10.1071/CH24006
Australian Journal of Chemistry

Supplementary Material

Liquid-assisted grinding (LAG) approach, metal-free synthesis of 2,3- dihydro-1,5-benzothiazepines and their electrochemical properties

Manjit Singh[A], *Kuldeep Kumar Maurya*[A] and *Manisha Malviya*[A,*]

[A]Department of Chemistry, Indian Institute of Technology (IIT) at Banaras Hindu University (BHU), Varanasi, India

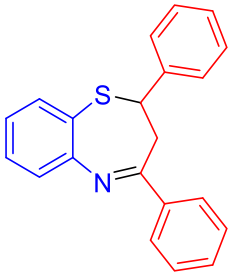
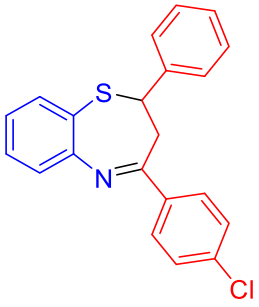
*Correspondence to: Email: manisha.apc@itbhu.ac.in

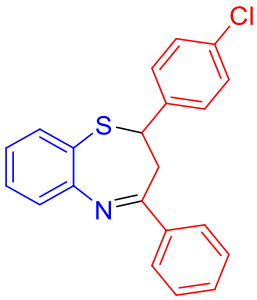
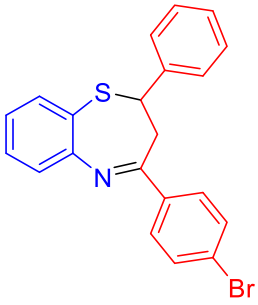
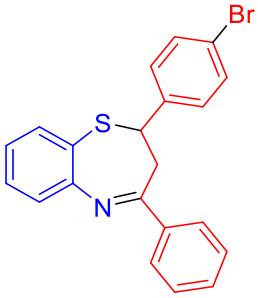
General information

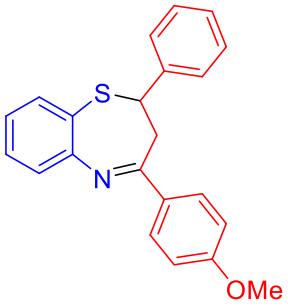
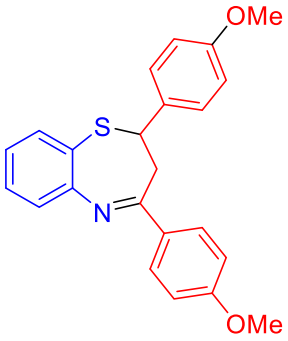
All the starting chemicals, chalcone, and ortho-amino thiophenol, were bought from Sigma–Aldrich and Merck Chemical and directly used as a reactant without purification. First, we synthesised **2,3-dihydro-1,5-benzothiazepine** (2a, 1 mmol) in the presence of a few drops of ethanol (5–6 drops or 0.3 mL) (3.5 mmol).

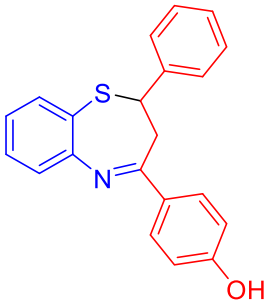
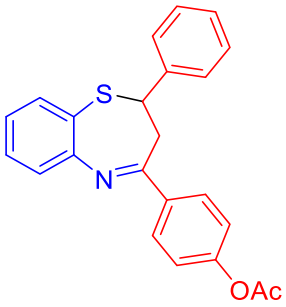
All the reactants were taken in the mortar and ground by pestle in the presence of ethanol. The progress of the reaction was monitored using (ethyl acetate: hexane) by thin-layer chromatography. The melting point was determined by the open glass capillary method is uncorrected. IR spectra in KBr were recorded on Perkin–Elmer 993 spectrophotometers. The structure of the synthesised compounds was determined by ^{1}H and ^{13}C NMR spectra recorded through Bruker 500-MHz spectrometer in DMSO-d6, $CDCl_3$ using TMS as reference. The chemical shift was indicated in δ ppm. Perkin–Elmer Micro analyser was used for elemental analysis (C, H, and N).

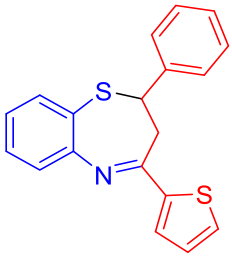
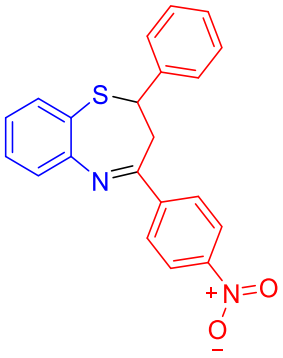
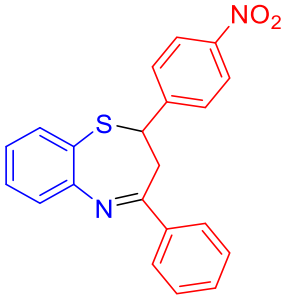
Table S1. Spectral data of desired products.

Scheme number	Compound	Supplementary data
1.		**2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine 1(a)**[1] Yellow solid; M.P. **115–117°C**. ^{1}H NMR (500 MHz, $CDCl_3$): 3.64 (dd, J = 4.5, 12.0 Hz, 1 H), 3.82 (dd, J = 4.7, 13.1 Hz, 1 H), 4.66 (t, J = 12.6 Hz, 1 H), 6.88 (m, 1 H), 7.25–7.04 (m, 5 H), 7.52 (m, 4 H), 7.63 (d, J = 6.1 Hz, 2 H), 7.95 (d, J = 7.5 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 43.46 (C), 46.62 (CH2), 128.52 (C), 128.71 (CH), 128.85 (CH), 128.07 (CH), 126.89 (CH), 128.52 (CH), 128.85 (CH), 129.00 (CH), 137.64 (CH), 148.64 (C), 149.44 (C), 166.82 (C). IR (KBr): 1598, 1690, 3000 cm^{-1}. **Isolated yield: 339 mg, 94%**.
2.		**2-(phenyl)-4(-4-Chlorophenyl)-2,3-dihydro-1,5-benzothiazepine 2(a)**[2] M.P. **125–127°C**. ^{1}H NMR (DMSO, 500 MHz): = 4.68 (t, *J* = 12.8 Hz, 1 H), 3.81 (dd, *J* = 4.8, 12.8 Hz, 1 H), 3.71 (dd, *J* = 4.8, 12.8 Hz, 1 H), 6.42 (t, *J* = 7.4 Hz 1 H), 6.72 (m, 5 H), 6.94–7.02 (m, 3 H), 7.29–7.55 (d, *J* = 7.6 Hz, 2 H), 7.63–7.96 (d, *J* = 7.6 Hz, 2 H). ^{13}C NMR (DMSO, 126 MHz): 48.86 (C), 56.62 (CH_2), 111.3 (C), 122.52 (CH), 134.60 (CH), 113.15 (CH), 113.75 (CH), 120.39 (CH), 125.18 (CH), 126.97 (CH), 137.40 (CH), 145.65 (C), 150.05 (C), 163.90 (C). IR (KBr): 1595, 1687, 2950 cm^{-1}. **Isolated yield: 319 mg, 73%**.

Scheme number	Compound	Supplementary data
3.		**2-(4-Chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 3(a)**[2,3] White solid; M.P. **127–130°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.83 (t, J = 12.8 Hz, 1 H), 3.68 (dd, J = 4.8, 12.8 Hz, 1 H), 3.07 (dd, J = 4.8, 12.8 Hz, 1 H), 5.80 (t, J = 7.4 Hz 1 H), 7.16–7.30 (m, 5 H), 7.31–7.33 (m, 3 H), 7.42 (d, J = 7.5 Hz, 2 H), 7.45 (d, J = 7.6 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 40.46 (C), 46.81 (CH2), 48.86 (C), 50.99 (CH), 123.80 (CH), 127.31 (CH), 127.33 (CH), 128.71 (CH), 130.71 (CH), 132.33 (CH), 132.50 (CH), 137.44. (C), 139.44 (C), 163.95, IR (KBr): 1597, 1688, 2955 cm^{-1}. **Isolated yield: 319 mg, 77%**.
4.		**2-Phenyl-4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepine 4(a)**[5] Pale yellow solid; M.P. **137°C**. ^{1}H NMR (DMSO, 500 MHz): δ = 4.68 (t, J = 12.7 Hz, 1 H), 3.81 (dd, J = 4.9, 13.0 Hz, 1 H), 3.67 (dd, J = 4.8, 12.4 Hz, 1 H), 6.88 (td, J = 1.5, 7.5 Hz 1 H), 7.04–7.25 (m, 6 H), 7.52 (td, J = 1.5, 7.6 Hz 1 H), 7.63 (d, J = 8.6 Hz, 3 H), 7.95 (d, J = 8.6 Hz, 2 H). ^{13}C NMR (DMSO, 126 MHz): 40.46 (C), 60.62 (CH_2), 111.60 (C), 126.62 (CH), 113.157 (CH), 113.75 (CH), 120.39 (CH), 125.19 (CH), 126.97 (CH), 137.40 (CH), 145.6 (CH), 149.05 (C), 149.09 (C), 150.90 (C), IR (KBr): 1599, 1686, 2953 cm^{-1}. **Isolated yield: 319 mg, 73%**.
5.		**2-(4-Bromophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 5(a)**[5] Pale yellow solid; M.P. **120–122°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.84 (t, J = 12.8 Hz, 1 H), 3.26 (dd, J = 4.8, 12.9 Hz, 1 H), 3.86 (dd, J = 4.8, 12.5 Hz, 1 H), 7.14–7.20 (m, 3 H), 7.33 (dd, J = 1.2, 7.9 Hz, 1 H), 7.42–7.46 (m, 6 H), 7.62 (dd, J = 1.3, 7.7 Hz, 1 H), 8.00 (d, J = 8.1 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 38.46 (C), 69.62 (CH2), 124.35 (C), 125.62 (CH), 127.07 (CH), 128.07 (CH), 128.89 (CH), 131.35 (CH), 130.98 (CH), 132.11 (CH), 133.61 (CH), 141.63 (C), 148.99 (C), 159.90 (C), IR (KBr): 1596, 1684, 2958 cm^{-1}. **Isolated yield: 321 mg, 76%**.

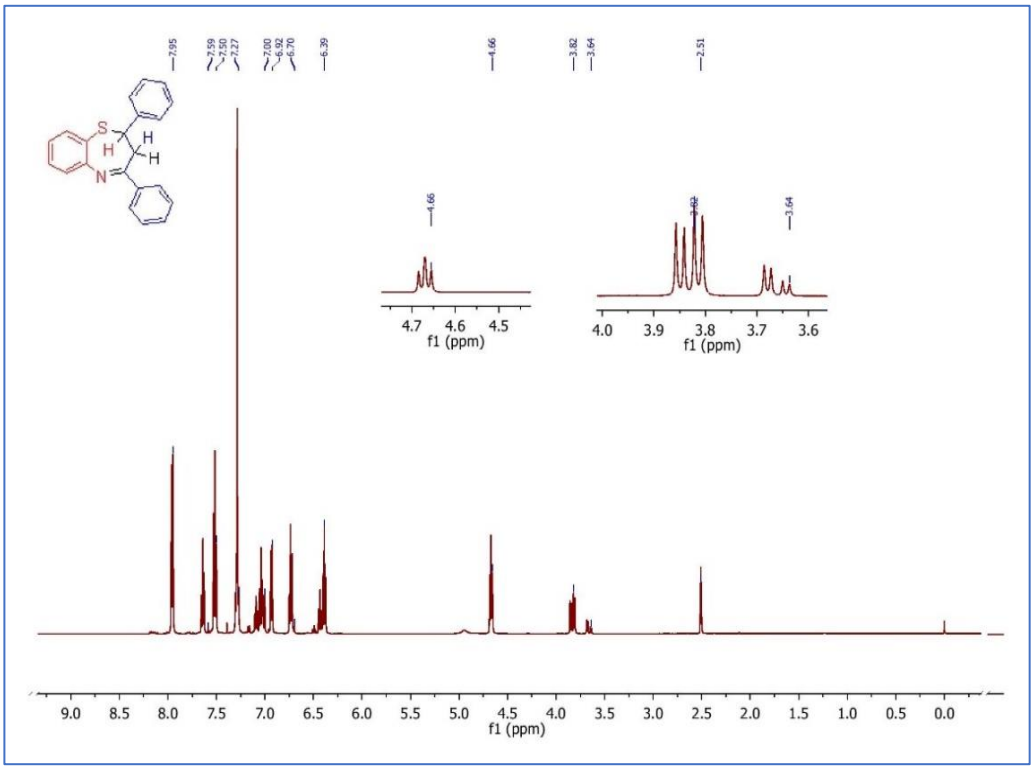
Scheme number	Compound	Supplementary data
6.		**2-phenyl-4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 6(a)**[3,5] Yellow solid; M.P. **106-109 °C**. ^{1}H NMR (DMSO, 500 MHz): δ = 4.66 (t, J = 12.8 Hz, 1 H), 3.86 (dd, J = 4.5, 13.0 Hz, 1 H), 3.75 (s, 3 H), 3.37 (s, 3 H), 6.37 (dd, J = 4.3, 12.1 Hz, 1 H), 6.70 (d, J = 8.3 Hz, 2 H), 6.89 (d, J = 8.4 Hz, 2 H), 7.03 (t, J = 7.5 Hz, 1 H), 7.25–7.30 (m, 3 H), 7.46 (t, J = 7.5 Hz, 1 H), 7.63 (d, J = 8.4 Hz, 1 H), 8.27 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (126 MHz, DMSO) δ 150.97 (s), 150.22 (s), 141.19 (s), 137.32 (s), 137.32 (s), 136.74 (dd, *J* = 15.3, 7.9 Hz), 133.95 (s), 131.86 (m), 131.61 (m), 130.91 (s), 130.04 (s), 129.23 (s), 128.48 (m), 116.93 (s), 115.46 (s), 40.31 (s). IR (KBr): 1596, 1687, 1320, 2955 cm^{-1}. **Isolated yield: 338 mg, 72%**.
7.		**2-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 7(a)**[4,5] Pale yellow solid; M.P. **128-129°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.41 (t, J = 12.8 Hz, 1 H), 3.44 (dd, J = 4.5, 13.0 Hz, 1 H), 3.49 (s, 3 H), 3.61 (s, 3 H), 3.94 (dd, J = 4.3, 12.1 Hz, 1 H), 6.85 (d, J = 8.2 Hz, 2 H), 6.94 (d, J = 8.4 Hz, 2 H), 7.12 (t, J = 7.5 Hz, 1 H), 7.21–7.30 (m, 3 H), 7.42 (t, J = 7.5 Hz, 1 H), 7.57 (d, J = 8.3 Hz, 1 H), 8.02 (d, J = 7.6 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 162.14 (s), 159.27 (s), 156.28 (s), 145.24 (s), 133.36 (s), 130.86 (dd, *J* = 15.3, 7.9 Hz), 130.02 (s), 129.96 (m), 128.19 (m), 125.27 (s), 120.15 (s), 114.80 (s), 114.30 (m), 56.04 (s), 49.92 (s), 38.32 (s). IR (KBr): 1596, 1687, 1320, 2955 cm^{-1}. **Isolated yield: 351 mg, 81%**.

Scheme number	Compound	Supplementary data
8.		**2-phenyl–4-(-4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine 8(a)**[5] Light brown solid; M.P. **130–132°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 5.38 (t, J = 12.7 Hz, 1 H), 3.18 (dd, J = 4.8, 12.9 Hz, 1 H), 2.93 (dd, J = 4.7, 12.5 Hz, 1 H), 7.11–716 (bs, 1 H), 7.19–7.25 (d, J = 8.5 Hz, 2 H), 7.25 (m, 3 H), 7.26 (d, J = 8.5 Hz, 1 H), 7.36 (m, 4 H), 7.37–7.38 (dd, J =1.5, 7.7 Hz, 1 H), 8.53 (m, 2 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 43.69 (CH_2), 60.05 (CH), 128.85 (CH), 129.10 (C), 130.48 (CH), 130.86 (CH), 141.24 (CH), 145.24 (C), 156.28 (C), 160.71(C). IR (KBr): 1640, 1684, 2920, 3351 cm^{-1}. MS (ESI): *m/z* = 332.26 (MH)+. Analytically calculated for $C_{21}H_{17}NOS$: C, 76.14; H, 5.16; N, 4.22, found: C, 76.20; H, 5.14; N, 4.23. **Isolated yield: 362 mg, 88%**
9.		**2-phenyl-4-(-4-acetoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 9(a)**[2,3] Yellow solid; M.P. **142–146°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 2.96(s, 3 H), 3.21(t, J = 12.8 Hz, 1 H), 5.09 dd, J = 4.8, 13.0 Hz, 1 H), 7.07(dd, J = 4.8, 13.0 Hz, 1 H), 7.13 (td, J = 1.4, 7.5 Hz, 1 H), 7.15–7.18 (m, 8 H), 7.26–7.28 (m, 1 H), 7.36 (dd, J = 1.4, 7.7 Hz, 1 H), 7.57 (d, J = 8.8 Hz, 2 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 43.69 (CH_3), 49.92 (CH_2), 120.15 (CH),123.35 (CH), 125.27 (CH), 127.35 (CH), 127.63 (CH), 129.10 (CH), 130.02 (CH), 133.75 (CH), 141.24 (C), 145.24 (C), 153.95 (C), 156.28 (C), 169.71 (C). IR (KBr): 1599, 1687, 1752, 2918 cm^{-1}. MS (ESI): *m/z* = 374.44 $(MH)^{+}$. Analytically calculated for $C_{23}H_{19}NO_2S$: C, 73.96; H, 5.12; N, 3.74, found: C, 74.08; H, 5.13; N, 3.75. **Isolated yield: 310 mg, 65%**

Scheme number	Compound	Supplementary data
10.		**2-Phenyl-4-(Thiophen-2-yl)-2,3-dihydro-1,5-benzothiazepine 10(a)**[3] Pale yellow solid. M.P. **124–126°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 6.42 (t, J = 12.6 Hz, 1 H), 5.23 (dd, J = 4.7, 12.8 Hz, 1 H), 3.20 (dd, J = 4.7, 12.0 Hz, 1 H), 7.11–7.13 (m, 2 H), 7.14– 7.20 (m, 6 H), 7.24–7.37 (m, 1 H), 7.62 (m, 3 H). ^{13}C NMR ($CDCl_3$, 126 MHz): 41.36 (CH2), 49.36 (CH), 112.60 (C), 120.15 (CH), 127.35 (CH), 127.63 (CH), 128.43 (CH), 130.02 (CH), 130.86 (CH), 144.24 (CH), 144.04 (C), 159.41 (C). IR (KBr): 1600, 1650, 2922 cm^{-1}. Analytically calculated for $C_{19}H_{15}NS_2$: C, 70.98; H, 4.71; N, 4.35, found: C, 71.14; H, 4.72; N, 4.36. **Isolated yield: 252 mg, 62%**.
11.		**2-phenyl-4-(-4-Nitrophenyl)-2,3-dihydro-1,5-benzothiazepine 11(a)**[2] Yellow solid; M.P. **124–126°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): δ = 4.81 (t, J = 13.1 Hz, 1 H), 3.75 (dd, J = 5.0, 13.2 Hz, 1 H), 3.64 (dd, J = 5.0, 12.0 Hz, 1 H), 6.94 (dt, J = 1.5, 7.5 Hz, 1 H), 7.15 (m, 6 H), 7.18 (dt, J = 1.5, 7.22 Hz, 1 H), 7.26 (dd, J = 1.5, 7.7 Hz, 1 H), 7.38 (m, 2 H), 8.11 (m 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 137.54 (s), 136.85 (s), 131.63 (s), 131.21(s), 128.92 (s), 128.81 (s), 128.52 (m), 127.38 (m), 127.04 (s), 124.22 (s), 123.63 (m), 118.21(s), 115.25 (s), 59.33 (s), 45.90 (s),43.35 (s). IR (KBr): 1360, 1600, 1695, 2922 cm^{-1}. **Isolated yield: 341 mg, 82%**.
12.		**2-(4-Nitrophenyl)-4-phenyl -2,3-dihydro-1,5-benzothiazepine 12(a)**[1] Pale yellow solid; M.P. **185–188°C**. ^{1}H NMR ($CDCl_3$, 500 MHz): = 5.01 (t, J = 12.7 Hz, 1 H), 3.22 (dd, J = 4.9, 12.8 Hz, 1 H), 2.88 (dd, J = 4.8, 12.5 Hz, 1 H), 7.49–7.32 (m, 1 H), 7.60 (m, 8 H), 8.22 (d, J = 8.7 Hz, 2 H). ^{13}C NMR (126 MHz, $CDCl_3$) δ 156.28 (s), 148.22 (s), 146.69 (s), 145.24 (s), 137.18 (s), 131.24 (s), 130.86 (m), 130.02 (m), 129.10 (s), 128.75 (s), 127.83 (m), 125.27 (s), 123.25 (s), 120.15 (s), 49.92 (s), 43.69(s). IR (KBr): 1355, 1602, 1685, 2920 cm^{-1}. **Isolated yield: 442 mg, 98%**.

^{1}H and ^{13}C NMR spectral data (Fig. S1–S12)

In this supplementary file, the structure and stereochemistry of the desired products were determined with two-dimensional NMR spectroscopy.



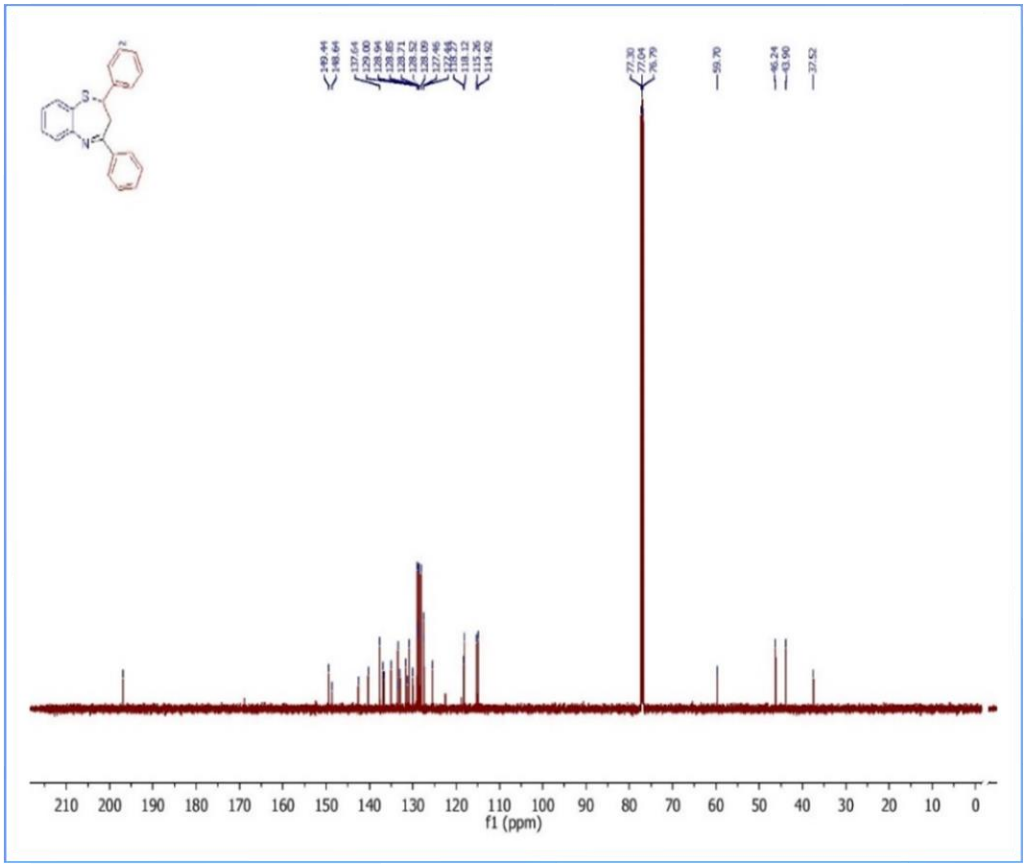
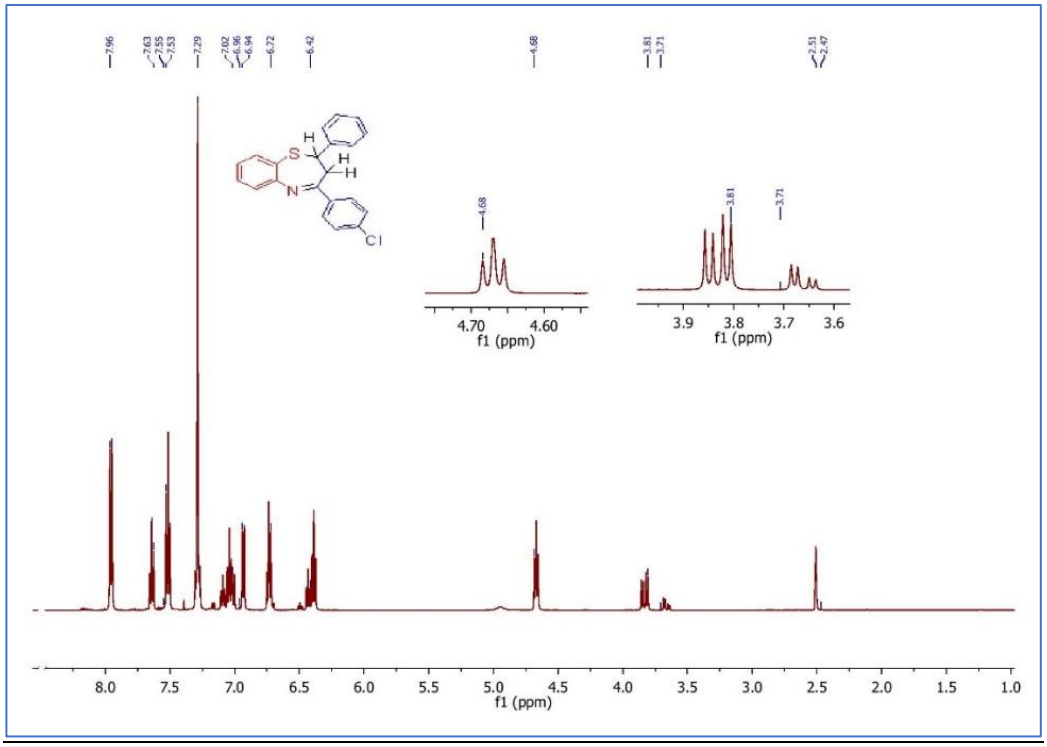


Fig S1. 2,4-Diphenyl-2,3-dihydro-1,5-benzothiazepine 1(a) of the ^{1}H & ^{13}C NMR.



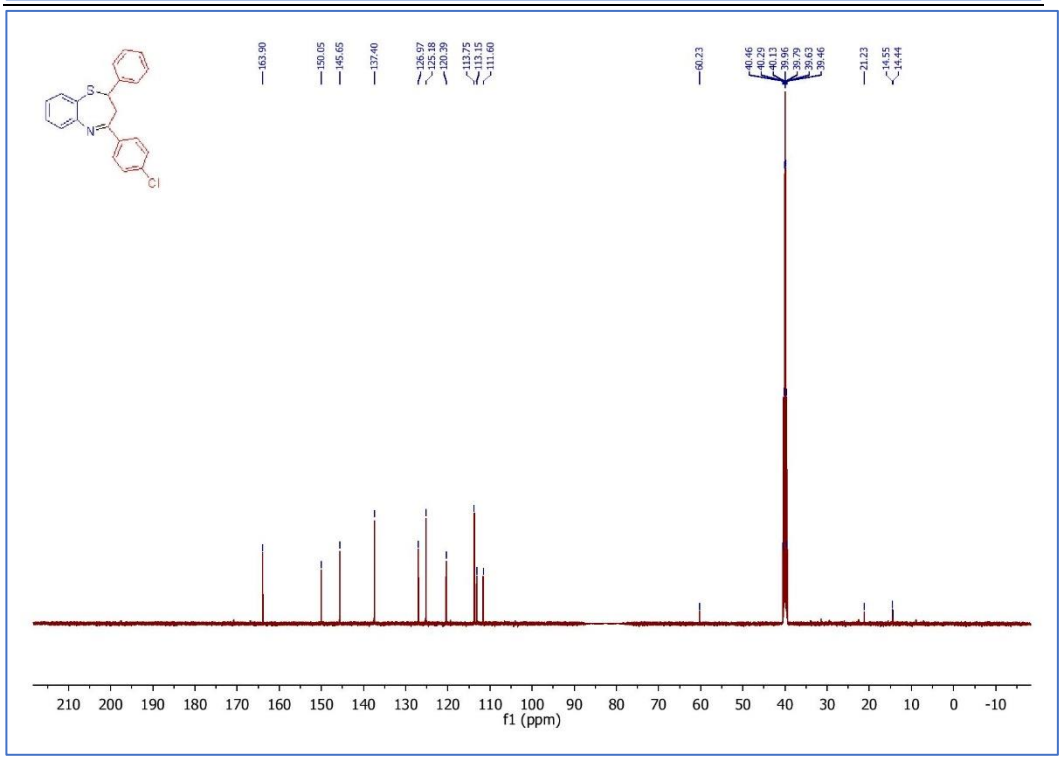


Fig S2. 2-(phenyl)-4(-4-Chlorophenyl) -2,3-dihydro-1,5-benzothiazepine 2(a) of ^{1}H & ^{13}C NMR.

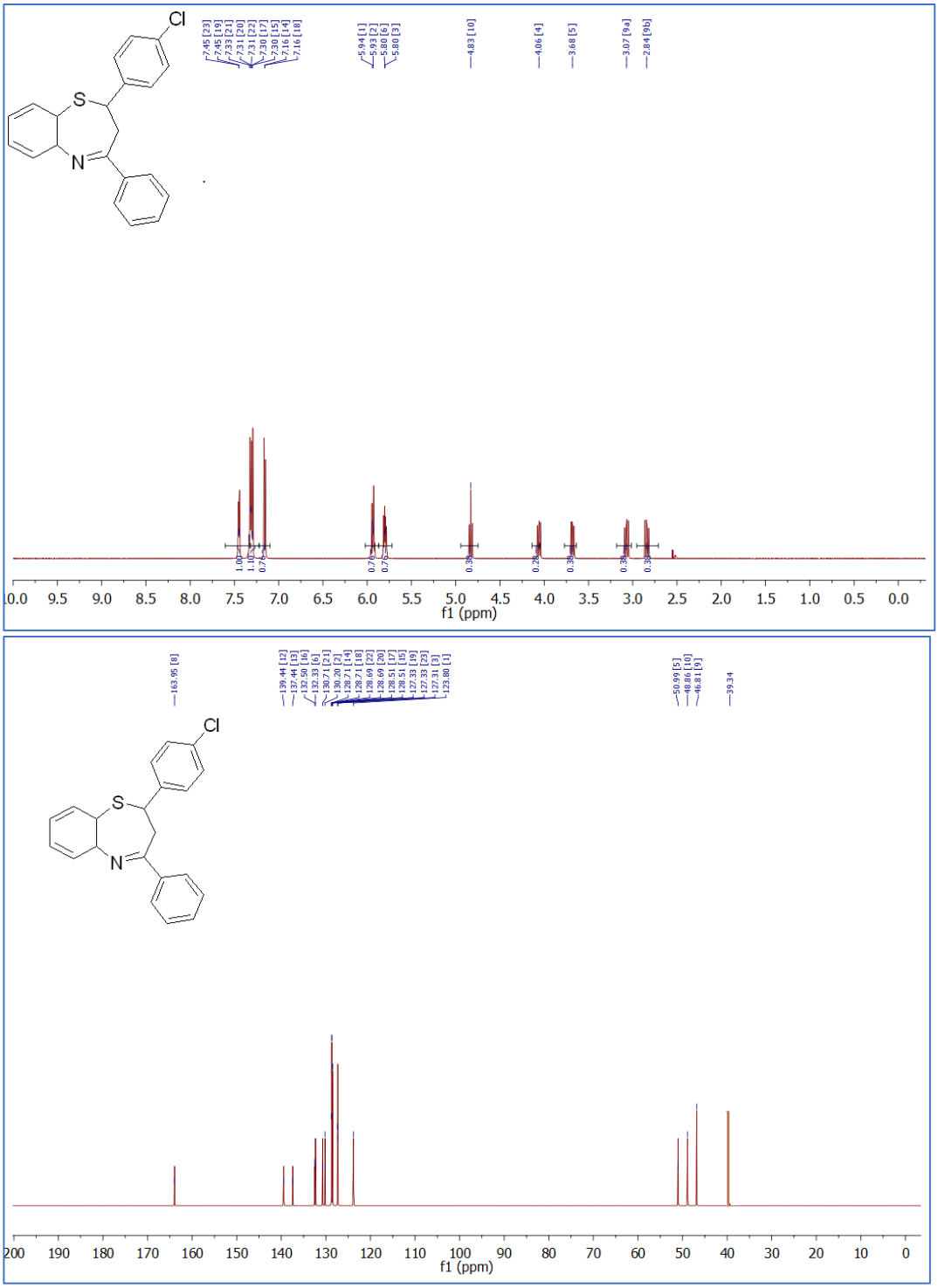


Fig S3. 2-(4-Chlorophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 3(a) of the ^{1}H & ^{13}C NMR.

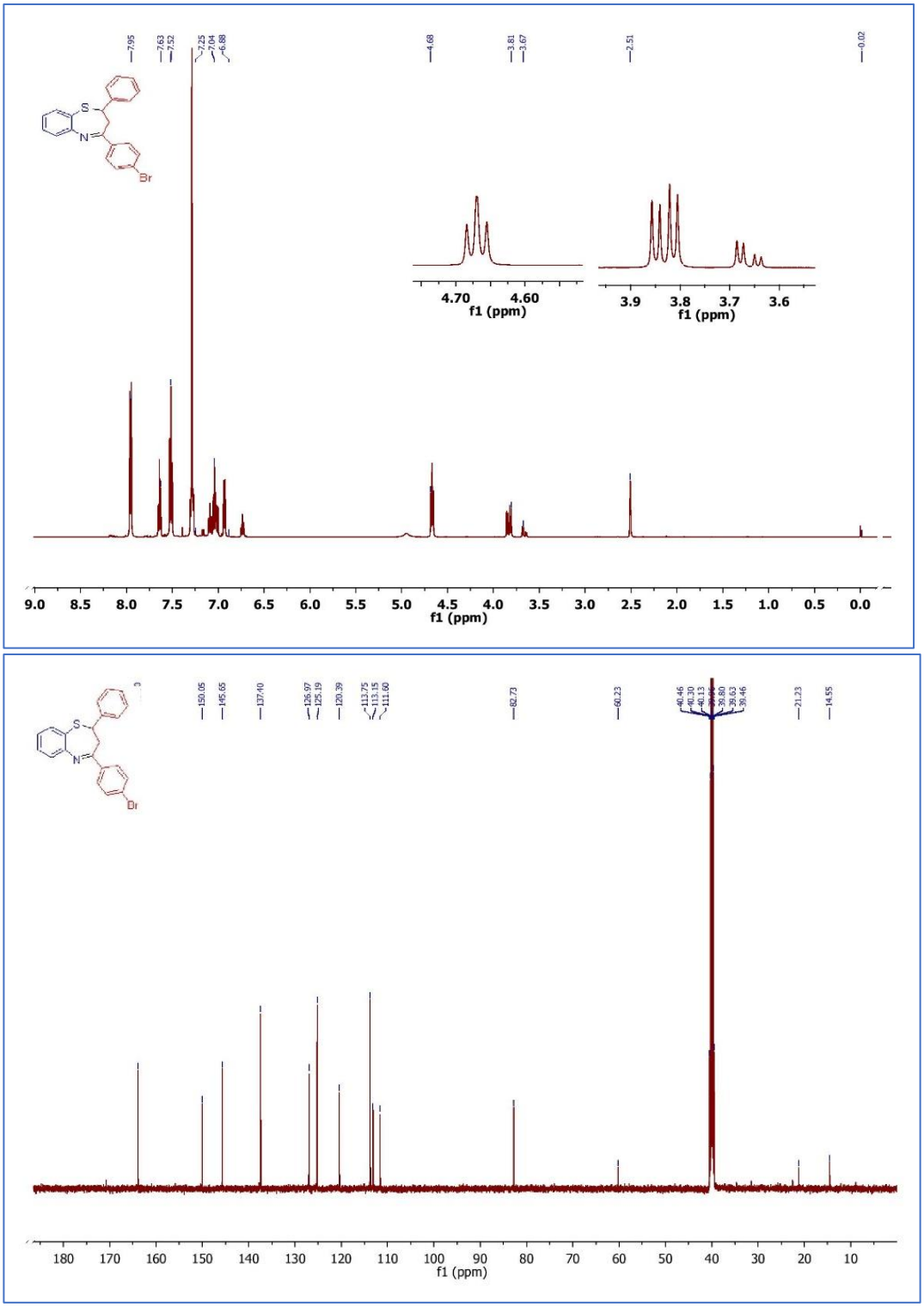


Fig S4. 2-Phenyl-4-(4-bromophenyl)-2,3-dihydro-1,5-benzothiazepine 4(a).

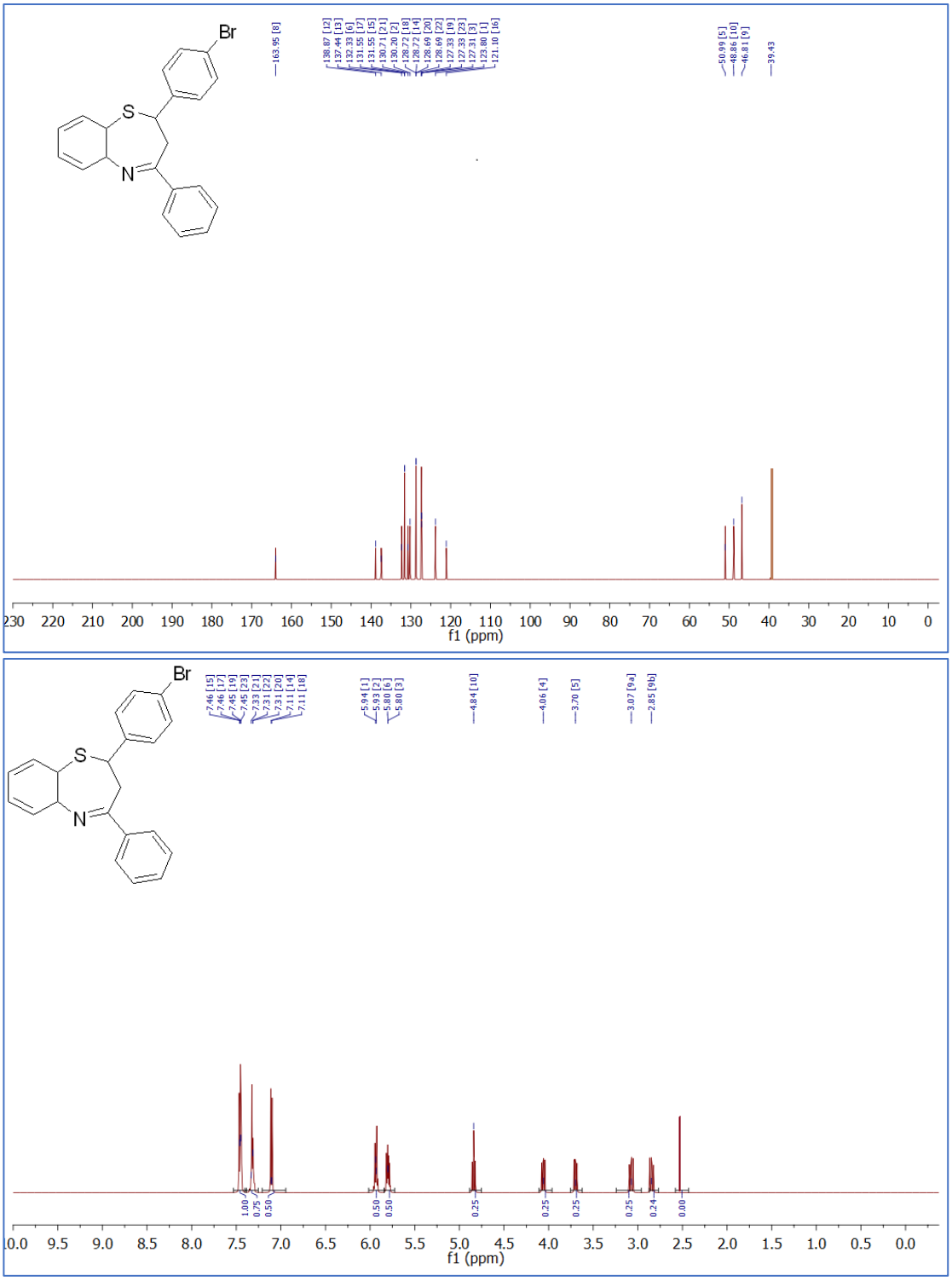


Fig S5. 2-(4-Bromophenyl)-4-phenyl-2,3-dihydro-1,5-benzothiazepine 5(a).

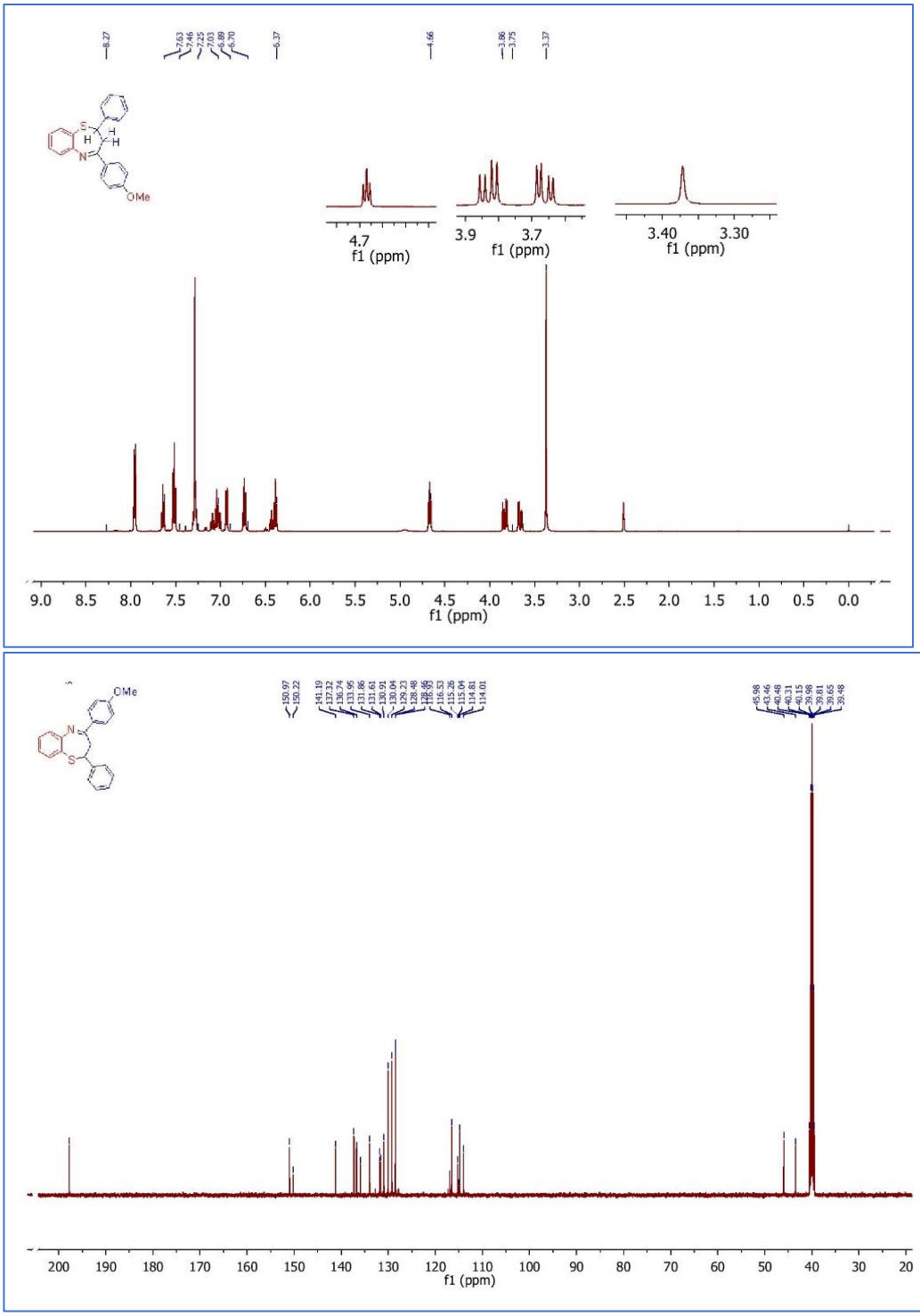


Fig S6. 2- phenyl-4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 6(a) of ^{1}H & ^{13}C NMR.

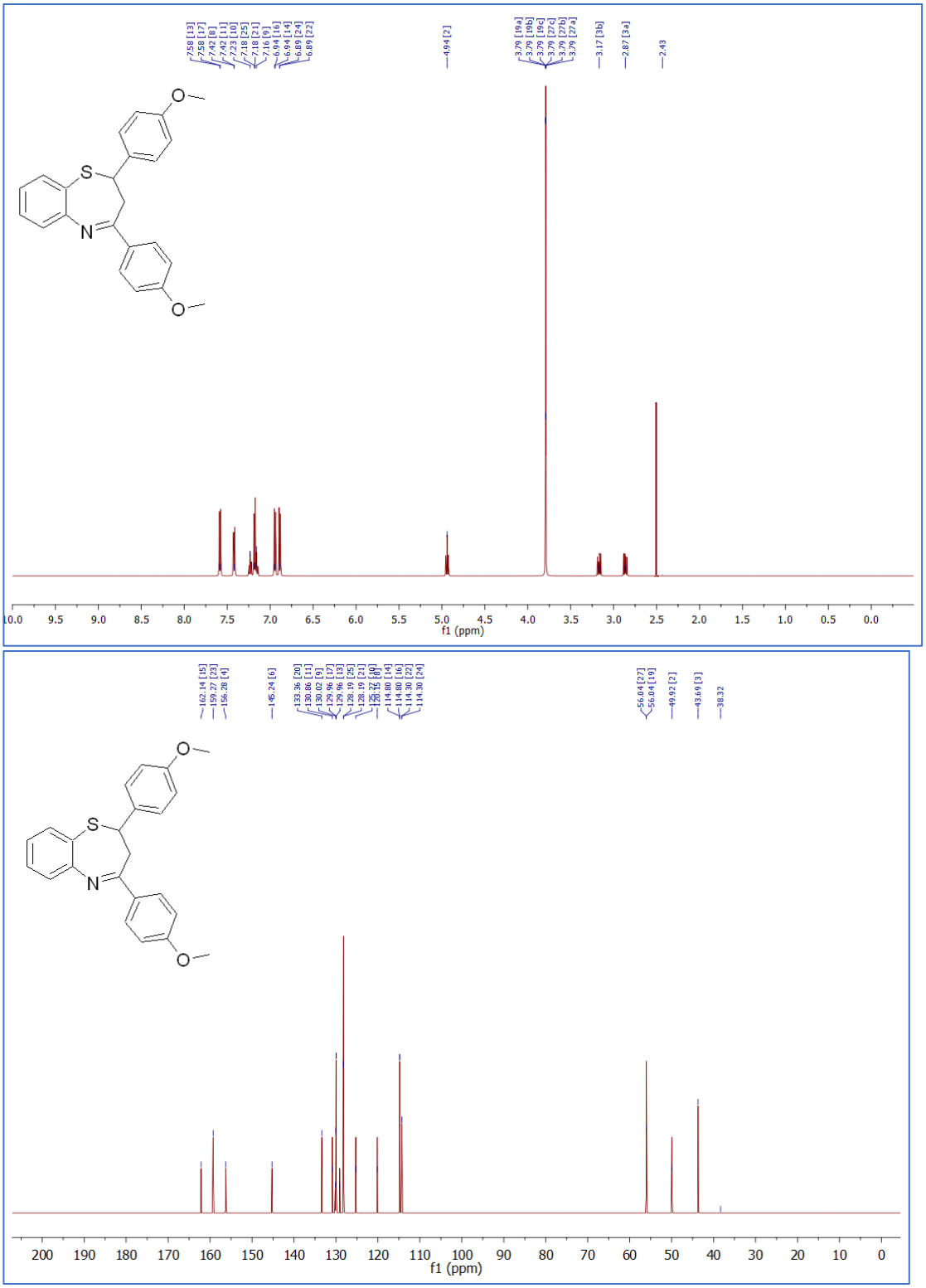


Fig S7. 2-(4-Methoxyphenyl)-4-(4-methoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 7(a).

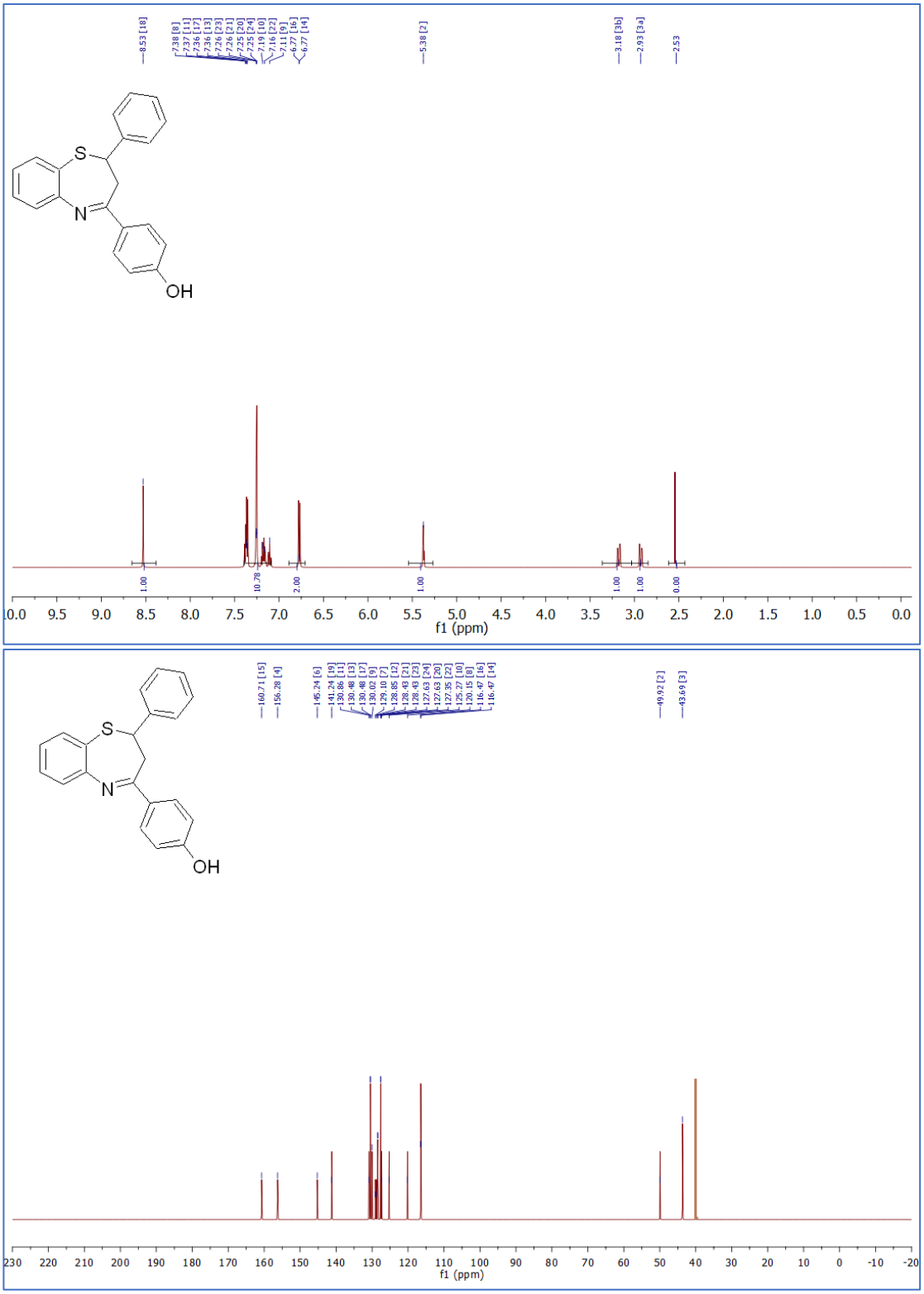


Fig S8. 2-phenyl–4-(-4-hydroxyphenyl)-2,3-dihydro-1,5-benzothiazepine 8(a) of the ^{1}H & ^{13}C NMR.

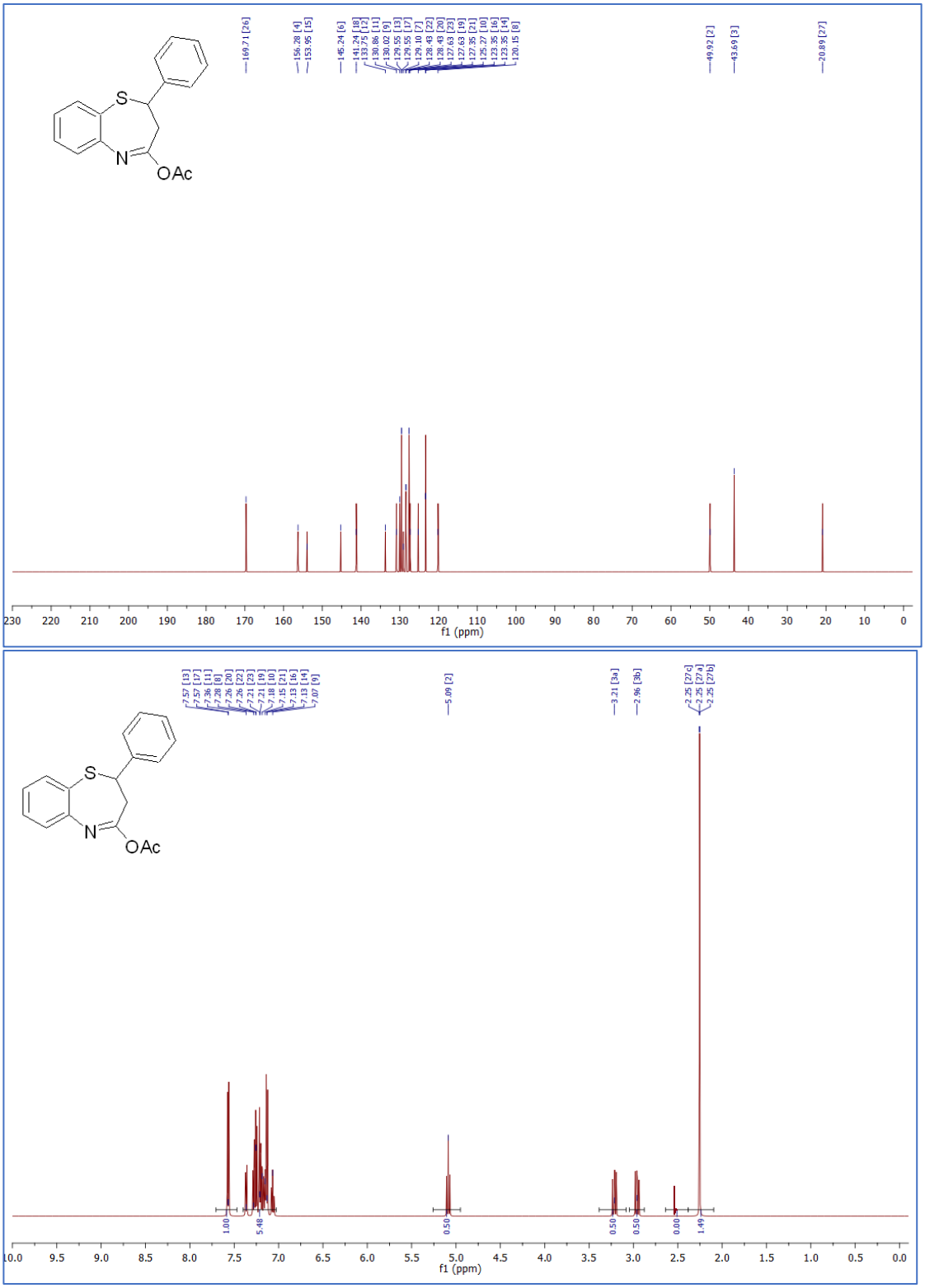


Fig S9. Phenyl-4-(-4-acetoxyphenyl)-2,3-dihydro-1,5-benzothiazepine 9(a) of the ^{1}H & ^{13}C NMR.

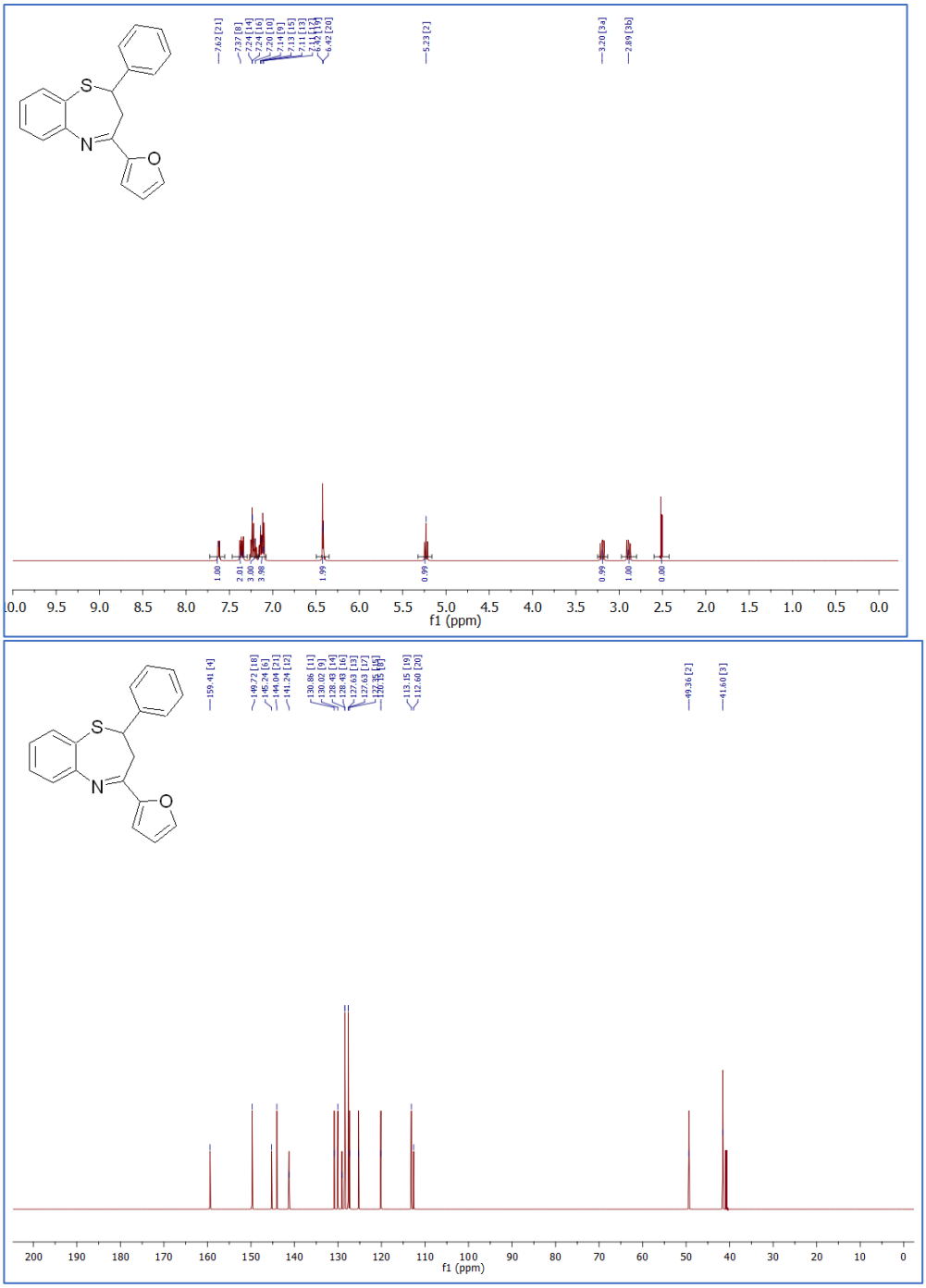


Fig S10. 2-Phenyl-4-(Thiophen-2-yl)-2,3-dihydro1,5-benzothiazepine 10(a)of the ^{1}H & ^{13}C NMR.

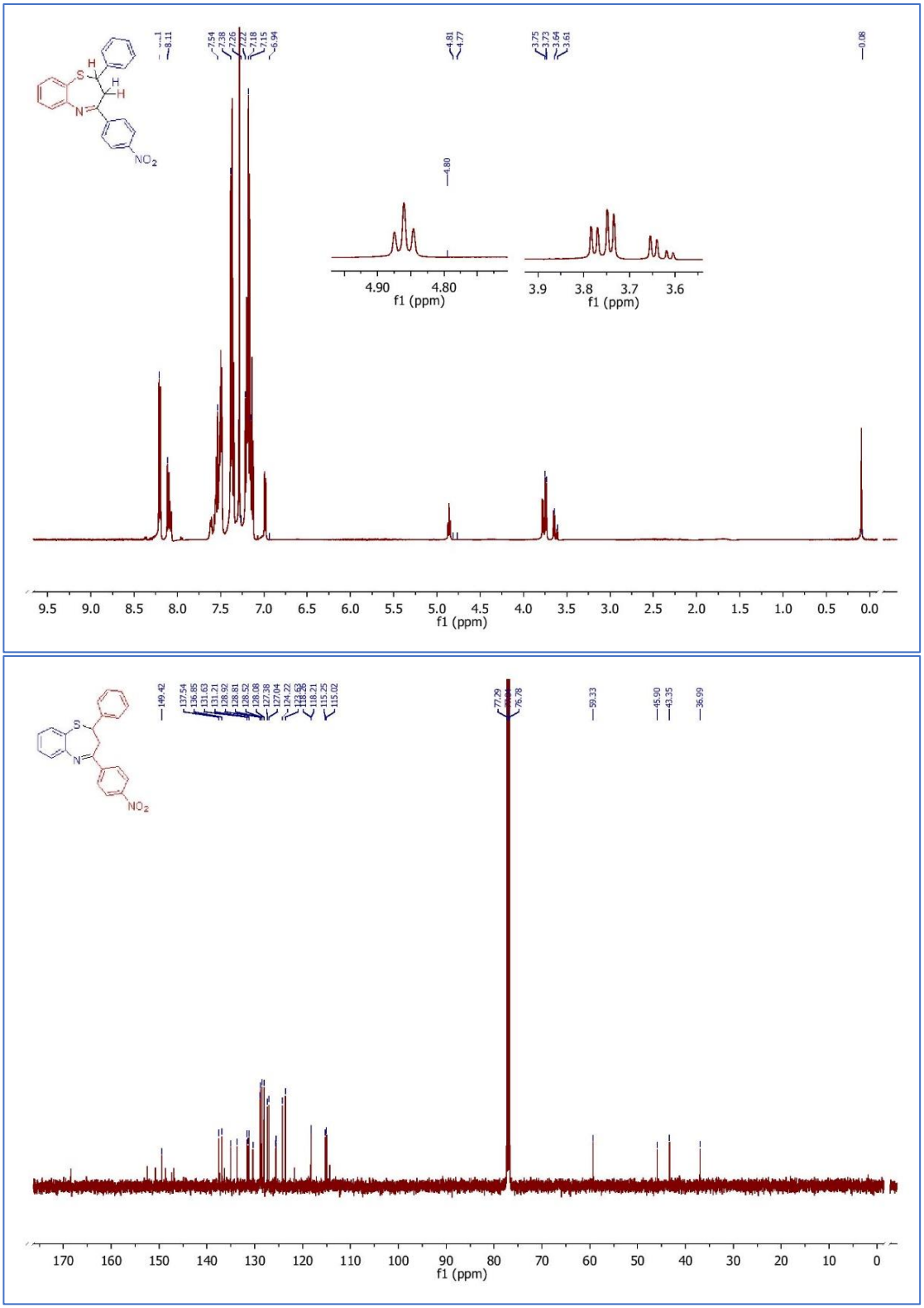


Fig S11. 2-phenyl-4-(-4-Nitrophenyl)-2,3-dihydro-1,5-benzothiazepine 11(a) of the ^{1}H & ^{13}C NMR.

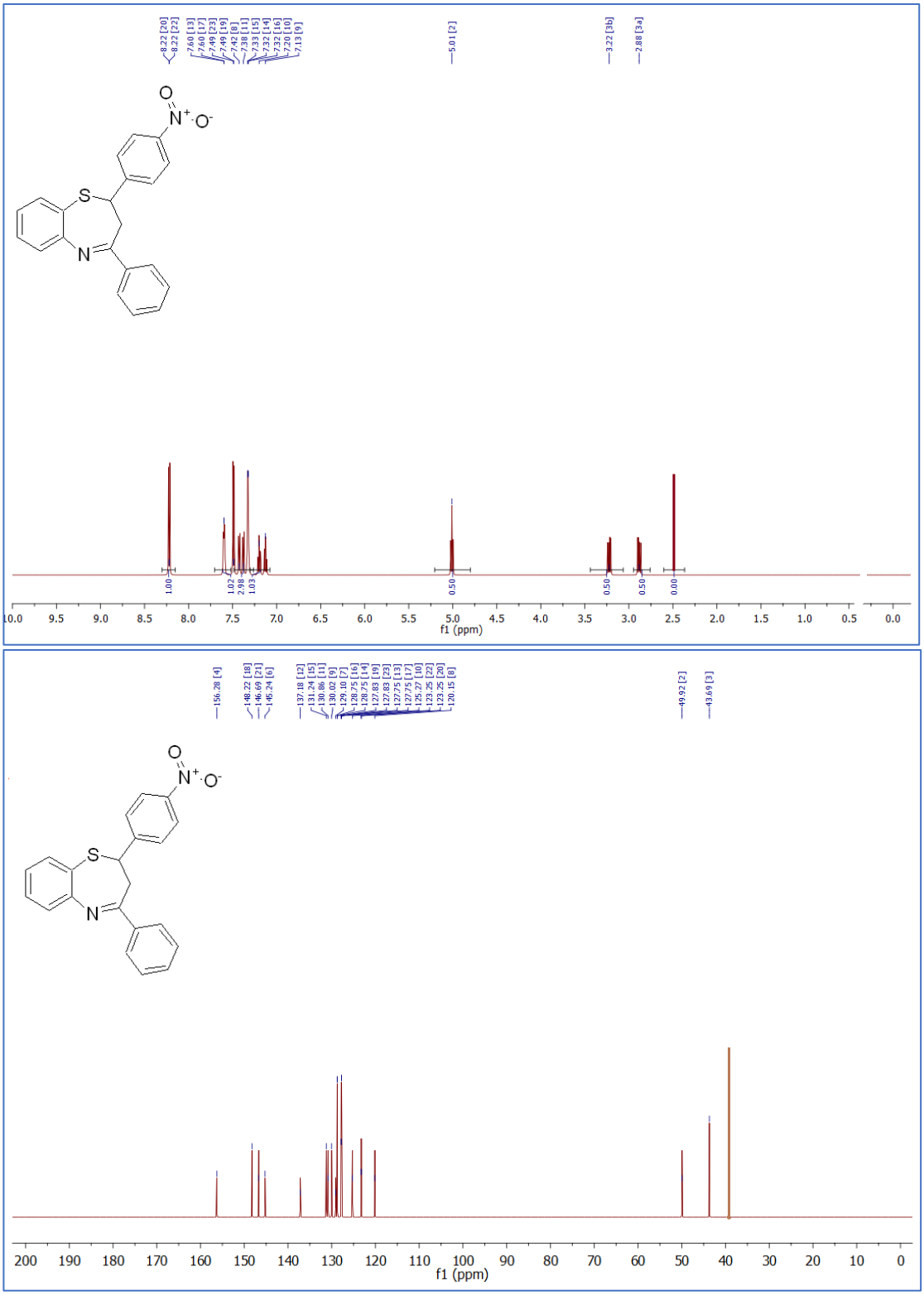


Fig S12. 2-(4-Nitrophenyl)-4-phenyl -2,3-dihydro-1,5-benzothiazepine 12(a) of the ^{1}H & ^{13}C NMR.

References

1 Albanese, DCM, Gaggero N, Fei M (2017) A practical synthesis of 2,3-dihydro-1,5-benzothiazepines. *Green Chemistry* 19, 23 (2017): 5703–5707. https://doi.org/10.1039/C7GC02097J

2 Pan X-Q, Zou J-P, Huang Z-H, Zhang W (2008) $Ga(OTf)_3$-promoted condensation reactions for 1,5-benzodiazepines and 1,5-benzothiazepines. *Tetrahedron Lett.* **49**, 36 (2008): 5302–5308. https://doi.org/10.1016/j.tetlet.2008.06.082

3 Kodomari M, Noguchi T, Aoyama T (2004) Solvent-free synthesis of 1,5-benzothiazepines and benzodiazepines on inorganic supports. *Synth. Commun.* **34**:10, 1783–1790. https://doi.org/10.1081/SCC-120034159

4 Ansari FL, Kalsoom S, Zaheer-ul-Haq, Ali Z, Jabeen F. (2012) *In silico* studies on 2,3-dihydro-1,5-benzothiazepines as cholinesterase inhibitors. *Med. Chem. Res.* 21: 2329–2339. https://doi.org/10.1007/s00044-011-9754-6

5 Saini RK, Joshi YC, Joshi P (2008) Solvent-free synthesis of some 1,5-benzothiazepines and benzodiazepines and their antibacterial activity. *Phosphorus Sulfur* **183**:9, 2181–2190. https://doi.org/10.1080/10426500701852661