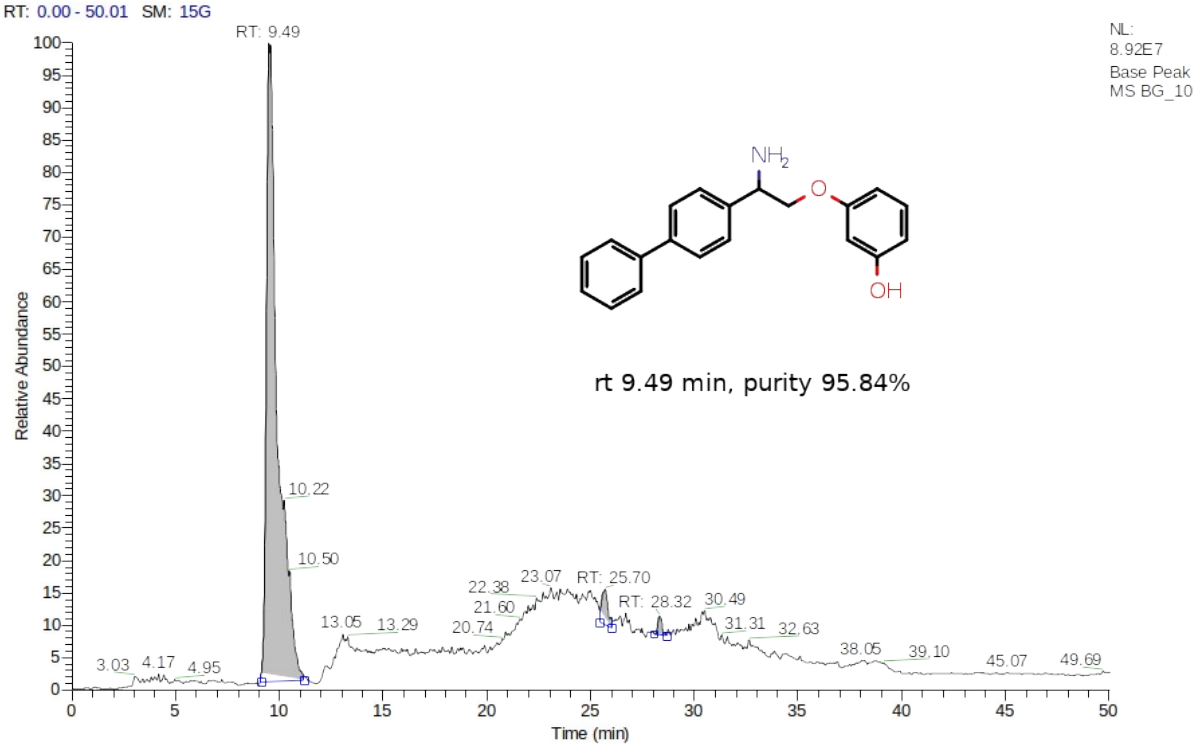
10h:


RT: 0.00 - 50.00 SM: 15G
NL:
3.41E9
TIC MS
BG_4
RT: 23.38
23.51
23.67
25.02
RT: 31.32
3.21
4.99
7.97
9.44
13.83
15.49
17.84
36.91
40.08
41.78
44.22
48.94
Relative Abundance
Time (min)
OH
H
N
HN
S
O
O
CH3
rt 23.38 min, purity: 99.53%

10i:



10j:



References

1. Trott, O.; Olson, A. J. AutoDock Vina: Improving the speed and accuracy of docking with a new scoring function, efficient optimization, and multithreading. *J. Comput. Chem.* **2010**, *31* (2), 455-461.

2. Regan, M. C.; Zhu, Z.; Yuan, H.; Myers, S. J.; Menaldino, D. S.; Tahirovic, Y. A.; Liotta, D. C.; Traynelis, S. F. and Furukawa H. Structural elements of a pH-sensitive inhibitor binding site in NMDA receptors. *Nat. Commun.* **2019**, *10*, 321.
3. Morris, G. M.; Huey, R.; Lindstrom, W.; Sanner, M. F.; Belew, R. K.; Goodsell, D. S. and Olson, A. J. AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility. *J. Comput. Chem.* **2009**, *30*, 2785-2791.
4. Wang, J.; Wolf, R.M.; Caldwell, J.W.; Kollman, P. A. and Case, D.A. Development and testing of a general amber force field. *J. Comput. Chem.* **2004**, *25*, 1157-1174.
5. Maier, J. A.; Martinez, C.; Kasavajhala, K.; Wickstrom, L.; Hauser, K. E. and Simmerling C. ff14SB: Improving the Accuracy of Protein Side Chain and Backbone Parameters from ff99SB. *J. Chem. Theory Comput.* **2015,** *11* (8), 3696-3713.
6. Jakalian, A.; Jack, D. B. and Bayly, C. I. Fast, efficient generation of high-quality atomic charges. AM1-BCC model: II. Parameterization and validation. *J. Comput. Chem.*, **2002**, *23*, 1623-1641.
7. Sindhikara, D. J.; Yoshida, N. and Hirata, F. *Placevent*: An algorithm for prediction of explicit solvent atom distribution - Application to HIV-1 protease and F-ATP synthase. *J. Comput. Chem.* **2012**, *33*, 1536-1543.
8. Salomon-Ferrer, R.; Case, D. A. and Walker, R. C. An overview of the Amber biomolecular simulation package. *WIREs Comput. Mol. Sci.* **2013**, *3*, 198-210.
9. Miller, B. R.; McGee, T. D.; Swails, J. M.; Homeyer, N.; Gohlke, H. and Roitberg A. E. MMPBSA.py: An Efficient Program for End-State Free Energy Calculations. *J. Chem. Theory Comput.* **2012**, *8* (9), 3314-3321.
10. Onufriev, A.; Bashford, D. and Case, D. A. Exploring protein native states and large-scale conformational changes with a modified generalized born model. *Proteins*. **2004**, *55*, 383-394.
11. Roe, D. R.; Cheatham, T. E. PTRAJ and CPPTRAJ: Software for Processing and Analysis of Molecular Dynamics Trajectory Data. J. Chem. Theory Comput. 2013, 9 (7), 3084-3095.
12. Vorobjev, V. S. Vibrodissociation of Sliced Mammalian Nervous Tissue. *J. Neurosci. Methods.* **1991**, *38*, 145-150.
13. Jones, S. M.; Snell, L. D.; Johnson, K. M. Characterization of the Binding of Radioligands to the N-Methyl-D-Aspartate, Phencyclidine, and Glycine Receptors in Buffy Coat Membranes. *J. Pharmacol. Methods.* **1989**, *21*, 161-168.
14. Jackson, G. R.; Werrbach-Perez, K.; Ezell, E.L; Post, J. F. M.; Perez-Polo, J.R. Nerve growth factor effects on pyridine nucleotides after oxidant injury of rat pheochromocytoma cells. *Brain Res.* **1992**, *592* (1–2), 239-248.
15. Ueda, Y.; Walsh, E.; Nakanishi, H.; Yoshida, K. A colorimetric assay method for the evaluation of neurotrophic activity in vitro. *Neurosci. Lett.* **1994**, *165* (1-2), 203-207.
16. Porsolt, R. D.; Pichon, M. L; Jalfre M. Depression: a new animal model sensitive to antidepressant treatments. *Nature.* **1977**, *266*, 730-732.
17. Porsolt, R. D.; Bertin, A.; Jalfre, M. Behavioural despair in mice: a primary screening test for antidepressants. *Arch. Int. Pharmocodyn. Ther.* **1977**, *229*, 327-336.
18. Porsolt, R. D.; Anton, G.; Blavet, N.; Jalfre, M. Behavioural despair in rats: a new model sensitive to antidepressant treatments. *Eur. J. Pharmacol.* **1978**, *47*, 379-391.
19. Borsini, F.; Meli, A. Is the forced swimming test a suitable model for revealing antidepressant activity? *Psychopharmacology* **1988**, *94*, 147-160.
20. Kourounakis, A. P.; Charitos, C.; Rekka, E. A.; Kourounakis P. N. Lipid-Lowering (Hetero)Aromatic Tetrahydro-1,4-Oxazine Derivatives with Antioxidant and Squalene Synthase Inhibitory Activity. *J. Med. Chem.* **2008**, *51*, 5861.

21. Temnyakova, N. S.; Vasilenko, D. A.; Barygin, O. I.; Dron, M. Y.; Averina, E. B.; Grishin, Y. K.; Grigoriev, V. V.; Palyulin, V. A.; Fedorov, M. V.; Karlov, D. S. Ifenprodil-like NMDA receptor modulator based on the biphenyl scaffold. *Mendeleev Commun*. **2020**, *30*, 324.
22. Moreira, D. R. M.; Leite, A. C. L.; Cardoso, M. V. O.; Srivastava, R. M.; Hernandes, M. Z.; Rabello, M. M.; Cruz, L. F.; Ferreira, R. S.; Simone, C. A.; Meira, C. S.; Guimaraes, E. T.; Silva, A. C.; Santos, T. A. R.; Pereira, V. R. A.; Soares, M. B. P. Structural Design, Synthesis and Structure-Activity Relationships of Thiazolidinones with Enhanced Anti-*Trypanosoma cruzi* Activity. *ChemMedChem*. **2014**, *9*, 177.
23. Kallmayer, H.; Wagner, E. Zur Farbe der N-(4′-Nitrophenacyl)-arylamine. *Arch. Pharm.* **1980**, *313*, 315.
24. Pan, S.; Jiang, M.; Hu, J.; Xu, R.; Zeng, X.; Zhong, G. Synthesis of 1,2-amino alcohols by decarboxylative coupling of amino acid derived α-amino radicals to carbonyl compounds *via* visible-light photocatalyst in water. *Green Chem.*, **2020**, *22*, 336.