

Supplementary data: Synthesis and Biological Evaluation of Highly Active 7-Anilino Triazolopyrimidines as Potent Antimicrotubule Agents

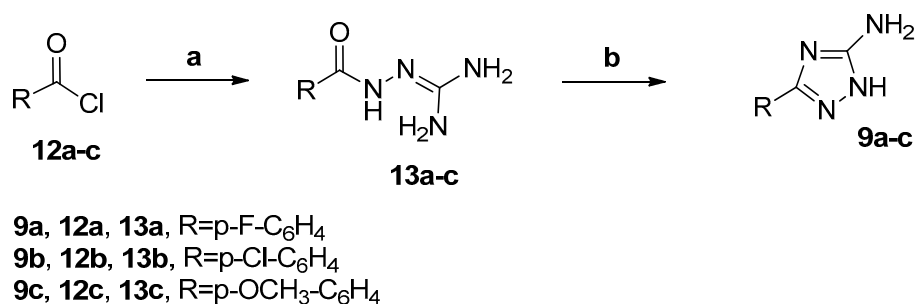
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Synthetic procedure for the preparation of 3-aryl-5-amino-1*H*-1,2,4-triazoles (9a-c)

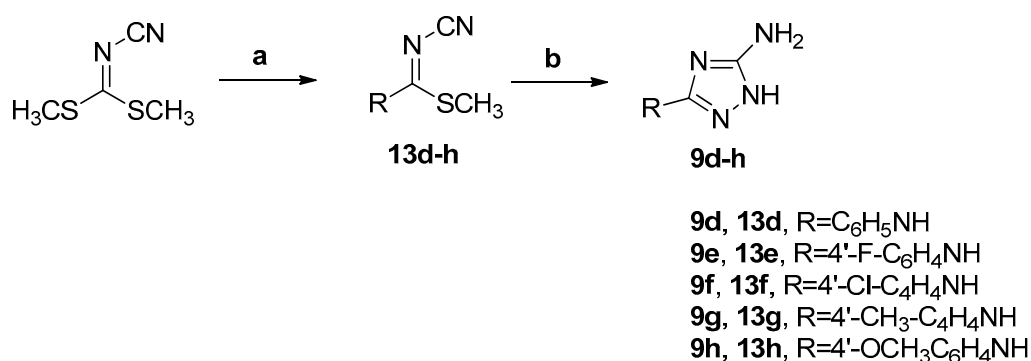


Scheme S1. Reagents. **a:** aminoguanidine hydrogen carbonate pyridine, 0 °C for 30 min. then 12 h rt; **b:** water, microwave irradiation, 100 W;

Synthesis of 3-aryl-5-amino-1*H*-1,2,4-triazoles **9a-c** (**9a**, R=p-F-C₆H₄; **9b**, R=p-Cl-C₆H₄; **9c**, R=p-OMe-C₆H₄) was accomplished using a three-step procedure reported in the Scheme S1 according to literature method previously described by us. Briefly, the reaction of aryl chloride **12a-c** with aminoguanidine hydrogen carbonate using pyridine as solvent furnished the corresponding aryl amidoguanidines **13a-c**, followed by subsequent ring closure of the intermediate in water under microwave irradiation, to yield 3-substituted-5-amino-1*H*-1,2,4-triazoles **9a-c**.

For the preparation and characterization of compounds **9a-c** and **13a-c** see: R. Romagnoli, F. Prencipe, P. Oliva, S. Baraldi, P.G Baraldi, A. Brancale, S. Ferla, E. Hamel, R. Bortolozzi, G. Viola. 3-Aryl/heteroaryl-5-amino-1-(3',4',5'-trimethoxybenzoyl)-1,2,4-triazoles as antimicrotubule agents. design, synthesis, antiproliferative activity and inhibition of tubulin polymerization. Bioorg. Chem. 80C (2018) 361-374.

Synthetic procedure for the preparation of 3-aryl-5-amino-1*H*-1,2,4-triazoles (**9d-h**)

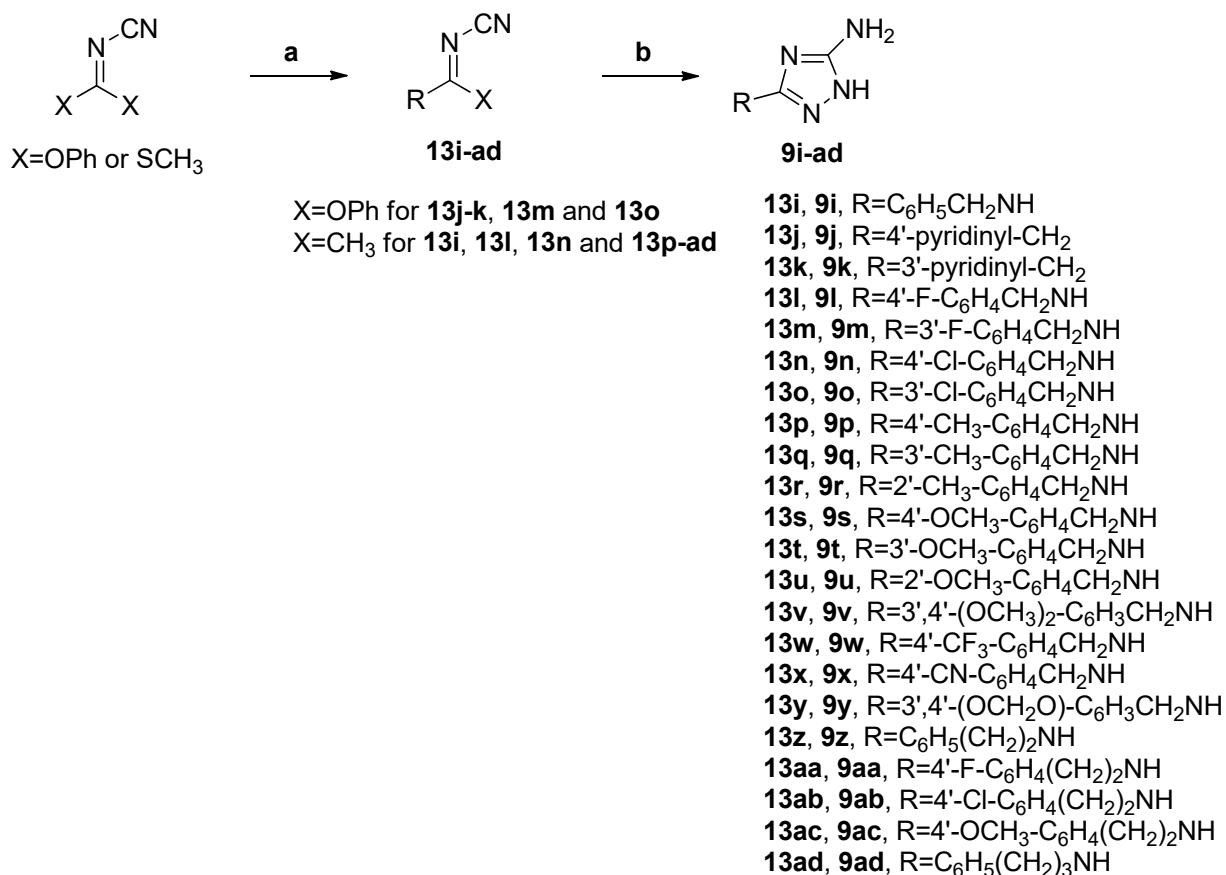


Scheme S2. Reagents. **a:** ArNH₂, *i*-PrOH, reflux; **b:** NH₂NH₂.H₂O, MeOH, rx, 18 h

Compounds **9d-h** were prepared according to the synthetic pathway reported in Scheme S2. The condensation of dimethyl cyanodithioimidocarbonate with the appropriate substituted aniline resulted in the formation of imidates **13d-h**, which were cyclized into the corresponding 5-amino-1*H*-[1,2,4]-triazole derivatives **9d-h** in the presence of hydrazine hydrate in refluxing methanol.

For the preparation and characterization of compounds **9d-h** and **13d-h** see: R. Romagnoli, P. G. Baraldi, M. Kimatrai Salvador, F. Prencipe, V. Bertolasi, M. Cancellieri, A. Brancale, E. Hamel, I. Castagliuolo, F. Consolaro, E. Porcu, G. Basso, G. Viola. Synthesis, antimitotic and antivascular activity of 1-(3',4',5'-trimethoxybenzoyl)-3-aryl-5-amino-1,2,4-triazoles. J. Med. Chem. 57 (2014) 6795-6808.

Synthetic procedure for the preparation of 3-substituted-5-amino-1*H*-1,2,4-triazoles (**9i-ad**)



Scheme S3. Reagents. **a:** Appropriate ArCH_2NH_2 or $\text{Ar}(\text{CH}_2)_2\text{NH}_2$ or $\text{C}_6\text{H}_5(\text{CH}_2)_3\text{NH}_2$, *i*-PrOH, room temperature; **b:** $\text{NH}_2\text{NH}_2\cdot\text{H}_2\text{O}$, MeOH, reflux, 18 h

Synthesis of compounds **9i-ad** was accomplished using a two-step protocol described in Scheme S3. The condensation of dimethyl cyanodithioimidocarbonate or diphenoxymethylidenecyanamide with the appropriate benzyl/phenylethylamine or 3-phenylpropylamine resulted in the formation of imidates **13i-ad**, which were cyclized into the corresponding 3-substituted-5-amino-1*H*-1,2,4-triazoles **9i-ad** with hydrazine hydrate in refluxing methanol.

General procedure (a) for the preparation of compounds 13i-ad. To a solution of dimethyl cyanodithioimidocarbonate (292 mg, 2 mmol) or diphenoxymethylidenecyanamide (500 mg, 2 mmol) in isopropanol (10 mL) was added the appropriate amine (2 mmol, 1 equiv.) and the mixture was stirred at room temperature for 24 h. After this time, the mixture was filtered, the solid residue washed with ethyl ether to furnish the final compound **13i-ad** that was used for the next reaction without any purification.

Compounds **13i**, **13l**, **13n**, **13p-q**, **13s-v**, **13z**, **13y** and **13ab-ad** ($\text{X}=\text{CH}_3$) have been already described and for their characterization see: P. Oliva, V. Onnis, E. Balboni, E. Hamel, F. Estévez-Sarmiento, J. Quintana, F. Estévez, A. Brancale, S. Ferla, S. Manfredini, R. Romagnoli. Synthesis and biological evaluation of 2-substituted benzyl/phenylethylamino-4-amino-5-aryl thiazoles as apoptosis inducing anticancer agents *Molecules*, 25 (2020) 2177.

(Z)- phenyl N'-cyano-N-(pyridin-4-ylmethyl)carbamimidate (**13j**). Following general procedure (a) reported in Scheme S3, by the condensation of diphenoxymethylidenecyanamide and pyridin-4-ylmethanamine, compound **13j** was obtained as a yellow solid, yield 67%, mp 110-112 °C. ¹H-NMR (DMSO-*d*₆) δ: 4.60 (bs, 2H), 7.02-7.10 (m, 2H), 7.26-7.45 (m, 6H), 7.51 (d, *J*=6.0 Hz, 1H), 8.57 (d, *J*=8.0 Hz, 1H). MS (ESI): [M+1]⁺=253.1.

(Z)- phenyl N'-cyano-N-(pyridin-3-ylmethyl)carbamimidate (**13k**). Following general procedure (a) reported in Scheme S3, by the condensation of diphenoxymethylidenecyanamide and pyridin-3-ylmethanamine, compound **13k** was obtained as a white solid, yield 56%, mp 167-169 °C. ¹H-NMR (DMSO-*d*₆) δ: 4.60 (bs, 2H), 7.08 (d, *J*=7.0 Hz, 1H), 7.24-7.57 (m, 5H), 7.69-7.86 (m, 1H), 8.62 (d, *J*=8.0 Hz, 1H). MS (ESI): [M+1]⁺=253.1.

(Z)-phenyl N'-cyano-N-(3-fluorobenzyl)carbamimidate (**13m**). Following general procedure (a) reported in Scheme S3, by the condensation of diphenoxymethylidenecyanamide and 3-fluorobenzylamine, compound **13m** was obtained as a white solid, yield 73%, mp 215-217 °C. ¹H-NMR (DMSO-*d*₆) δ: 4.54 (bs, 2H), 7.02-7.56 (m, 9H), 8.92 (bs, 1H). MS (ESI): [M+1]⁺=270.1.

(Z)-phenyl N'-cyano-N-(3-chlorobenzyl)carbamimidate (**13o**). Following general procedure (a) reported in Scheme S3, by the condensation of diphenoxymethylidenecyanamide and 3-chlorobenzylamine, compound **13o** was obtained as a white solid, yield 68%, mp 201-203 °C. ¹H-NMR (DMSO-*d*₆) δ: 4.44 (bs, 2H), 7.06 (d, *J*=8.0 Hz, 1H), 7.33-7.55 (m, 8H), 8.54 (bs, 1H). MS (ESI): [M+1]⁺=288.1.

(Z)-methyl N'-cyano-N-(2-methylbenzyl)carbamimidothioate (**13r**). Following general procedure (a) reported in Scheme S3, by the condensation of dimethyl cyanodithioimidocarbonate and 2-methylbenzylamine, compound **13r** was obtained as a white solid, yield 92%, mp 185-188 °C. ¹H-NMR (CDCl₃) δ: 2.30 (s, 3H), 2.64 (s, 3H), 4.42 (d, *J*=6.2 Hz, 2H), 6.90-6.94 (m, 3H), 7.36 (t, *J*=8.2 Hz, 1H). MS (ESI): [M+1]⁺=220.2.

(Z)-methyl N'-cyano-N-(4-trifluoromethylbenzyl)carbamimidothioate (**13w**). Following general (a) procedure reported in Scheme S3, by the condensation of dimethyl cyanodithioimidocarbonate and 4-trifluoromethylbenzylamine, compound **13w** was obtained as a yellow solid, yield >95%, mp 173-175 °C. ¹H-NMR (CDCl₃) δ: 2.52 (s, 3H), 4.58 (d, *J*=5.6 Hz, 2H), 7.40 (d, *J*=8.2 Hz, 2H), 7.61 (d, *J*=8.2 Hz, 2H). MS (ESI): [M+1]⁺=274.3.

(Z)-methyl N'-cyano-N-(4-cyanobenzyl)carbamimidothioate (**13x**). Following general procedure (a) reported in Scheme S3, by the condensation of dimethyl cyanodithioimidocarbonate and 4-cyanobenzylamine, compound **13x** was obtained as a yellow solid, yield: 76%, mp 225-227 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.62 (s, 3H), 4.54 (bs, 2H), 7.44 (d, *J*=8.2 Hz, 2H), 7.78 (d, *J*=8.2 Hz, 2H), 8.86 (bs, 1H). MS (ESI): [M+1]⁺=231.3.

(Z)-methyl N'-cyano-N-(4-fluorophenethyl)carbamimidothioate (**13aa**). Following general (a) procedure reported in Scheme S3, by the condensation of dimethyl cyanodithioimidocarbonate and 4-fluorophenylethylamine, compound **13aa** was obtained as a white solid, yield 90%, mp 173-175 °C. ¹H-NMR (CDCl₃) δ: 2.46 (s, 3H), 2.91 (t, *J*=7.2 Hz, 2H), 3.60 (bs, 2H), 7.07 (t, *J*=8.4 Hz, 2H), 7.20-7.22 (m, 2H). MS (ESI): [M+1]⁺=238.3.

General procedure (b) for the preparation of 3-substituted-5-amino-1*H*-1,2,4-triazoles (9i-ad).

To a stirred suspension of compound **13i-ad** (2 mmol) in methanol (10 mL) was added hydrazine monohydrate (0.2 mL, 4 mmol, 2 equiv.) and the mixture was heated under reflux for 18 h. After this time, the volatiles were removed and the residue suspended with ethyl ether (10 mL) was sonicated for 10 min. The resultant solid was collected by filtration and then used for the next reaction without any purification.

Compounds **9i**, **9n**, **9s**, **9v** and **9ad** have already been reported and for their characterization see: V.M. Chernyshev, V.A. Rakitov, A.V. Astakhov, A.N. Sokolov, N.D. Zemlyakov, V.A. Taranushich. Regioselective synthesis of alkyl derivatives of 3,5-diamino-1,2,4-triazole. Russ. J. Appl. Chem. 79. (2006), 624-630.

Compound **9z** was previously described and for its characterization see: A.V. Dolzhenko, A.V. Dolzhenko, W.K. Chui. Synthesis of 5,7-diamino[1,2,4]triazolo[1,2-*a*][1,3,5]triazines via annulation of 1,3,5-triazine ring onto 3(5)-amino-1,2,4-triazoles. Heterocycles 71 (2007) 429-436.

*N*³-(pyridin-4-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9j**). Following general procedure (b) reported in the Scheme S3, compound **9j** was obtained as a white solid. Yield 63%; mp 210-212 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.24 (d, *J*=6.38 Hz, 2H), 5.39 (br. s., 2H), 6.19 (br. s., 1H), 7.25-7.32, (m, 2H), 8.42 - 8.49 (m, 2H). MS (ESI): [M+1]⁺=191.08.

*N*³-(pyridin-3-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9k**). Following general procedure (b) reported in the Scheme S3, compound **9k** was obtained as a white solid. Yield 67%; mp 198-200 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.23 (d, *J*=6.2 Hz, 2H), 5.43-5.91 (m, 2H) 7.31 (dd, *J*=7.70 and 4.84 Hz, 1H) 7.71 (dt, *J*=7.87 and 1.90 Hz, 1H) 8.38-8.45 (m, 1H) 8.52 (d, *J*=1.76 Hz, 1H), 10.64 (br. s., 1H). MS (ESI): [M+1]⁺=191.2.

*N*³-(4-fluorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9l**). Following general procedure (b) reported in the Scheme S3, compound **9l** was obtained as a white solid. Yield 87%; mp 178-180 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.20 (d, *J*=6.4 Hz, 2H), 5.43 (bs, 2H), 5.77-6.11 (m, 1H), 7.06-7.14 (m, 2H), 7.30-7.37 (m, 2H), 10.35 - 10.45 (bs, 1H). MS (ESI): [M+1]⁺=208.3.

*N*³-(3-fluorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9m**). Following general procedure (b) reported in the Scheme S3, compound **9m** was obtained as a white solid. Yield 53%; mp 184-186 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.23 (d, *J*=6.4 Hz, 2H), 5.48 (bs, 1H), 7.01 (dt, *J*=8.6 and 2.2 Hz, 1H), 7.08-7.17 (m, 2H), 7.28-7.37 (m, 1H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=208.2.

*N*³-(3-chlorophenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9o**). Following general procedure (b) reported in the Scheme S3 compound **9o** was obtained as a white solid. Yield 93%; mp 186-188 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.22 (d, *J*=6.2 Hz, 2H), 5.27-5.68 (m, 2H), 7.22-7.28 (m, 2H), 7.31 (d, *J*=7.5 Hz, 1H), 7.36 (s, 1H), 10.4 (bs, 1H). MS (ESI): [M+1]⁺=224.3.

*N*³-(4-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9p**). Following general procedure (b) reported in the Scheme S3, compound **9p** was obtained as a white solid. Yield 87%; mp 188-190 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.25 (s, 3H), 4.14 (d, *J*=6.2 Hz, 2H), 5.27 (bs, 2H), 5.85 (t, *J*=6.2 Hz, 1H), 7.05 (d, *J*=8.0 Hz, 2H), 7.16 (d, *J*=8.0 Hz, 2H), 10.7 (bs, 1H). MS (ESI): [M+1]⁺=203.9.

*N*³-(3-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9q**). Following general procedure (b) reported in the Scheme S3, compound **9q** was obtained as a white solid. Yield >95%; mp 173-175 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.23 (s, 3H), 4.17 (d, *J*=6.4 Hz, 2H), 4.56 (bs, 1H), 5.62 (bs, 2H), 6.96 (t, *J*=6.4 Hz, 1H), 7.00 (dd, *J*=8.4 and 2.6 Hz, 1H), 7.08 (dd, *J*=8.4 and 2.6 Hz, 1H), 7.14 (s, 1H), 7.20 (t, *J*=8.4 Hz, 1H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=204.2.

*N*³-(2-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9r**). Following general procedure (b) reported in the Scheme S3, compound **9r** was obtained as a white solid. Yield 92%; mp 162-164 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.28 (s, 3H), 4.18 (d, *J*=6.4 Hz, 2H), 5.62 (bs, 2H), 6.96 (t, *J*=6.4 Hz, 1H), 7.10-7.15 (m, 2H), 7.20-7.24 (m, 2H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=204.2.

*N*³-(3-methoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9t**). Following general procedure (b) reported in the Scheme S3, compound **9t** was obtained as a white solid. Yield 88%; mp 178-180 °C. ¹H-NMR (CD₃OD) δ: 3.82 (s, 3H), 4.34 (s, 2H), 6.80 (dd, *J*=7.4 and 2.4 Hz, 1H), 6.90-6.95 (m, 2H), 7.22 (t, *J*=7.4 Hz, 1H). MS (ESI): [M+1]⁺=220.3.

*N*³-(2-methoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9u**). Following general procedure (b) reported in the Scheme S3, compound **9u** was obtained as a white solid. Yield 89%; mp 201-203 °C. ¹H-NMR (CD₃OD) δ: 3.80 (s, 3H), 4.32 (s, 2H), 6.86 (t, *J*=8.2 Hz, 1H), 6.94 (d, *J*=8.2 Hz, 1H), 7.18-7.22 (m, 2H). MS (ESI): [M+1]⁺=220.2.

*N*³-(4-(trifluoromethyl)benzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9w**). Following general procedure (b) reported in the Scheme S3, compound **9w** was obtained as a yellow solid. Yield 86%; mp 173-175 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.28 (d, *J*=6.3 Hz, 2H), 5.64 (bs, 2H), 6.22 (bs, 1H), 7.49 (d, *J*=8.1 Hz, 2H), 7.63 (d, *J*=8.1 Hz, 2H), 10.7 (bs, 1H). MS (ESI): [M+1]⁺=258.3.

4-(((5-amino-1*H*-1,2,4-triazol-3-yl)amino)methyl)benzonitrile (**9x**). Following general procedure (b) reported in the Scheme S3, compound **9x** was obtained as a white solid. Yield 74%; mp 258-260 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.27 (d, *J*=6.0 Hz, 2H), 5.62 (bs, 2H), 6.03 (bs, 1H), 7.46 (d, *J*=8.1 Hz, 2H), 7.74 (d, *J*=8.1 Hz, 2H), 10.8 (bs, 1H). MS (ESI): [M+1]⁺=215.3.

*N*³-(benzo[d][1,3]dioxol-5-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9y**). Following general procedure (b) reported in the Scheme S3, compound **9y** was obtained as a white solid. Yield 93%; mp 204-206 °C. ¹H-NMR (*d*₆-DMSO) δ: 4.12 (d, *J*=6.4 Hz, 2H), 4.24 (bs, 1H), 5.38 (bs, 2H), 5.97 (s, 2H), 6.74 (dd, *J*=8.2 and 2.2 Hz, 1H), 6.80 (d, *J*=8.2 Hz, 1H), 6.88 (d, *J*=2.2 Hz, 1H), 10.8 (bs, 1H). MS (ESI): [M+1]⁺=234.2.

*N*³-(4-Fluorophenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9aa**). Following general procedure (b) reported in the Scheme S3, compound **9aa** was obtained as a white solid. Yield >95%; mp 210-212 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.74 (t, *J*=7.5 Hz, 2H), 3.16 (m, 2H), 3.31 (m, 2H), 5.22 (bs, 2H), 5.80 (bs, 1H), 7.04 (t, *J*=8.4 Hz, 2H), 7.20-7.22 (m, 2H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=222.2.

*N*³-(4-chlorophenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9ab**). Following general procedure (b) reported in the Scheme S3, compound **9ab** was obtained as a white solid. Yield 95%; mp 202-204 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.70 (t, *J*=7.2 Hz, 2H), 3.16 (m, 2H), 3.36 (t, *J*=6.4 Hz, 2H), 5.24 (bs, 2H), 5.84 (bs, 1H), 6.83 (d, *J*=8.4 Hz, 2H), 7.11 (d, *J*=8.4 Hz, 2H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=224.3.

*N*³-(4-methoxyphenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9ac**). Following general procedure (b) reported in the Scheme S3, compound **9ac** was obtained as a pink solid. Yield >95%; mp 252-254 °C. ¹H-NMR (*d*₆-DMSO) δ: 2.71 (t, *J*=7.2 Hz, 2H), 3.16 (m, 2H), 3.32 (t, *J*=6.4 Hz, 2H), 3.71 (s, 3H), 5.24 (bs, 2H), 5.84 (bs, 1H), 6.85 (d, *J*=8.4 Hz, 2H), 7.13 (d, *J*=8.4 Hz, 2H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=234.3.

Characterization of compounds 10a-ad

2-(4-Fluorophenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10a**). Following general procedure A, starting from 3-(4-fluorophenyl)-1*H*-1,2,4-triazol-5-amine (**9a**), compound **10a** was obtained as a white solid. Yield: 74%, mp 234-236 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.31 (s, 3H), 5.83 (s, 1H), 7.32 (t, *J*=8.8 Hz, 2H), 8.10-8.14 (m, 2H), 13.2 (bs, 1H). MS (ESI): [M+1]⁺=245.3.

2-(4-Chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10b**). Following general procedure A, starting from 3-(4-chlorophenyl)-1*H*-1,2,4-triazol-5-amine (**9b**), compound **10b** was obtained as a white solid. Yield: 90%, mp 270-272 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.32 (s, 3H), 5.84 (s, 1H), 7.56 (dd, *J*=8.8 and 2.0 Hz, 2H), 8.07 (dd, *J*=8.8 and 2.0 Hz, 2H), 13.3 (bs, 1H). MS (ESI): [M+1]⁺=261.2.

5-Methyl-2-(*p*-tolyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10c**). Following general procedure A, starting from 3-(*p*-tolyl)-1*H*-1,2,4-triazol-5-amine (**9c**), compound **10c** was obtained as a pink solid. Yield: 68%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.33 (s, 3H), 2.38 (s, 3H), 5.84 (s, 1H), 7.33 (d, *J*=7.6 Hz, 2H), 7.99 (d, *J*=7.6 Hz, 2H), 13.4 (bs, 1H). MS (ESI): [M+1]⁺=241.4.

5-Methyl-2-(phenylamino)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10d**). Following general procedure A, starting from *N*³-phenyl-4*H*-1,2,4-triazole-3,5-diamine **9d**, compound **10d** was obtained as a white solid. Yield: 88%, mp 250-252 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.26 (s, 3H), 5.73 (s, 1H), 6.84 (t, *J*=7.6 Hz, 1H), 7.26 (t, *J*=7.6 Hz, 2H), 7.62 (d, *J*=6.8 Hz, 2H), 9.50 (s, 1H), 12.8 (bs, 1H). MS (ESI): [M+1]⁺=242.3.

2-((4-Fluorophenyl)amino)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10e**). Following general procedure A, starting from *N*³-(4-fluorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (**9e**), compound **10e** was obtained as a white solid. Yield: 75%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.26 (s, 3H), 5.72 (s, 1H), 7.11 (t, *J*=9.2 Hz, 2H), 7.62-7.65 (m, 2H), 9.54 (s, 1H), 11.8 (bs, 1H). MS (ESI): [M+1]⁺=260.3.

2-((4-Chlorophenyl)amino)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10f**). Following general procedure A, starting from *N*³-(4-chlorophenyl)-1*H*-1,2,4-triazole-3,5-diamine (**9f**), compound **10f** was obtained as a white solid. Yield: 82%, mp 260-262 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.26 (s, 3H), 5.75 (s, 1H), 7.31 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 9.71 (s, 1H), 12.9 (bs, 1H). MS (ESI): [M+1]⁺=276.3.

5-Methyl-2-(*p*-tolylamino)-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10g**). Following general procedure A, starting from *N*³-(*p*-tolyl)-1*H*-1,2,4-triazole-3,5-diamine (**9g**), compound **10g** was obtained as a white solid. Yield: 87%, mp 250-252 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 2.26 (s, 3H), 5.71 (s, 1H), 7.05 (d, *J*=8.4 Hz, 2H), 7.51 (d, *J*=8.4 Hz, 2H), 9.38 (s, 1H), 12.8 (bs, 1H). MS (ESI): [M+1]⁺=256.3.

2-((4-Methoxyphenyl)amino)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-7-ol (**10h**). Following general procedure A, starting from *N*³-(4-methoxyphenyl)-1*H*-1,2,4-triazole-3,5-diamine (**9h**), compound **10h** was obtained as a pink solid. Yield: 76%, mp 234-236 °C. ¹H-NMR (DMSO-*d*₆) δ:

2.26 (s, 3H), 3.70 (s, 3H), 5.71 (s, 1H), 6.85 (d, J=9.2 Hz, 2H), 7.53 (d, J=9.2 Hz, 2H), 9.27 (s, 1H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=272.3.

2-(Benzylamino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10i). Following general procedure A, starting from *N*³-benzyl-1*H*-1,2,4-triazole-3,5-diamine (**9i**), compound **10i** was obtained as a white solid. Yield: 72%, mp 232-234 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 4.37 (d, J=6.4 Hz, 2H), 5.64 (s, 1H), 7.13 (t, J=6.4 Hz, 1H), 7.20-7.21 (m, 1H), 7.30-7.34 (m, 4H), 12.8 (bs, 1H). MS (ESI): [M+1]⁺=256.4.

5-Methyl-2-((pyridin-4-ylmethyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10j). Following general procedure A, starting from *N*³-(pyridin-4-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9j**), compound **10j** was obtained as a pink solid. Yield: 72%, mp 263-265 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 4.41 (d, J=6.4 Hz, 2H), 5.64 (s, 1H), 7.22 (s, 1H), 7.32 (d, J=6.2 Hz, 2H), 8.45-8.51 (m, 2H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=257.2.

5-Methyl-2-((pyridin-3-ylmethyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10k). Following general procedure A, starting from *N*³-(pyridin-3-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9k**), compound **10k** was obtained as a pink solid. Yield: 76%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.64 (s, 3H), 4.41 (d, J=6.2 Hz, 2H), 5.64 (s, 1H), 7.17 (t, J=6.2 Hz, 1H), 7.34 (dd, J=7.2 and 4.8 Hz, 1H), 7.74 (d, J=7.70 Hz, 1H), 8.44 (dd, J=4.8 and 1.6 Hz, 1H), 8.56 (d, J=1.6 Hz, 1H), 12.8 (bs, 1H). MS (ESI): [M+1]⁺=257.1.

2-((4-Fluorobenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10l). Following general procedure A, starting from *N*³-(4-fluorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9l**), compound **10l** was obtained as a pink solid. Yield: 81%, mp 240-242 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 4.36 (d, J=6.4 Hz, 2H), 5.63 (s, 1H), 7.08-7.13 (m, 3H), 7.34-7.41 (m, 2H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=274.1.

2-((3-Fluorobenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10m). Following general procedure A, starting from *N*³-(3-fluorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9m**), compound **10m** was obtained as a pink solid. Yield: 61%, mp 250-252 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 4.40 (d, J=6.4 Hz, 2H), 5.64 (s, 1H), 7.04 (dt, J=8.5 and 2.9 Hz, 1H), 7.11-7.21 (m, 3H), 7.32-7.39 (m, 1H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=274.1.

2-((4-Chlorobenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10n). Following general procedure A, starting from *N*³-(4-chlorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9n**), compound **10n** was obtained as a pink solid. Yield: 82%, mp 258-260 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 4.34 (d, J=6.4 Hz, 2H), 5.61 (s, 1H), 7.11 (t, J=6.4 Hz, 1H), 7.34 (s, 4H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=290.7.

2-((3-Chlorobenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10o). Following general procedure A, starting from *N*³-(3-chlorobenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9o**), compound **10o** was obtained as a pink solid. Yield: 83%, mp 234-236 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.32 (s, 3H), 4.39 (d, J=6.4 Hz, 2H), 5.64 (s, 1H), 7.17 (s, 1H), 7.28-7.36 (m, 4H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=290.1.

5-Methyl-2-((4-methylbenzyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10p). Following general procedure A, starting from *N*³-(4-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9p**), compound **10p** was obtained as a pink solid. Yield: 68%, mp 262-264 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 2.26 (s, 3H), 4.32 (d, J=6.4 Hz, 2H), 5.62 (s, 1H), 7.02 (t, J=6.4 Hz, 1H), 7.11 (d, J=8.0 Hz, 2H), 7.20 (d, J=8.0 Hz, 2H), 13.2 (bs, 1H). MS (ESI): [M+1]⁺=270.3.

5-Methyl-2-((3-methylbenzyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10q). Following general procedure A, starting from *N*³-(3-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9q**), compound **10q** was obtained as a pink solid. Yield: 65%, mp 180-182 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 2.46 (s, 3H), 4.32 (d, *J*=6.4 Hz, 2H), 5.61 (s, 1H), 7.01 (t, *J*=6.4 Hz, 1H), 7.02-7.12 (m, 4H), 12.6 (bs, 1H). MS (ESI): [*M*+1]⁺=270.3.

5-Methyl-2-((2-methylbenzyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10r). Following general procedure A, starting from *N*³-(2-methylbenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9r**), compound **10r** was obtained as a pink solid. Yield: 64%, mp 236-238 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 2.29 (s, 3H), 4.32 (d, *J*=6.4 Hz, 2H), 5.61 (s, 1H), 7.00 (t, *J*=6.4 Hz, 1H), 7.08-7.14 (m, 3H), 7.32 (t, *J*=8.4 Hz, 1H), 12.6 (bs, 1H). MS (ESI): [*M*+1]⁺=270.4.

2-((4-Methoxybenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10s). Following general procedure A, starting from *N*³-(4-methoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9s**), compound **9s** was obtained as a white solid. Yield: 70%, mp 270-272 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 3.71 (s, 3H), 4.29 (d, *J*=6.4 Hz, 2H), 5.63 (s, 1H), 6.85 (d, *J*=8.4 Hz, 2H), 7.03 (t, *J*=6.4 Hz, 1H), 7.24 (d, *J*=8.4 Hz, 2H), 12.8 (bs, 1H). MS (ESI): [*M*+1]⁺=286.4.

2-((3-Methoxybenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10t). Following general procedure A, starting from *N*³-(3-methoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9t**), compound **10t** was obtained as a pink solid. Yield: 84%, mp 260-262 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.21 (s, 3H), 3.71 (s, 3H), 4.33 (d, *J*=6.4 Hz, 2H), 5.62 (s, 1H), 6.77 (dd, *J*=8.4 and 2.0 Hz, 1H), 6.88-6.91 (m, 2H), 7.09 (t, *J*=8.4 Hz, 1H), 7.20 (t, *J*=8.4 Hz, 1H), 12.7 (bs, 1H). MS (ESI): [*M*+1]⁺=286.4.

2-((2-Methoxybenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10u). Following general procedure A, starting from *N*³-(2-methoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9u**), compound **10u** was obtained as a pink solid. Yield: 75%, mp 148-150 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 3.80 (s, 3H), 4.33 (d, *J*=6.0 Hz, 2H), 5.61 (s, 1H), 6.85-6.90 (m, 2H), 6.94 (d, *J*=7.6 Hz, 1H), 7.18-7.21 (m, 2H), 12.6 (bs, 1H). MS (ESI): [*M*+1]⁺=286.4.

2-((3,4-dimethoxybenzyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10v). Following general procedure A, starting from *N*³-(3,4-dimethoxybenzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9v**), compound **10v** was obtained as a purple solid. Yield: 75%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 3.69 (s, 3H), 3.71 (s, 3H), 4.27 (d, *J*=6.4 Hz, 2H), 5.61 (s, 1H), 6.84-6.86 (m, 2H), 6.96-6.98 (m, 2H), 12.7 (bs, 1H). MS (ESI): [*M*+1]⁺=316.4.

5-Methyl-2-((4-(trifluoromethyl)benzyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (10w). Following general procedure A, starting from *N*³-(4-(trifluoromethyl)benzyl)-1*H*-1,2,4-triazole-3,5-diamine (**9w**), compound **10w** was obtained as a white solid. Yield: 78%, mp 202-204 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 4.44 (d, *J*=6.4 Hz, 2H), 5.62 (s, 1H), 7.02 (t, *J*=6.4 Hz, 1H), 7.51 (d, *J*=8.4 Hz, 2H), 7.64 (d, *J*=8.4 Hz, 2H), 13.0 (bs, 1H). MS (ESI): [*M*+1]⁺=324.7.

4-(((7-Hydroxy-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)amino)methyl)benzonitrile (10x). Following general procedure A, starting from 4-((5-amino-1*H*-1,2,4-triazol-3-yl)amino)methyl)benzonitrile (**9x**), compound **10x** was obtained as a pink solid. Yield: 83%, mp 250-252 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 4.43 (d, *J*=6.4 Hz, 2H), 5.62 (s, 1H), 7.24 (t, *J*=6.4 Hz, 1H), 7.48 (d, *J*=8.4 Hz, 2H), 7.75 (d, *J*=8.4 Hz, 2H), 12.6 (bs, 1H). MS (ESI): [*M*+1]⁺=281.3.

2-((Benzo[d][1,3]dioxol-5-ylmethyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10y**). Following general procedure A, starting from *N*³-(benzo[d][1,3]dioxol-5-ylmethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9y**), compound **10y** was obtained as a white solid. Yield: 78%, mp 263-265 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.20 (s, 3H), 4.24 (d, *J*=6.4 Hz, 2H), 5.62 (s, 1H), 5.94 (s, 2H), 6.78-6.82 (m, 2H), 6.88 (s, 1H), 7.04 (t, *J*=5.6 Hz, 1H), 12.7 (bs, 1H). MS (ESI): [M+1]⁺=300.4.

5-Methyl-2-(phenethylamino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10z**). Following general procedure A, starting from *N*³-phenethyl-1*H*-1,2,4-triazole-3,5-diamine (**9z**), compound **10z** was obtained as a pink solid. Yield: 88%, mp 204-206 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.23 (s, 3H), 2.85 (t, *J*=7.2 Hz, 2H), 3.37-3.39 (m, 2H), 5.64 (s, 1H), 6.61 (t, *J*=6.4 Hz, 1H), 7.20-7.29 (m, 5H), 12.6 (bs, 1H). MS (ESI): [M+1]⁺=270.6.

2-((4-Fluorophenethyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10aa**). Following general procedure A, starting from *N*³-(4-fluorophenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9aa**), compound **10aa** was obtained as a pink solid. Yield: 81%, mp 270-272 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.21 (s, 3H), 2.82 (t, *J*=7.2 Hz, 2H), 3.30-3.36 (m, 2H), 5.62 (s, 1H), 6.59 (t, *J*=6.4 Hz, 1H), 7.08 (t, *J*=8.4 Hz, 2H), 7.24 (t, *J*=8.4 Hz, 2H), 12.6 (bs, 1H). MS (ESI): [M+1]⁺=288.3.

2-((4-Chlorophenethyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10ab**). Following general procedure A, starting from *N*³-(4-chlorophenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9ab**), compound **10ab** was obtained as a white solid. Yield: 84%, mp 262-264 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.21 (s, 3H), 2.75 (t, *J*=7.2 Hz, 2H), 3.16-3.22 (m, 2H), 5.60 (s, 1H), 5.84 (t, *J*=6.4 Hz, 1H), 7.20 (d, *J*=8.4 Hz, 2H), 7.30 (d, *J*=8.4 Hz, 2H), 10.6 (bs, 1H). MS (ESI): [M+1]⁺=304.7.

2-((4-Methoxyphenethyl)amino)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10ac**). Following general procedure A, starting from *N*³-(4-methoxyphenethyl)-1*H*-1,2,4-triazole-3,5-diamine (**9ac**), compound **10ac** was obtained as a pink solid. Yield: 85%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.21 (s, 3H), 2.76 (t, *J*=7.2 Hz, 2H), 3.28-3.30 (m, 2H), 3.70 (s, 3H), 5.62 (s, 1H), 6.56 (t, *J*=6.4 Hz, 1H), 6.82 (d, *J*=8.7 Hz, 2H), 7.30 (d, *J*=8.7 Hz, 2H), 10.7 (bs, 1H). MS (ESI): [M+1]⁺=300.3.

5-Methyl-2-((3-phenylpropyl)amino)-[1,2,4]triazolo[1,5-a]pyrimidin-7-ol (**10ad**). Following general procedure A, starting from *N*³-(3-phenylpropyl)-1*H*-1,2,4-triazole-3,5-diamine (**9ad**), compound **10ad** was obtained as a pink solid. Yield: 68%, mp 252-254 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.79-1.84 (m, 2H), 2.20 (s, 3H), 2.62 (t, *J*=7.2 Hz, 2H), 3.14 (t, *J*=7.2 Hz, 2H), 5.61 (s, 1H), 6.62 (t, *J*=6.4 Hz, 1H), 7.14-7.26 (m, 5H), 12.6 (bs, 1H). MS (ESI): [M+1]⁺=284.3.

Characterization of compounds 11a-ad

7-Chloro-2-(4-fluorophenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine (**11a**). Following general procedure B, compound **11a** was obtained as a yellow solid. Yield: 78%, mp 154-156 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.63 (s, 3H), 7.40 (t, *J*=8.8 Hz, 2H), 7.64 (s, 1H), 8.24-8.27 (m, 2H). MS (ESI): [M+1]⁺=263.5.

7-Chloro-2-(4-chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidine (**11b**). Following general procedure B, compound **11b** was obtained as a yellow solid. Yield: 81%, mp 173-175 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.64 (s, 3H), 7.63 (dd, *J*=8.4 and 2.0 Hz, 2H), 7.91 (s, 1H), 8.21 (dd, *J*=8.4 and 2.0 Hz, 2H). MS (ESI): [M+1]⁺=279.4.

7-Chloro-5-methyl-2-(*p*-tolyl)-[1,2,4]triazolo[1,5-*a*]pyrimidine (**11c**). Following general procedure B, **11c** was obtained as an orange solid. Yield: 57%, mp 173-175 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.39 (s, 3H), 2.62 (s, 3H), 7.36 (d, *J*=8.4 Hz, 2H), 7.62 (s, 1H), 8.09 (d, *J*=8.4 Hz, 2H). MS (ESI): [M+1]⁺=259.2.

7-Chloro-5-methyl-*N*-phenyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11d**). Following general procedure B, compound **11d** was obtained as a brownish solid. Yield: 75%, mp 135-136 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.55 (s, 3H), 6.93 (t, *J*=8.4 Hz, 1H), 7.32 (t, *J*=8.4 Hz, 2H), 7.41 (s, 1H), 7.69 (d, *J*=8.4 Hz, 2H), 9.98 (s, 1H). MS (ESI): [M+1]⁺=260.2.

7-Chloro-*N*-(4-fluorophenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11e**). Following general procedure B, compound **11e** was obtained as a yellow solid. Yield: 53%, mp 192-194 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.55 (s, 3H), 7.16 (t, *J*=8.8 Hz, 2H), 7.41 (s, 1H), 7.68-7.72 (m, 2H), 10.0 (s, 1H). MS (ESI): [M+1]⁺=278.3.

7-Chloro-*N*-(4-chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11f**). Following general procedure B, compound **11f** was obtained as a yellow solid. Yield: 69%, mp 186-188 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.34 (s, 3H), 6.96 (d, *J*=8.4 Hz, 2H), 7.12 (s, 1H), 7.56 (d, *J*=8.4 Hz, 2H), 9.74 (s, 1H). MS (ESI): [M+1]⁺=295.2.

7-Chloro-5-methyl-*N*-(*p*-tolyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11g**). Following general procedure B, compound **11g** was obtained as a yellow solid. Yield: 54%, mp 201-202 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.25 (s, 3H), 2.55 (s, 3H), 7.10 (d, *J*=8.8 Hz, 2H), 7.39 (s, 1H), 7.57 (d, *J*=8.8 Hz, 2H), 9.87 (s, 1H). MS (ESI): [M+1]⁺=274.3.

7-Chloro-*N*-(4-methoxyphenyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11h**). Following general procedure B, compound **11h** was obtained as a brownish solid. Yield: 73%, mp 242-244 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.42 (s, 3H), 3.72 (s, 3H), 6.90 (d, *J*=8.8 Hz, 2H), 7.38 (s, 1H), 7.59 (d, *J*=8.8 Hz, 2H), 9.77 (s, 1H). MS (ESI): [M+1]⁺=290.4.

N-Benzyl-7-chloro-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11i**). Following general procedure B, compound **11i** was obtained as a white solid. Yield: 72%, mp 232-234 °C. ¹H-NMR (CDCl₃) δ: 2.62 (s, 3H), 4.67 (s, 2H), 3.50 (bs, 1H), 6.92 (s, 1H), 7.28 (d, *J*=6.4 Hz, 2H), 7.29 (t, *J*=6.4 Hz, 1H), 7.39 (d, *J*=6.4 Hz, 2H). MS (ESI): [M+1]⁺=274.2.

7-Chloro-5-methyl-*N*-(pyridin-4-ylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11j**). Following general procedure B, compound **11j** was obtained as a brown solid. Yield: 44%, mp 210-212 °C. ¹H-NMR (DMSO-*d*₆) δ: 3.12 (s, 3H), 4.44 (d, *J*=6.4 Hz, 2H), 5.78 (s, 1H), 7.34 (d, *J*=6.2 Hz, 2H), 7.34 (d, *J*=6.2 Hz, 2H), 7.83 (t, *J*=6.4 Hz, 1H). MS (ESI): [M+1]⁺=275.1.

7-Chloro-5-methyl-*N*-(pyridin-3-ylmethyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11k**). Following general procedure B, compound **11k** was obtained as a brown solid. Yield: 57%, mp 234-236 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.22 (s, 3H), 4.54 (d, *J*=6.2 Hz, 2H), 7.26 (s, 1H), 7.36 (dd, *J*=7.2 and 4.8 Hz, 1H), 7.82 (d, *J*=7.70 Hz, 1H), 8.46 (dd, *J*=4.8 and 1.6 Hz, 1H), 8.56 (d, *J*=1.6 Hz, 1H), 8.63 (t, *J*=6.2 Hz, 1H). MS (ESI): [M+1]⁺=275.1.

7-Chloro-*N*-(4-fluorobenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11l**). Following general procedure B, compound **11l** was obtained as a brown solid. Yield: 72%, mp 156-158 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.50 (s, 3H), 4.46 (d, *J*=6.4 Hz, 2H), 7.11-7.18 (m, 1H), 7.25-7.27 (m, 1H), 7.26 (s, 1H), 7.38-7.43 (m, 2H), 7.68 (t, *J*=6.5 Hz, 1H). MS (ESI): [M+1]⁺=292.05.

7-Chloro-*N*-(3-fluorobenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11m**). Following general procedure B, compound **11m** was obtained as a brown solid. Yield: 58%, mp 162-164 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.52 (s, 3H), 4.46 (d, *J*=6.4 Hz, 2H), 5.74 (s, 1H), 7.22 (dt, *J*=8.5 and 2.9 Hz, 1H), 7.13-7.22 (m, 2H), 7.32-7.42 (m, 1H), 7.72 (t, *J*=6.5 Hz, 1H). MS (ESI): [M+1]⁺=292.01.

7-Chloro-*N*-(4-chlorobenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11n**). Following general procedure B, compound **11n** was obtained as a brown solid. Yield: 55%, mp 174-176 °C. ¹H-NMR (CDCl₃) δ: 2.62 (s, 3H), 4.63 (s, 2H), 5.84 (bs, 1H), 6.93 (s, 1H), 7.30 (d, *J*=9.2 Hz, 2H), 7.36 (d, *J*=9.2 Hz, 2H). MS (ESI): [M+1]⁺=307.9.

7-Chloro-*N*-(3-chlorobenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11o**). Following general procedure B, compound **11o** was obtained as a brown solid. Yield: 52%, mp 163-165 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.23 (s, 3H), 4.47 (d, *J*=6.4 Hz, 2H), 5.76 (s, 1H), 7.26-7.40 (m, 3H), 7.42 (s, 1H), 7.75 (t, *J*=6.5 Hz, 1H). MS (ESI): [M+1]⁺=308.0.

7-Chloro-5-methyl-*N*-(4-methylbenzyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11p**). Following general procedure B, **11p** was obtained as a pink solid. Yield: 58%, mp 180-182 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.24 (s, 3H), 2.46 (s, 3H), 4.39 (d, *J*=6.0 Hz, 2H), 7.08 (d, *J*=7.6 Hz, 2H), 7.21 (d, *J*=7.6 Hz, 2H), 7.23 (s, 1H), 7.60 (t, *J*=6.0 Hz, 1H). MS (ESI): [M+1]⁺=288.4.

7-Chloro-5-methyl-*N*-(3-methylbenzyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11q**). Following general procedure B, **11q** was obtained as a pink solid. Yield: 73%, mp 154-156 °C. ¹H-NMR (CDCl₃) δ: 2.34 (s, 3H), 2.61 (s, 3H), 4.63 (s, 2H), 5.62 (bs, 1H), 6.90 (s, 1H), 7.02 (dd, *J*=7.6 and 1.8 Hz, 1H), 7.16-7.21 (m, 3H). MS (ESI): [M+1]⁺=287.8.

7-Chloro-5-methyl-*N*-(2-methylbenzyl)-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11r**). Following general procedure B, **11r** was obtained as a pink solid. Yield: 78%, mp 120-122 °C. ¹H-NMR (CDCl₃) δ: 2.40 (s, 3H), 2.63 (s, 3H), 4.64 (s, 2H), 6.16 (bs, 1H), 6.98 (s, 1H), 7.16-7.19 (m, 3H), 7.36 (dd, *J*=6.0 and 1.6 Hz, 1H). MS (ESI): [M+1]⁺=287.8.

7-Chloro-*N*-(4-methoxybenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11s**). Following general procedure B, compound **11s** was obtained as a pink solid. Yield: 63%, mp 210-212 °C. ¹H-NMR (DMSO-*d*₆) δ: 2.46 (s, 3H), 3.69 (s, 3H), 4.37 (d, *J*=6.4 Hz, 2H), 6.84 (d, *J*=8.4 Hz, 2H), 7.23 (s, 1H), 7.25 (d, *J*=8.4 Hz, 2H), 7.59 (t, *J*=6.4 Hz, 1H). MS (ESI): [M+1]⁺=303.8.

7-Chloro-*N*-(3-methoxybenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11t**). Following general procedure B, compound **11t** was obtained as a purple solid. Yield: 54%, mp 180-182 °C. ¹H-NMR (CDCl₃) δ: 2.61 (s, 3H), 3.80 (s, 3H), 4.64 (s, 2H), 6.12 (bs, 1H), 6.84 (d, *J*=8.4 Hz, 1H), 6.93-6.97 (m, 3H), 7.24 (t, *J*=8.4 Hz, 1H). MS (ESI): [M+1]⁺=303.8.

7-Chloro-*N*-(2-methoxybenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11u**). Following general procedure B, compound **11u** was obtained as a purple solid. Yield: 61%, mp 192-194 °C. ¹H-NMR (CDCl₃) δ: 2.59 (s, 3H), 3.87 (s, 3H), 4.64 (s, 2H), 5.74 (bs, 1H), 6.81-6.94 (m, 3H), 7.21-7.32 (m, 1H), 7.42 (d, *J*=8.2 Hz, 1H). MS (ESI): [M+1]⁺=303.7.

7-Chloro-*N*-(3,4-dimethoxybenzyl)-5-methyl-[1,2,4]triazolo[1,5-*a*]pyrimidin-2-amine (**11v**). Following general procedure B, compound **11v** was obtained as a pink solid. Yield: 68%, mp 148-150 °C. ¹H-NMR (CDCl₃) δ: 2.64 (s, 3H), 3.84 (s, 3H), 3.88 (s, 3H), 4.58 (s, 2H), 6.80 (d, *J*=8.0 Hz, 1H), 6.94 (d, *J*=8.0 Hz, 1H), 6.96 (s, 1H), 7.06 (s, 1H). MS (ESI): [M+1]⁺=334.8.

7-Chloro-5-methyl-N-(4-(trifluoromethyl)benzyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11w**). Following general procedure B, compound **11w** was obtained as a pink solid. Yield: 66%, mp 166-168 °C. ¹H-NMR (CDCl₃) δ: 2.64 (s, 3H), 3.00 (bs, 1H), 4.72 (s, 2H), 7.02 (s, 1H), 7.54 (d, J=8.4 Hz, 2H), 7.58 (d, J=8.4 Hz, 2H). MS (ESI): [M+1]⁺=342.3.

4-(((7-Chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-yl)amino)methyl)benzonitrile (**11x**). Following general procedure B, compound **11x** was obtained as an orange solid. Yield: 66%, mp 208-210 °C. ¹H-NMR (CDCl₃) δ: 2.62 (s, 3H), 4.73 (s, 2H), 6.00 (bs, 1H), 6.95 (s, 1H), 7.50 (d, J=8.4 Hz, 2H), 7.61 (d, J=8.4 Hz, 2H). MS (ESI): [M+1]⁺=299.7.

N-(benzo[d][1,3]dioxol-5-ylmethyl)-7-chloro-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11y**). Following general procedure B, compound **11y** was obtained as a pink solid. Yield: 74%, mp 168-170 °C. ¹H-NMR (CDCl₃) δ: 2.60 (s, 3H), 4.56 (s, 2H), 5.63 (s, 1H), 5.94 (s, 2H), 6.75 (d, J=8.0 Hz, 1H), 6.82 (dd, J=8.0 and 2,4 Hz, 1H), 6.89-6.91 (m, 2H). MS (ESI): [M+1]⁺=318.7.

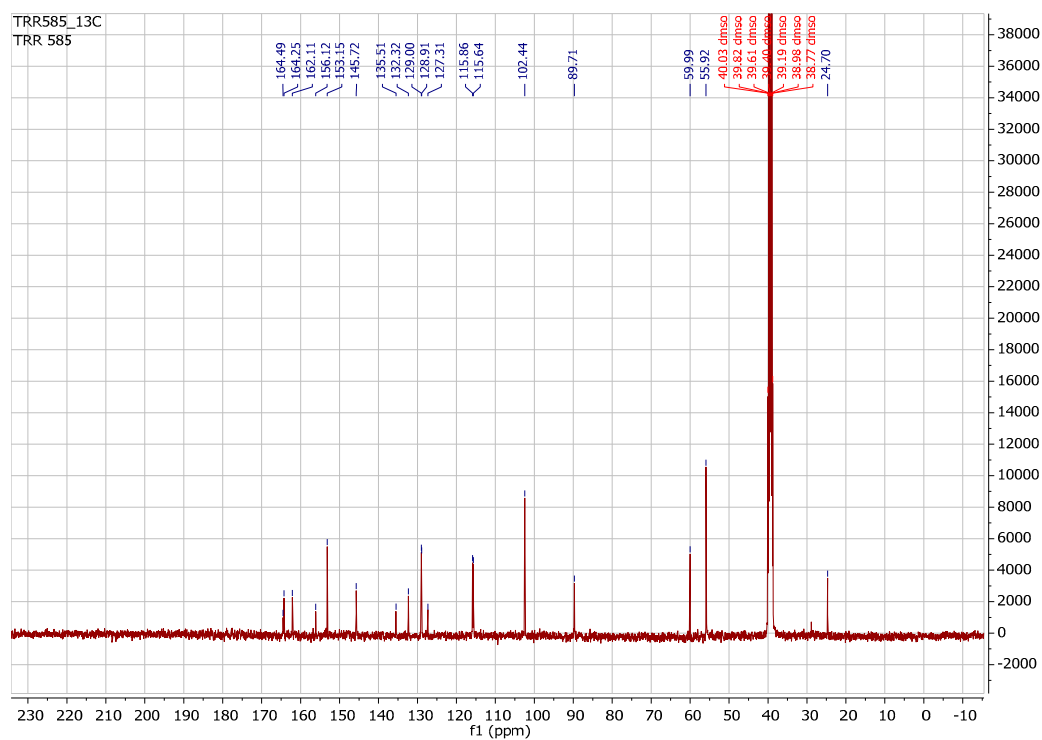
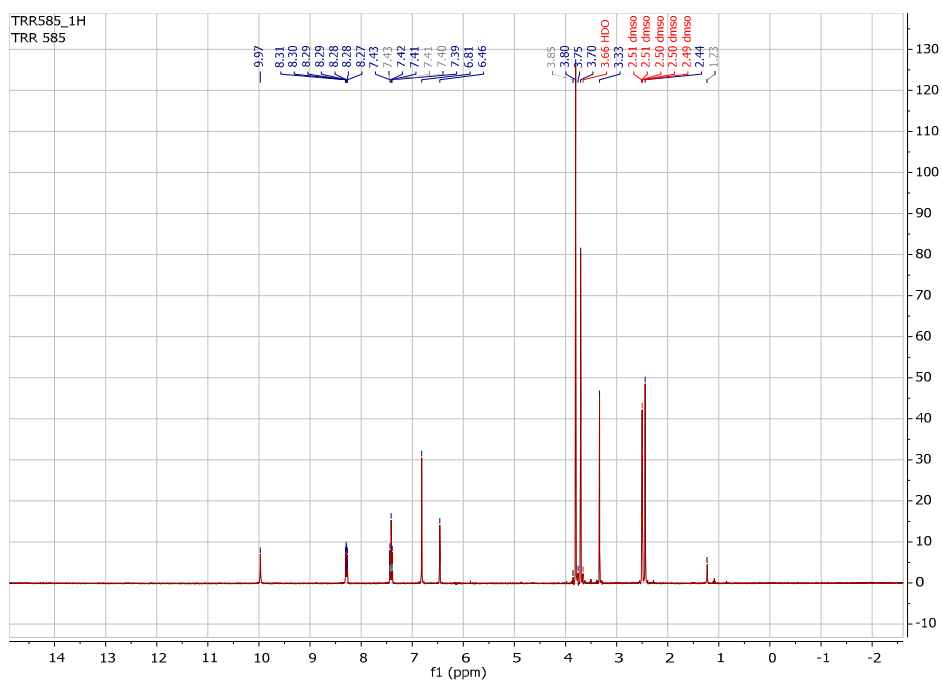
7-Chloro-5-methyl-N-phenethyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11z**). Following general procedure B, compound **11z** was obtained as a white solid. Yield: 67%, mp 118-120 °C. ¹H-NMR (CDCl₃) δ: 2.61 (s, 3H), 2.98 (t, J=7.2 Hz, 2H), 3.70 (t, J=7.2 Hz, 2H), 5.42 (bs, 1H), 6.90 (s, 1H), 7.23-7.32 (m, 5H). MS (ESI): [M+1]⁺=288.5.

7-Chloro-N-(4-fluorophenethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11aa**). Following general procedure B, compound **11aa** was obtained as a brown solid. Yield: 58%, mp 186-188 °C. ¹H-NMR (CDCl₃) δ: 2.61 (s, 3H), 2.95 (t, J=7.2 Hz, 2H), 3.70 (t, J=7.2 Hz, 2H), 5.28 (bs, 1H), 6.88 (s, 1H), 6.99 (d, J=8.4 Hz, 2H), 7.18-7.23 (m, 2H). MS (ESI): [M+1]⁺=306.7.

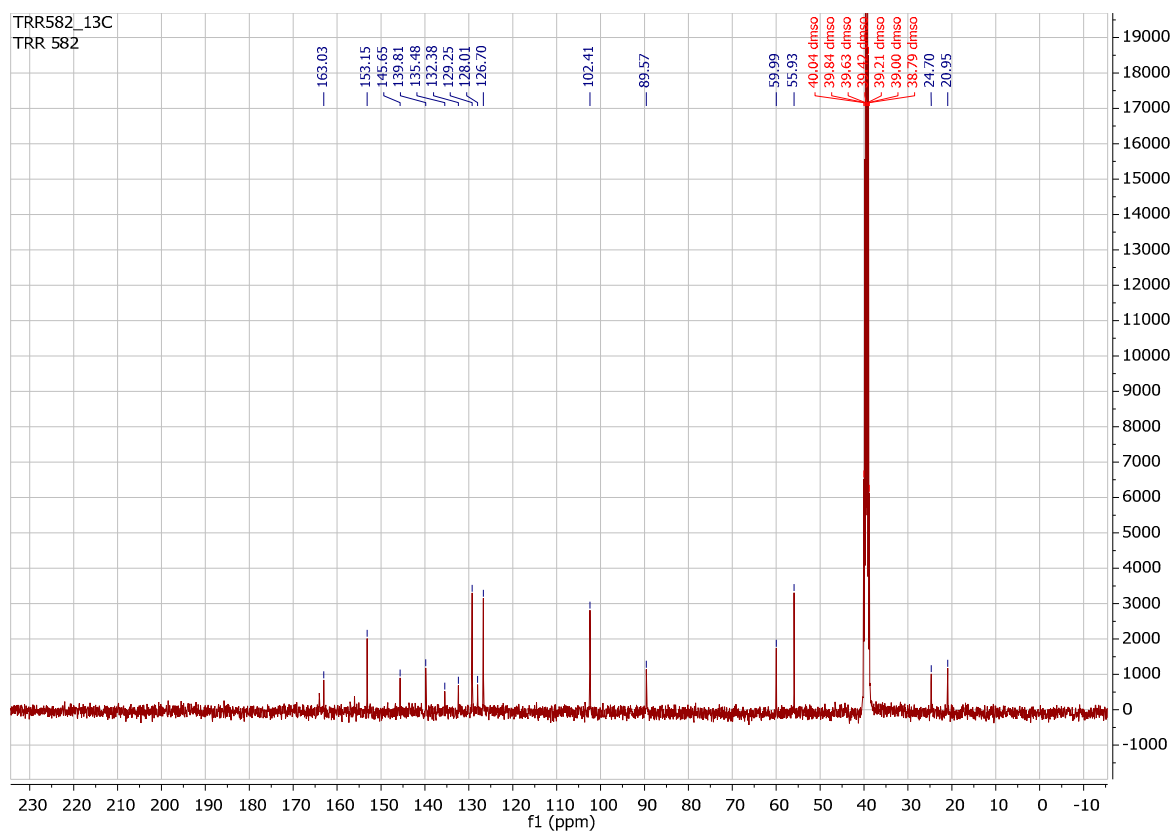
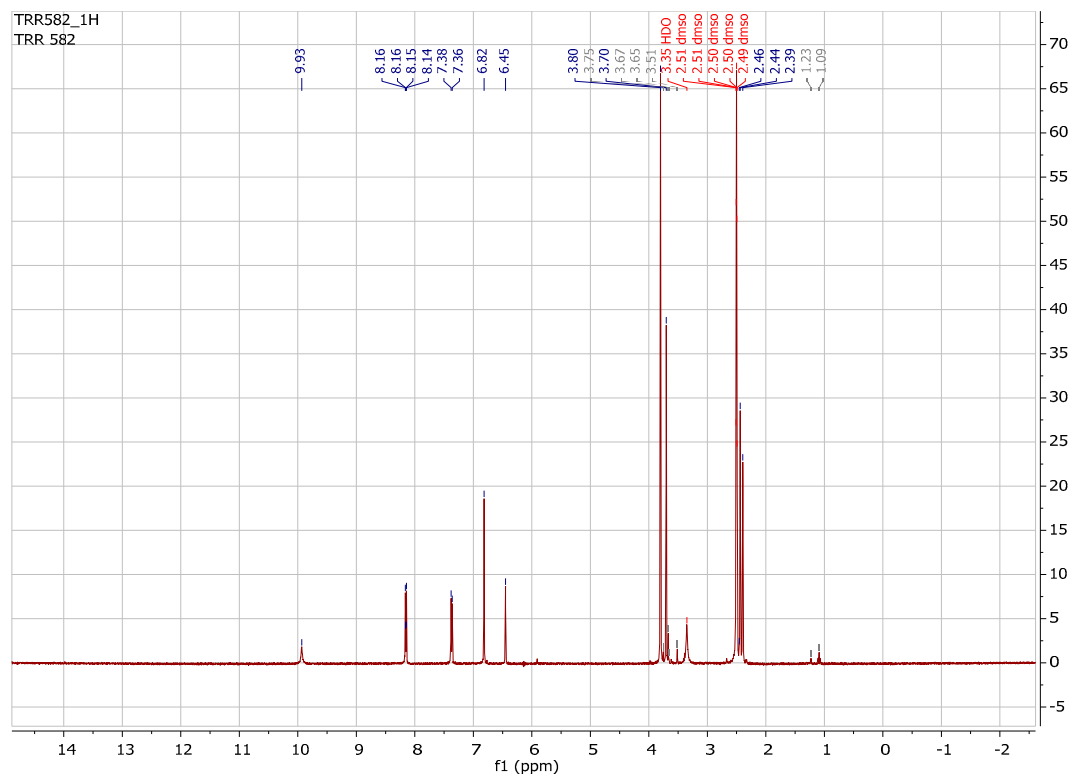
7-Chloro-N-(4-chlorophenethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11ab**). Following general procedure B, compound **11ab** was obtained as a pink solid. Yield: 64%, mp 180-182 °C. ¹H-NMR (CDCl₃) δ: 2.63 (s, 3H), 2.96 (t, J=7.2 Hz, 2H), 3.70 (t, J=7.2 Hz, 2H), 5.82 (bs, 1H), 6.97 (s, 1H), 7.17 (d, J=8.4 Hz, 2H), 7.26 (d, J=8.4 Hz, 2H). MS (ESI): [M+1]⁺=323.3.

7-Chloro-N-(4-methoxyphenethyl)-5-methyl-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11ac**). Following general procedure B, compound **11ac** was obtained as a white solid. Yield: 64%, mp 186-188 °C. ¹H-NMR (CDCl₃) δ: 2.60 (s, 3H), 2.91 (t, J=7.2 Hz, 2H), 3.69 (t, J=7.2 Hz, 2H), 3.79 (s, 3H), 5.22 (bs, 1H), 6.83 (d, J=8.4 Hz, 2H), 6.86 (s, 1H), 7.15 (d, J=8.4 Hz, 2H). MS (ESI): [M+1]⁺=318.3.

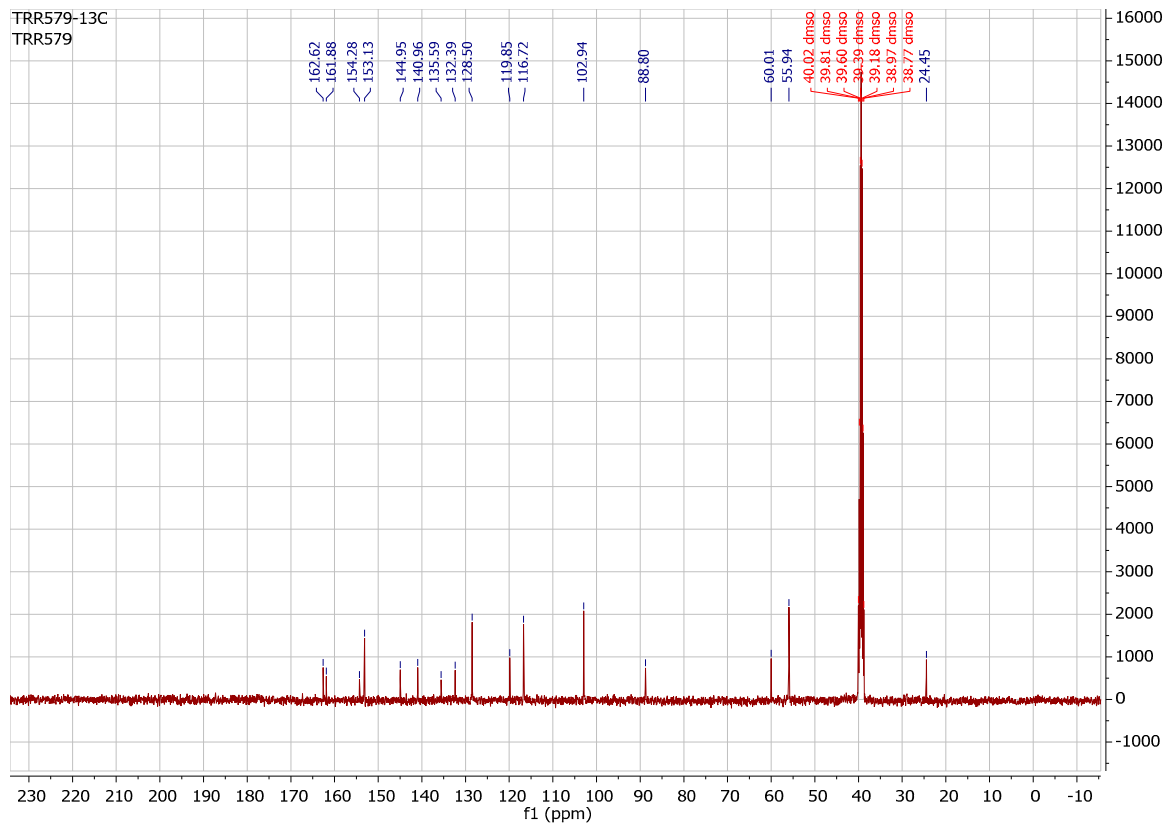
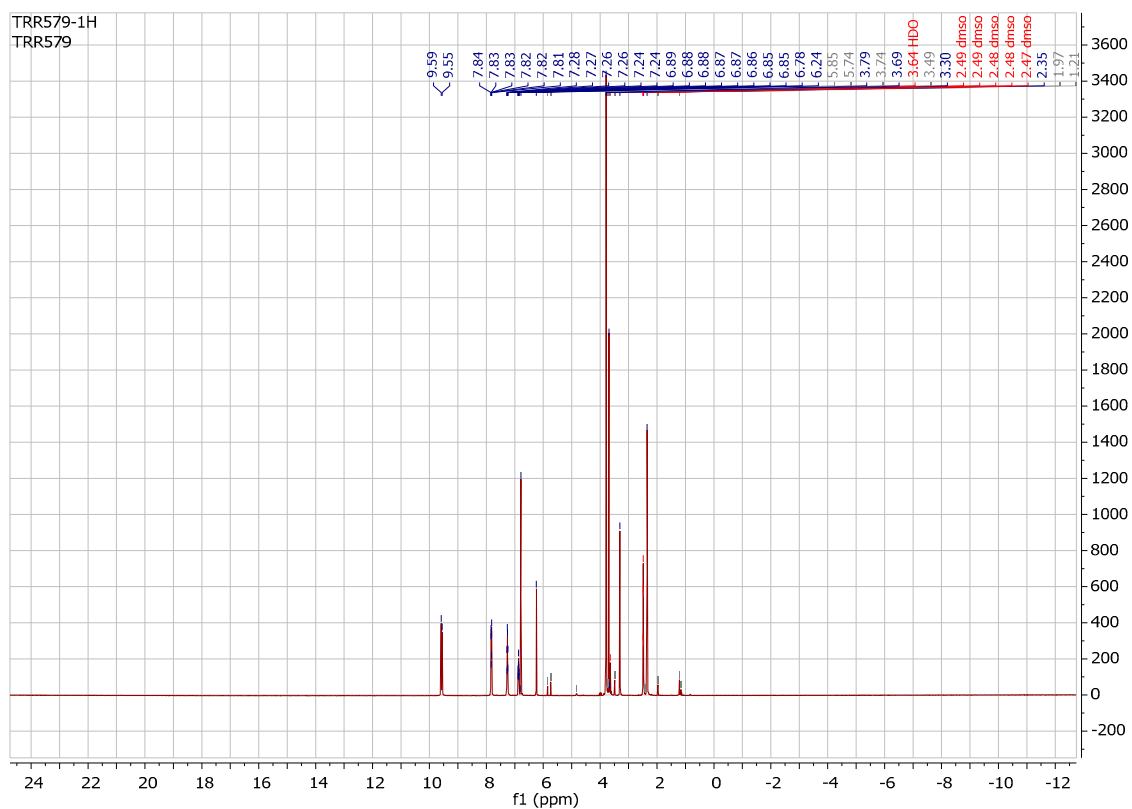
7-Chloro-5-methyl-N-(3-phenylpropyl)-[1,2,4]triazolo[1,5-a]pyrimidin-2-amine (**11ad**). Following general procedure B, compound **11ad** was obtained as a black solid. Yield: 54%, mp 142-144 °C. ¹H-NMR (DMSO-*d*₆) δ: 1.96-2.04 (m, 2H), 2.61 (s, 3H), 2.74 (t, J=7.2 Hz, 2H), 3.47 (t, J=7.2 Hz, 2H), 5.60 (bs, 1H), 7.16-7.26 (m, 6H). MS (ESI): [M+1]⁺=302.3.



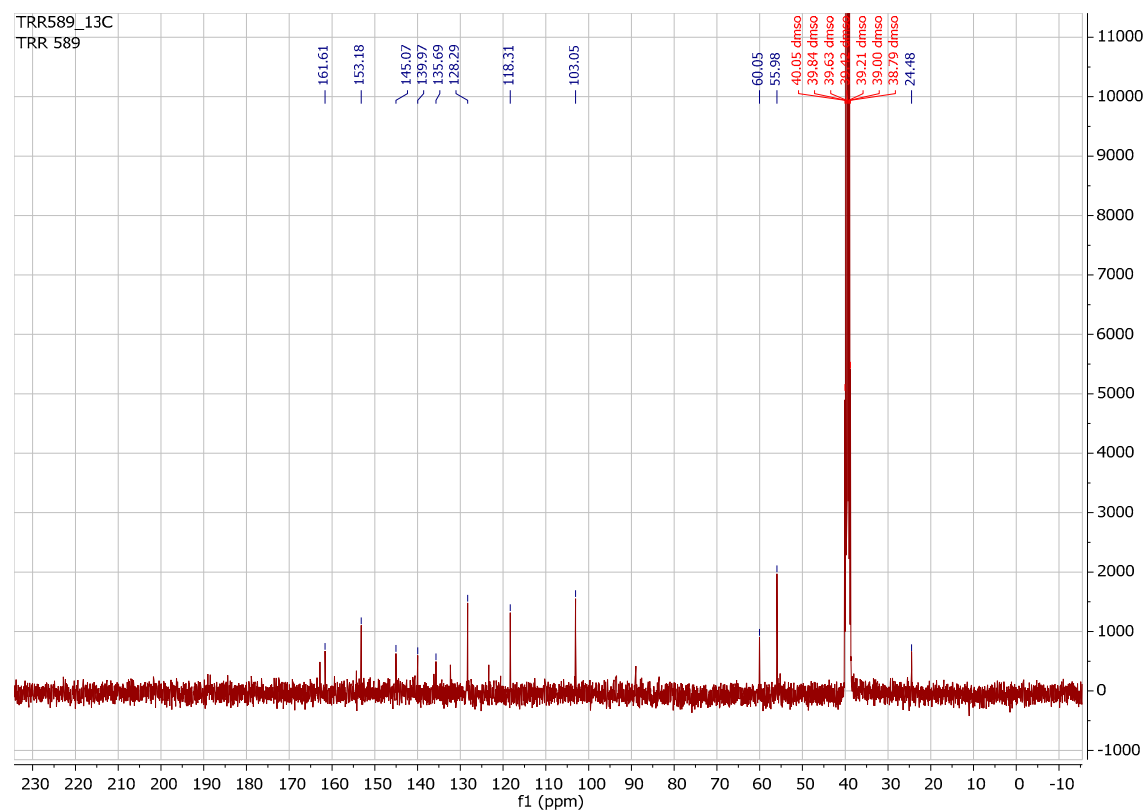
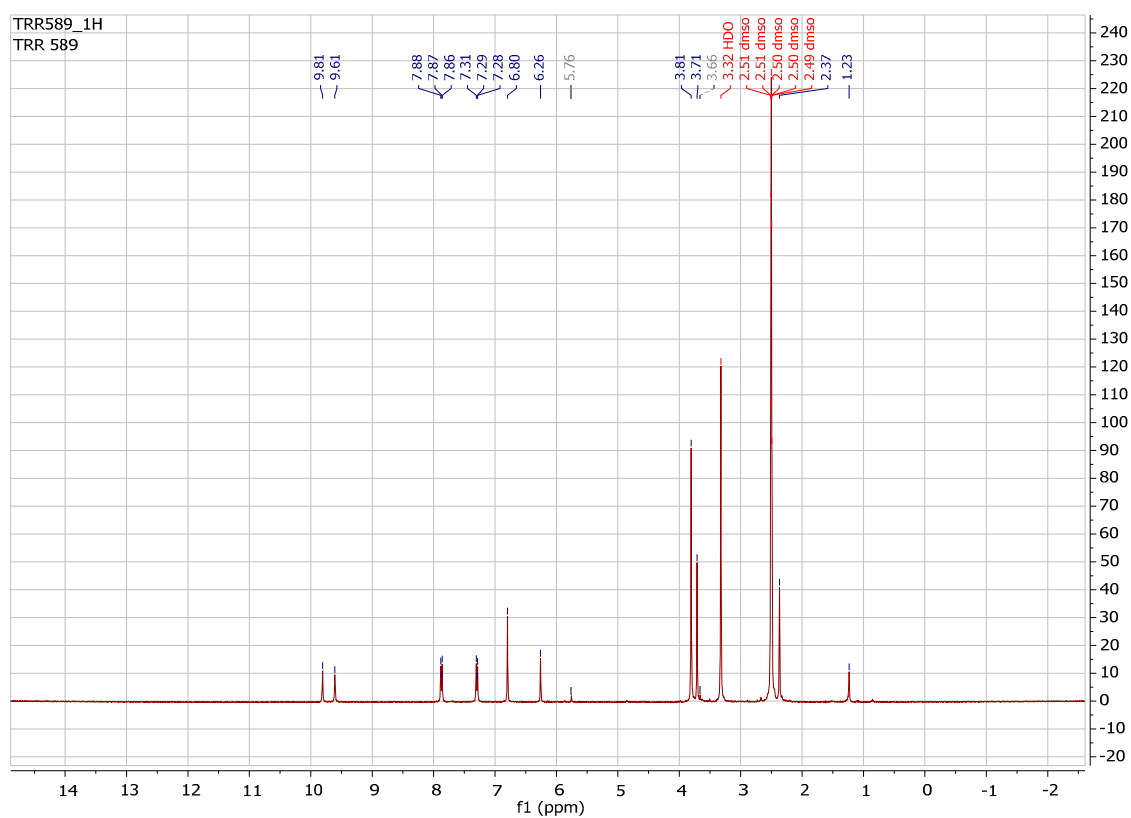
^1H -NMR and ^{13}C -NMR spectra of compound **7a**



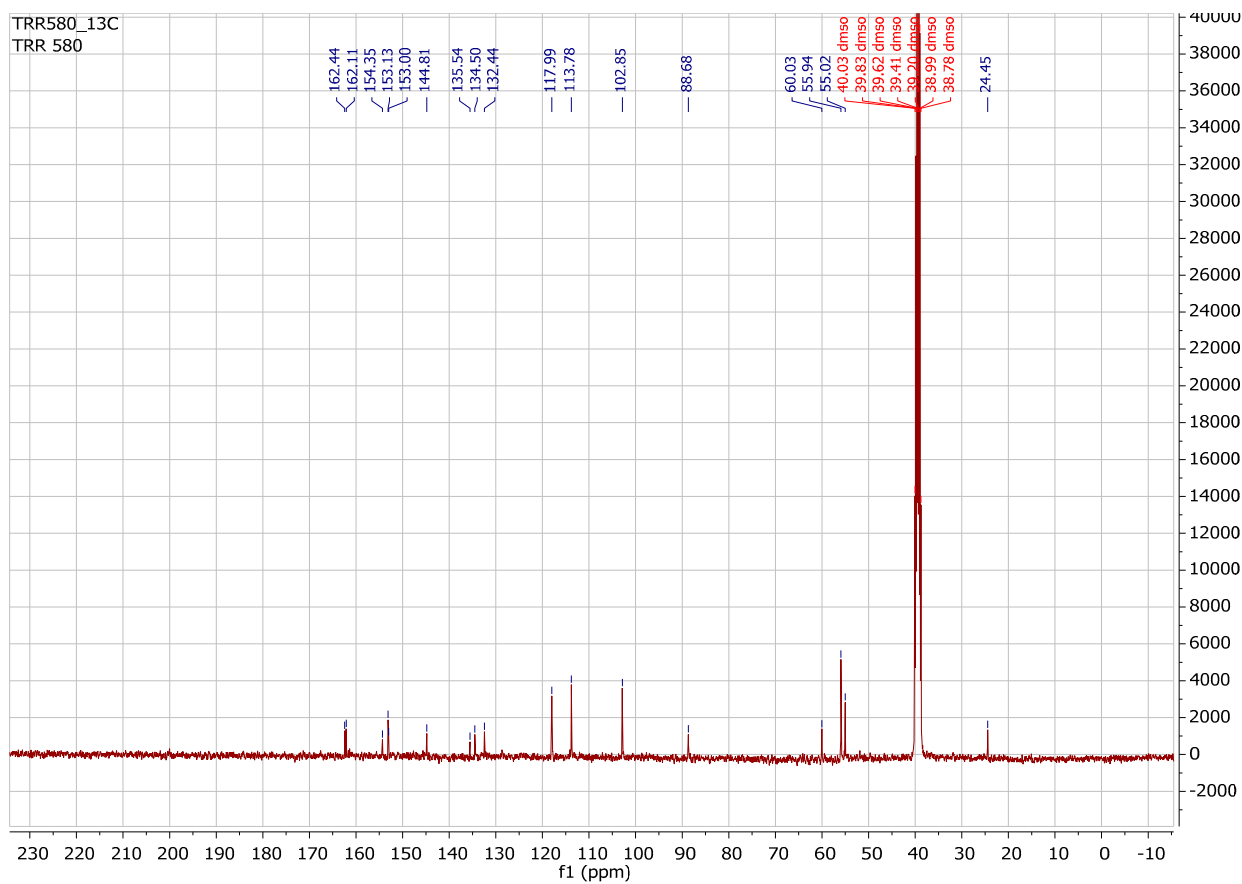
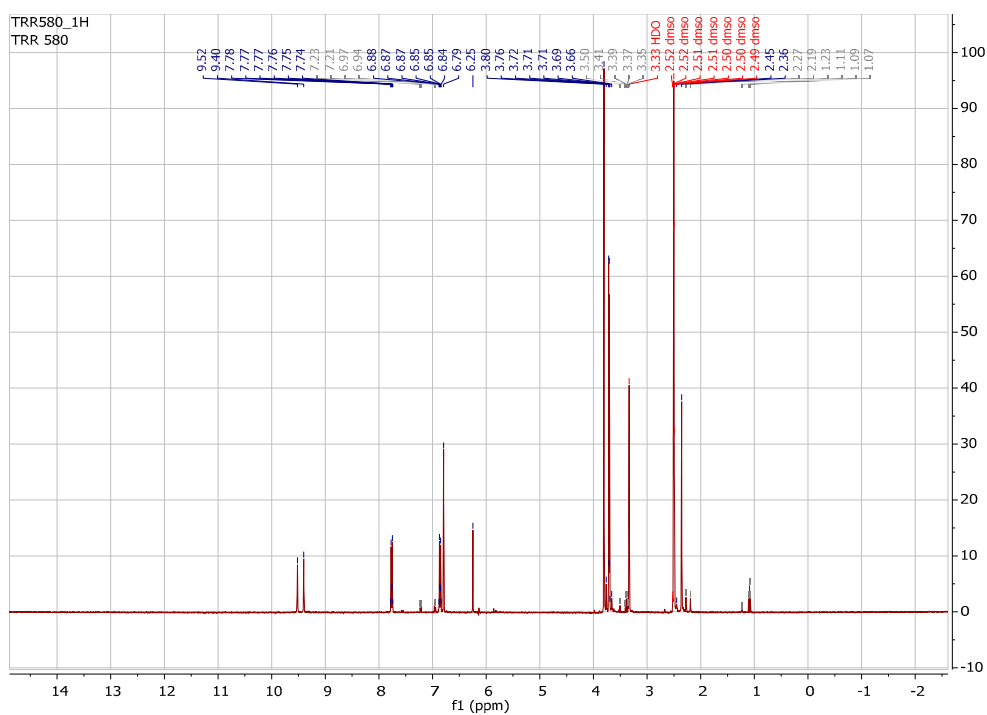
¹H-NMR and ¹³C-NMR spectra of compound **7c**



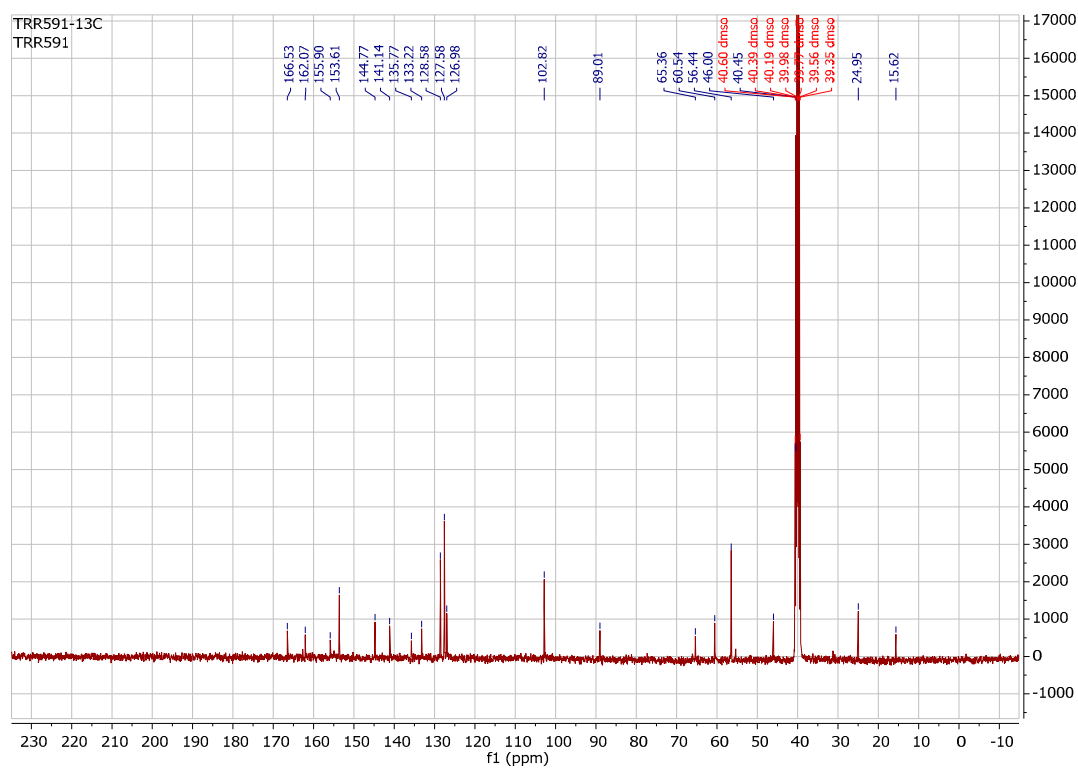
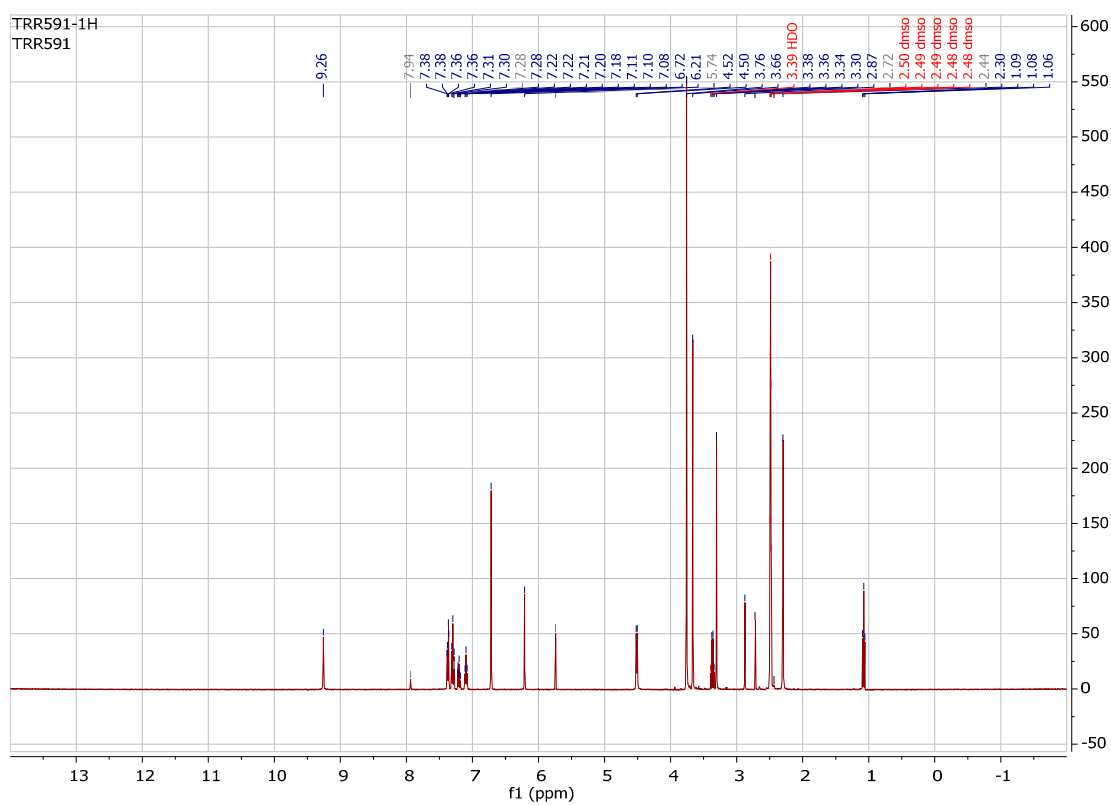
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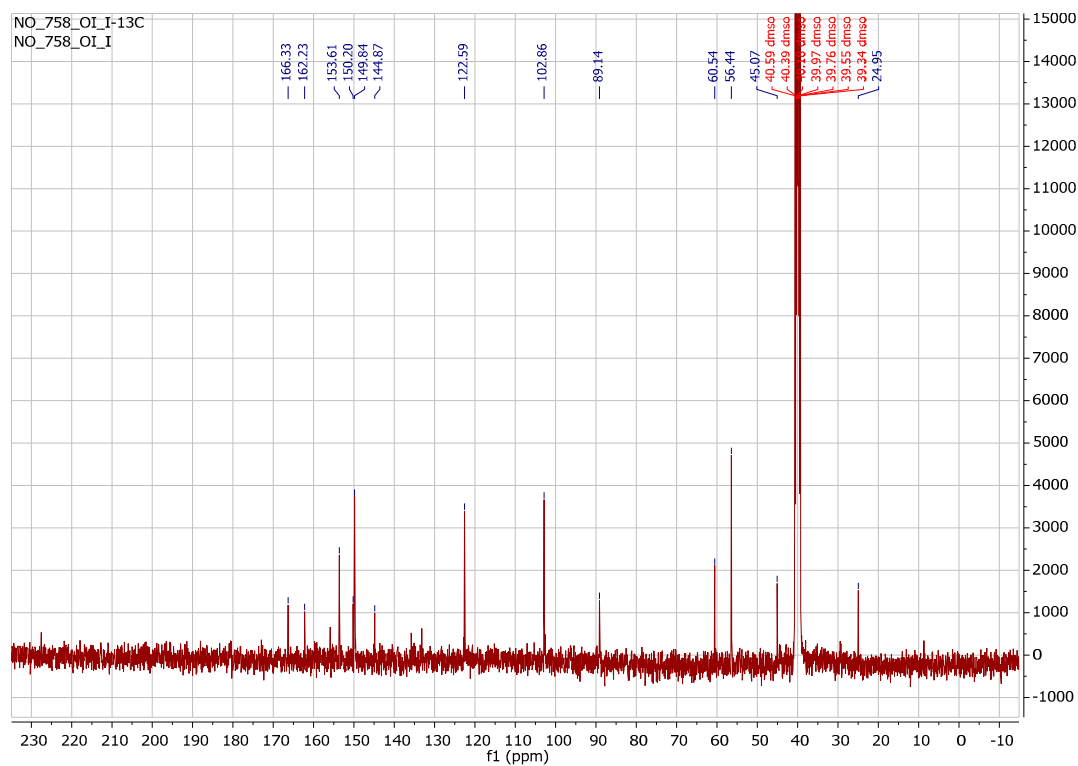
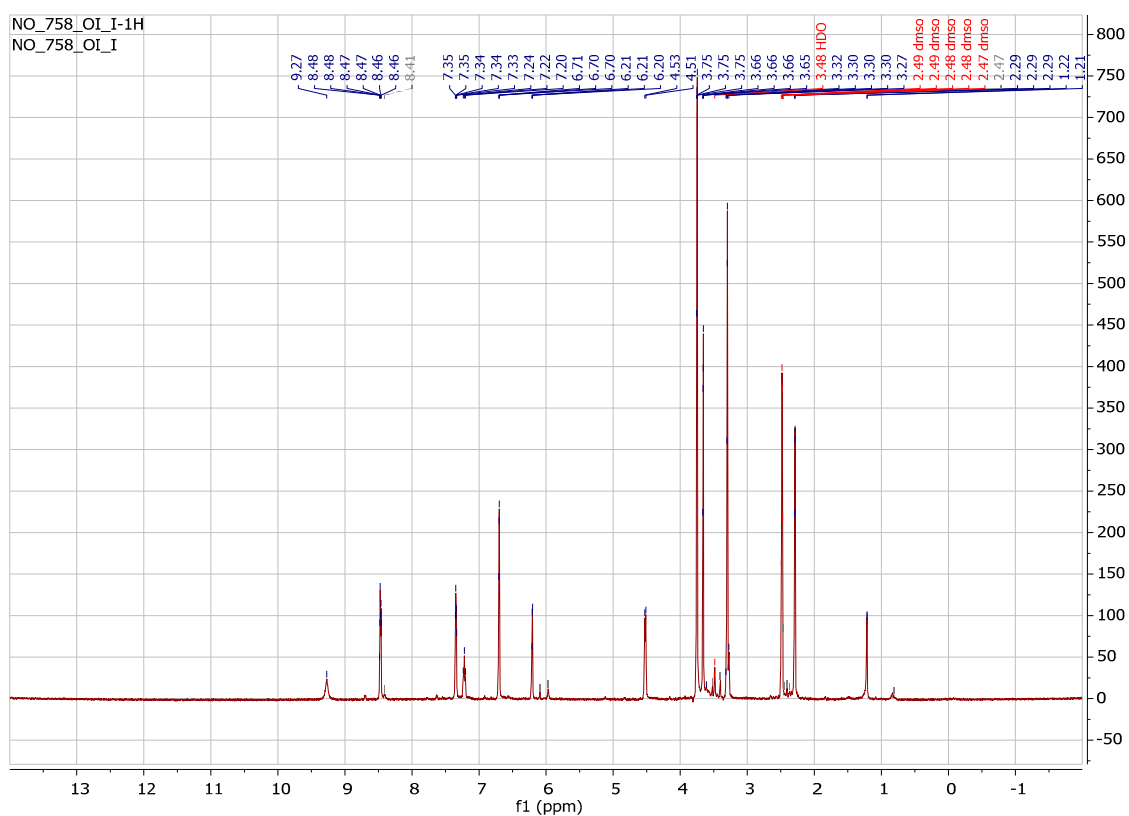
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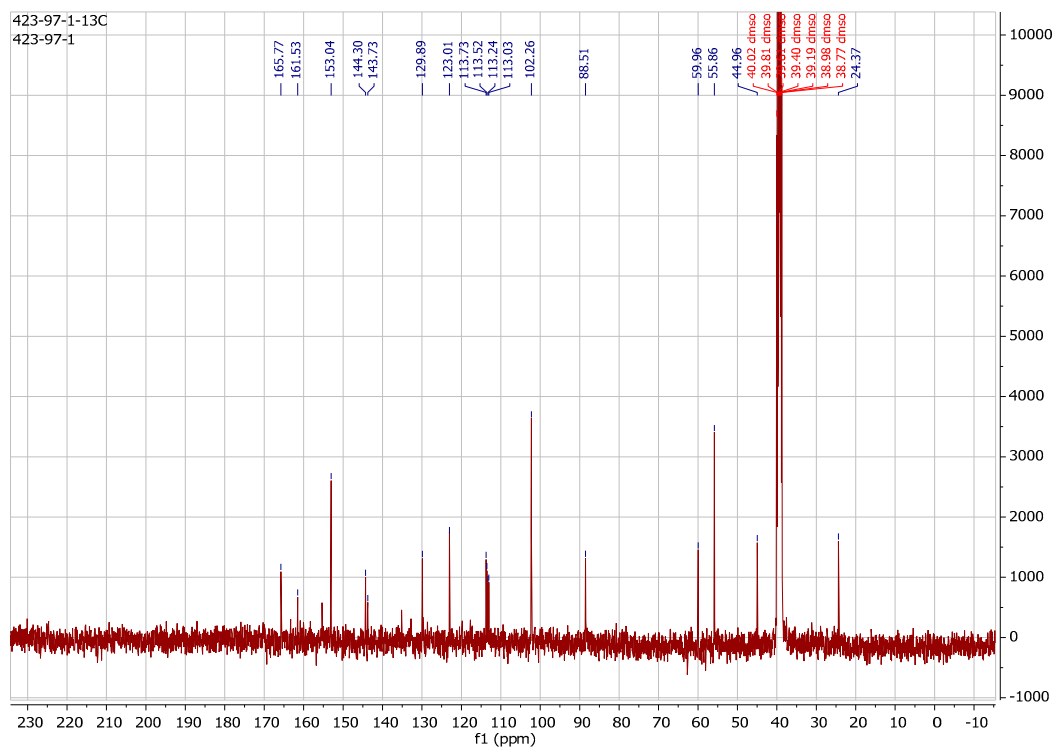
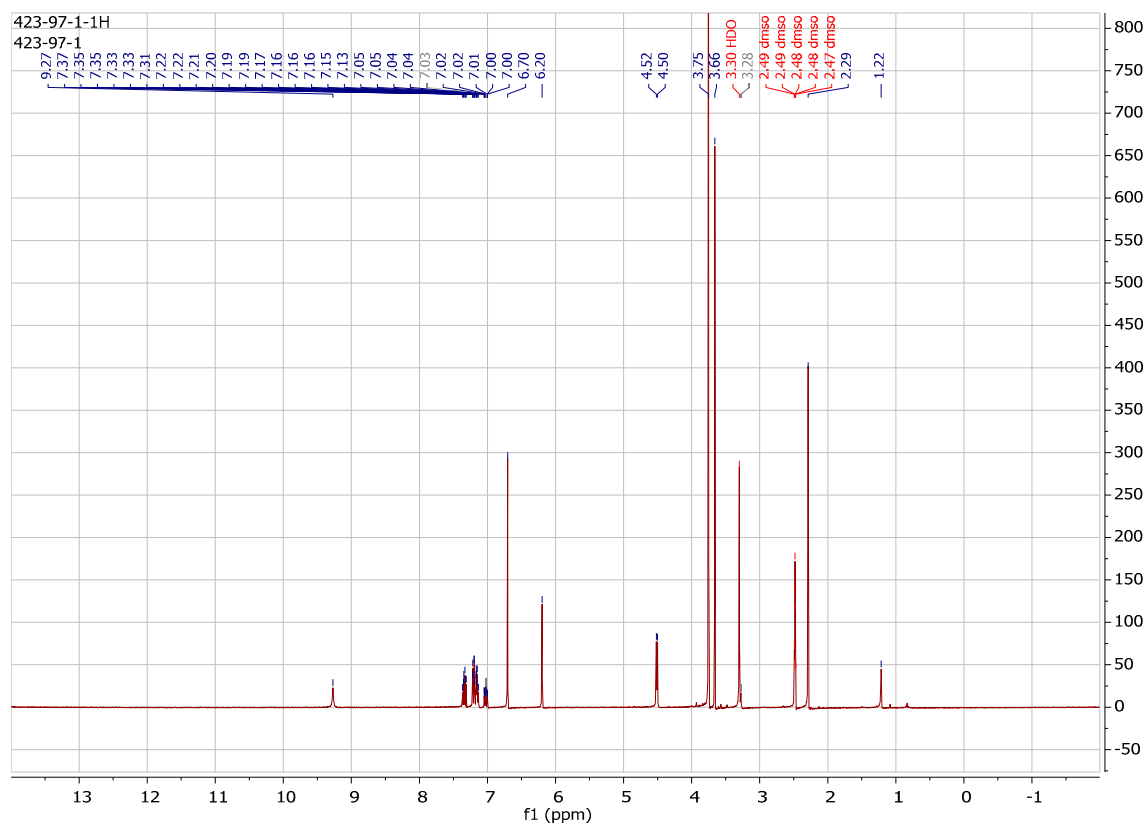
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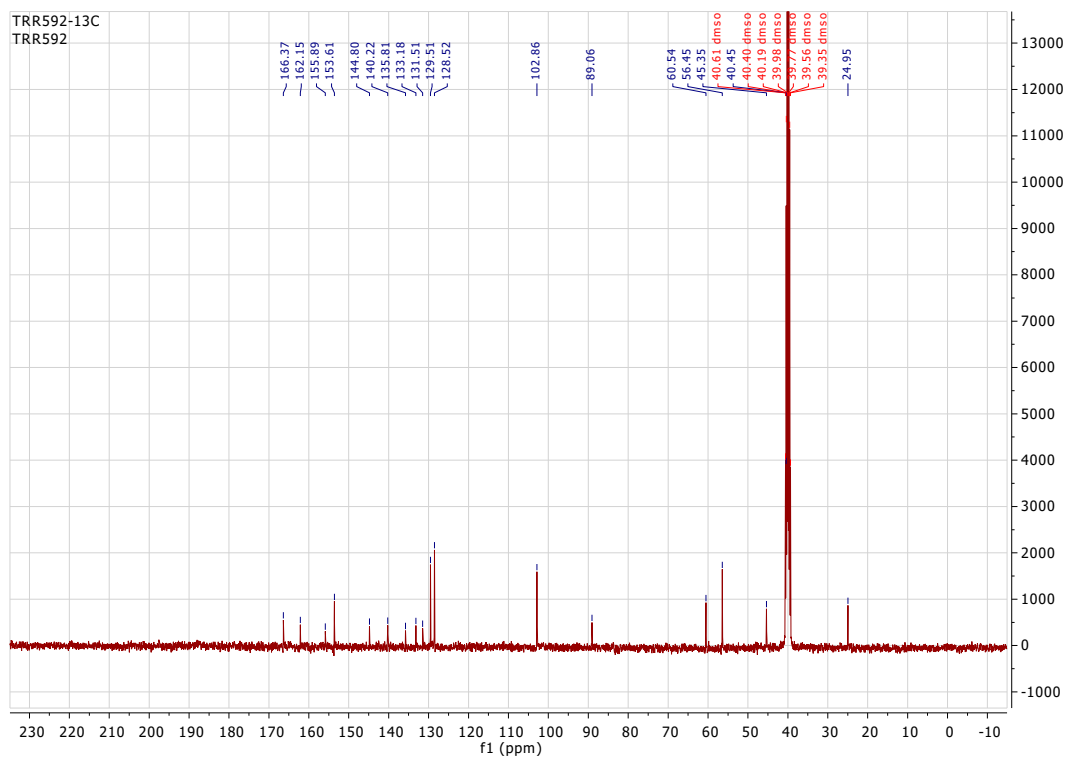
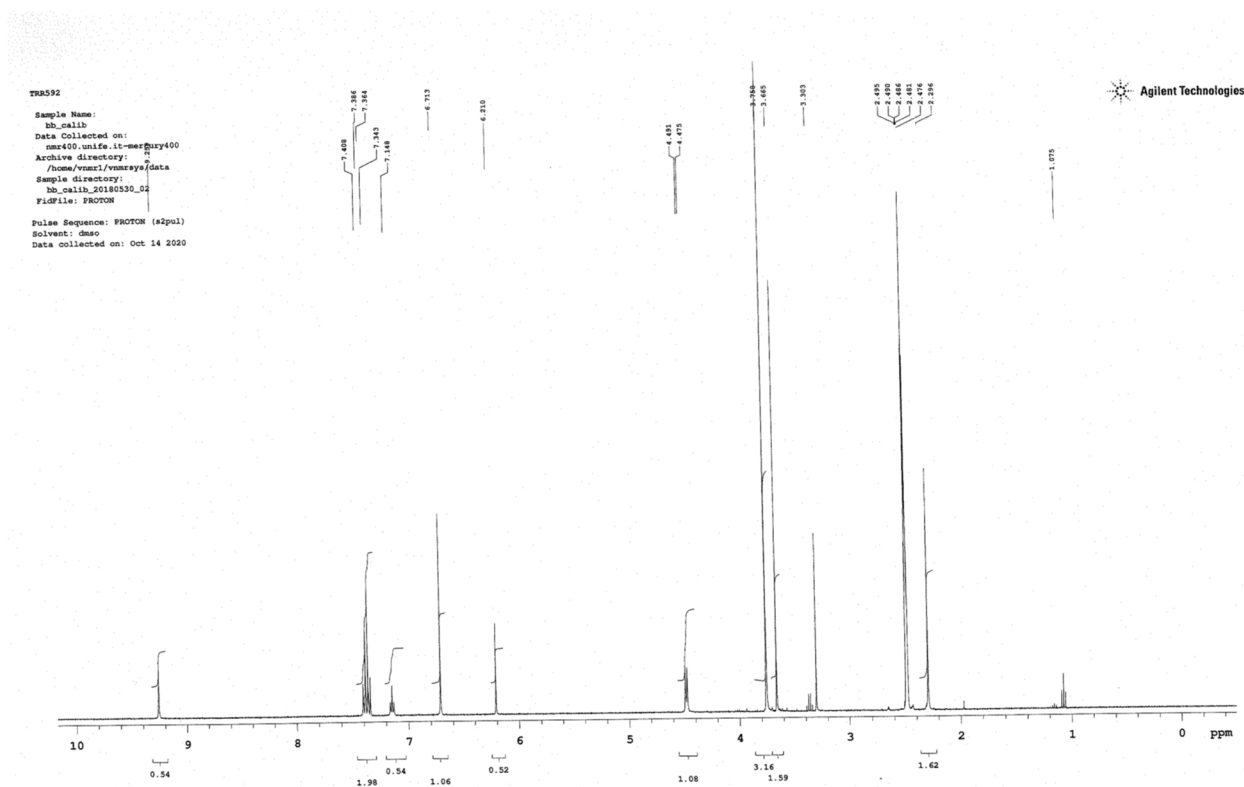
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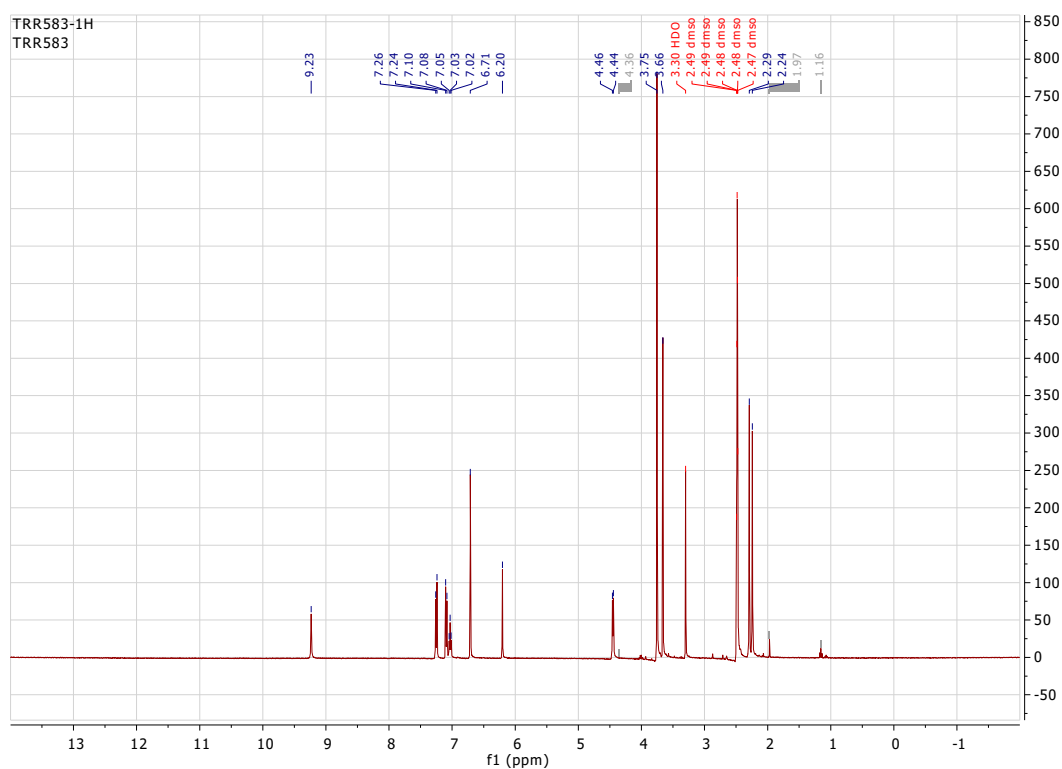
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^1H -NMR and ^{13}C -NMR spectra of compound **7m**

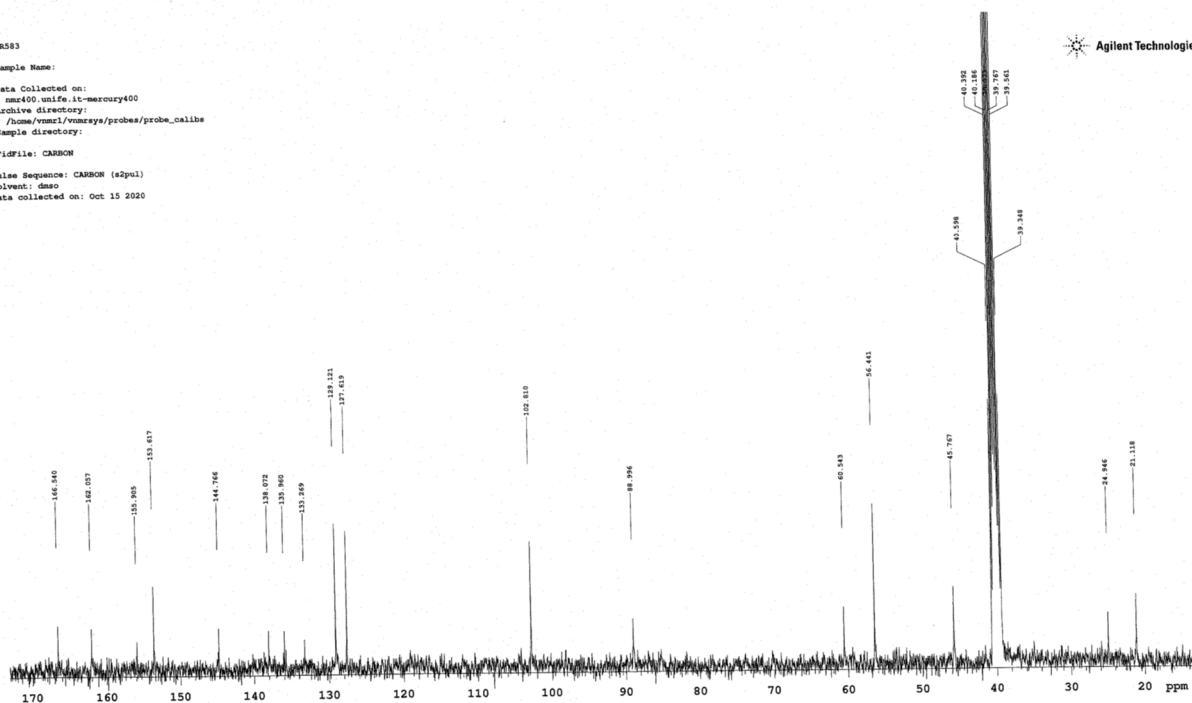


^1H -NMR and ^{13}C -NMR spectra of compound **7n**



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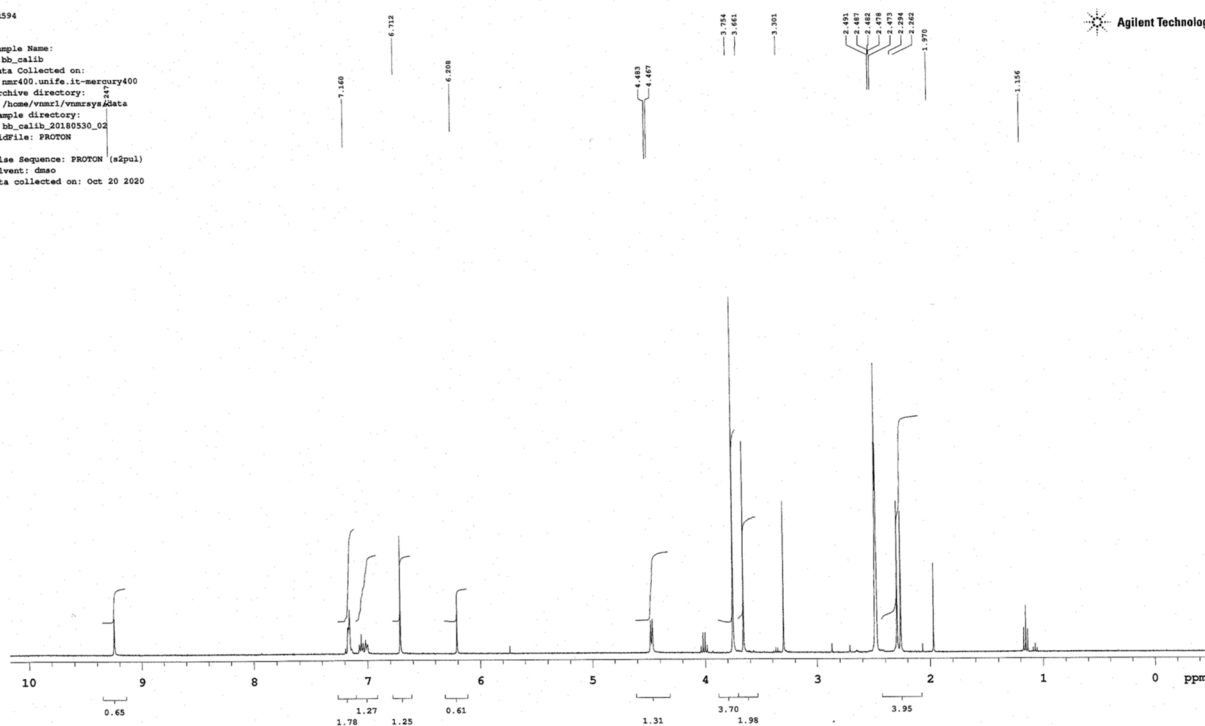


^1H -NMR and ^{13}C -NMR spectra of compound **7p**

TKR594

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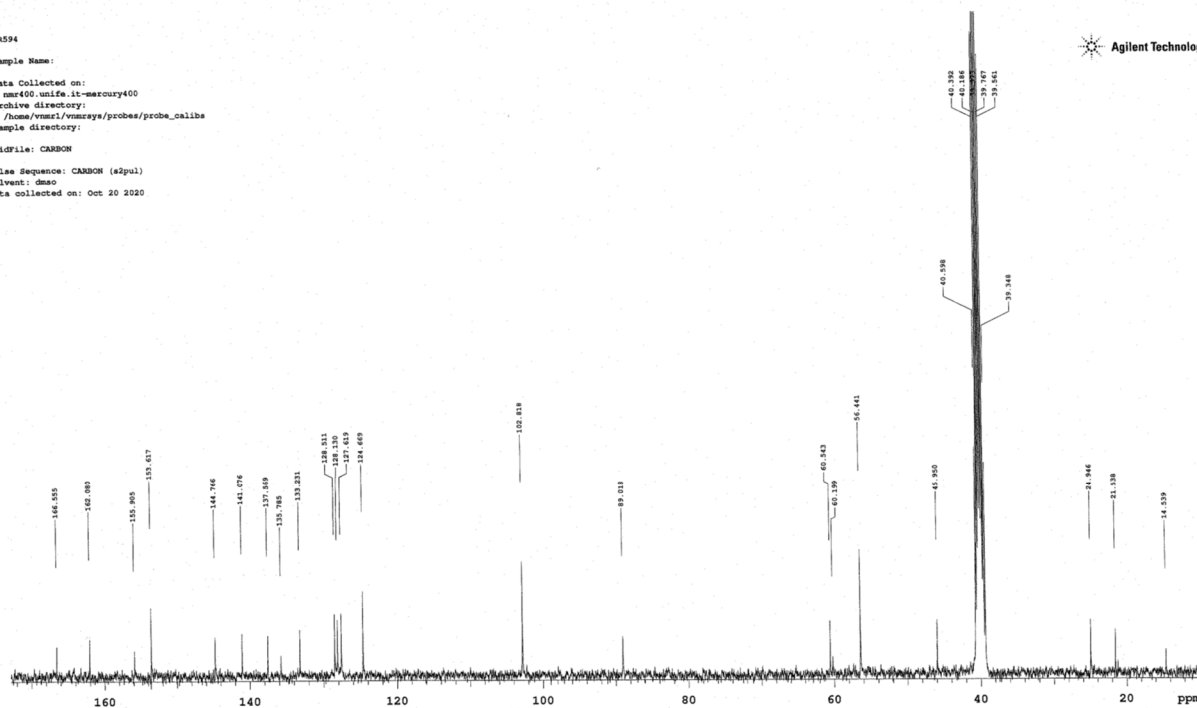
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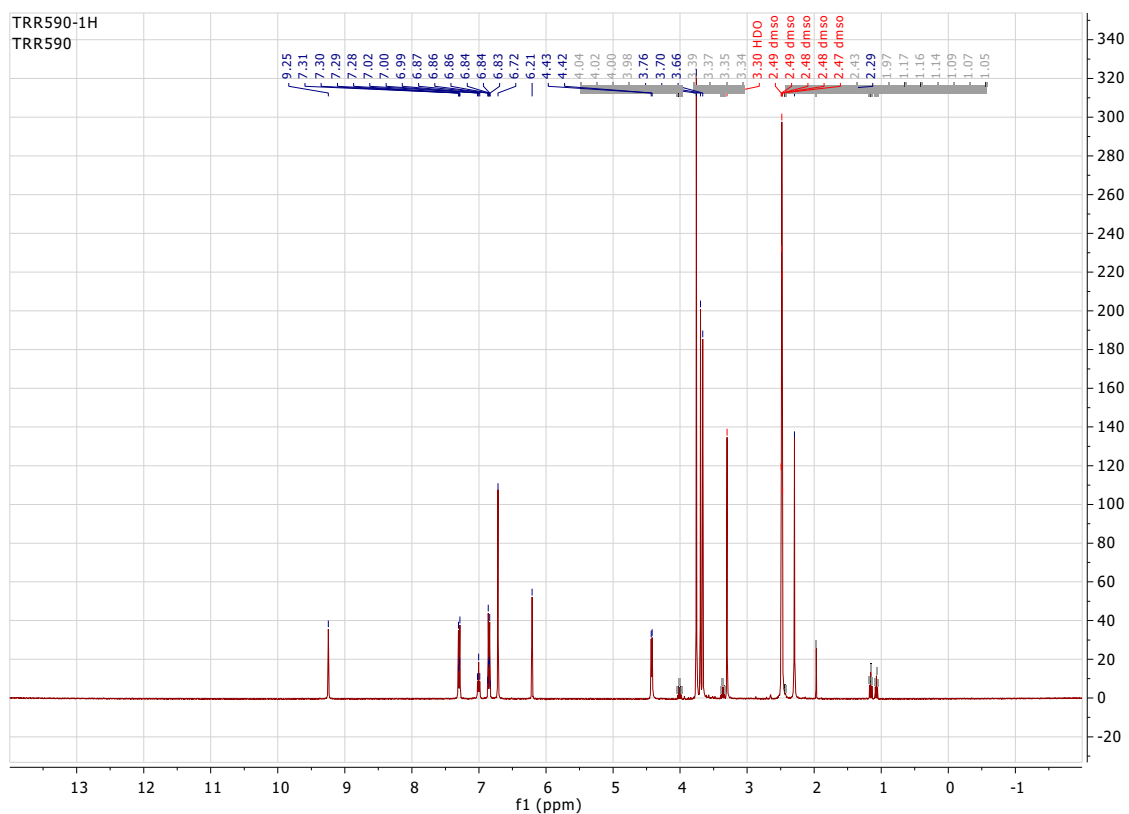
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Agilent Technologies



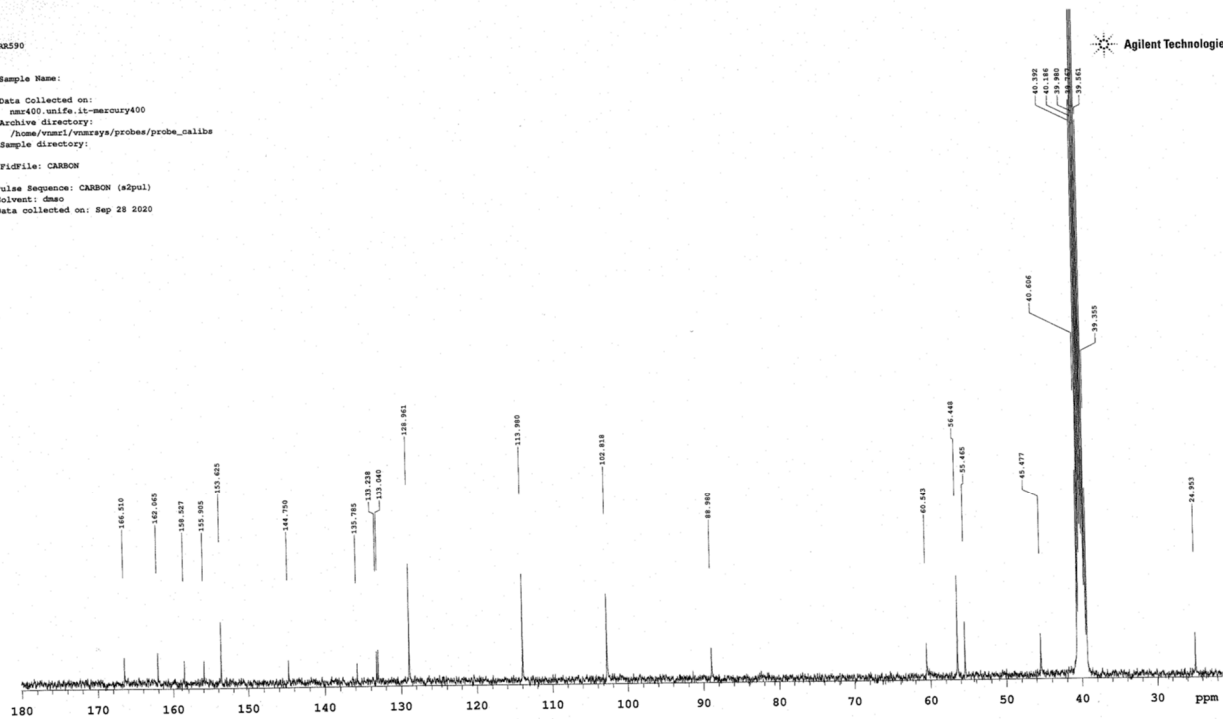
^1H -NMR and ^{13}C -NMR spectra of compound **7q**



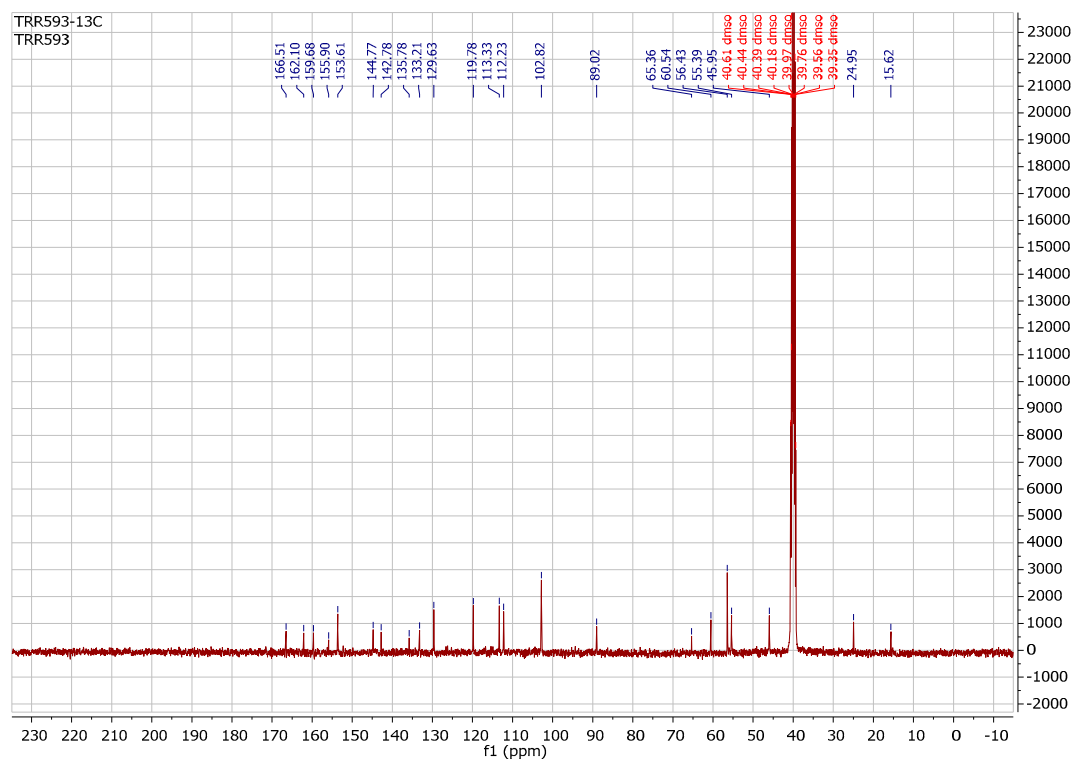
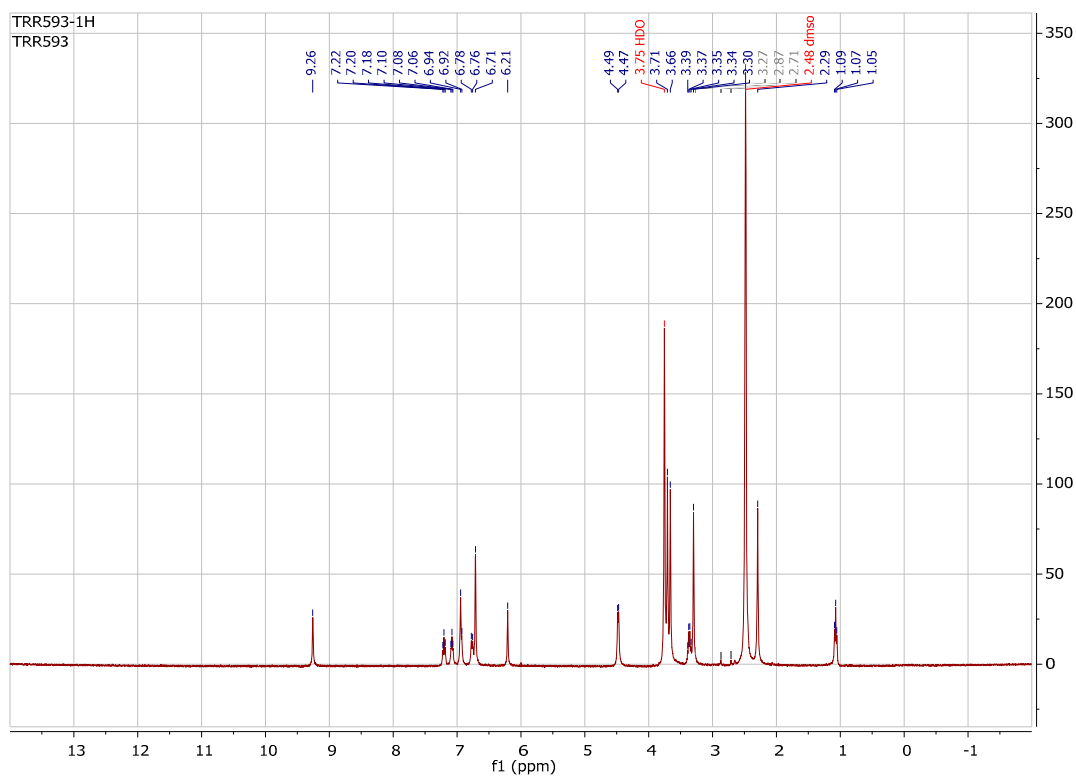
TRR590

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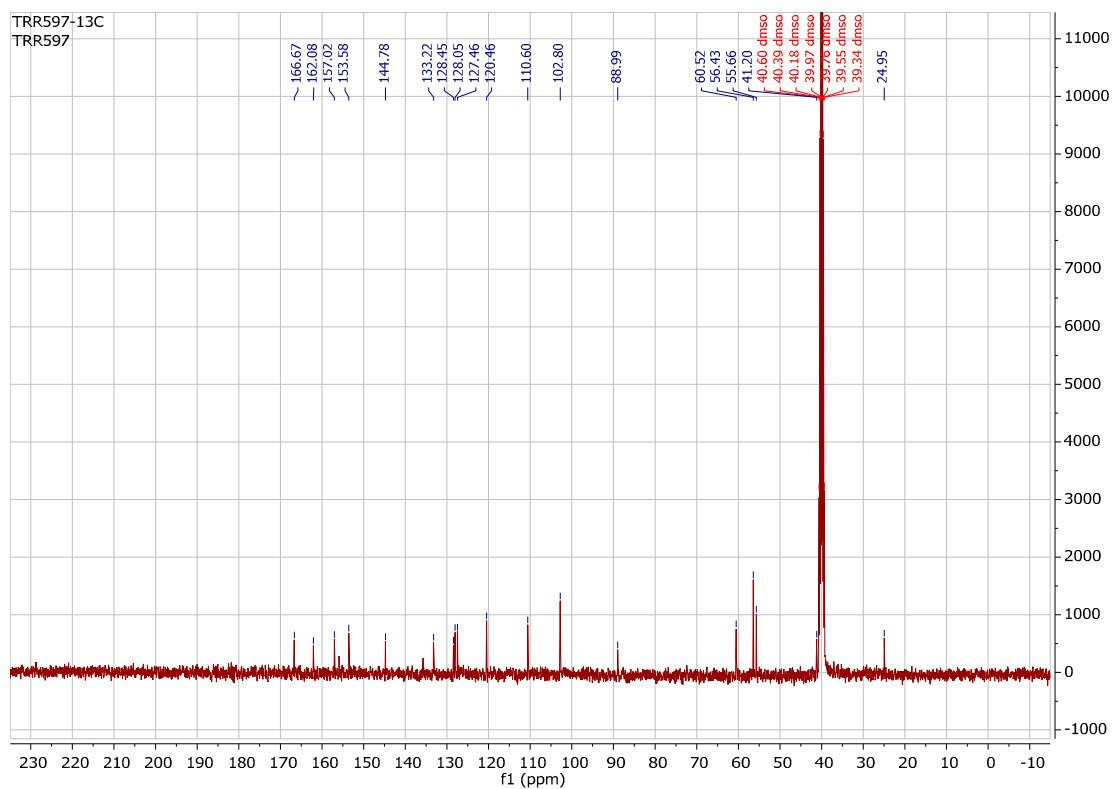
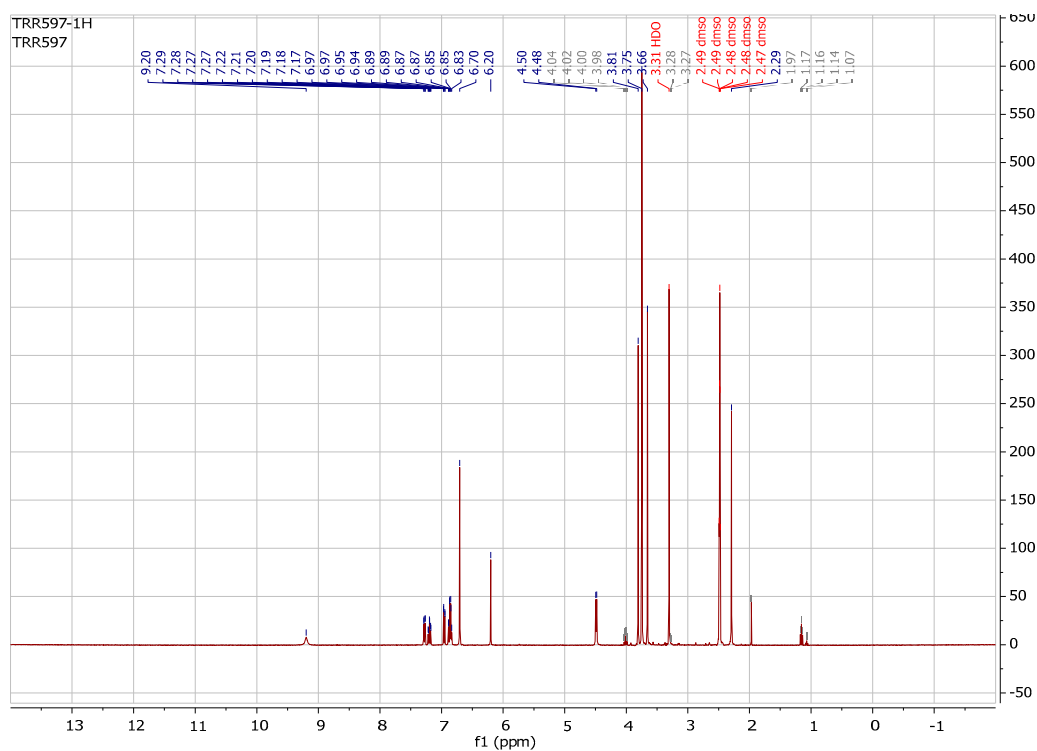
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^1H -NMR and ^{13}C -NMR spectra of compound **7s**



^1H -NMR and ^{13}C -NMR spectra of compound **7t**

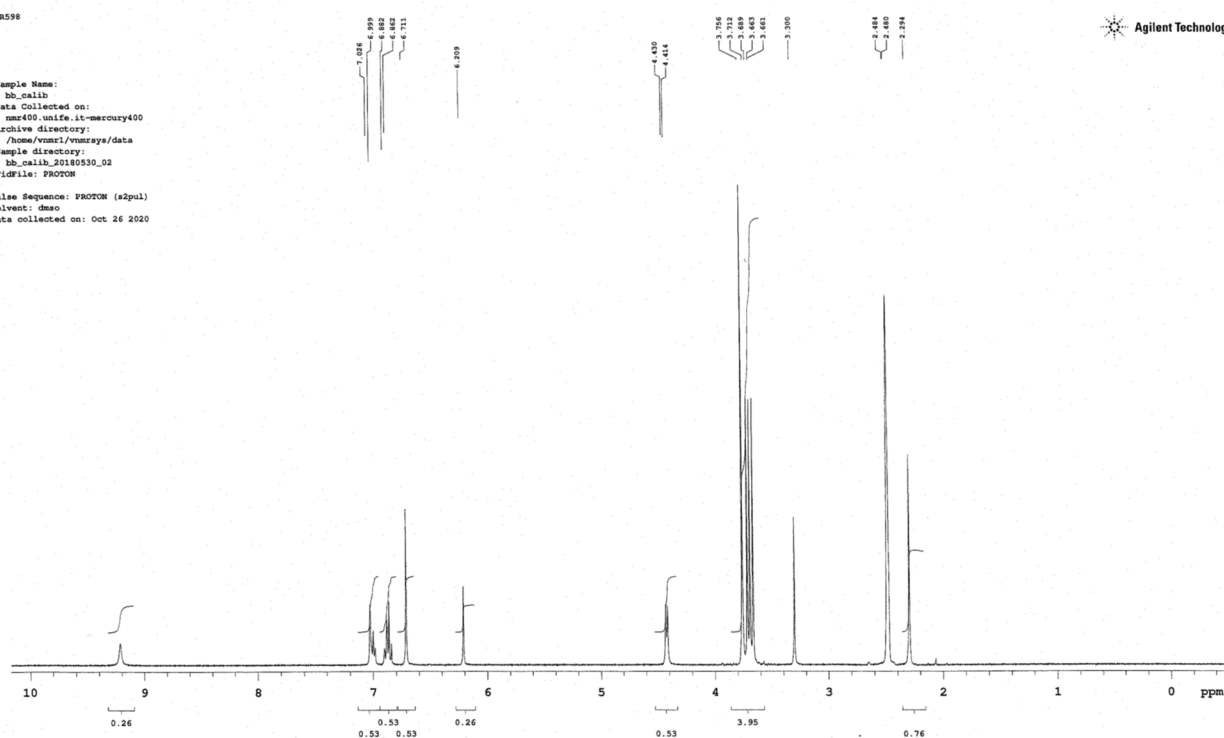


^1H -NMR and ^{13}C -NMR spectra of compound **7u**

TR5598



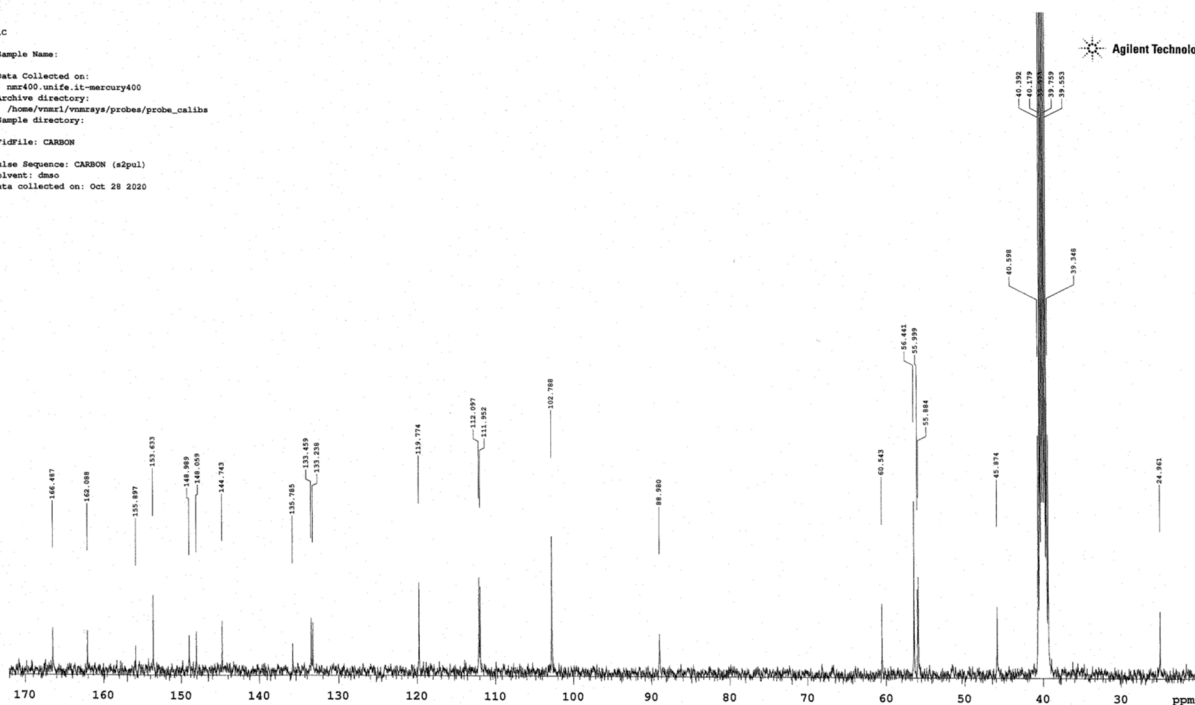
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Solvent: dms
Data collected on: Oct 26 2020



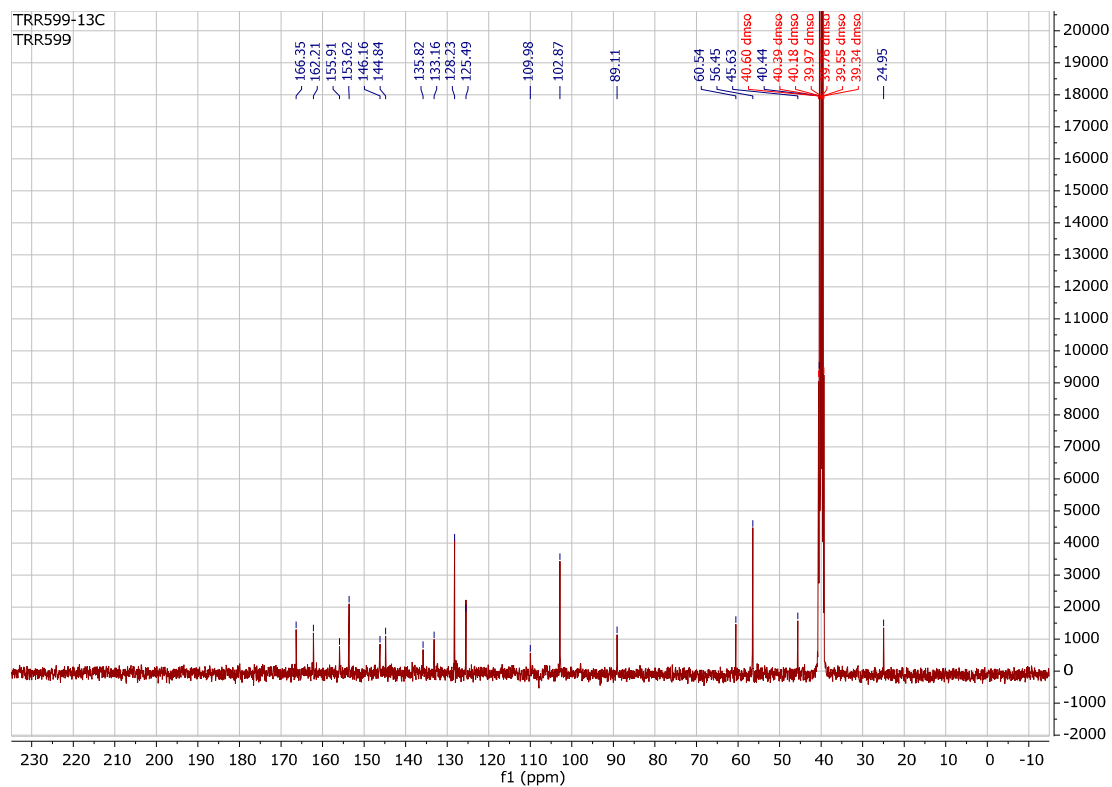
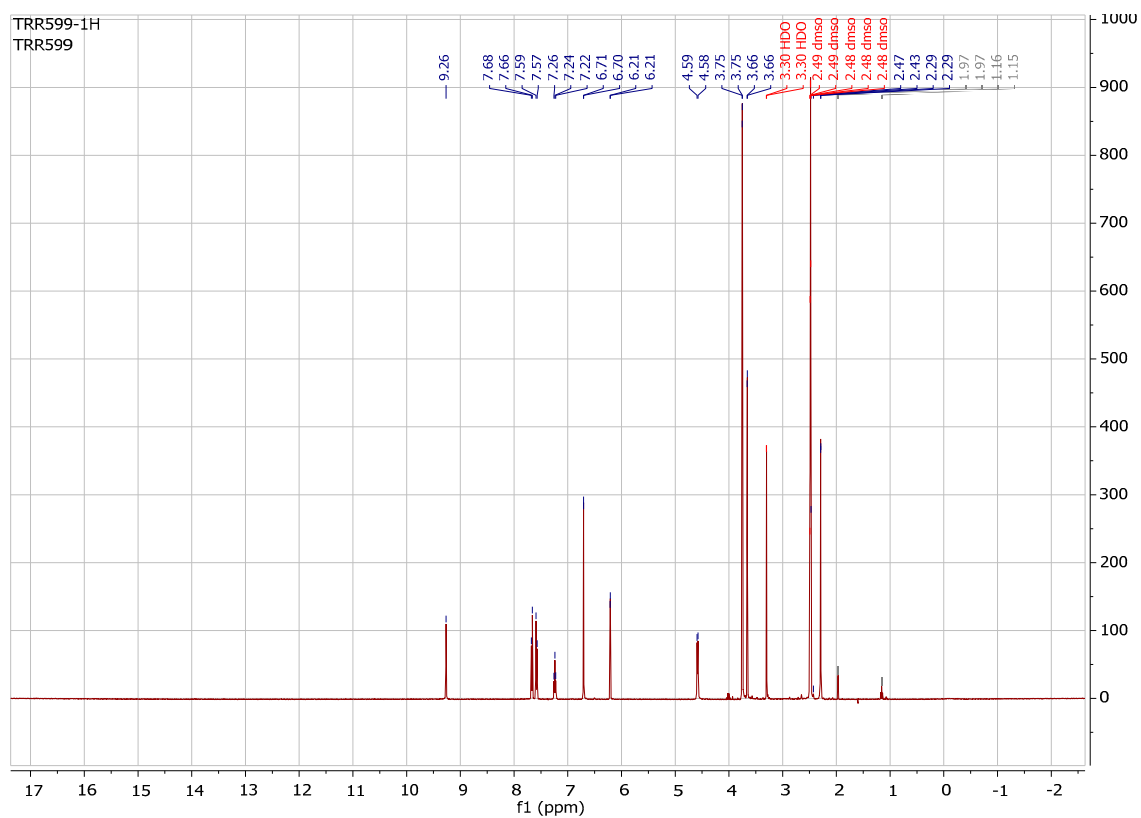
21C



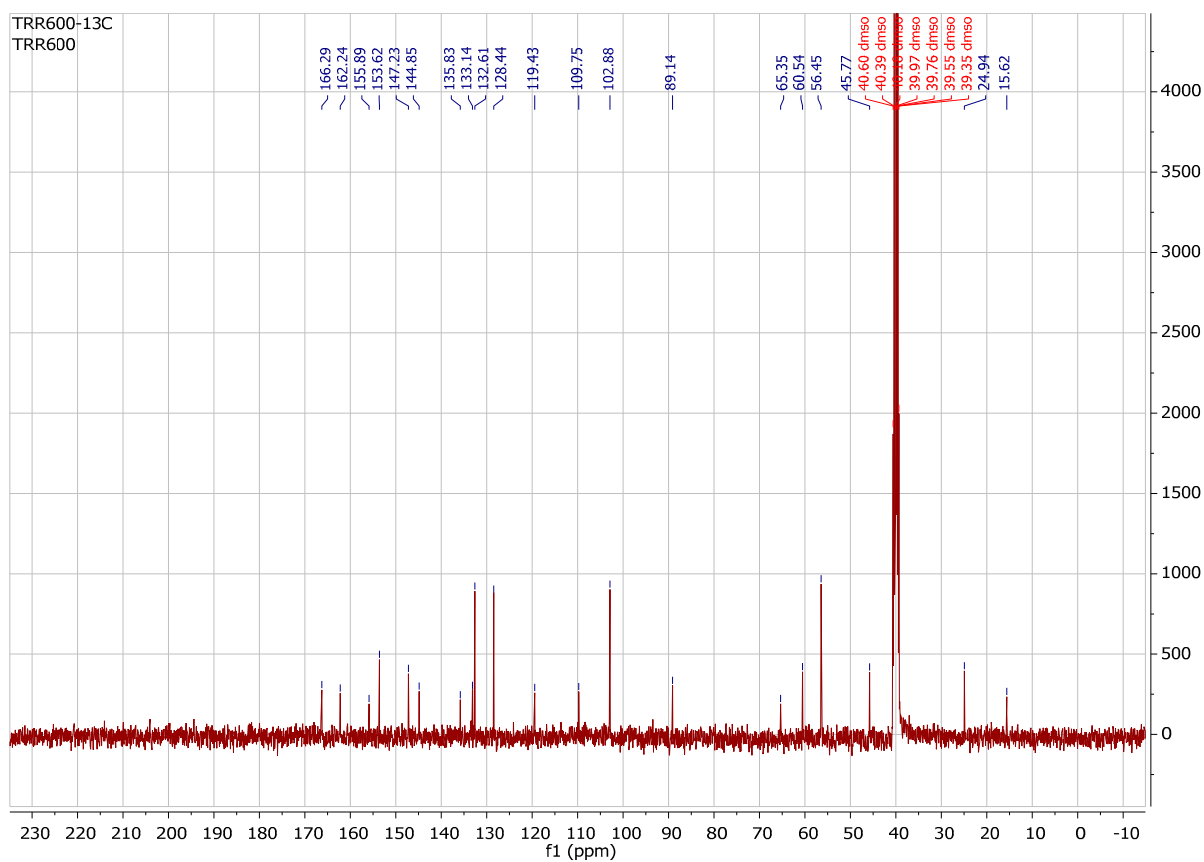
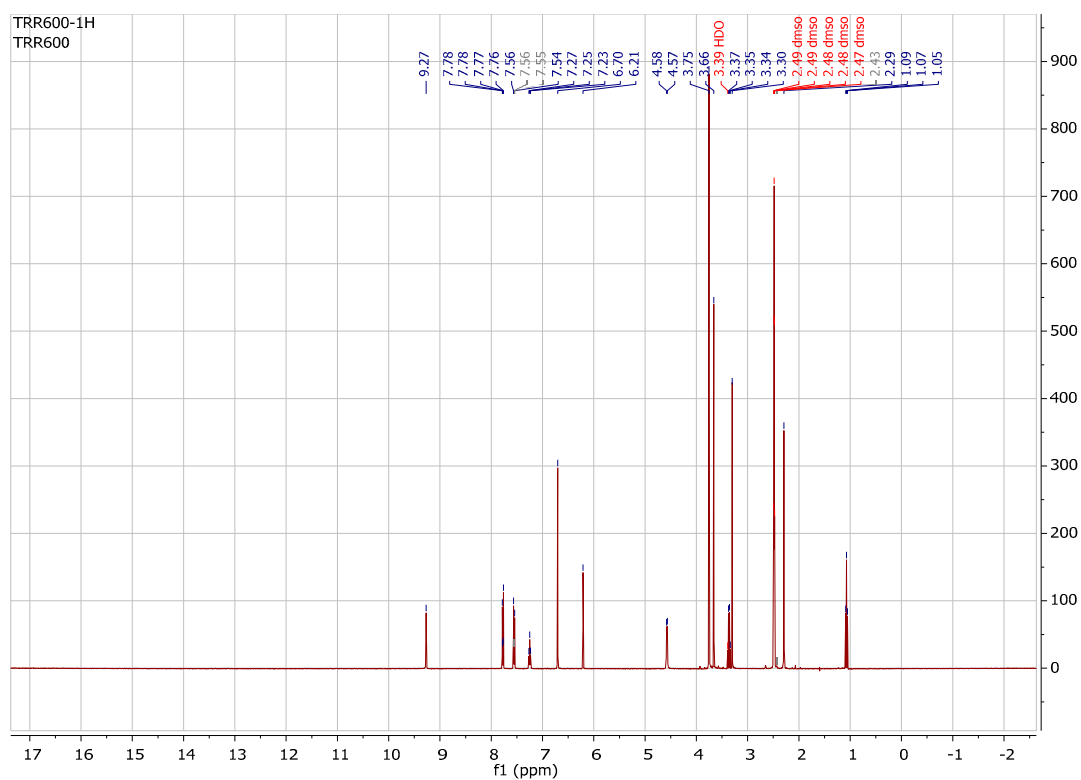
Sample Name:
Data Collected on:
nmr400.unif.it-mercury400
Archive directory:
/home/vmci/vmrays/probes/probe_calib
Sample directory:
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Pulse Sequence: CARBON (s2pul)
Solvent: dms
Data collected on: Oct 28 2020

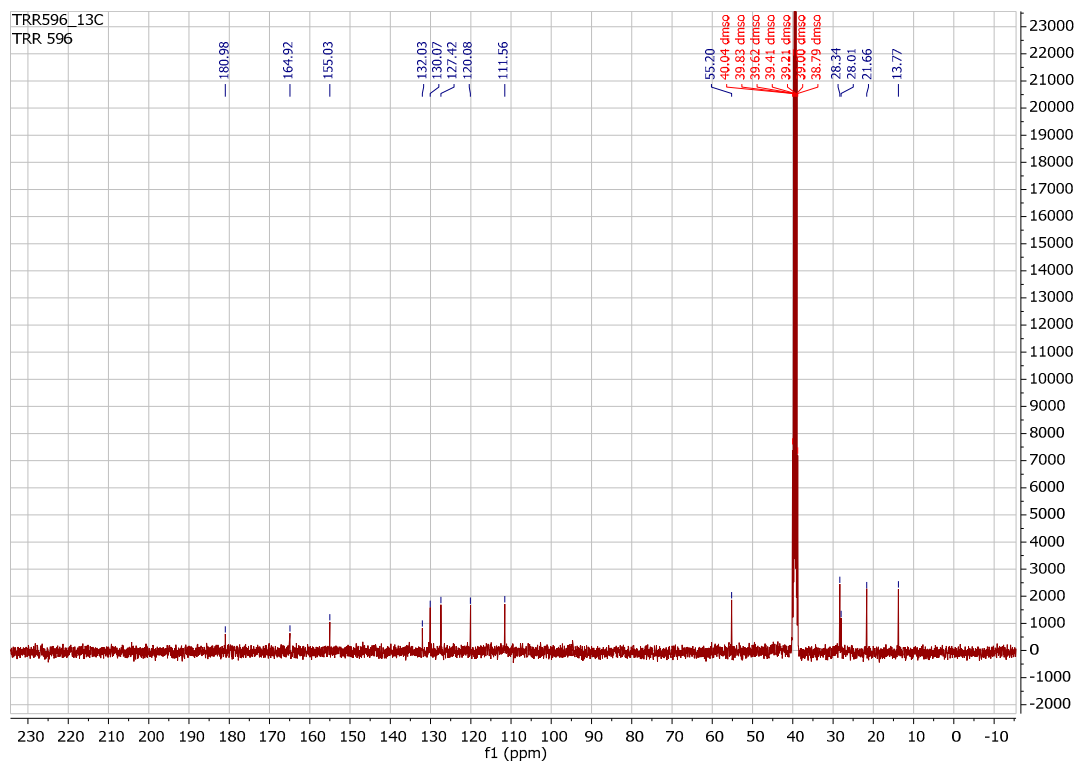
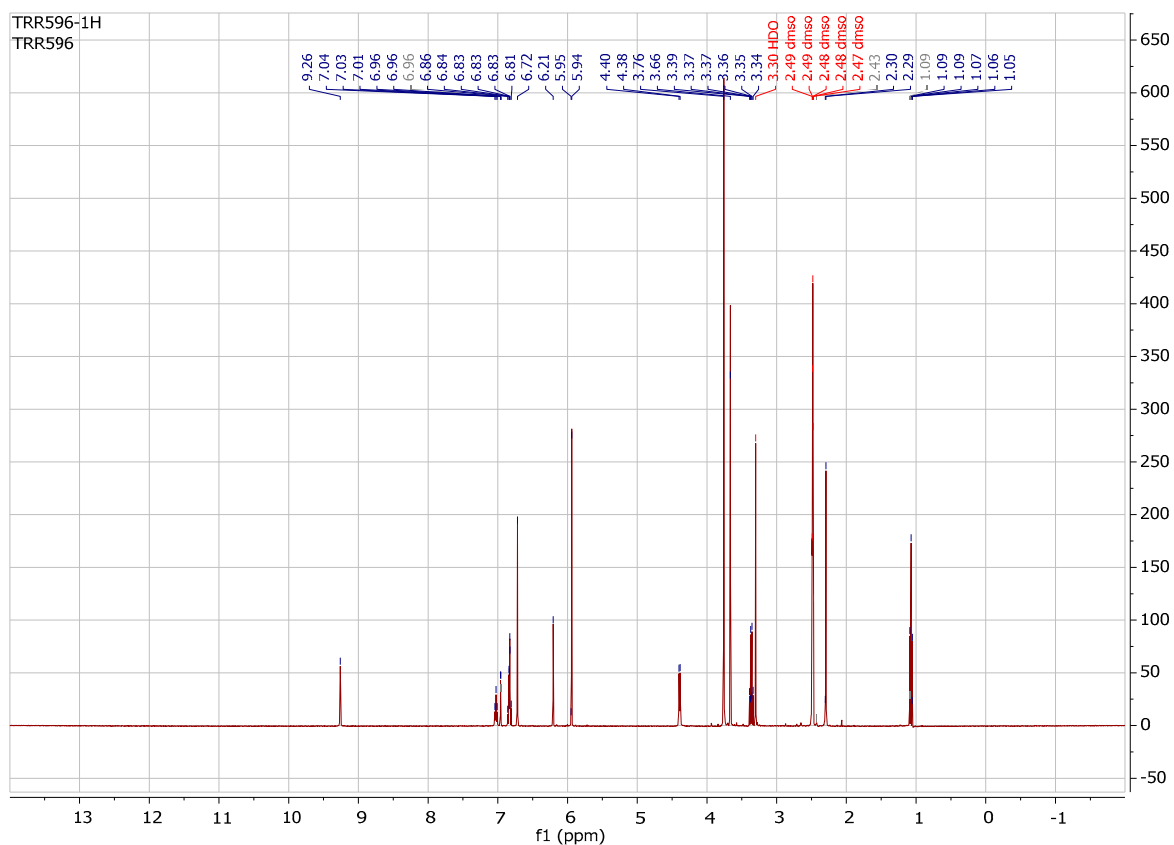


^1H -NMR and ^{13}C -NMR spectra of compound **7v**

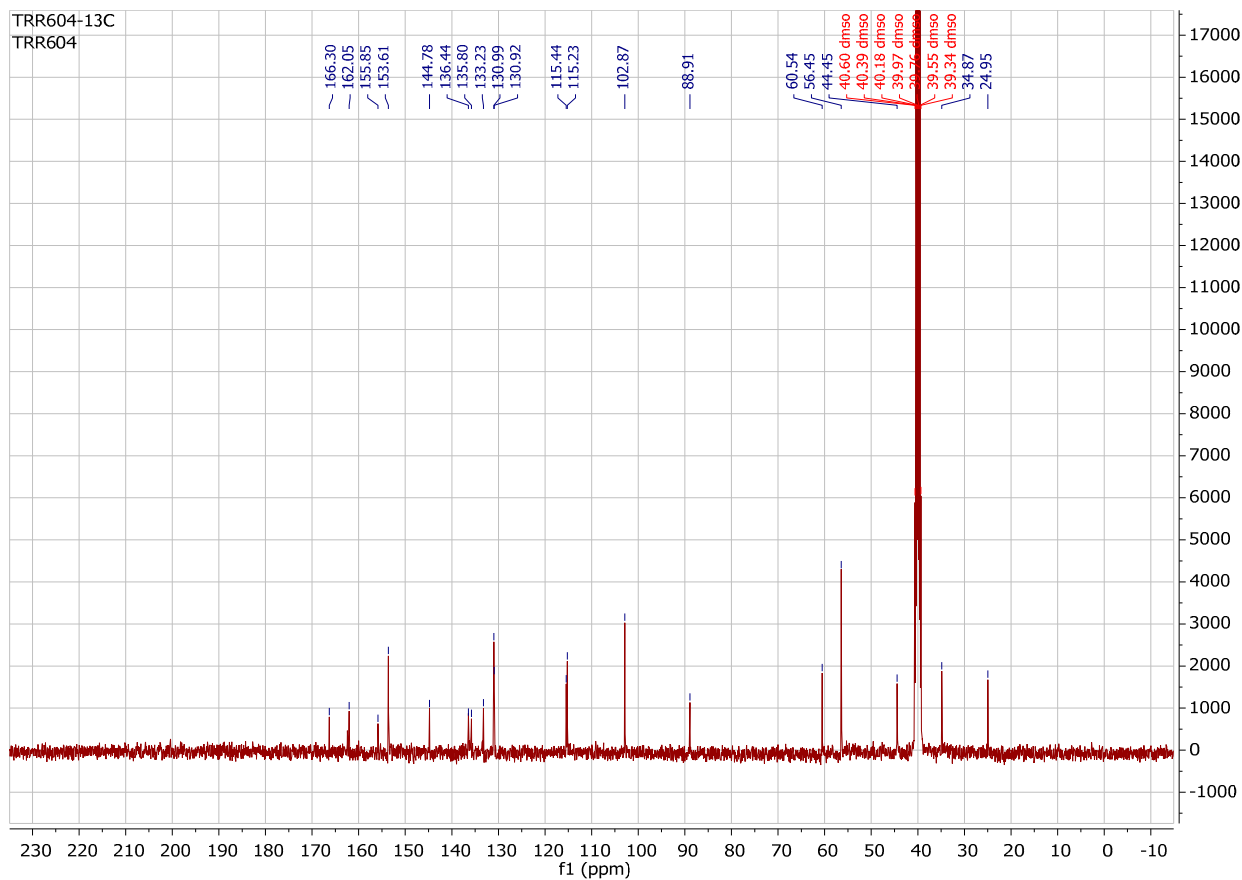
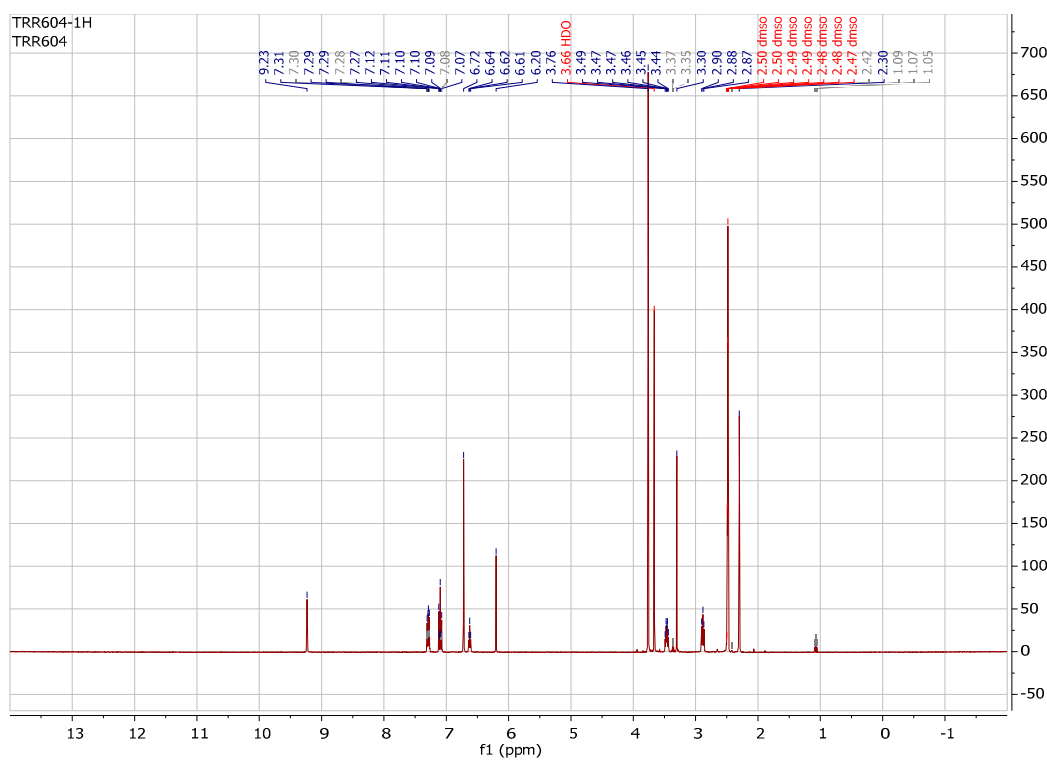


^1H -NMR and ^{13}C -NMR spectra of compound **7w**

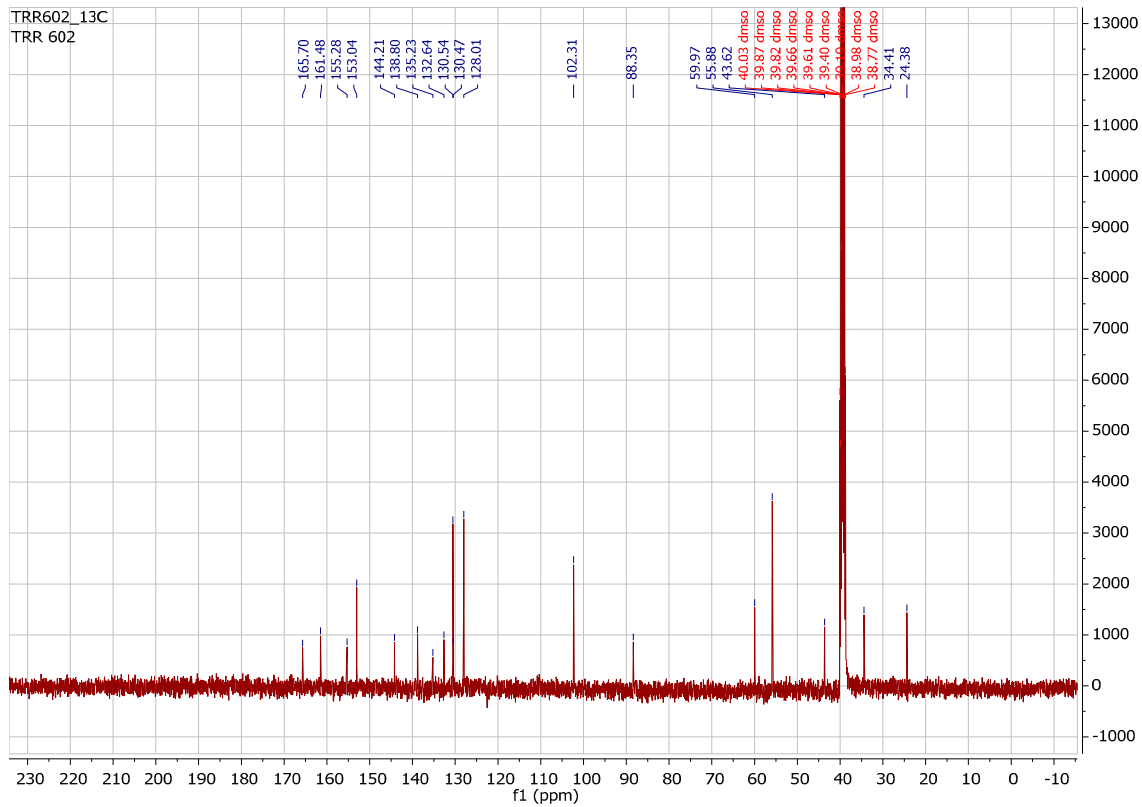
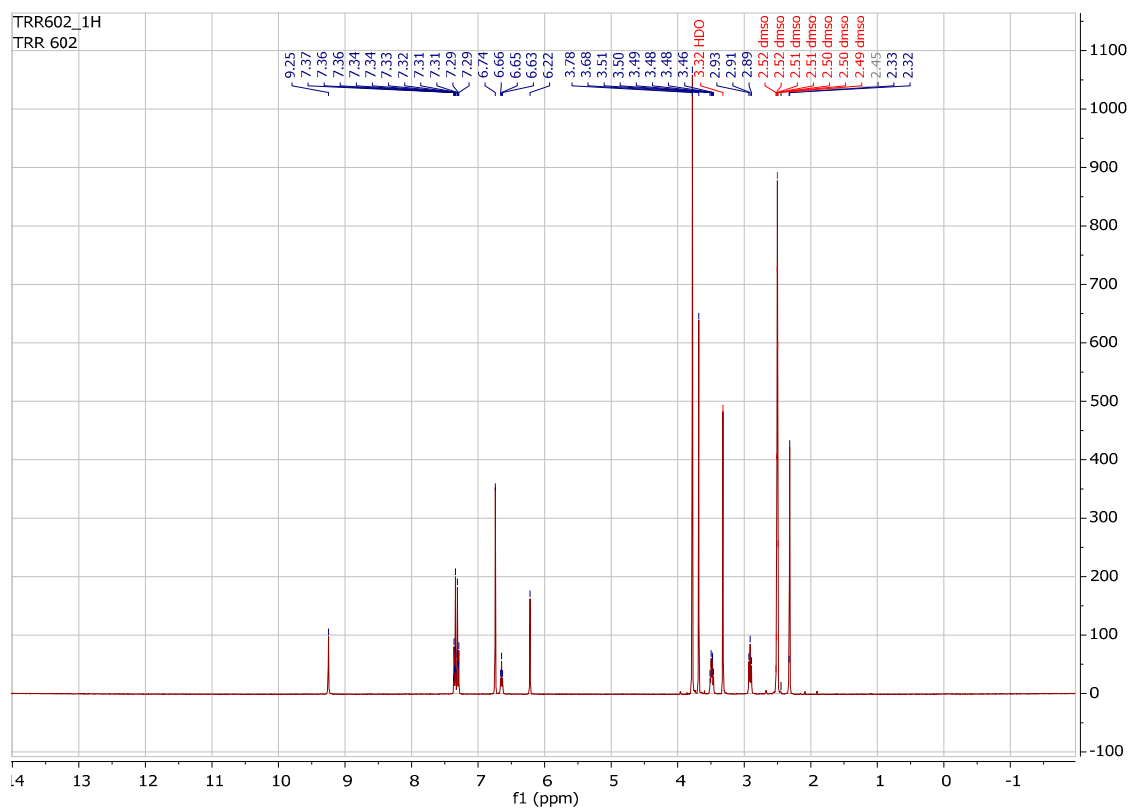
¹H-NMR and ¹³C-NMR spectra of compound 7x



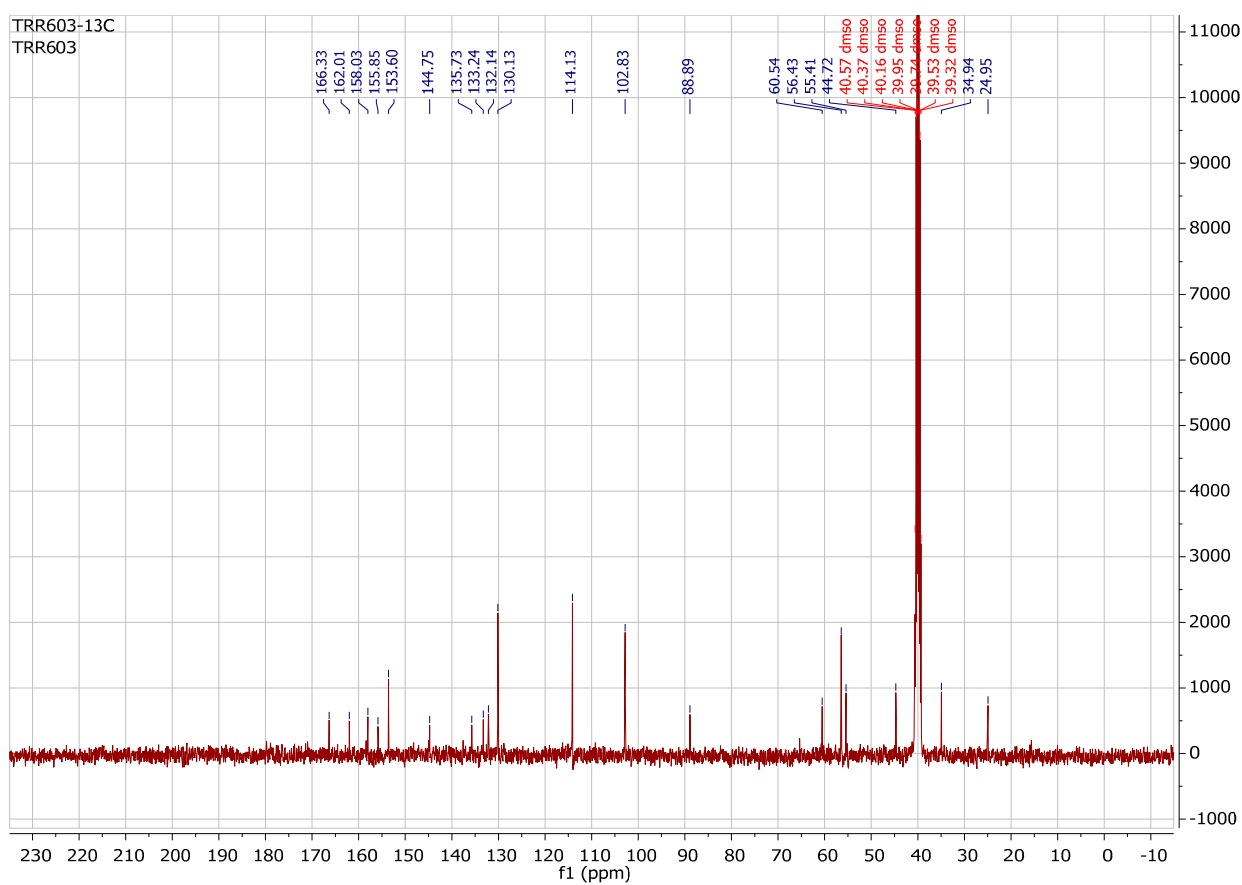
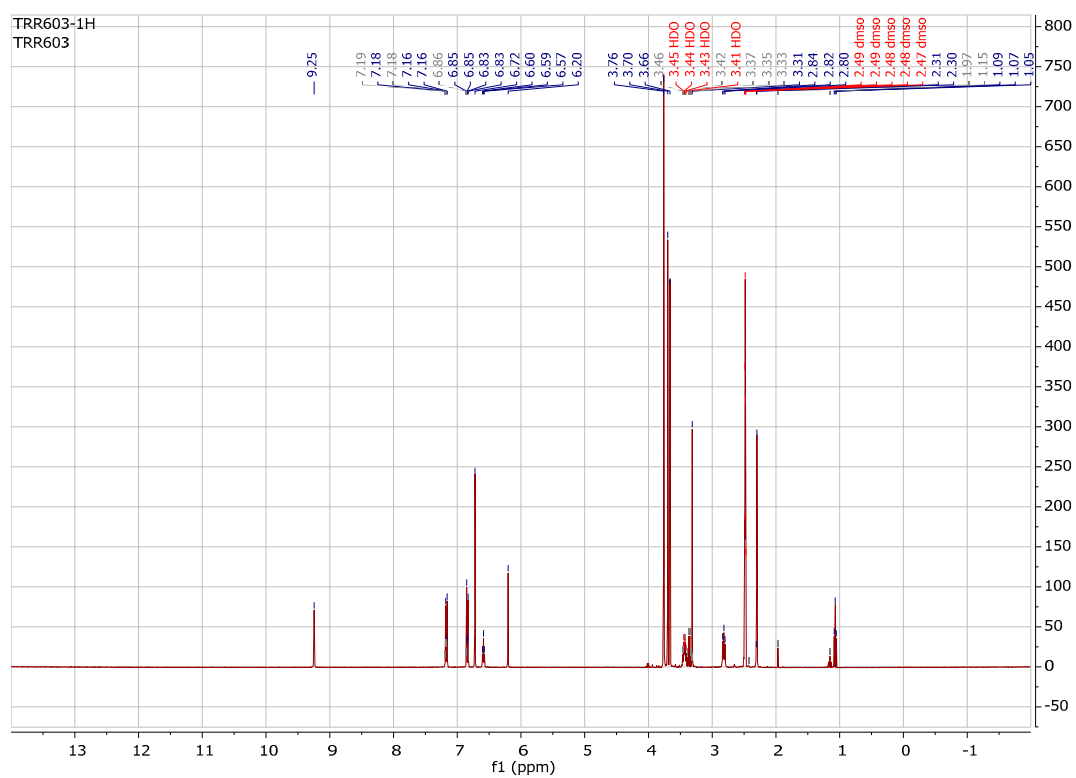
^1H -NMR and ^{13}C -NMR spectra of compound **7y**



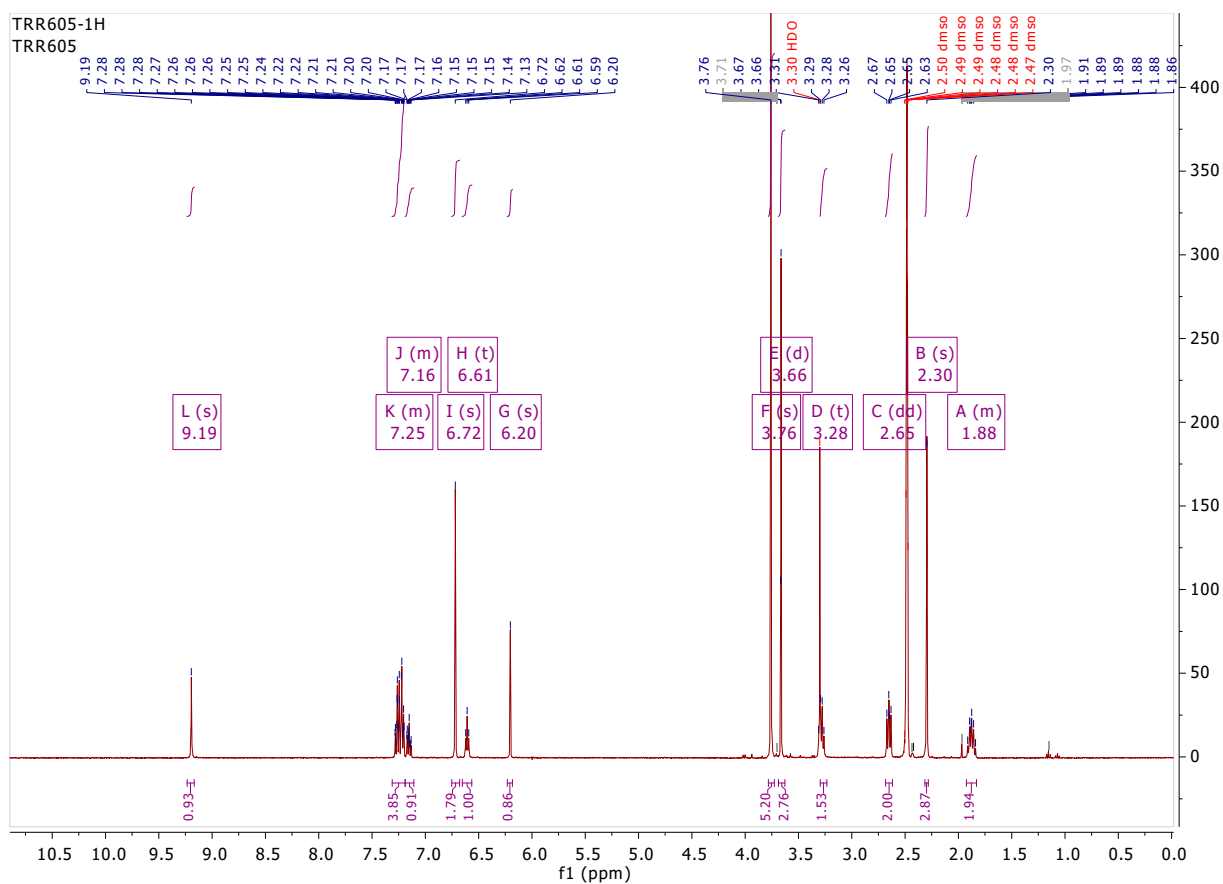
^1H -NMR and ^{13}C -NMR spectra of compound **7aa**



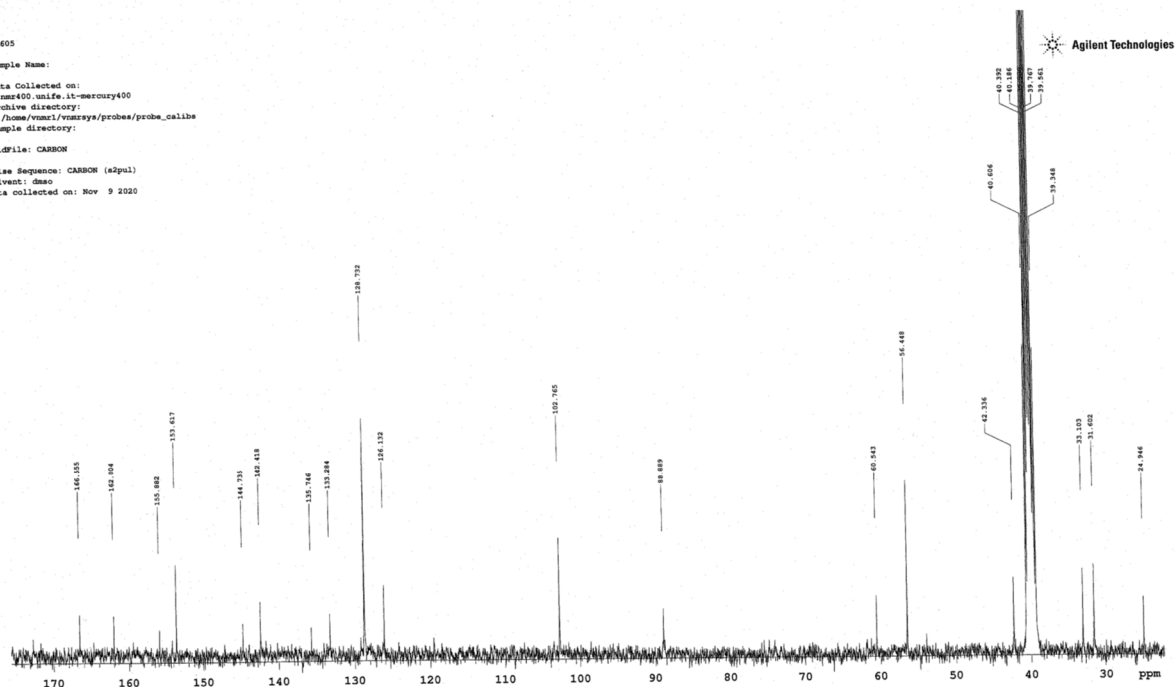
^1H -NMR and ^{13}C -NMR spectra of compound **7ab**



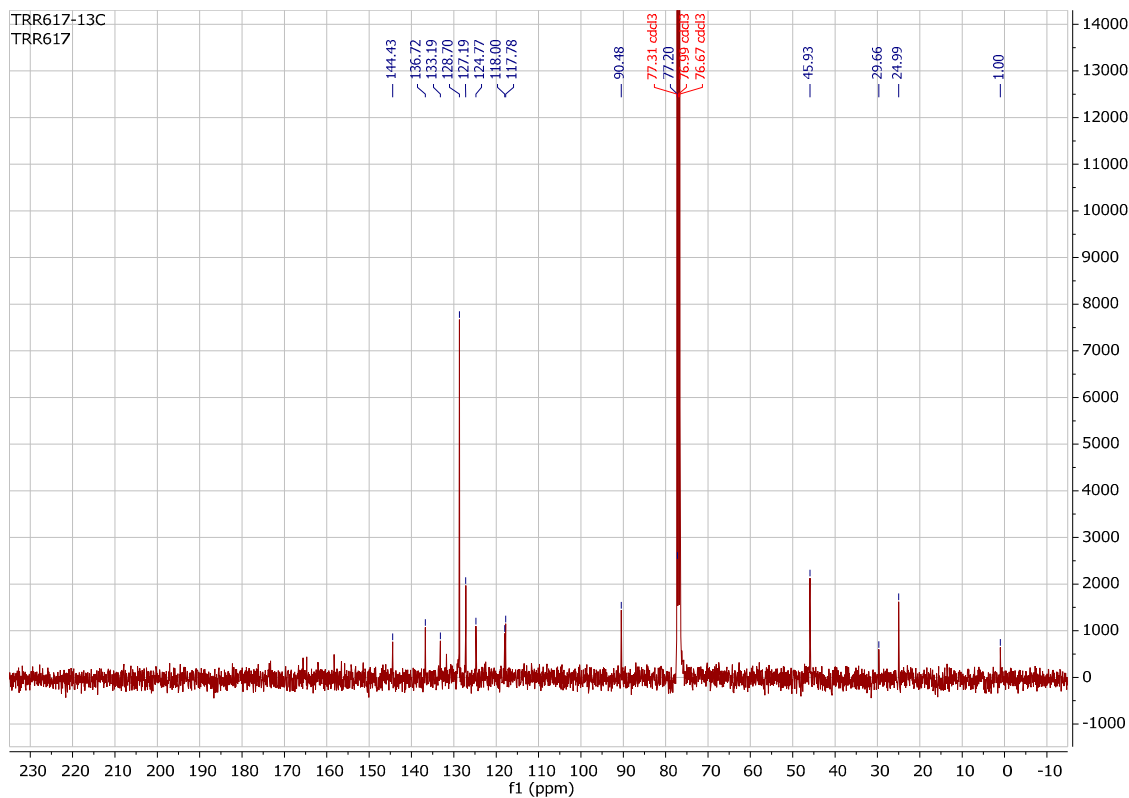
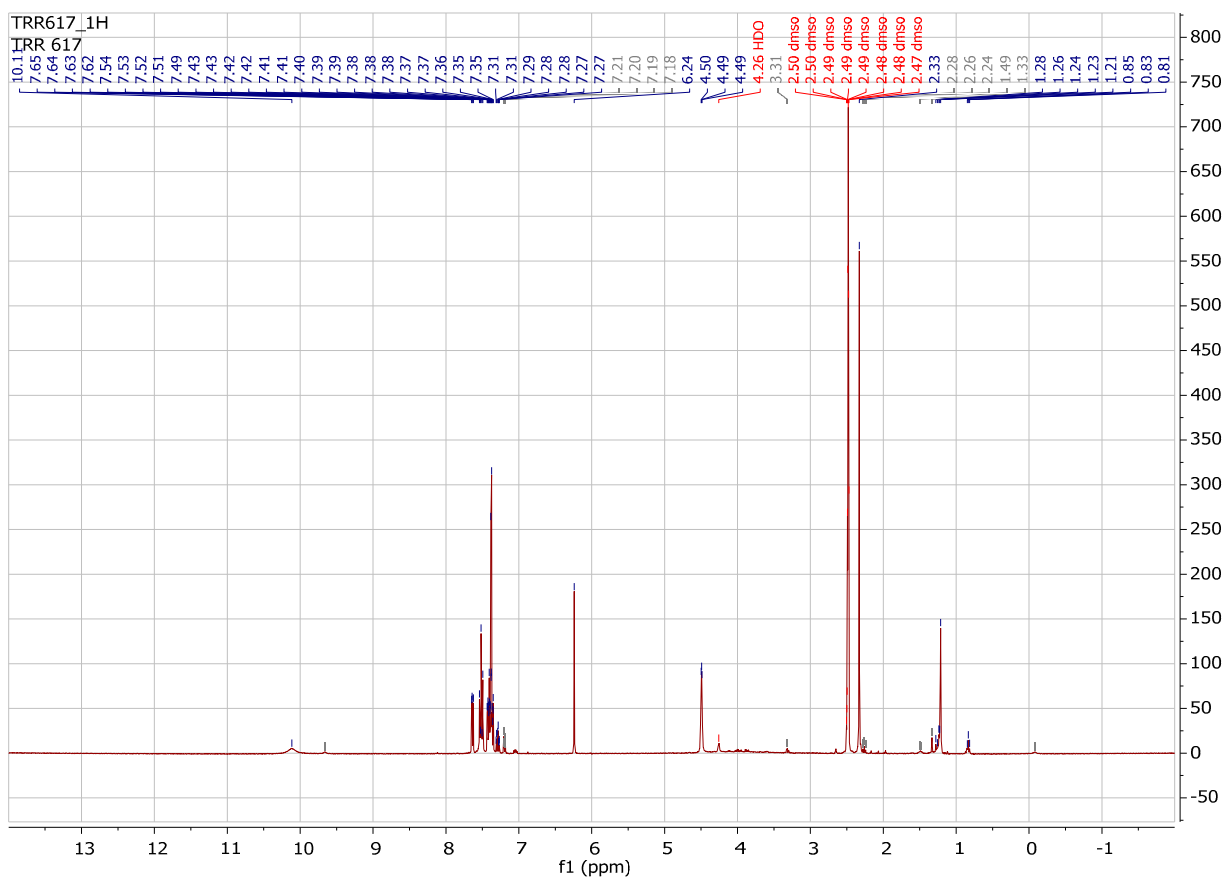
^1H -NMR and ^{13}C -NMR spectra of compound **7ac**



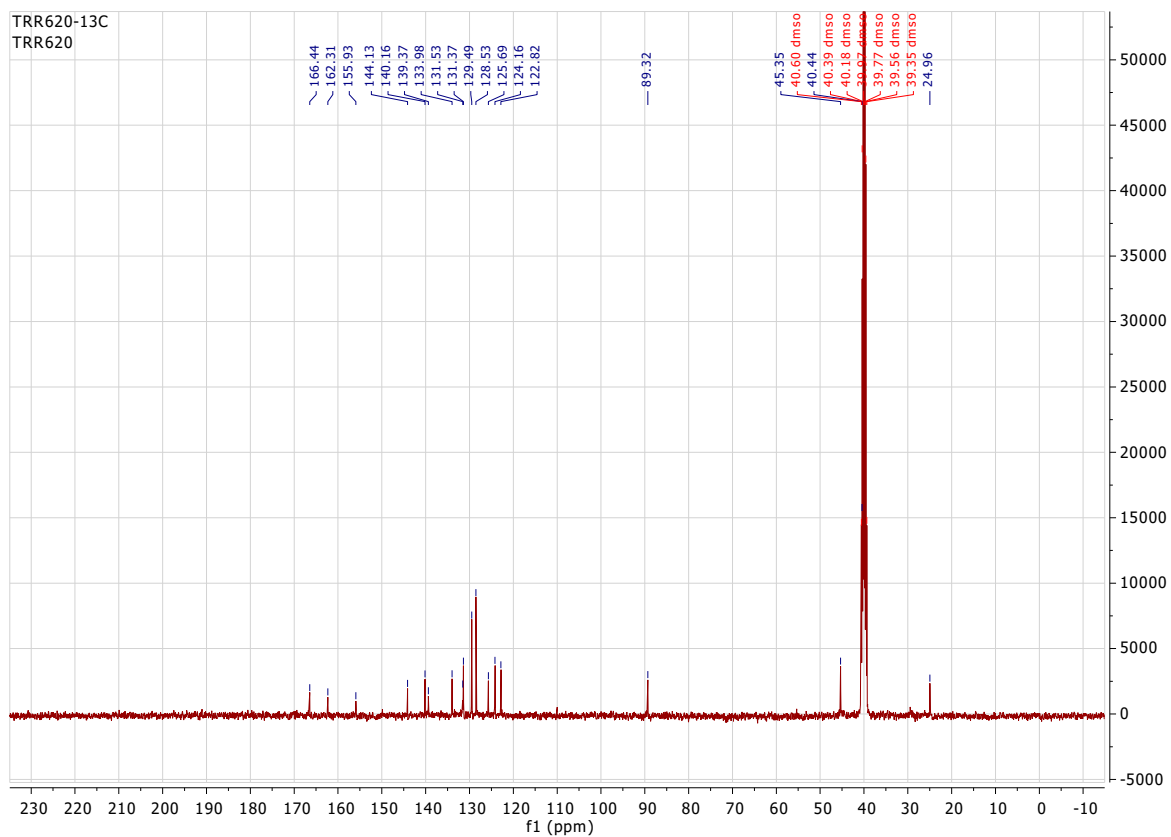
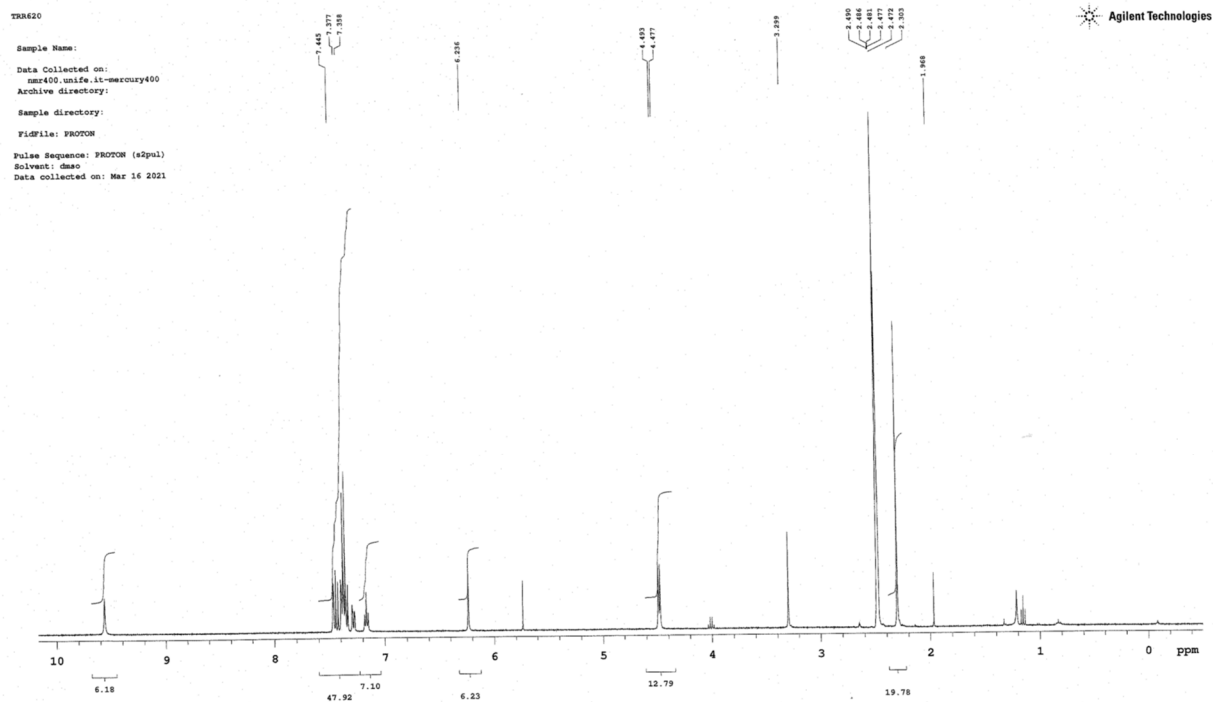
TRR605
Sample Name:
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Archive directory:
/home/ruvif/vmrays/probes/probe_calibe
Sample directory:
File: CARBON
Pulse Sequence: CARBON (a2p2)
Solvent: dms
Data collected on: Nov 9 2020



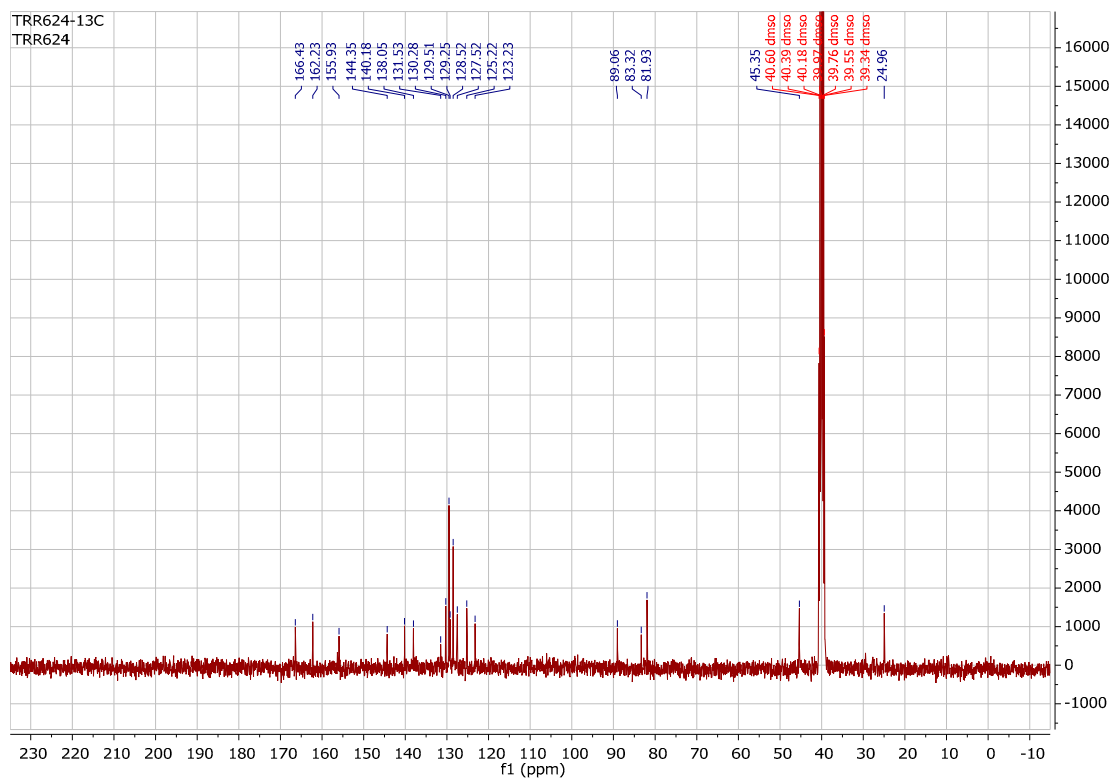
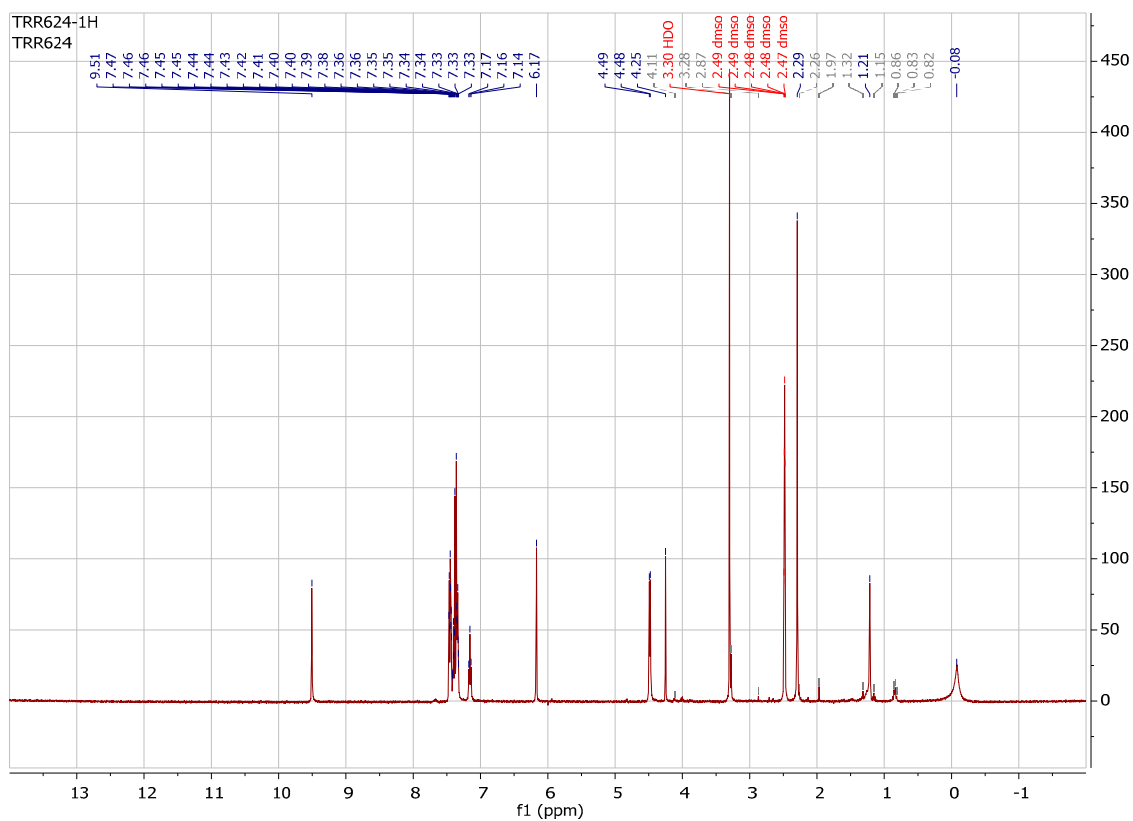
¹H-NMR and ¹³C-NMR spectra of compound **7ad**



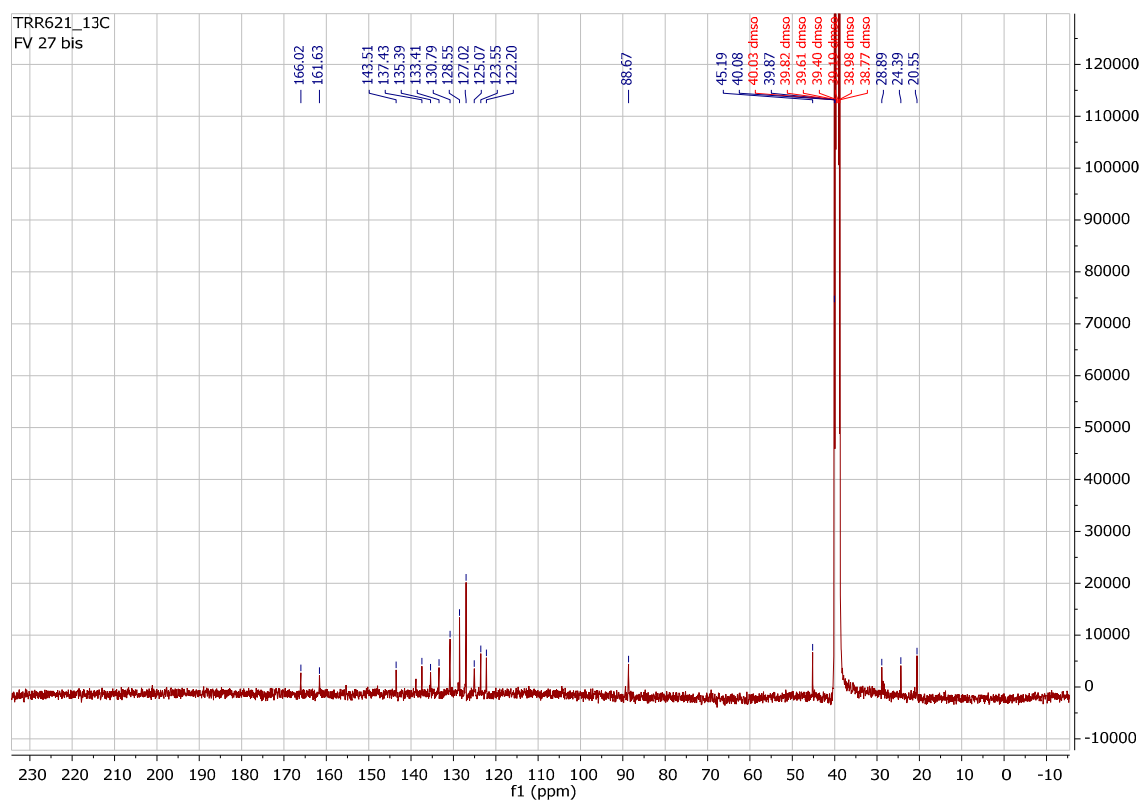
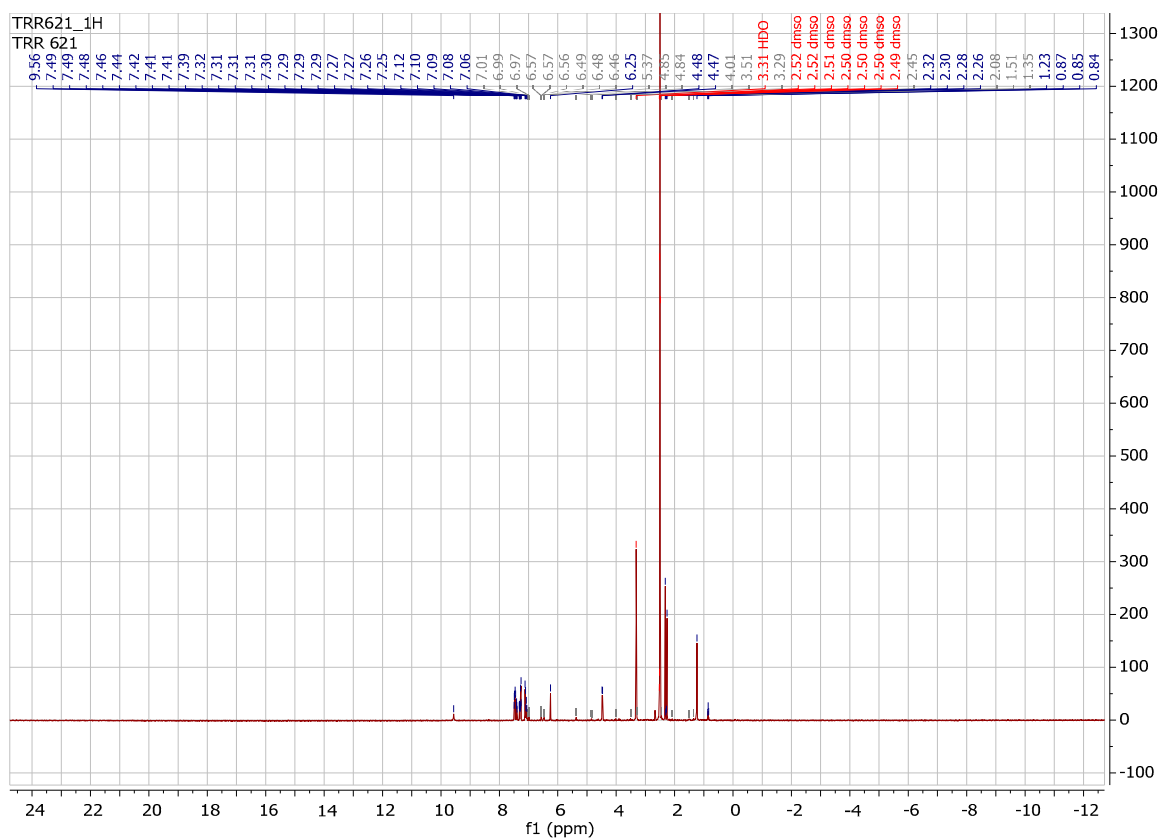
^1H -NMR and ^{13}C -NMR spectra of compound **8a**



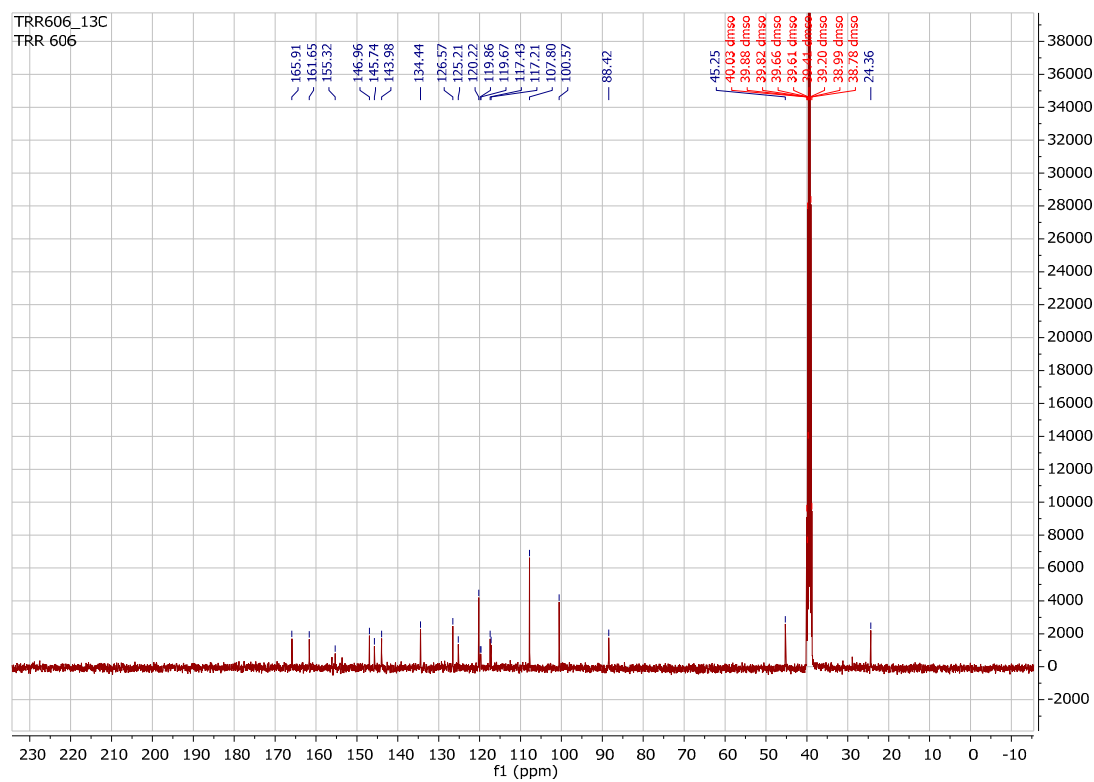
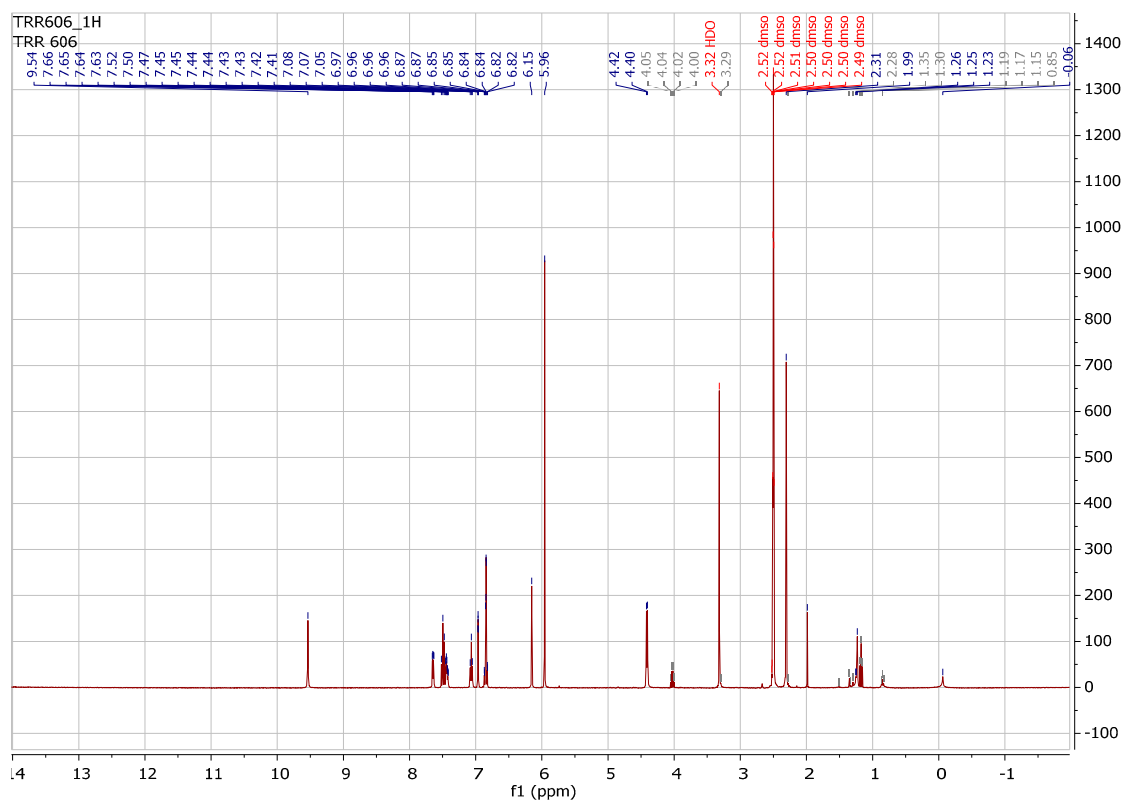
^1H -NMR and ^{13}C -NMR spectra of compound **8b**



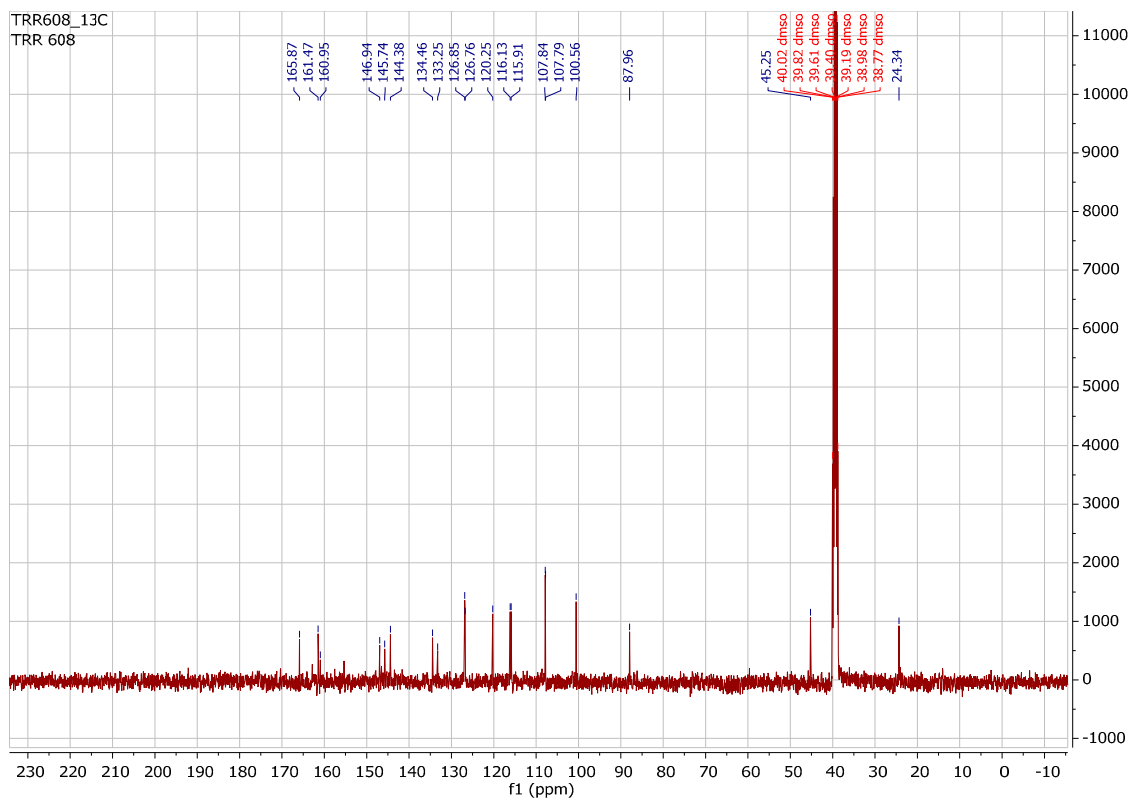
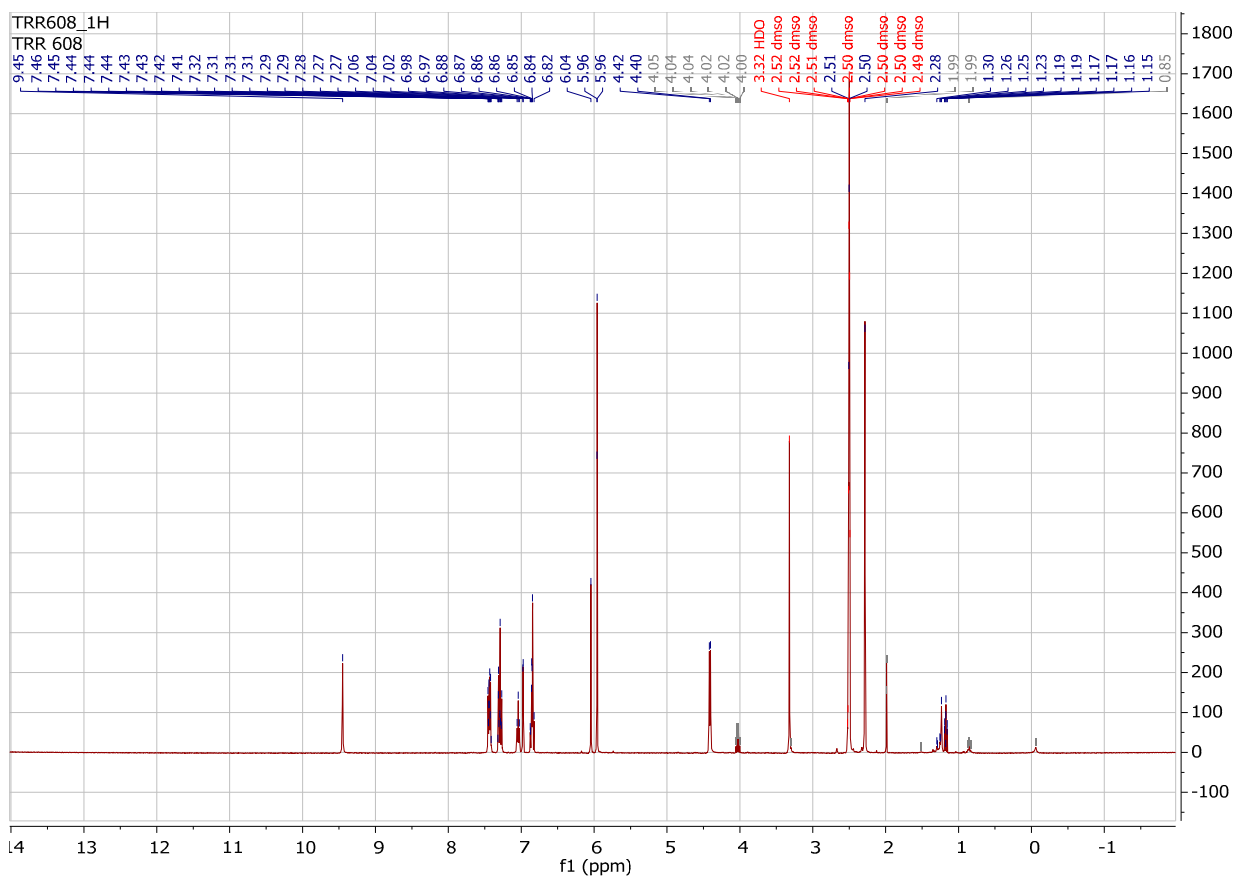
^1H -NMR and ^{13}C -NMR spectra of compound **8c**



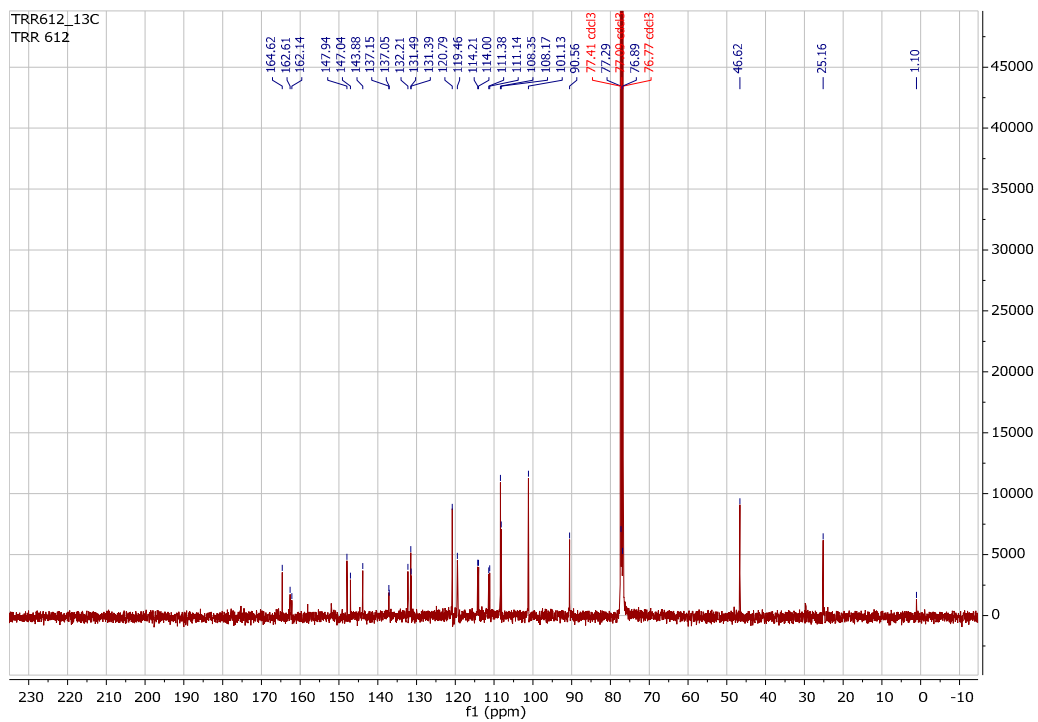
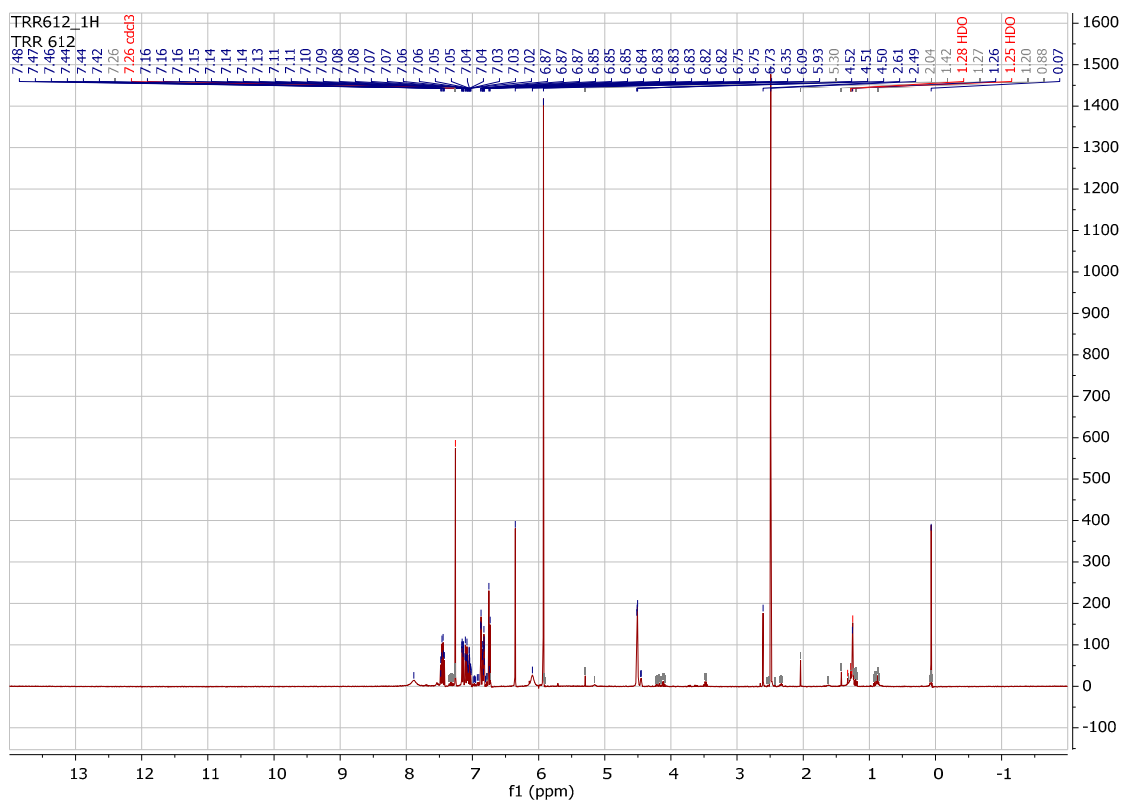
^1H -NMR and ^{13}C -NMR spectra of compound **8e**



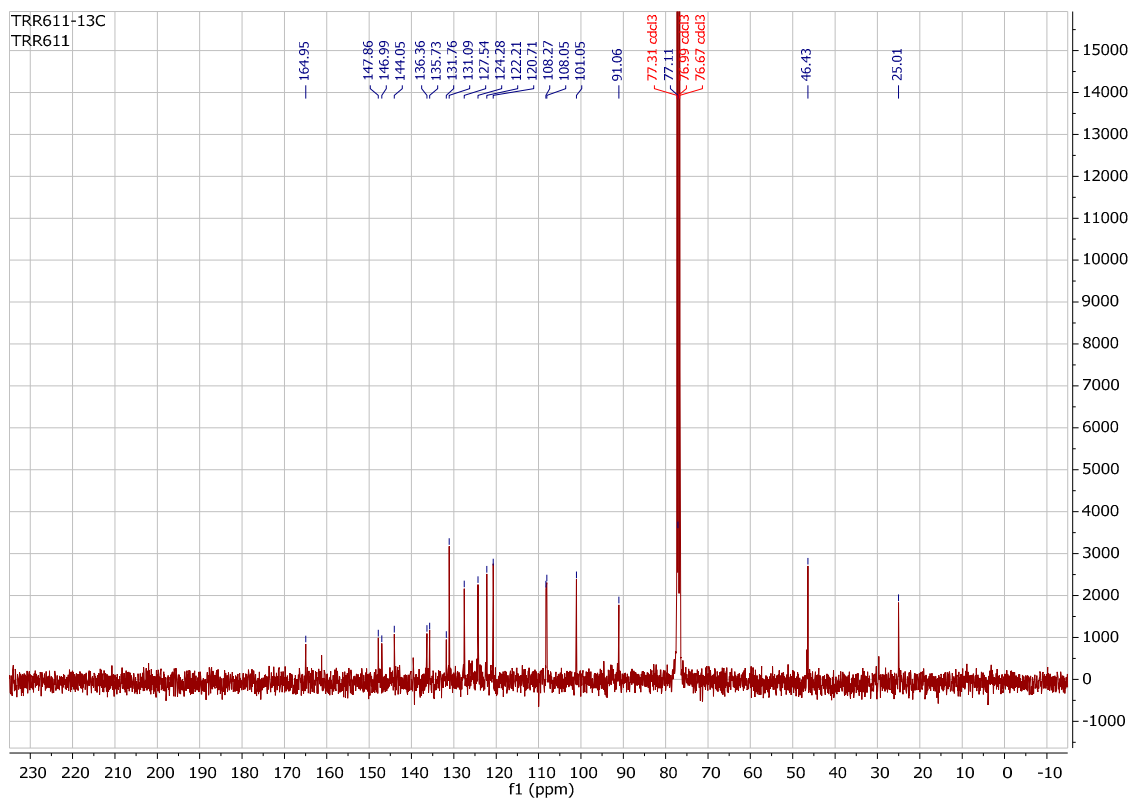
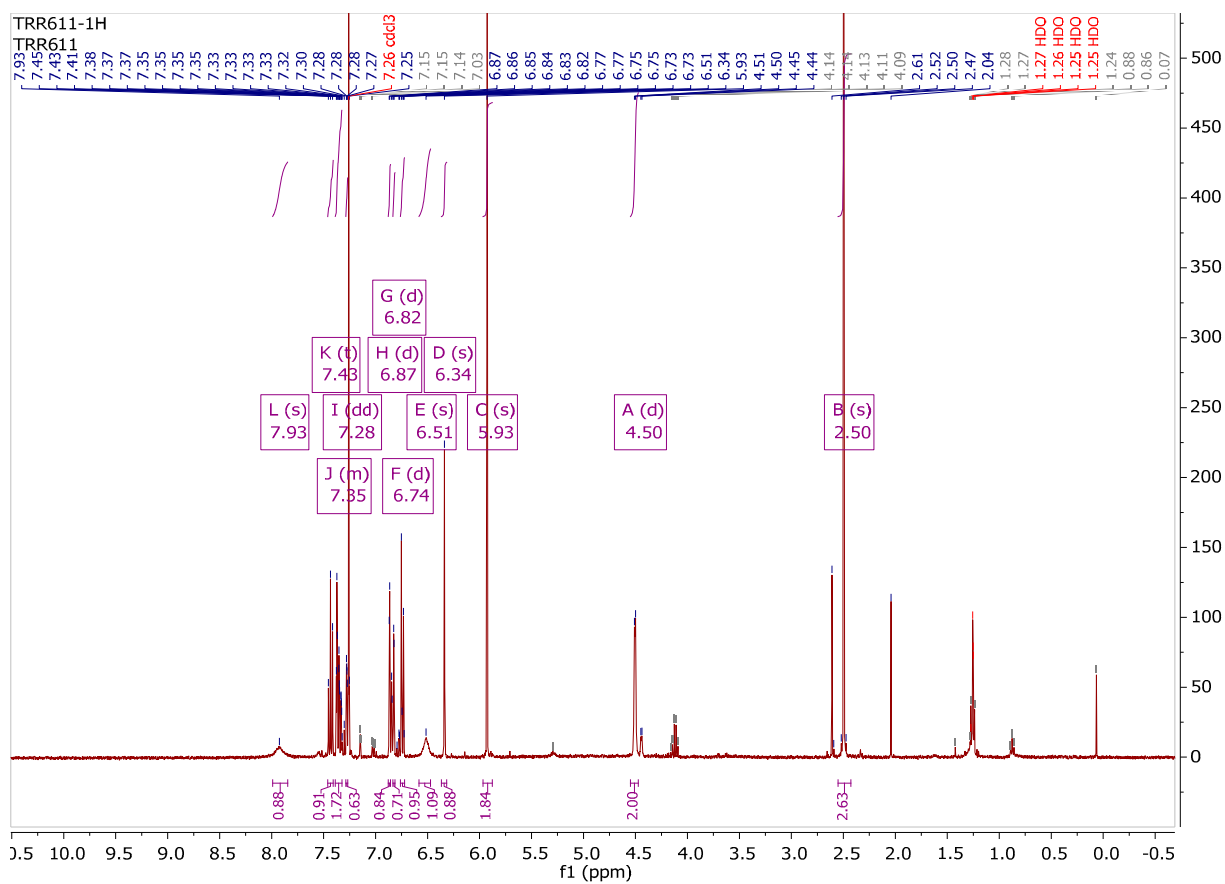
^1H -NMR and ^{13}C -NMR spectra of compound **8f**



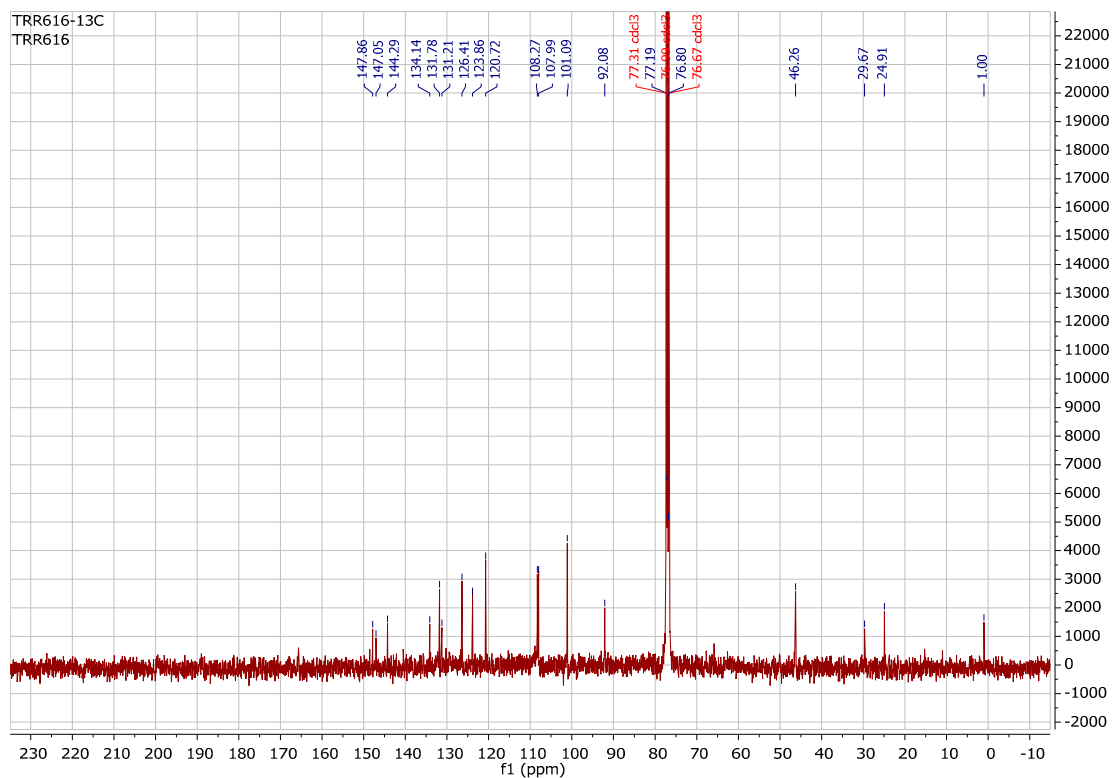
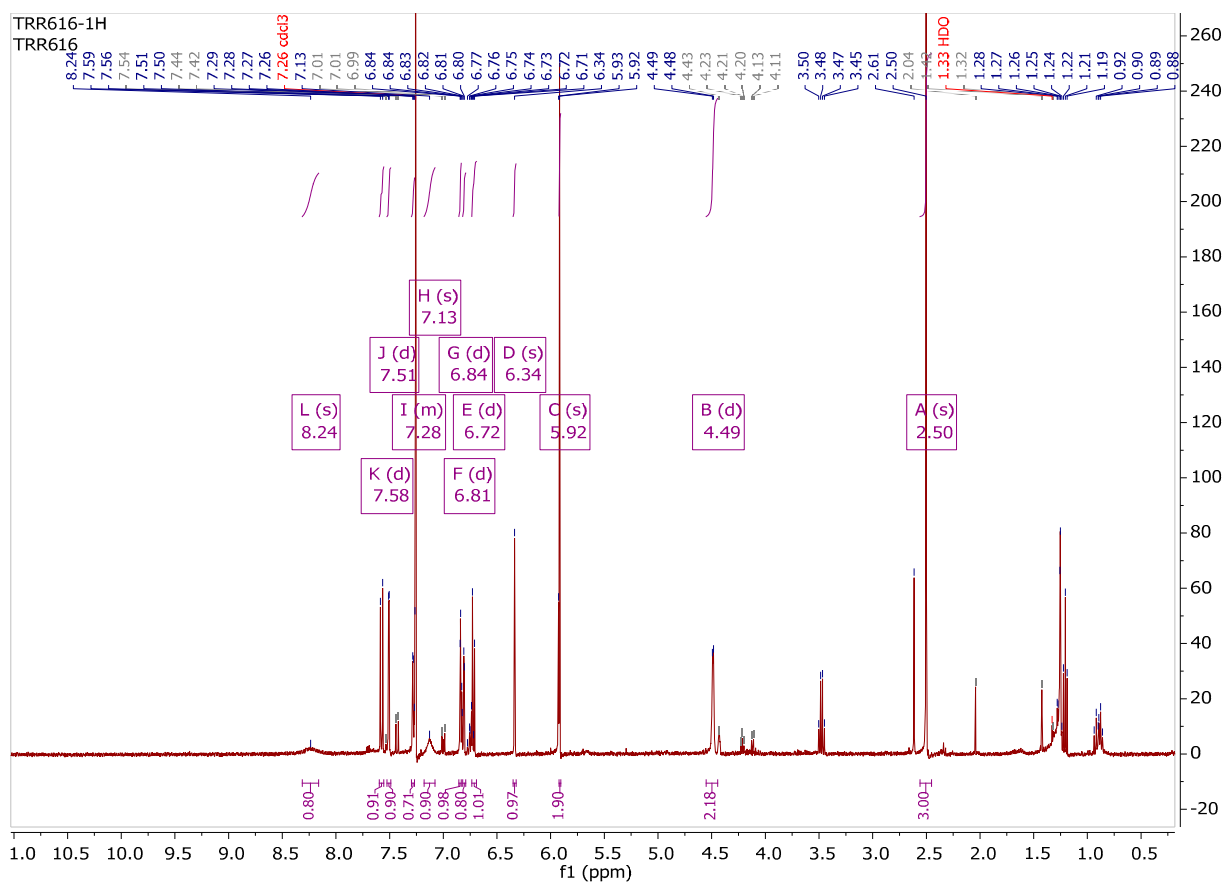
¹H-NMR and ¹³C-NMR spectra of compound **8g**



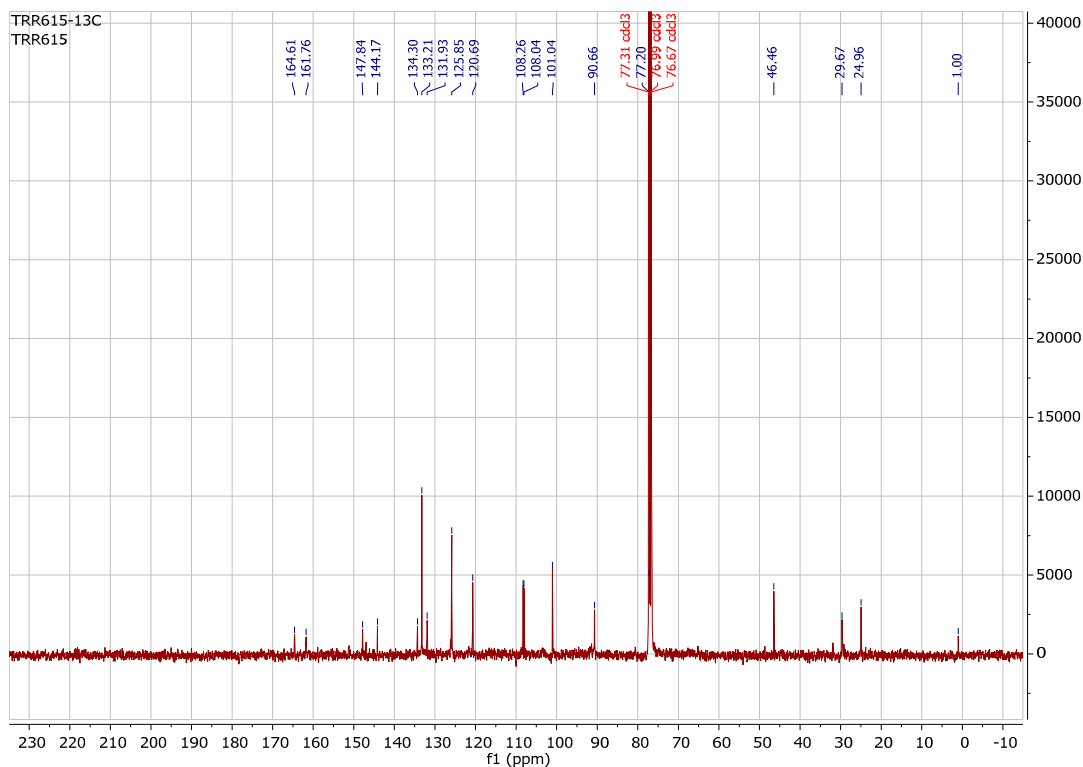
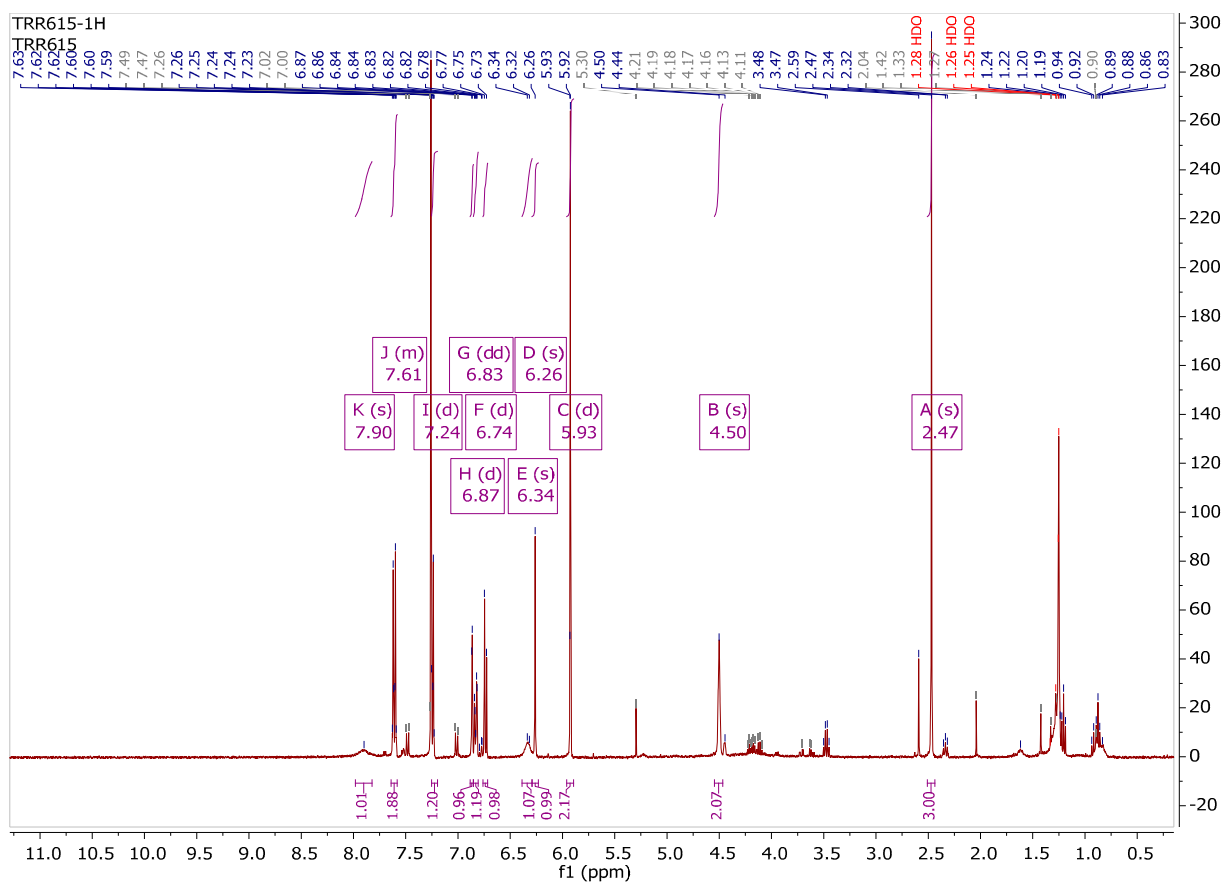
^1H -NMR and ^{13}C -NMR spectra of compound **8h**



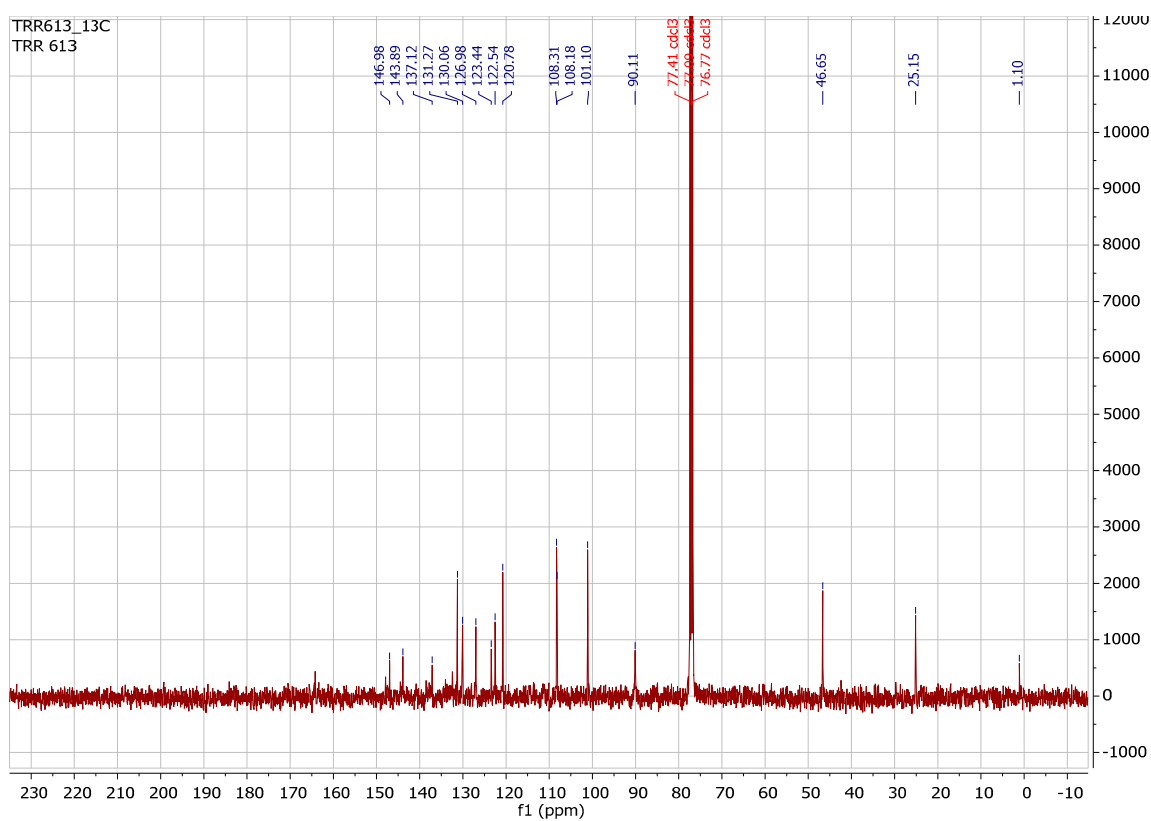
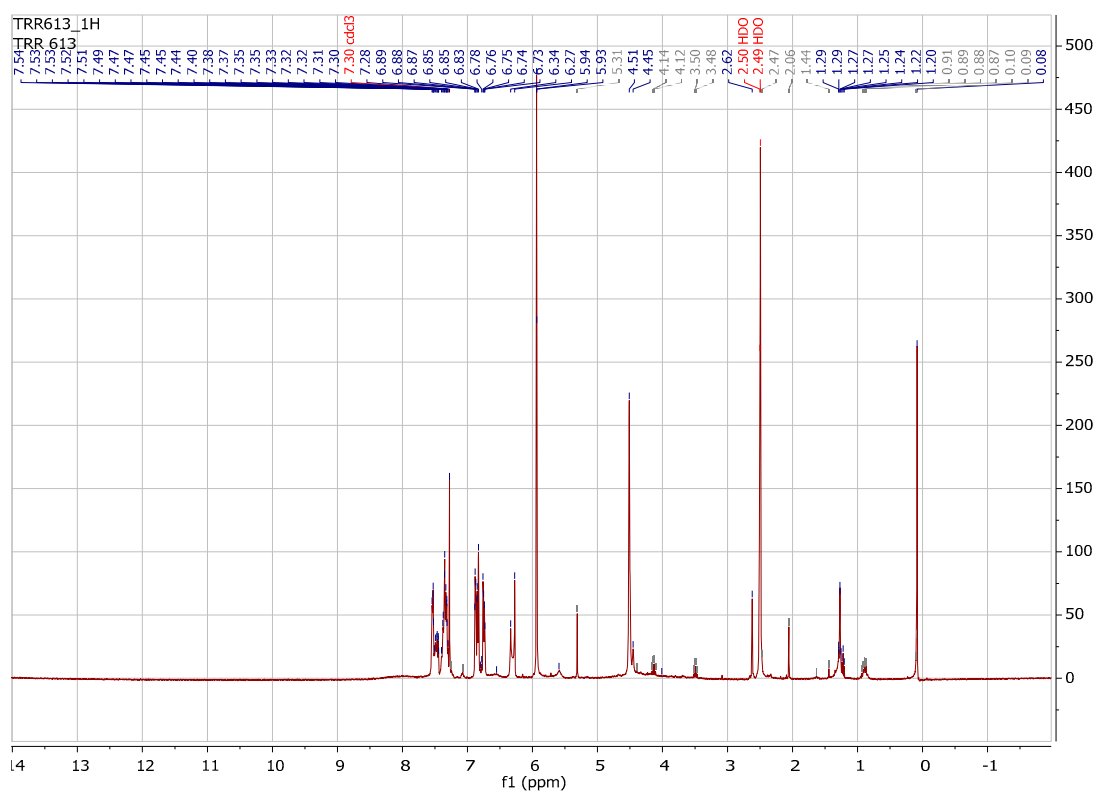
^1H -NMR and ^{13}C -NMR spectra of compound **8j**



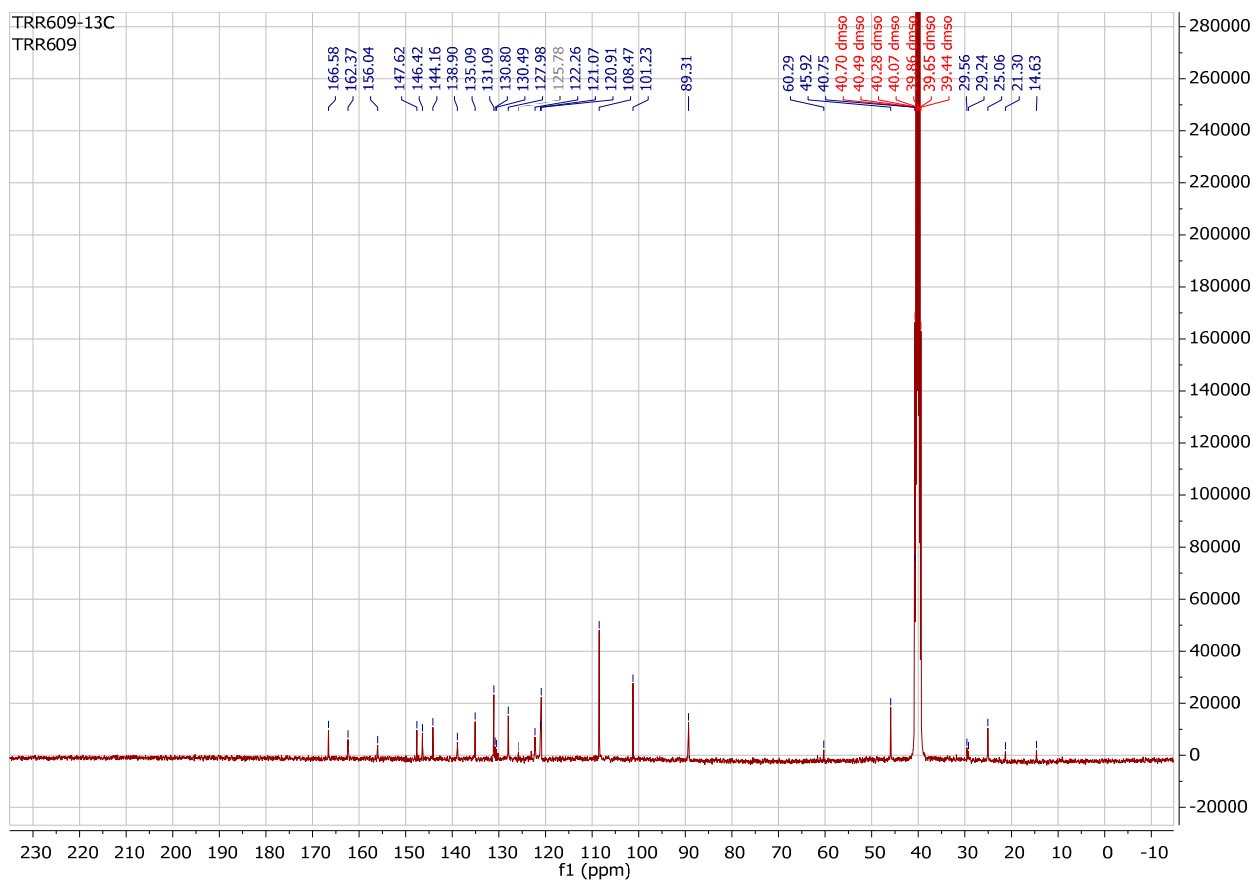
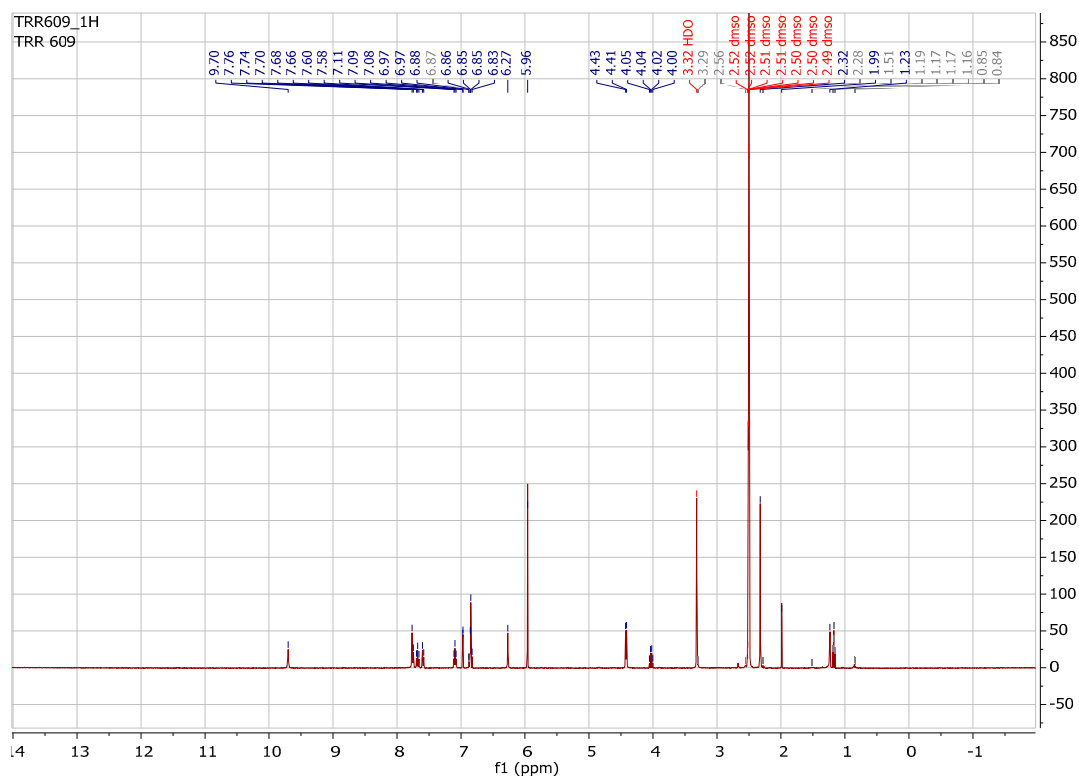
¹H-NMR and ¹³C-NMR spectra of compound **8k**



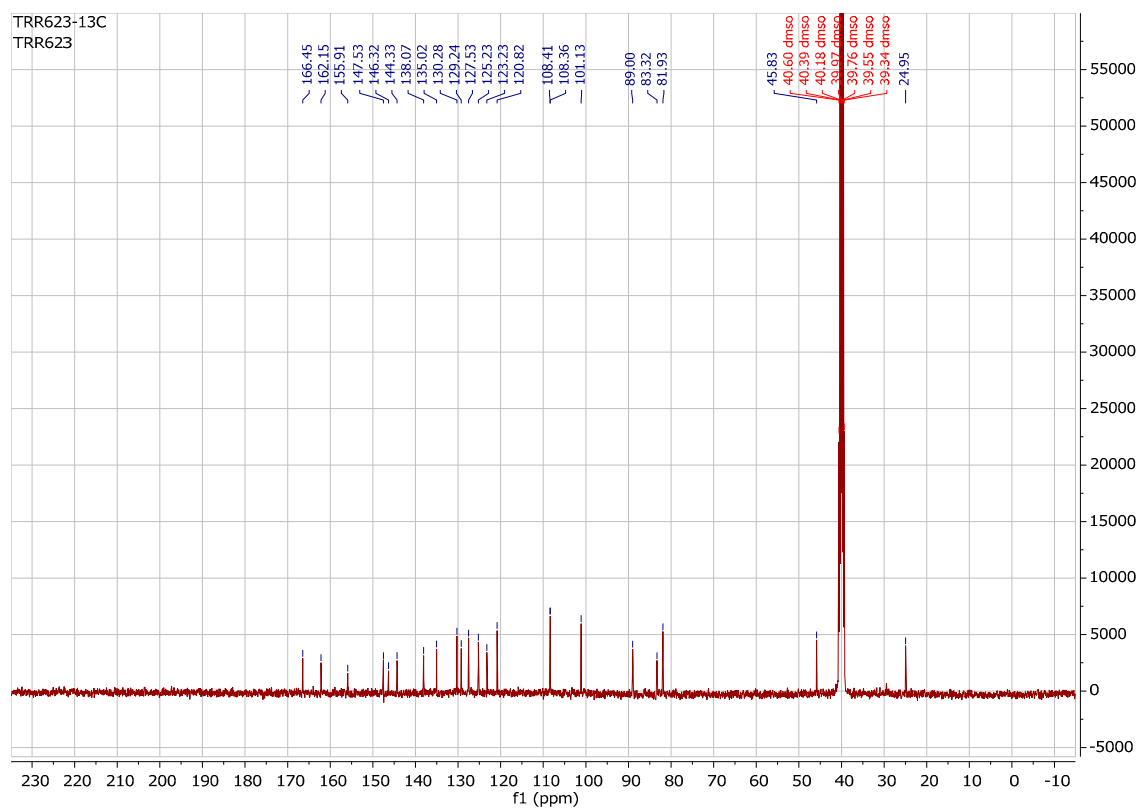
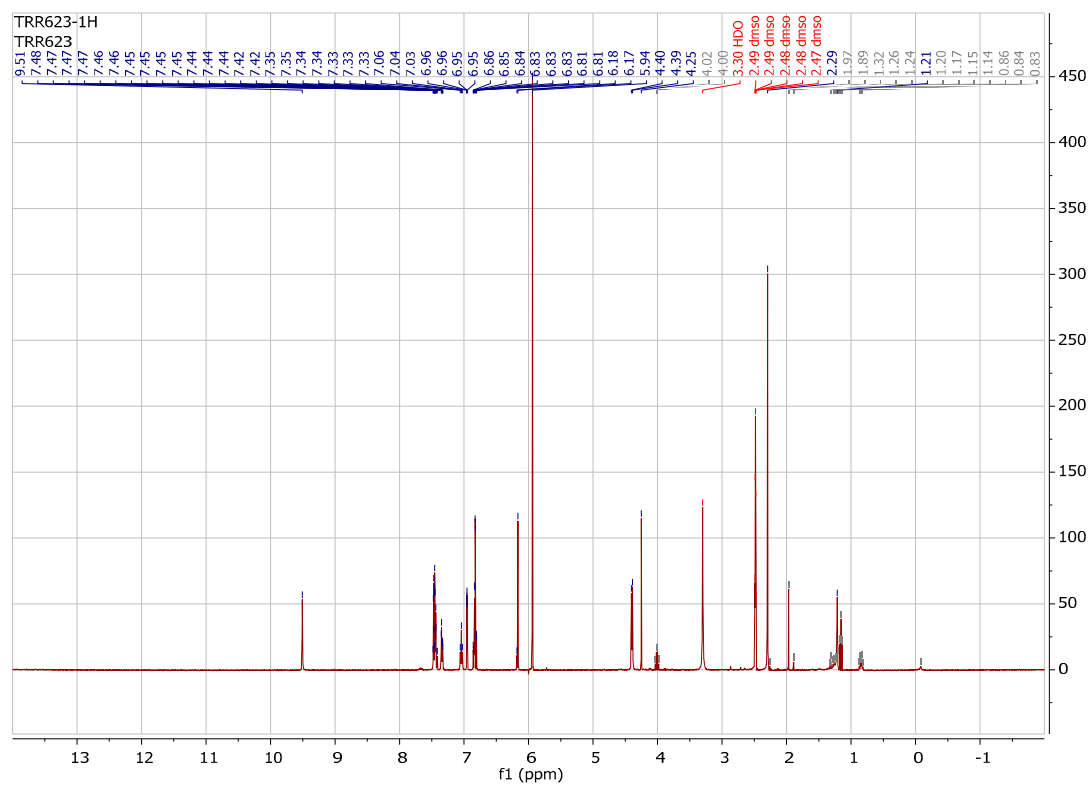
^1H -NMR and ^{13}C -NMR spectra of compound **81**



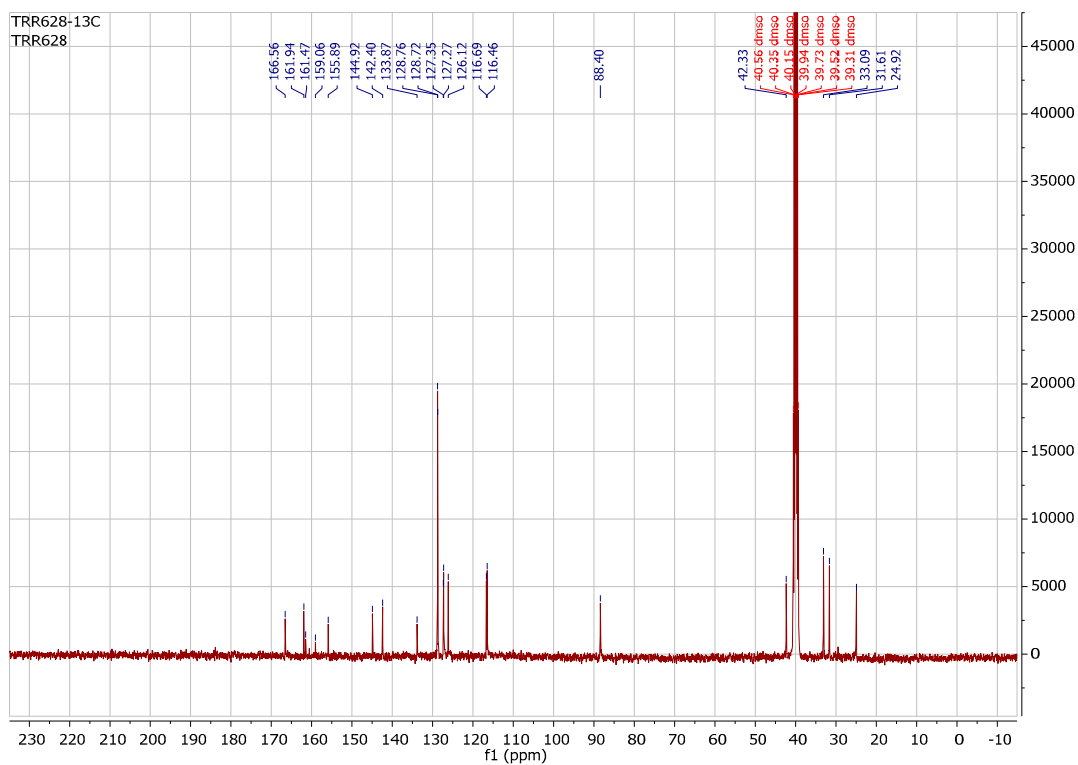
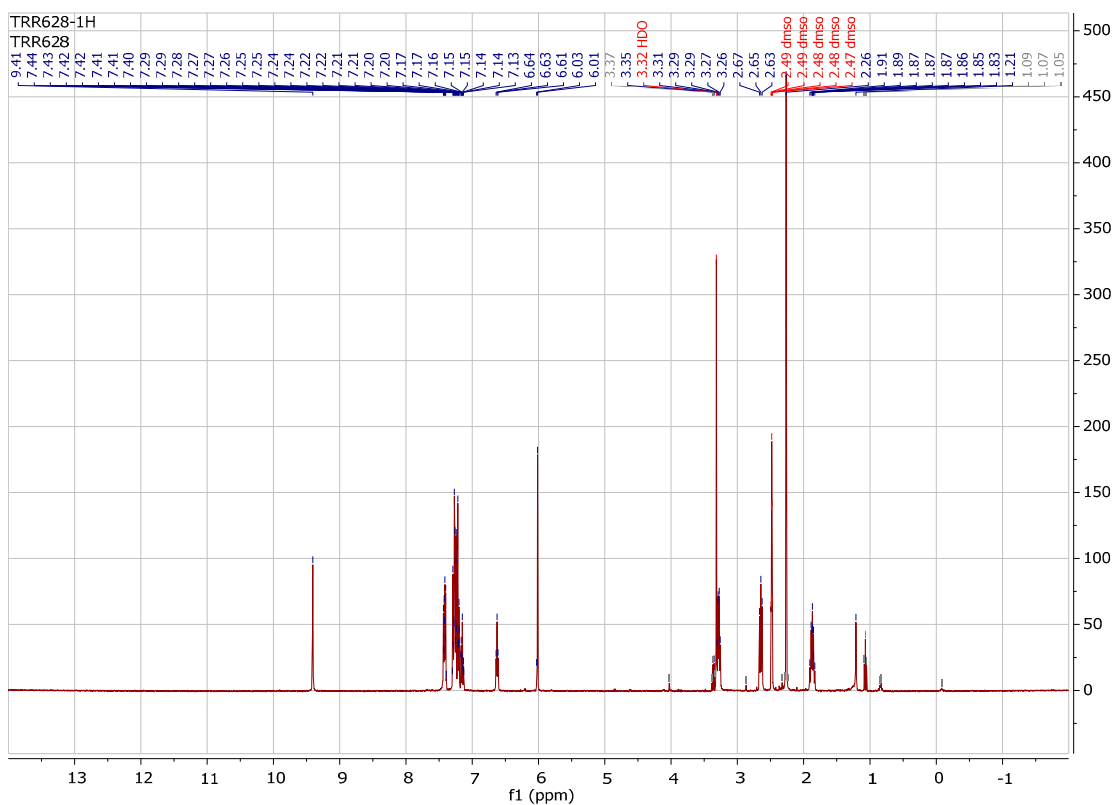
^1H -NMR and ^{13}C -NMR spectra of compound **8m**



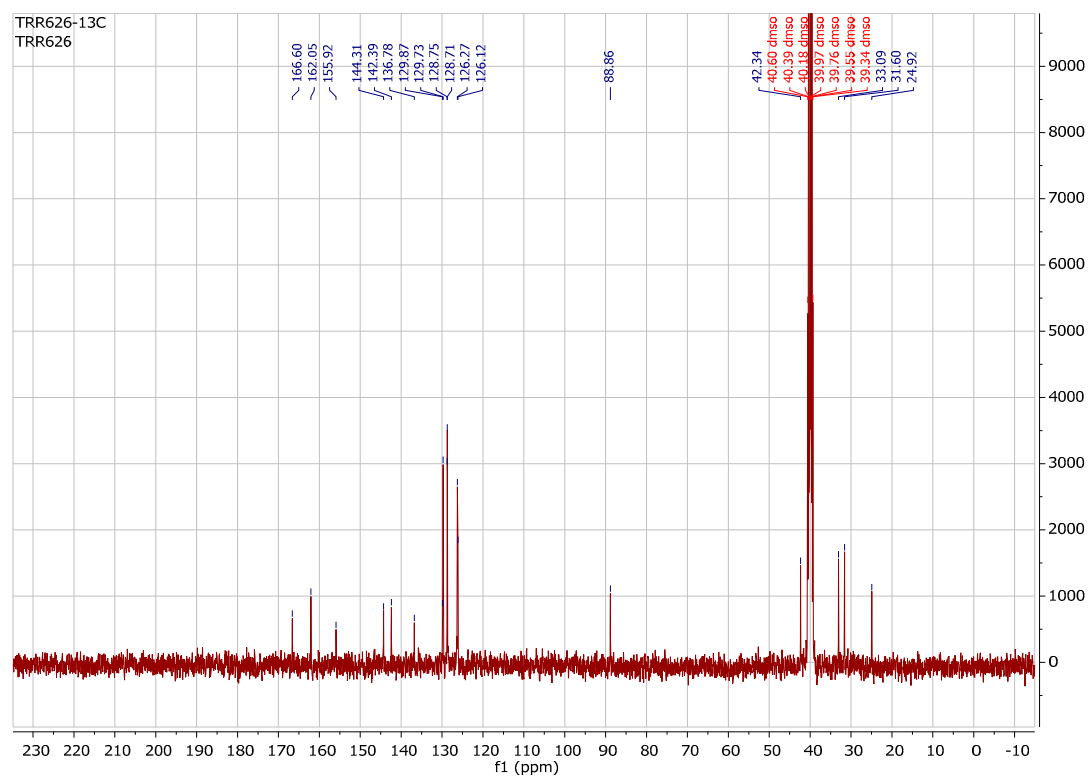
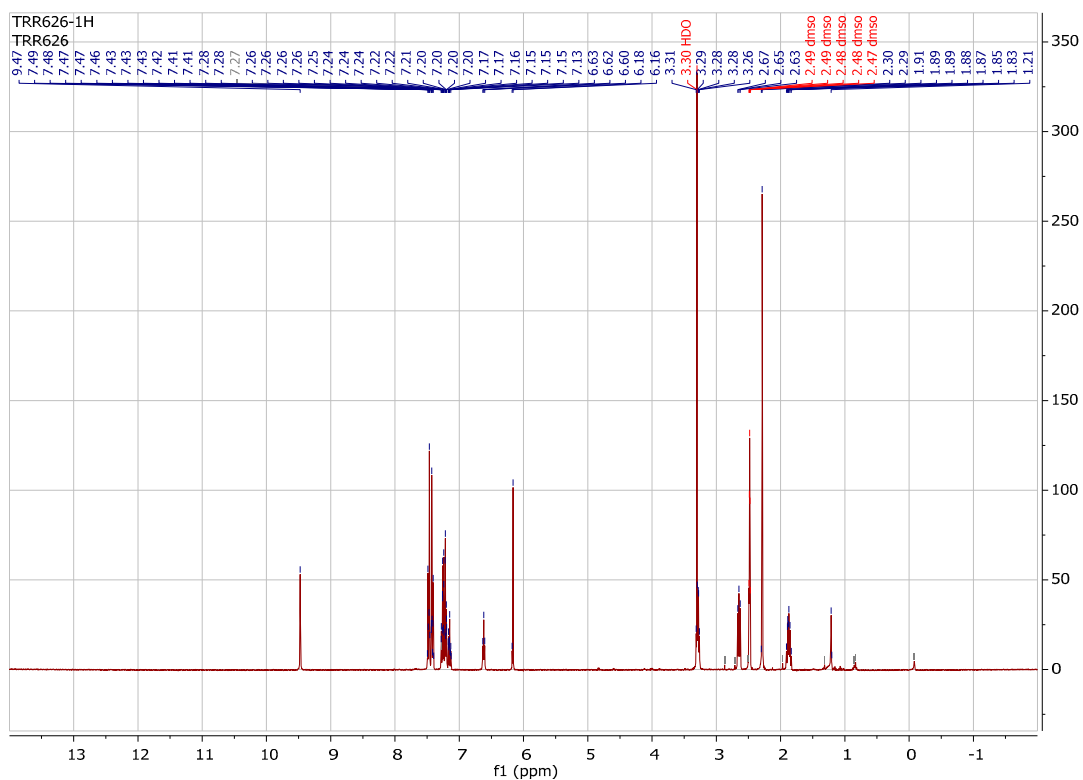
¹H-NMR and ¹³C-NMR spectra of compound **80**



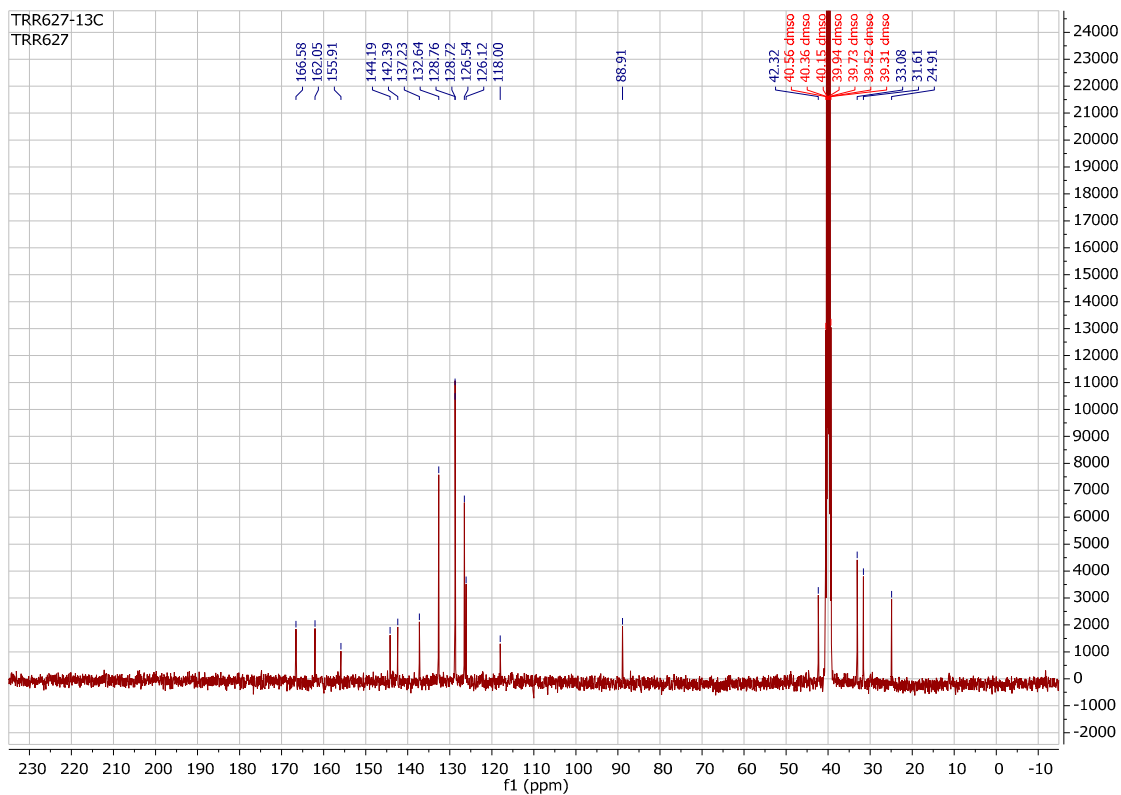
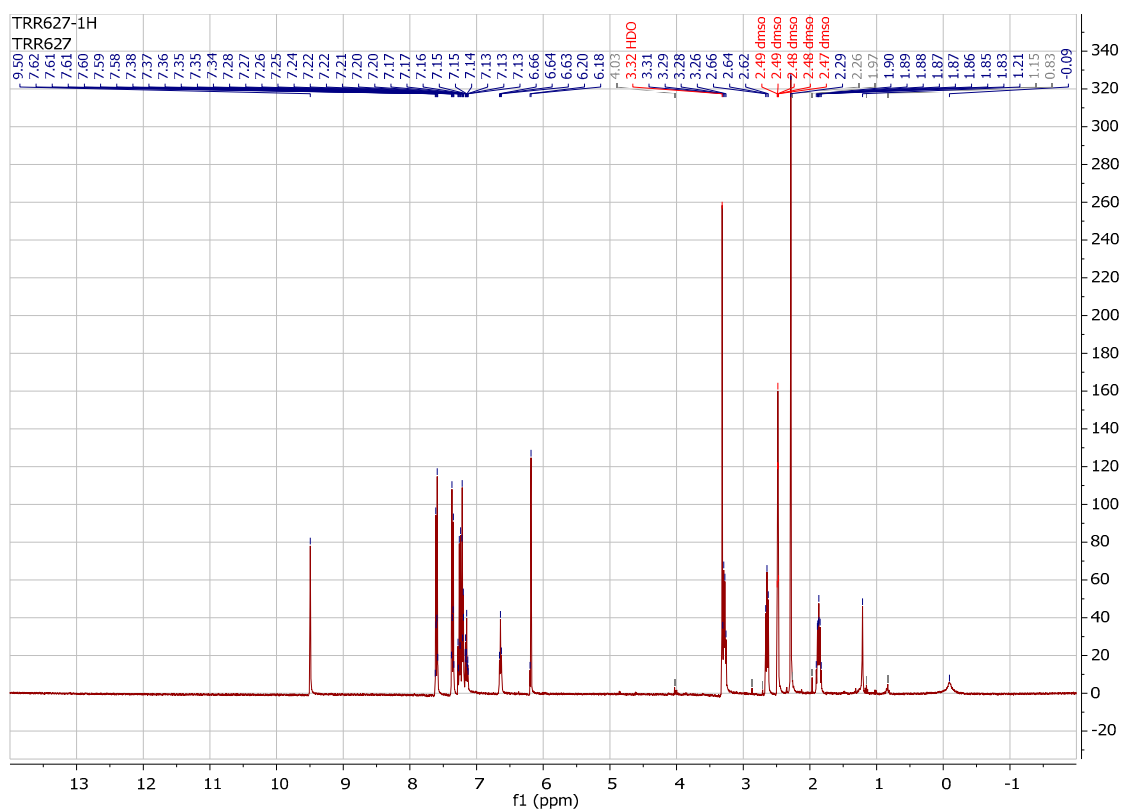
^1H -NMR and ^{13}C -NMR spectra of compound **8p**



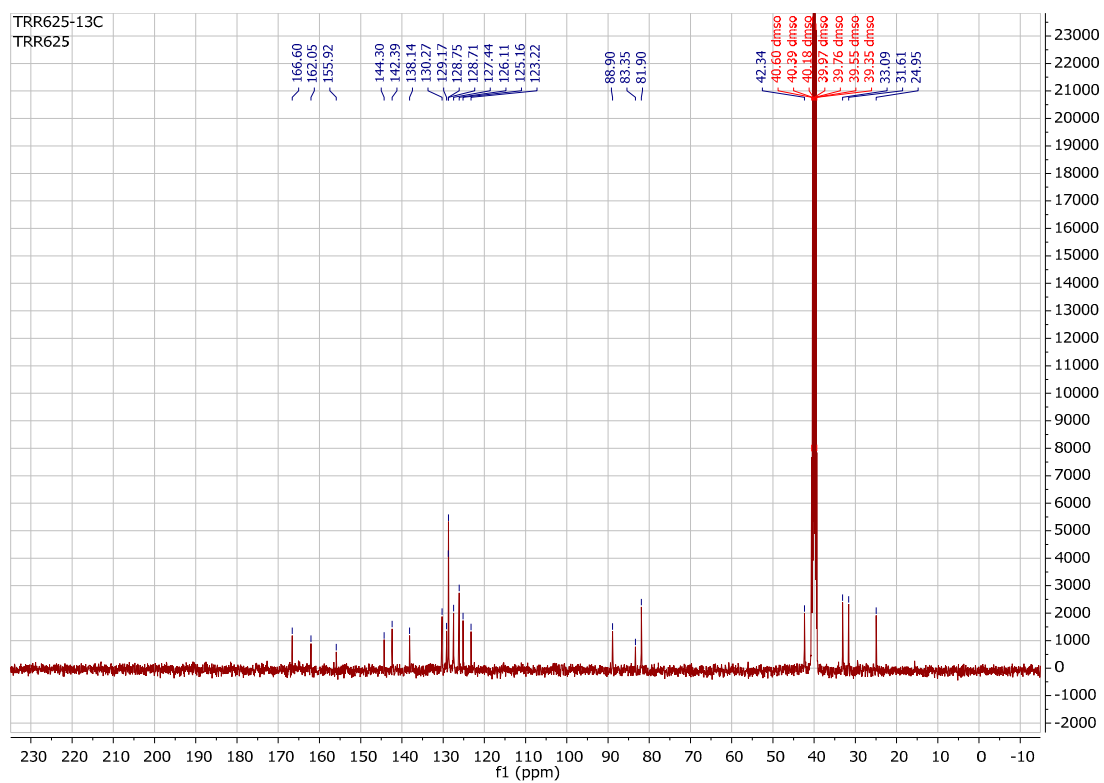
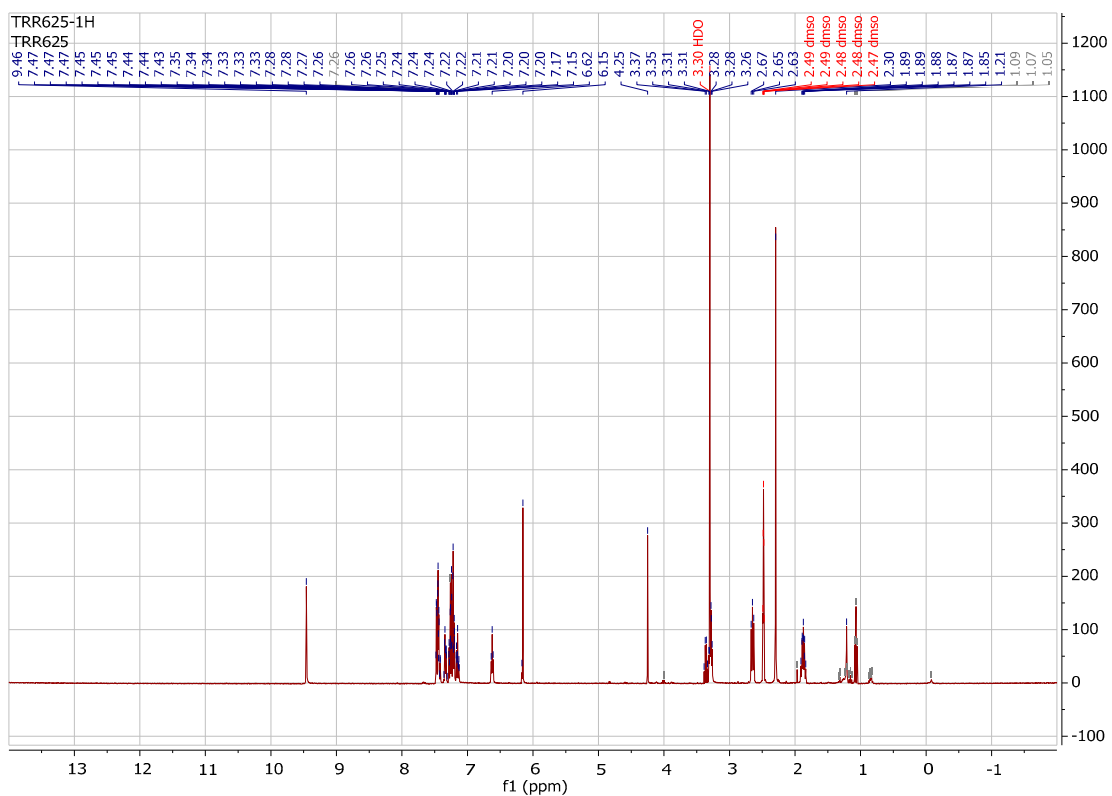
^1H -NMR and ^{13}C -NMR spectra of compound **8q**



^1H -NMR and ^{13}C -NMR spectra of compound **8s**



^1H -NMR and ^{13}C -NMR spectra of compound **8u**



^1H -NMR and ^{13}C -NMR spectra of compound **8v**