

References

- [1] A.D. Gitler, P. Dhillon, J. Shorter, Neurodegenerative disease: models, mechanisms, and a new hope, *Dis Model Mech.* 10 (2017) 499. <https://doi.org/10.1242/DMM.030205>.
- [2] J. Brettschneider, K. Del Tredici, V.M.Y. Lee, J.Q. Trojanowski, Spreading of pathology in neurodegenerative diseases: a focus on human studies, *Nat Rev Neurosci.* 16 (2015) 109. <https://doi.org/10.1038/NRN3887>.
- [3] B.N. Dugger, D.W. Dickson, *Pathology of Neurodegenerative Diseases*, Cold Spring Harb Perspect Biol. 9 (2017). <https://doi.org/10.1101/CSHPERSPECT.A028035>.
- [4] S. Tiwari, V. Atluri, A. Kaushik, A. Yndart, M. Nair, Alzheimer's disease: pathogenesis, diagnostics, and therapeutics, *Int J Nanomedicine.* 14 (2019) 5541. <https://doi.org/10.2147/IJN.S200490>.
- [5] J.H. Shin, Dementia Epidemiology Fact Sheet 2022, *Ann Rehabil Med.* 46 (2022) 53. <https://doi.org/10.5535/ARM.22027>.
- [6] S. Chaturvedi, J. Porter, G.K.G. Pillai, L. Abraham, D. Shankar, B. Patwardhan, India and its pluralistic health system – a new philosophy for Universal Health Coverage, *The Lancet Regional Health. Southeast Asia.* 10 (2023) 100136. <https://doi.org/10.1016/J.LANSEA.2022.100136>.
- [7] I. Arevalo-Rodriguez, N. Smailagic, M. Roquéi Figuls, A. Ciapponi, E. Sanchez-Perez, A. Giannakou, O.L. Pedraza, X. Bonfill Cosp, S. Cullum, Mini-Mental State Examination (MMSE) for the detection of Alzheimer's disease and other dementias in people with mild cognitive impairment (MCI), *Cochrane Database Syst Rev.* 2015 (2015). <https://doi.org/10.1002/14651858.CD010783>.
- [8] A. Serrano-Pozo, M.P. Frosch, E. Masliah, B.T. Hyman, Neuropathological Alterations in Alzheimer Disease, *Cold Spring Harb Perspect Med.* 1 (2011). <https://doi.org/10.1101/CSHPERSPECT.A006189>.
- [9] T.H. Ferreira-Vieira, I.M. Guimaraes, F.R. Silva, F.M. Ribeiro, Alzheimer's Disease: Targeting the Cholinergic System, *Curr Neuropharmacol.* 14 (2016) 101. <https://doi.org/10.2174/1570159X13666150716165726>.

- [10] K.G. Yiannopoulou, S.G. Papageorgiou, Current and future treatments for Alzheimer's disease, *Ther Adv Neurol Disord.* 6 (2013) 19. <https://doi.org/10.1177/1756285612461679>.
- [11] J. Knowles, Donepezil in Alzheimer's disease: an evidence-based review of its impact on clinical and economic outcomes, *Core Evid.* 1 (2006) 195. [/pmc/articles/PMC3321665/](https://pubmed.ncbi.nlm.nih.gov/17562856/) (accessed June 18, 2023).
- [12] M. Samochocki, A. Höffle, A. Fehrenbacher, R. Jostock, J. Ludwig, C. Christner, M. Radina, M. Zerlin, C. Ullmer, E.F.R. Pereira, H. Lübbert, E.X. Albuquerque, A. Maelicke, Galantamine is an allosterically potentiating ligand of neuronal nicotinic but not of muscarinic acetylcholine receptors, *J Pharmacol Exp Ther.* 305 (2003) 1024–1036. <https://doi.org/10.1124/JPET.102.045773>.
- [13] S. Reardon, FDA approves Alzheimer's drug lecanemab amid safety concerns, *Nature.* 613 (2023) 227–228. <https://doi.org/10.1038/D41586-023-00030-3>.
- [14] van D. CH, S. CJ, A. P, B. RJ, C. C, G. M, K. M, L. D, R. L, C. S, F. L, K. S, S. M, V. B, W. D, D. S, I. M, K. LD, I. T, Lecanemab in Early Alzheimer's Disease, *N Engl J Med.* 388 (2023) 142–143. <https://doi.org/10.1056/NEJM0A2212948>.
- [15] A. Rahman, M.A. Hossen, M.F.I. Chowdhury, S. Bari, N. Tamanna, S.S. Sultana, S.N. Haque, A. Al Masud, K.M. Saif-Ur-Rahman, Aducanumab for the treatment of Alzheimer's disease: a systematic review, *Psychogeriatrics.* 23 (2023) 512–522. <https://doi.org/10.1111/PSYG.12944>.
- [16] J.S. Birks, R.J. Harvey, Donepezil for dementia due to Alzheimer's disease, *Cochrane Database Syst Rev.* 2018 (2018). <https://doi.org/10.1002/14651858.CD001190.PUB3>.
- [17] J.S. Birks, L.Y. Chong, J. Grimley Evans, Rivastigmine for Alzheimer's disease, *Cochrane Database Syst Rev.* 2015 (2015). <https://doi.org/10.1002/14651858.CD001191.PUB4>.
- [18] B.S. Williams, A. Buvanendran, Memantine, *The Essence of Analgesia and Analgesics.* (2022) 319–321. <https://doi.org/10.1017/CBO9780511841378.077>.
- [19] J. Olin, L. Schneider, Galantamine for Alzheimer's disease., *Cochrane Database Syst Rev.* (2001) CD001747. <https://doi.org/10.1002/14651858.CD001747>.

- [20] L. Golchin, M. Shabani, S. Harandi, M. Razavinasab, Pistachio supplementation attenuates motor and cognition impairments induced by cisplatin or vincristine in rats, *Adv Biomed Res.* 4 (2015) 92. <https://doi.org/10.4103/2277-9175.156656>.
- [21] M. Ammari, H. Othman, A. Hajri, M. Sakly, H. Abdelmelek, Pistacia lentiscus oil attenuates memory dysfunction and decreases levels of biomarkers of oxidative stress induced by lipopolysaccharide in rats, *Brain Res Bull.* 140 (2018) 140–147. <https://doi.org/10.1016/J.BRAINRESBULL.2018.04.014>.
- [22] M. Zahoor, R. Zafar, N.U. Rahman, Isolation and identification of phenolic antioxidants from Pistacia integerrima gall and their anticholine esterase activities, *Heliyon.* 4 (2018).
- [23] M.S. Uddin, A. Al Mamun, M.S. Hossain, M. Ashaduzzaman, M.A.A. Noor, M.S. Hossain, M.J. Uddin, J. Sarker, M. Asaduzzaman, Neuroprotective effect of Phyllanthus acidus L. on learning and memory impairment in scopolamine-induced animal model of dementia and oxidative stress: natural wonder for regulating the development and progression of Alzheimer's disease, *Adv Alzheimer Dis.* 5 (2016) 53–72.
- [24] H.-J. Kim, S.-W. Jung, S.-Y. Kim, I.-H. Cho, H.-C. Kim, H. Rhim, M. Kim, S.-Y. Nah, Panax ginseng as an adjuvant treatment for Alzheimer's disease, *J Ginseng Res.* 42 (2018) 401–411.
- [25] H. Benamar, A. Marouf, M. Bennaceur, Phytochemical composition, antioxidant and acetylcholinesterase inhibitory activities of aqueous extract and fractions of Pistacia atlantica subsp. atlantica from Algeria, *J Herbs Spices Med Plants.* 24 (2018) 229–244.
- [26] M.K. Sarkar, P.C. Sil, Hepatocytes are protected by herb Phyllanthus niruri protein isolate against thioacetamide toxicity, *Pathophysiology.* 14 (2007) 113–120.
- [27] M.S. Uddin, A. Al Mamun, M.S. Hossain, F. Akter, M.A. Iqbal, M. Asaduzzaman, Exploring the effect of Phyllanthus emblica L. on cognitive performance, brain antioxidant markers and acetylcholinesterase activity in rats: promising natural gift for the mitigation of Alzheimer's disease, *Ann Neurosci.* 23 (2016) 218–229.
- [28] C. Shi, J. Liu, F. Wu, D.T. Yew, Ginkgo biloba extract in Alzheimer's disease: from action mechanisms to medical practice, *Int J Mol Sci.* 11 (2010) 107–123.

- [29] R.A. El-Shiekh, R.M. Ashour, E.A. Abd El-Haleim, K.A. Ahmed, E. Abdel-Sattar, *Hibiscus sabdariffa* L.: A potent natural neuroprotective agent for the prevention of streptozotocin-induced Alzheimer's disease in mice, *Biomedicine & Pharmacotherapy*. 128 (2020) 110303.
- [30] W.J. Hashmi, H. Ismail, L. Jafri, B. Mirza, Ethnopharmacological activity of *Hedera nepalensis* K. Koch extracts and lupeol against alloxan-induced type I diabetes, *Brazilian Journal of Pharmaceutical Sciences*. 56 (2020).
- [31] H. Yu, L. Yao, H. Zhou, S. Qu, X. Zeng, D. Zhou, Y. Zhou, X. Li, Z. Liu, Neuroprotection against A β 25–35-induced apoptosis by *Salvia miltiorrhiza* extract in SH-SY5Y cells, *Neurochem Int*. 75 (2014) 89–95.
- [32] Q.F. Liu, Y. Jeon, Y. Sung, J.H. Lee, H. Jeong, Y.-M. Kim, H.S. Yun, Y.-W. Chin, S. Jeon, K.S. Cho, *Nardostachys jatamansi* ethanol extract ameliorates A β 42 cytotoxicity, *Biol Pharm Bull*. 41 (2018) 470–477.
- [33] X. Chen, J. Drew, W. Berney, W. Lei, Neuroprotective natural products for Alzheimer's disease, *Cells*. 10 (2021) 1309.
- [34] T.T. Bui, T.H. Nguyen, Natural product for the treatment of Alzheimer's disease, *J Basic Clin Physiol Pharmacol*. 28 (2017) 413–423.
- [35] M.P. Murphy, H. Levine, Alzheimer's Disease and the β -Amyloid Peptide, *J Alzheimers Dis*. 19 (2010) 311. <https://doi.org/10.3233/JAD-2010-1221>.
- [36] S.E.B. Tyler, L.D.K. Tyler, Therapeutic roles of plants for 15 hypothesised causal bases of Alzheimer's disease, *Nat Prod Bioprospect*. 12 (2022). <https://doi.org/10.1007/S13659-022-00354-Z>.
- [37] A.F.G. Cicero, M. Ruscica, M. Banach, Resveratrol and cognitive decline: a clinician perspective, *Arch Med Sci*. 15 (2019) 936. <https://doi.org/10.5114/AOMS.2019.85463>.
- [38] T.Y.C. Tan, X.Y. Lim, N.A. Norahmad, H. Chanthira Kumar, B.P. Teh, N.M. Lai, A.F. Syed Mohamed, Neurological Applications of Celery (*Apium graveolens*): A Scoping Review, *Molecules*. 28 (2023). <https://doi.org/10.3390/MOLECULES28155824/S1>.

- [39] S. Witter, R. Witter, R. Vilu, A. Samoson, Medical Plants and Nutraceuticals for Amyloid- β Fibrillation Inhibition, *J Alzheimers Dis Rep.* 2 (2018) 239. <https://doi.org/10.3233/ADR-180066>.
- [40] Q. Wang, B. Xiao, S. Cui, H. Song, Y. Qian, L. Dong, H. An, Y. Cui, W. Zhang, Y. He, J. Zhang, J. Yang, F. Zhang, G. Hu, X. Gong, Z. Yan, Y. Zheng, X. Wang, Triptolide treatment reduces Alzheimer's disease (AD)-like pathology through inhibition of BACE1 in a transgenic mouse model of AD, *Dis Model Mech.* 7 (2014) 1385–1395. <https://doi.org/10.1242/DMM.018218>.
- [41] T. Saido, M.A. Leissring, Proteolytic Degradation of Amyloid β -Protein, *Cold Spring Harb Perspect Med.* 2 (2012). <https://doi.org/10.1101/CSHPERSPECT.A006379>.
- [42] O.O. Ogunraku, G. Oboh, S. Passamonti, F. Tramer, A.A. Boligon, Capsicum annum var. grossum (Bell Pepper) Inhibits β -Secretase Activity and β -Amyloid1–40 Aggregation, <https://Home.Liebertpub.Com/Jmf>. 20 (2017) 124–130. <https://doi.org/10.1089/JMF.2016.0077>.
- [43] S. Kumar, E.J. Okello, J.R. Harris, Experimental inhibition of fibrillogenesis and neurotoxicity by amyloid-beta ($A\beta$) and other disease-related peptides/proteins by plant extracts and herbal compounds, *Subcell Biochem.* 65 (2012) 295–326. https://doi.org/10.1007/978-94-007-5416-4_13.
- [44] J.H. Lee, N.H. Ahn, S. Bin Choi, Y. Kwon, S.H. Yang, Natural Products Targeting Amyloid Beta in Alzheimer's Disease, *Int J Mol Sci.* 22 (2021) 1–17. <https://doi.org/10.3390/IJMS22052341>.
- [45] N. Sehgal, A. Gupta, R.K. Valli, S.D. Joshi, J.T. Mills, E. Hamel, P. Khanna, S.C. Jain, S.S. Thakur, V. Ravindranath, Withania somnifera reverses Alzheimer's disease pathology by enhancing low-density lipoprotein receptor-related protein in liver, *Proc Natl Acad Sci U S A.* 109 (2012) 3510–3515. <https://doi.org/10.1073/PNAS.1112209109>.
- [46] Z. Wang, Z. Zhang, J. Liu, M. Guo, H. Li, Panax Ginseng in the treatment of Alzheimer's disease and vascular dementia, *J Ginseng Res.* 47 (2023) 506. <https://doi.org/10.1016/J.JGR.2023.03.001>.

- [47] Y. Wu, P. Mumford, S. Noy, K. Cleverley, A. Mrzyglod, D. Luo, F. van Dalen, M. Verdoes, E.M.C. Fisher, F.K. Wiseman, Cathepsin B abundance, activity and microglial localisation in Alzheimer's disease-Down syndrome and early onset Alzheimer's disease; the role of elevated cystatin B, *Acta Neuropathol Commun.* 11 (2023) 132. <https://doi.org/10.1186/S40478-023-01632-8/FIGURES/6>.
- [48] P. Barbier, O. Zejneli, M. Martinho, A. Lasorsa, V. Belle, C. Smet-Nocca, P.O. Tsvetkov, F. Devred, I. Landrieu, Role of Tau as a Microtubule-Associated Protein: Structural and Functional Aspects, *Front Aging Neurosci.* 11 (2019). <https://doi.org/10.3389/FNAGI.2019.00204>.
- [49] A.L. Hobday, M.S. Parmar, The Link Between Diabetes Mellitus and Tau Hyperphosphorylation: Implications for Risk of Alzheimer's Disease, *Cureus.* 13 (2021). <https://doi.org/10.7759/CUREUS.18362>.
- [50] Z.F. Wang, J. Yin, Y. Zhang, L.Q. Zhu, Q. Tian, X.C. Wang, H.L. Li, J.Z. Wang, Overexpression of Tau Proteins Antagonizes Amyloid- β -Potentiated Apoptosis Through Mitochondria-Caspase-3 Pathway in N2a Cells, *Journal of Alzheimer's Disease.* 20 (2010) 145–157. <https://doi.org/10.3233/JAD-2010-1351>.
- [51] L. Calcul, B. Zhang, U.K. Jinwal, C.A. Dickey, B.J. Baker, Natural products as a rich source of tau-targeting drugs for Alzheimer's disease, *Future Med Chem.* 4 (2012) 1751. <https://doi.org/10.4155/FMC.12.124>.
- [52] A.D. Snow, G.M. Castillo, B.P. Nguyen, P.Y. Choi, J.A. Cummings, J. Cam, Q. Hu, T. Lake, W. Pan, A.J. Kastin, D.A. Kirschner, S.G. Wood, E. Rockenstein, E. Masliah, S. Lorimer, R.E. Tanzi, L. Larsen, The Amazon rain forest plant *Uncaria tomentosa* (cat's claw) and its specific proanthocyanidin constituents are potent inhibitors and reducers of both brain plaques and tangles, *Sci Rep.* 9 (2019). <https://doi.org/10.1038/S41598-019-38645-0>.
- [53] S. Schweiger, F. Matthes, K. Posey, E. Kickstein, S. Weber, M.M. Hettich, S. Pfurtsheller, D. Ehninger, R. Schneider, S. Krauß, Resveratrol induces dephosphorylation of Tau by interfering with the MID1-PP2A complex, *Sci Rep.* 7 (2017). <https://doi.org/10.1038/S41598-017-12974-4>.
- [54] J.R. Jones, M.D. Lebar, U.K. Jinwal, J.F. Abisambra, J. Koren, L. Blair, J.C. O'Leary, Z. Davey, J. Trotter, A.G. Johnson, E. Weeber, C.B. Eckman, B.J. Baker, C.A. Dickey, The

Diarylheptanoid (+)-aR,11S-Myricanol and Two Flavones from Bayberry (*Myrica cerifera*) Destabilize the Microtubule Associated Protein Tau, *J Nat Prod.* 74 (2011) 38. <https://doi.org/10.1021/NP100572Z>.

[55] A. Ciechanover, P. Brundin, The Ubiquitin Proteasome System in Neurodegenerative Diseases: Sometimes the Chicken, Sometimes the Egg, *Neuron.* 40 (2003) 427–446. [https://doi.org/10.1016/S0896-6273\(03\)00606-8](https://doi.org/10.1016/S0896-6273(03)00606-8).

[56] A. Ciechanover, Y.T. Kwon, Protein quality control by molecular chaperones in neurodegeneration, *Front Neurosci.* 11 (2017) 245345. <https://doi.org/10.3389/FNINS.2017.00185>.

[57] Y. Li, S. Li, H. Wu, Ubiquitination-Proteasome System (UPS) and Autophagy Two Main Protein Degradation Machineries in Response to Cell Stress, *Cells.* 11 (2022). <https://doi.org/10.3390/CELLS11050851>.

[58] L. Huang, P. Ho, C.H. Chen, Activation and inhibition of proteasomes by betulinic acid and its derivatives, *FEBS Lett.* 581 (2007) 4955. <https://doi.org/10.1016/J.FEBSLET.2007.09.031>.

[59] Y. Liu, C.L. Hettinger, D. Zhang, K. Rezvani, X. Wang, H. Wang, Sulforaphane enhances proteasomal and autophagic activities in mice and is a potential therapeutic reagent for Huntington's disease, *J Neurochem.* 129 (2014) 539–547. <https://doi.org/10.1111/JNC.12647>.

[60] R. Santín-Márquez, A. Alarcón-Aguilar, N.E. López-Diazguerrero, N. Chondrogianni, M. Königsberg, Sulforaphane - role in aging and neurodegeneration, *Geroscience.* 41 (2019) 655. <https://doi.org/10.1007/S11357-019-00061-7>.

[61] S.F. Funderburk, B.K. Marcellino, Z. Yue, Cell “Self-Eating” (Autophagy) Mechanism in Alzheimer's Disease, *Mt Sinai J Med.* 77 (2010) 59. <https://doi.org/10.1002/MSJ.20161>.

[62] N.L. Wankhede, M.B. Kale, A.B. Upaganlawar, B.G. Taksande, M.J. Umekar, T. Behl, A.A.H. Abdellatif, P.M. Bhaskaran, S.R. Dachani, A. Sehgal, S. Singh, N. Sharma, H.A. Makeen, M. Albratty, H.G. Dailah, S. Bhatia, A. Al-Harrasi, S. Bungau, Involvement of molecular chaperone in protein-misfolding brain diseases, *Biomedicine & Pharmacotherapy.* 147 (2022) 112647. <https://doi.org/10.1016/J.BIOPHA.2022.112647>.

- [63] D. Park, H. Jeong, M.N. Lee, A. Koh, O. Kwon, Y.R. Yang, J. Noh, P.G. Suh, H. Park, S.H. Ryu, Resveratrol induces autophagy by directly inhibiting mTOR through ATP competition, *Sci Rep.* 6 (2016). <https://doi.org/10.1038/SREP21772>.
- [64] Z. Shi, H. Chen, X. Zhou, W. Yang, Y. Lin, Pharmacological effects of natural medicine ginsenosides against Alzheimer's disease, *Front Pharmacol.* 13 (2022). <https://doi.org/10.3389/FPHAR.2022.952332>.
- [65] D. Fan, L. Liu, Z. Wu, M. Cao, Combating Neurodegenerative Diseases with the Plant Alkaloid Berberine: Molecular Mechanisms and Therapeutic Potential, *Curr Neuropharmacol.* 17 (2019) 563. <https://doi.org/10.2174/1570159X16666180419141613>.
- [66] S. Zhang, Z. Yu, J. Xia, X. Zhang, K. Liu, A. Sik, M. Jin, Anti-Parkinson's disease activity of phenolic acids from *Eucommia ulmoides* Oliver leaf extracts and their autophagy activation mechanism, *Food Funct.* 11 (2020) 1425–1440. <https://doi.org/10.1039/C9FO02288K>.
- [67] Y.D. Boakye, L. Groyer, E.H. Heiss, An increased autophagic flux contributes to the anti-inflammatory potential of urolithin A in macrophages, *Biochim Biophys Acta Gen Subj.* 1862 (2018) 61–70. <https://doi.org/10.1016/J.BBAGEN.2017.10.006>.
- [68] L. Chen, H. Deng, H. Cui, J. Fang, Z. Zuo, J. Deng, Y. Li, X. Wang, L. Zhao, Inflammatory responses and inflammation-associated diseases in organs, *Oncotarget.* 9 (2018) 7204. <https://doi.org/10.18632/ONCOTARGET.23208>.
- [69] M. Sochocka, B.S. Diniz, J. Leszek, Inflammatory Response in the CNS: Friend or Foe?, *Mol Neurobiol.* 54 (2017) 8071. <https://doi.org/10.1007/S12035-016-0297-1>.
- [70] D. Nayak, T.L. Roth, D.B. McGavern, Microglia Development and function, *Annu Rev Immunol.* 32 (2014) 367. <https://doi.org/10.1146/ANNUREV-IMMUNOL-032713-120240>.
- [71] J.M. Zhang, J. An, Cytokines, Inflammation and Pain, *Int Anesthesiol Clin.* 45 (2007) 27. <https://doi.org/10.1097/AIA.0B013E318034194E>.
- [72] W.S. Chung, N.J. Allen, C. Eroglu, Astrocytes Control Synapse Formation, Function, and Elimination, *Cold Spring Harb Perspect Biol.* 7 (2015). <https://doi.org/10.1101/CSHPERSPECT.A020370>.

- [73] G.R. Frost, Y.M. Li, The role of astrocytes in amyloid production and Alzheimer's disease, *Open Biol.* 7 (2017). <https://doi.org/10.1098/RSOB.170228>.
- [74] P.L. McGeer, E.G. McGeer, The amyloid cascade-inflammatory hypothesis of Alzheimer disease: implications for therapy, *Acta Neuropathol.* 126 (2013) 479–497. <https://doi.org/10.1007/S00401-013-1177-7>.
- [75] M.A. Meraz-Ríos, D. Toral-Rios, D. Franco-Bocanegra, J. Villeda-Hernández, V. Campos-Peña, Inflammatory process in Alzheimer's Disease, *Front Integr Neurosci.* 7 (2013) 55461. <https://doi.org/10.3389/FNINT.2013.00059>.
- [76] V. Gupta, R. Guleri, M. Gupta, N. Kaur, K. Kaur, P. Kumar, M. Anand, G. Kaur, P.K. Pati, Anti-neuroinflammatory potential of *Tylophora indica* (Burm. f) Merrill and development of an efficient in vitro propagation system for its clinical use, *PLoS One.* 15 (2020) e0230142. <https://doi.org/10.1371/JOURNAL.PONE.0230142>.
- [77] D. Singh, Astrocytic and microglial cells as the modulators of neuroinflammation in Alzheimer's disease, *J Neuroinflammation.* 19 (2022) 206. <https://doi.org/10.1186/S12974-022-02565-0>.
- [78] R. Das, D.K. Mehta, M. Dhanawat, Medicinal Plants in Cancer Treatment: Contribution of Nuclear Factor- Kappa B (NF-kB) Inhibitors, *Mini Rev Med Chem.* 22 (2022) 1938–1962. <https://doi.org/10.2174/1389557522666220307170126>.
- [79] Z. Blach-Olszewska, J. Leszek, Mechanisms of over-activated innate immune system regulation in autoimmune and neurodegenerative disorders, *Neuropsychiatr Dis Treat.* 3 (2007) 365. <https://pubmed.ncbi.nlm.nih.gov/1654796/>.
- [80] B. Alberts, A. Johnson, J. Lewis, M. Raff, K. Roberts, P. Walter, *Lymphocytes and the Cellular Basis of Adaptive Immunity*, (2002). <https://www.ncbi.nlm.nih.gov/books/NBK26921>.
- [81] X. Zhu, J. Zhu, CD4 T Helper Cell Subsets and Related Human Immunological Disorders, *Int J Mol Sci.* 21 (2020) 1–26. <https://doi.org/10.3390/IJMS21218011>.
- [82] J. Xie, L. Van Hoecke, R.E. Vandembroucke, The Impact of Systemic Inflammation on Alzheimer's Disease Pathology, *Front Immunol.* 12 (2021). <https://doi.org/10.3389/FIMMU.2021.796867>.

- [83] J. Fu, Y. Huang, T. Bao, C. Liu, X. Liu, X. Chen, The role of Th17 cells/IL-17A in AD, PD, ALS and the strategic therapy targeting on IL-17A, *J Neuroinflammation*. 19 (2022). <https://doi.org/10.1186/S12974-022-02446-6>.
- [84] M. Moutia, F. Seghrouchni, O. Abouelazz, A. Elouaddari, A. Al Jahid, A. Elhou, S. Nadifi, J. Jamal Eddine, N. Habti, A. Badou, *Allium sativum* L. regulates in vitro IL-17 gene expression in human peripheral blood mononuclear cells, *BMC Complement Altern Med*. 16 (2016). <https://doi.org/10.1186/S12906-016-1365-9>.
- [85] X. Li, L. Zhao, J.J. Han, F. Zhang, S. Liu, L. Zhu, Z.Z. Wang, G.X. Zhang, Y. Zhang, Carnosol modulates Th17 cell differentiation and microglial switch in experimental autoimmune encephalomyelitis, *Front Immunol*. 9 (2018) 1807. <https://doi.org/10.3389/FIMMU.2018.01807>.
- [86] J.M. Damsker, A.M. Hansen, R.R. Caspi, Th1 and Th17 cells: Adversaries and collaborators, *Ann N Y Acad Sci*. 1183 (2010) 211. <https://doi.org/10.1111/J.1749-6632.2009.05133.X>.
- [87] A. Berger, Science commentary: Th1 and Th2 responses: what are they?, *BMJ : British Medical Journal*. 321 (2000) 424. <https://doi.org/10.1136/BMJ.321.7258.424>.
- [88] E. Ricciotti, G.A. Fitzgerald, Prostaglandins and Inflammation, *Arterioscler Thromb Vasc Biol*. 31 (2011) 986. <https://doi.org/10.1161/ATVBAHA.110.207449>.
- [89] P.S. Minhas, A. Latif-Hernandez, M.R. McReynolds, A.S. Durairaj, Q. Wang, A. Rubin, A.U. Joshi, J.Q. He, E. Gauba, L. Liu, C. Wang, M. Linde, Y. Sugiura, P.K. Moon, R. Majeti, M. Suematsu, D. Mochly-Rosen, I.L. Weissman, F.M. Longo, J.D. Rabinowitz, K.I. Andreasson, Restoring metabolism of myeloid cells reverses cognitive decline in ageing, *Nature*. 590 (2021) 122. <https://doi.org/10.1038/S41586-020-03160-0>.
- [90] K. Nakatani, N. Nakahata, T. Arakawa, H. Yasuda, Y. Ohizumi, Inhibition of cyclooxygenase and prostaglandin E2 synthesis by γ -mangostin, a xanthone derivative in mangosteen, in C6 rat glioma cells, *Biochem Pharmacol*. 63 (2002) 73–79. [https://doi.org/10.1016/S0006-2952\(01\)00810-3](https://doi.org/10.1016/S0006-2952(01)00810-3).
- [91] G.L. He, Z. Luo, J. Yang, T.T. Shen, Y. Chen, X. Sen Yang, Curcumin Ameliorates the Reduction Effect of PGE2 on Fibrillar β -Amyloid Peptide (1-42)-Induced Microglial

Phagocytosis through the Inhibition of EP2-PKA Signaling in N9 Microglial Cells, *PLoS One*. 11 (2016). <https://doi.org/10.1371/JOURNAL.PONE.0147721>.

[92] E. Tönnies, E. Trushina, Oxidative Stress, Synaptic Dysfunction, and Alzheimer's Disease, *Journal of Alzheimer's Disease*. 57 (2017) 1105–1121. <https://doi.org/10.3233/JAD-161088>.

[93] S. Di Meo, T.T. Reed, P. Venditti, V.M. Victor, Role of ROS and RNS Sources in Physiological and Pathological Conditions, *Oxid Med Cell Longev*. 2016 (2016). <https://doi.org/10.1155/2016/1245049>.

[94] B.L. Tan, M.E. Norhaizan, W.P.P. Liew, H.S. Rahman, Antioxidant and Oxidative Stress: A Mutual Interplay in Age-Related Diseases, *Front Pharmacol*. 9 (2018) 1162. <https://doi.org/10.3389/FPHAR.2018.01162>.

[95] L. Zhao, J.L. Wang, R. Liu, X.X. Li, J.F. Li, L. Zhang, Neuroprotective, Anti-Amyloidogenic and Neurotrophic Effects of Apigenin in an Alzheimer's Disease Mouse Model, *Molecules*. 18 (2013) 9949. <https://doi.org/10.3390/MOLECULES18089949>.

[96] P. Mucha, A. Skoczyńska, M. Małecka, P. Hikiş, E. Budzisz, Overview of the Antioxidant and Anti-Inflammatory Activities of Selected Plant Compounds and Their Metal Ions Complexes, *Molecules*. 26 (2021). <https://doi.org/10.3390/MOLECULES26164886>.

[97] J. Kim, Y.N. Cha, Y.J. Surh, A protective role of nuclear factor-erythroid 2-related factor-2 (Nrf2) in inflammatory disorders, *Mutat Res*. 690 (2010) 12–23. <https://doi.org/10.1016/J.MRFMMM.2009.09.007>.

[98] B. Salehi, L. Machin, L. Monzote, J. Sharifi-Rad, S.M. Ezzat, M.A. Salem, R.M. Merghany, N.M. El Mahdy, C.S. Killıç, O. Sytar, M. Sharifi-Rad, F. Sharopov, N. Martins, M. Martorell, W.C. Cho, Therapeutic Potential of Quercetin: New Insights and Perspectives for Human Health, *ACS Omega*. 5 (2020) 11849. <https://doi.org/10.1021/ACSOMEGA.0C01818>.

[99] T.P. Xu, H. Shen, L.X. Liu, Y.Q. Shu, Plumbagin from *Plumbago Zeylanica* L induces apoptosis in human non-small cell lung cancer cell lines through NF- κ B inactivation, *Asian Pac J Cancer Prev*. 14 (2013) 2325–2331. <https://doi.org/10.7314/APJCP.2013.14.4.2325>.

- [100] R.H. Swerdlow, J.M. Burns, S.M. Khan, The Alzheimer's Disease Mitochondrial Cascade Hypothesis, *J Alzheimers Dis.* 20 (2010) 265. <https://doi.org/10.3233/JAD-2010-100339>.
- [101] J.M. Perez Ortiz, R.H. Swerdlow, Mitochondrial dysfunction in Alzheimer's disease: Role in pathogenesis and novel therapeutic opportunities, *Br J Pharmacol.* 176 (2019) 3489. <https://doi.org/10.1111/BPH.14585>.
- [102] A. Atlante, G. Amadoro, V. Latina, D. Valenti, Therapeutic Potential of Targeting Mitochondria for Alzheimer's Disease Treatment, *J Clin Med.* 11 (2022). <https://doi.org/10.3390/JCM11226742>.
- [103] T.H. Chung, J.H. Kim, S.Y. Seol, Y.J. Kim, Y.J. Lee, The Effects of Korean Red Ginseng on Biological Aging and Antioxidant Capacity in Postmenopausal Women: A Double-Blind Randomized Controlled Study, *Nutrients.* 13 (2021). <https://doi.org/10.3390/NU13093090>.
- [104] D.L. Barton, H. Liu, S.R. Dakhil, B. Linqvist, J.A. Sloan, C.R. Nichols, T.W. McGinn, P.J. Stella, G.R. Seeger, A. Sood, C.L. Loprinzi, Wisconsin Ginseng (*Panax quinquefolius*) to improve cancer-related fatigue: a randomized, double-blind trial, N07C2, *J Natl Cancer Inst.* 105 (2013) 1230–1238. <https://doi.org/10.1093/JNCI/DJT181>.
- [105] Y. Wang, Y. Wang, S. Li, H. Jin, J. Duan, X. Lu, Y. Qin, J. Song, X. Li, X. Jin, Insights of Chinese herbal medicine for mitochondrial dysfunction in chronic cerebral hypoperfusion induced cognitive impairment: Existed evidences and potential directions, *Front Pharmacol.* 14 (2023). <https://doi.org/10.3389/FPHAR.2023.1138566>.
- [106] D. Kang, N. Hamasaki, Maintenance of mitochondrial DNA integrity: repair and degradation, *Curr Genet.* 41 (2002) 311–322. <https://doi.org/10.1007/S00294-002-0312-0>.
- [107] J. Tian, G. Li, Z. Liu, F. Fu, Hydroxysafflor yellow A inhibits rat brain mitochondrial permeability transition pores by a free radical scavenging action, *Pharmacology.* 82 (2008) 121–126. <https://doi.org/10.1159/000141653>.
- [108] H.G. Kim, J.H. Cho, S.R. Yoo, J.S. Lee, J.M. Han, N.H. Lee, Y.C. Ahn, C.G. Son, Antifatigue Effects of *Panax ginseng* C.A. Meyer: A Randomised, Double-Blind, Placebo-

Controlled Trial, PLoS One. 8 (2013) e61271. <https://doi.org/10.1371/JOURNAL.PONE.0061271>.

[109] A.M. Bond, G.L. Ming, H. Song, Adult Mammalian Neural Stem Cells and Neurogenesis: Five Decades Later, *Cell Stem Cell*. 17 (2015) 385. <https://doi.org/10.1016/J.STEM.2015.09.003>.

[110] M. Demars, Y.S. Hu, A. Gadadhar, O. Lazarov, Impaired Neurogenesis is an early event in the etiology of Familial Alzheimer's disease in transgenic mice, *J Neurosci Res*. 88 (2010) 2103. <https://doi.org/10.1002/JNR.22387>.

[111] E.P. Moreno-Jiménez, M. Flor-García, J. Terreros-Roncal, A. Rábano, F. Cafini, N. Pallas-Bazarra, J. Ávila, M. Llorens-Martín, Adult hippocampal neurogenesis is abundant in neurologically healthy subjects and drops sharply in patients with Alzheimer's disease, *Nat Med*. 25 (2019) 554–560. <https://doi.org/10.1038/S41591-019-0375-9>.

[112] S. Zafar, A. Rasul, J. Iqbal, H. Anwar, A. Imran, F. Jabeen, A. Shabbir, R. Akram, J. Maqbool, F. Sajid, M.U. Arshad, G. Hussain, S. Islam, *Calotropis procera* (leaves) supplementation exerts curative effects on promoting functional recovery in a mouse model of peripheral nerve injury., *Food Sci Nutr*. 9 (2021) 5016–5027. <https://doi.org/10.1002/fsn3.2455>.

[113] S.J. Park, Y.J. Ahn, H.E. Lee, E. Hong, J.H. Ryu, Standardized *Prunella vulgaris* var. *lilacina* Extract Enhances Cognitive Performance in Normal Naive Mice, *Phytother Res*. 29 (2015) 1814–1821. <https://doi.org/10.1002/PTR.5449>.

[114] C. Tohda, E. Joyashiki, Somnifene enhances neurite outgrowth and spatial memory mediated by the neurotrophic factor receptor, RET, *Br J Pharmacol*. 157 (2009) 1427. <https://doi.org/10.1111/J.1476-5381.2009.00313.X>.

[115] S. Sen Leow, S.D. Sekaran, Y.A. Tan, K. Sundram, R. Sambanthamurthi, Oil palm phenolics confer neuroprotective effects involving cognitive and motor functions in mice, *Nutr Neurosci*. 16 (2013) 207. <https://doi.org/10.1179/1476830512Y.0000000047>.

[116] M.B. Colovic, D.Z. Krstic, T.D. Lazarevic-Pasti, A.M. Bondzic, V.M. Vasic, Acetylcholinesterase Inhibitors: Pharmacology and Toxicology, *Curr Neuropharmacol*. 11 (2013) 315. <https://doi.org/10.2174/1570159X11311030006>.

- [117] L.M.T. Lam, M.T.T. Nguyen, H.X. Nguyen, P.H. Dang, N.T. Nguyen, H.M. Tran, H.T. Nguyen, N.M. Nguyen, B.S. Min, J.A. Kim, J.S. Choi, M. Can, Anti-cholinesterases and memory improving effects of Vietnamese *Xylia xylocarpa*, *Chem Cent J.* 10 (2016). <https://doi.org/10.1186/S13065-016-0197-5>.
- [118] P.M.K. Sundaramoorthy, K.K. Packiam, In vitro enzyme inhibitory and cytotoxic studies with *Evolvulus alsinoides* (Linn.) Linn. Leaf extract: a plant from Ayurveda recognized as Dasapushpam for the management of Alzheimer's disease and diabetes mellitus, *BMC Complement Med Ther.* 20 (2020). <https://doi.org/10.1186/S12906-020-02922-7>.
- [119] M. He, J. Kim, C. Park, E. Cho, Herbal Mixture of *Carthamus tinctorius* L. Seed and *Taraxacum coreanum* Attenuates Amyloid Beta-Induced Cognitive Dysfunction In Vivo, *Foods.* 11 (2022). <https://doi.org/10.3390/FOODS11020142>.
- [120] P. Kashyap, K. Muthusamy, M. Niranjana, S. Tripathi, S. Kumar, Sarsasapogenin: A steroidal saponin from *Asparagus racemosus* as multi target directed ligand in Alzheimer's disease, *Steroids.* 153 (2020) 108529. <https://doi.org/10.1016/J.STEROIDS.2019.108529>.
- [121] V.P. Menon, A.R. Sudheer, Antioxidant and anti-inflammatory properties of curcumin, *Adv Exp Med Biol.* 595 (2007) 105–125. https://doi.org/10.1007/978-0-387-46401-5_3.
- [122] J. Yan, J. Hu, A. Liu, L. He, X. Li, H. Wei, Design, synthesis, and evaluation of multitarget-directed ligands against Alzheimer's disease based on the fusion of donepezil and curcumin, *Bioorg Med Chem.* 25 (2017) 2946–2955. <https://doi.org/10.1016/J.BMC.2017.02.048>.
- [123] S. Wang, X. Peng, L. Cui, T. Li, B. Yu, G. Ma, X. Ba, Synthesis of water-soluble curcumin derivatives and their inhibition on lysozyme amyloid fibrillation, *Spectrochim Acta A Mol Biomol Spectrosc.* 190 (2018) 89–95. <https://doi.org/10.1016/J.SAA.2017.09.010>.
- [124] L. Cui, S. Wang, J. Zhang, M. Wang, Y. Gao, L. Bai, H. Zhang, G. Ma, X. Ba, Effect of curcumin derivatives on hen egg white lysozyme amyloid fibrillation and their interaction study by spectroscopic methods, *Spectrochim Acta A Mol Biomol Spectrosc.* 223 (2019). <https://doi.org/10.1016/J.SAA.2019.117365>.
- [125] J. Lakey-Beitia, Y. González, D. Doens, D.E. Stephens, R. Santamaría, E. Murillo, M. Gutiérrez, P.L. Fernández, K.S. Rao, O. V. Larionov, A.A. Durant-Archibold, Assessment of

Novel Curcumin Derivatives as Potent Inhibitors of Inflammation and Amyloid- β Aggregation in Alzheimer's Disease, *Journal of Alzheimer's Disease*. 60 (2017) S59–S68. <https://doi.org/10.3233/JAD-170071>.

[126] M. Okuda, I. Hijikuro, Y. Fujita, T. Teruya, H. Kawakami, T. Takahashi, H. Sugimoto, Design and synthesis of curcumin derivatives as tau and amyloid β dual aggregation inhibitors, *Bioorg Med Chem Lett*. 26 (2016) 5024–5028. <https://doi.org/10.1016/J.BMCL.2016.08.092>.

[127] Y. Li, P. Peng, L. Tang, Y. Hu, Y. Hu, R. Sheng, Design, synthesis and evaluation of rivastigmine and curcumin hybrids as site-activated multitarget-directed ligands for Alzheimer's disease therapy, *Bioorg Med Chem*. 22 (2014) 4717–4725. <https://doi.org/10.1016/J.BMC.2014.07.009>.

[128] Z. Liu, L. Fang, H. Zhang, S. Gou, L. Chen, Design, synthesis and biological evaluation of multifunctional tacrine-curcumin hybrids as new cholinesterase inhibitors with metal ions-chelating and neuroprotective property, *Bioorg Med Chem*. 25 (2017) 2387–2398. <https://doi.org/10.1016/J.BMC.2017.02.049>.

[129] K.S.T. Dias, C.T. de Paula, T. dos Santos, I.N.O. Souza, M.S. Boni, M.J.R. Guimarães, F.M.R. da Silva, N.G. Castro, G.A. Neves, C.C. Veloso, M.M. Coelho, I.S.F. de Melo, F.C.V. Giusti, A. Giusti-Paiva, M.L. da Silva, L.E. Dardenne, I.A. Guedes, L. Pruccoli, F. Morroni, A. Tarozzi, C. Viegas, Design, synthesis and evaluation of novel feruloyl-donepezil hybrids as potential multitarget drugs for the treatment of Alzheimer's disease, *Eur J Med Chem*. 130 (2017) 440–457. <https://doi.org/10.1016/J.EJMECH.2017.02.043>.

[130] R. Jagannathan, P.M. Abraham, P. Poddar, Temperature-dependent spectroscopic evidences of curcumin in aqueous medium: a mechanistic study of its solubility and stability, *J Phys Chem B*. 116 (2012) 14533–14540. <https://doi.org/10.1021/JP3050516>.

[131] P.H. Reddy, M. Manczak, X. Yin, M.C. Grady, A. Mitchell, S. Tonk, C.S. Kuruva, J.S. Bhatti, R. Kandimalla, M. Vijayan, S. Kumar, R. Wang, J.A. Pradeepkiran, G. Ogunmokun, K. Thamarai, K. Quesada, A. Boles, A.P. Reddy, Protective Effects of Indian Spice Curcumin Against Amyloid Beta in Alzheimer's Disease, *J Alzheimers Dis*. 61 (2018) 843. <https://doi.org/10.3233/JAD-170512>.

[132] L.F. Pan, X.B. Wang, S.S. Xie, S.Y. Li, L.Y. Kong, Multitarget-directed resveratrol derivatives: anti-cholinesterases, anti- β -amyloid aggregation and monoamine oxidase

inhibition properties against Alzheimer's disease, *Medchemcomm.* 5 (2014) 609–616. <https://doi.org/10.1039/C3MD00376K>.

[133] C. Lu, Y. Guo, J. Yan, Z. Luo, H. Bin Luo, M. Yan, L. Huang, X. Li, Design, synthesis, and evaluation of multitarget-directed resveratrol derivatives for the treatment of Alzheimer's disease, *J Med Chem.* 56 (2013) 5843–5859. <https://doi.org/10.1021/JM400567S>.

[134] M. Przybyłowska, S. Kowalski, K. Dzierzbicka, I. Inkielewicz-Stepniak, Therapeutic Potential of Multifunctional Tacrine Analogues, *Curr Neuropharmacol.* 17 (2019) 472. <https://doi.org/10.2174/1570159X16666180412091908>.

[135] G. Cheng, P. Xu, M. Zhang, J. Chen, R. Sheng, Y. Ma, Resveratrol-maltol hybrids as multi-target-directed agents for Alzheimer's disease, *Bioorg Med Chem.* 26 (2018) 5759–5765. <https://doi.org/10.1016/J.BMC.2018.08.011>.

[136] T. Puksasook, S. Kimura, S. Tadtong, J. Jiaranaikulwanitch, J. Pratuangdejkul, W. Kitphati, K. Suwanborirux, N. Saito, V. Nukoolkarn, Semisynthesis and biological evaluation of prenylated resveratrol derivatives as multi-targeted agents for Alzheimer's disease, *J Nat Med.* 71 (2017) 665–682. <https://doi.org/10.1007/S11418-017-1097-2>.

[137] Y.W. Tang, C.J. Shi, H.L. Yang, P. Cai, Q.H. Liu, X.L. Yang, L.Y. Kong, X.B. Wang, Synthesis and evaluation of isoprenylation-resveratrol dimer derivatives against Alzheimer's disease, *Eur J Med Chem.* 163 (2019) 307–319. <https://doi.org/10.1016/J.EJMECH.2018.11.040>.

[138] P. Xu, M. Zhang, R. Sheng, Y. Ma, Synthesis and biological evaluation of deferiprone-resveratrol hybrids as antioxidants, A β 1-42 aggregation inhibitors and metal-chelating agents for Alzheimer's disease, *Eur J Med Chem.* 127 (2017) 174–186. <https://doi.org/10.1016/J.EJMECH.2016.12.045>.

[139] X. Yang, X. Qiang, Y. Li, L. Luo, R. Xu, Y. Zheng, Z. Cao, Z. Tan, Y. Deng, Pyridoxine-resveratrol hybrids Mannich base derivatives as novel dual inhibitors of AChE and MAO-B with antioxidant and metal-chelating properties for the treatment of Alzheimer's disease, *Bioorg Chem.* 71 (2017) 305–314. <https://doi.org/10.1016/J.BIOORG.2017.02.016>.

[140] S.Y. Li, X.B. Wang, S.S. Xie, N. Jiang, K.D.G. Wang, H.Q. Yao, H. Bin Sun, L.Y. Kong, Multifunctional tacrine-flavonoid hybrids with cholinergic, β -amyloid-reducing, and metal

chelating properties for the treatment of Alzheimer's disease, *Eur J Med Chem.* 69 (2013) 632–646. <https://doi.org/10.1016/J.EJMECH.2013.09.024>.

[141] X.B. Wang, F.C. Yin, M. Huang, N. Jiang, J.S. Lan, L.Y. Kong, Chromone and donepezil hybrids as new multipotent cholinesterase and monoamine oxidase inhibitors for the potential treatment of Alzheimer's disease, *RSC Med Chem.* 11 (2020) 225–233. <https://doi.org/10.1039/C9MD00441F>.

[142] I. Pachón-Angona, B. Refouvelet, R. Andrýs, H. Martín, V. Luzet, I. Iriepa, I. Moraleda, D. Díez-Iriepa, M.J. Oset-Gasque, J. Marco-Contelles, K. Musilek, L. Ismaili, Donepezil + chromone + melatonin hybrids as promising agents for Alzheimer's disease therapy, *J Enzyme Inhib Med Chem.* 34 (2019) 479–489. <https://doi.org/10.1080/14756366.2018.1545766>.

[143] F. Li, J.J. Wu, J. Wang, X.L. Yang, P. Cai, Q.H. Liu, L.Y. Kong, X.B. Wang, Synthesis and pharmacological evaluation of novel chromone derivatives as balanced multifunctional agents against Alzheimer's disease, *Bioorg Med Chem.* 25 (2017) 3815–3826. <https://doi.org/10.1016/J.BMC.2017.05.027>.

[144] J. Reis, F. Cagide, M.E. Valencia, J. Teixeira, D. Bagetta, C. Pérez, E. Uriarte, P.J. Oliveira, F. Ortuso, S. Alcaro, M.I. Rodríguez-Franco, F. Borges, Multi-target-directed ligands for Alzheimer's disease: Discovery of chromone-based monoamine oxidase/cholinesterase inhibitors., *Eur J Med Chem.* 158 (2018) 781–800. <https://doi.org/10.1016/J.EJMECH.2018.07.056>.

[145] K.R. Valasani, G. Hu, M.O. Chaney, S.S. Yan, Structure-based design and synthesis of benzothiazole phosphonate analogues with inhibitors of human ABAD-A β for treatment of Alzheimer's disease, *Chem Biol Drug Des.* 81 (2013) 238–249. <https://doi.org/10.1111/CBDD.12068>.

[146] S. Shaikh, P. Dhavan, M.M.V. Ramana, B.L. Jadhav, Design, synthesis and evaluation of new chromone-derived aminophosphonates as potential acetylcholinesterase inhibitor, *Mol Divers.* 25 (2021) 811–825. <https://doi.org/10.1007/S11030-020-10060-Y>.

[147] X.T. Luo, C.M. Wang, Y. Liu, Z.G. Huang, New multifunctional melatonin-derived benzylpyridinium bromides with potent cholinergic, antioxidant, and neuroprotective properties as innovative drugs for Alzheimer's disease, *Eur J Med Chem.* 103 (2015) 302–311. <https://doi.org/10.1016/J.EJMECH.2015.08.052>.

- [148] J. Wang, Z.M. Wang, X.M. Li, F. Li, J.J. Wu, L.Y. Kong, X.B. Wang, Synthesis and evaluation of multi-target-directed ligands for the treatment of Alzheimer's disease based on the fusion of donepezil and melatonin, *Bioorg Med Chem.* 24 (2016) 4324–4338. <https://doi.org/10.1016/J.BMC.2016.07.025>.
- [149] D. Puzzo, A. Staniszewski, S. XianDeng, L. Privitera, E. Leznik, S. Liu, H. Zhang, Y. Feng, A. Palmeri, D.W. Landry, O. Arancio, Phosphodiesterase 5 inhibition improves synaptic function, memory, and amyloid-beta load in an Alzheimer's disease mouse model, *J Neurosci.* 29 (2009) 8075–8086. <https://doi.org/10.1523/JNEUROSCI.0864-09.2009>.
- [150] F. Mao, H. Wang, W. Ni, X. Zheng, M. Wang, K. Bao, D. Ling, X. Li, Y. Xu, H. Zhang, J. Li, Design, Synthesis, and Biological Evaluation of Orally Available First-Generation Dual-Target Selective Inhibitors of Acetylcholinesterase (AChE) and Phosphodiesterase 5 (PDE5) for the Treatment of Alzheimer's Disease, *ACS Chem Neurosci.* 9 (2018) 328–345. <https://doi.org/10.1021/ACSCHEMNEURO.7B00345>.
- [151] J. Lalut, G. Santoni, D. Karila, C. Lecoutey, A. Davis, F. Nachon, I. Silman, J. Sussman, M. Weik, T. Maurice, P. Dallemagne, C. Rochais, Novel multitarget-directed ligands targeting acetylcholinesterase and σ_1 receptors as lead compounds for treatment of Alzheimer's disease: Synthesis, evaluation, and structural characterization of their complexes with acetylcholinesterase, *Eur J Med Chem.* 162 (2019) 234–248. <https://doi.org/10.1016/J.EJMECH.2018.10.064>.
- [152] J. Rodríguez-Lavado, C. Gallardo-Garrido, M. Mallea, V. Bustos, R. Osorio, M. Hödar-Salazar, H. Chung, R. Araya-Maturana, M. Lorca, C.D. Pessoa-Mahana, J. Mella-Raipán, C. Saitz, P. Jaque, M. Reyes-Parada, P. Iturriaga-Vásquez, H. Pessoa-Mahana, Synthesis, in vitro evaluation and molecular docking of a new class of indolylpropyl benzamidopiperazines as dual AChE and SERT ligands for Alzheimer's disease, *Eur J Med Chem.* 198 (2020) 112368. <https://doi.org/10.1016/J.EJMECH.2020.112368>.
- [153] A. Shoaib, A systematic ethnobotanical review of *Adhatoda vasica* (L.), Nees, *Cell Mol Biol (Noisy-Le-Grand).* 67 (2022) 248–263. <https://doi.org/10.14715/CMB/2021.67.4.28>.
- [154] R. Khan, Y. Shamsi, S. Nikhat, MEDICINAL BENEFITS OF ADHATODA VASICA NEES.-IN UNANI AND CONTEMPORARY MEDICINE, *CELLMED.* 10 (2020) 13.1-13.7. <https://doi.org/10.5667/CELLMED.2020.0013>.

- [155] W. Liu, Y. Wang, D.D. He, S.P. Li, Y.D. Zhu, B. Jiang, X.M. Cheng, Z.T. Wang, C.H. Wang, Antitussive, expectorant, and bronchodilating effects of quinazoline alkaloids (\pm)-vasicine, deoxyvasicine, and (\pm)-vasicinone from aerial parts of *Peganum harmala* L, *Phytomedicine*. 22 (2015) 1088–1095. <https://doi.org/10.1016/J.PHYMED.2015.08.005>.
- [156] A. Tiwari, K.R. Mahadik, S.Y. Gabhe, Piperine: A comprehensive review of methods of isolation, purification, and biological properties, *Med Drug Discov*. 7 (2020) 100027. <https://doi.org/10.1016/J.MEDIDD.2020.100027>.
- [157] L. V. Vieira, M.E. Maria, M. Krause, O.A. Heringer, J.S. Ribeiro, G.P. Brandão, R.M. Kuster, M.T.W.D. Carneiro, The effects of drying methods and harvest season on piperine, essential oil composition, and multi-elemental composition of black pepper, *Food Chem*. 390 (2022) 133148. <https://doi.org/10.1016/J.FOODCHEM.2022.133148>.
- [158] R.K. Bhardwaj, H. Glaeser, L. Becquemont, U. Klotz, S.K. Gupta, M.F. Fromm, Piperine, a major constituent of black pepper, inhibits human P-glycoprotein and CYP3A4, *J Pharmacol Exp Ther*. 302 (2002) 645–650. <https://doi.org/10.1124/JPET.102.034728>.
- [159] A.K. Tripathi, A.K. Ray, S.K. Mishra, Molecular and pharmacological aspects of piperine as a potential molecule for disease prevention and management: evidence from clinical trials, *Beni Suef Univ J Basic Appl Sci*. 11 (2022) 16. <https://doi.org/10.1186/S43088-022-00196-1>.
- [160] J.S. Bang, D.H. Oh, H.M. Choi, B.J. Sur, S.J. Lim, J.Y. Yeon, H.I. Yang, M.C. Chul, D.H. Hahm, K.S. Kim, Anti-inflammatory and antiarthritic effects of piperine in human interleukin 1 β -stimulated fibroblast-like synoviocytes and in rat arthritis models, *Arthritis Res Ther*. 11 (2009) R49. <https://doi.org/10.1186/AR2662>.
- [161] G. Singh, *International Journal of Pharmacognosy and Chinese Medicine Piperine: A Remarkable Marker with Intense Biological Activity*, (n.d.).
- [162] R. Prasad, A. Singh, N. Gupta, C. Tarke, Role of Bioenhancers in Tuberculosis, *International Journal of Health Sciences & Research (Www.Ijhsr.Org)*. 6 (2016) 307. www.ijhsr.org.
- [163] U.H. Park, H.S. Jeong, E.Y. Jo, T. Park, S.K. Yoon, E.J. Kim, J.C. Jeong, S.J. Um, Piperine, a component of black pepper, inhibits adipogenesis by antagonizing PPAR γ activity

in 3T3-L1 cells, *J Agric Food Chem.* 60 (2012) 3853–3860. <https://doi.org/10.1021/JF204514A>.

[164] N. Atal, K.L. Bedi, Bioenhancers: Revolutionary concept to market, *J Ayurveda Integr Med.* 1 (2010) 96. <https://doi.org/10.4103/0975-9476.65073>.

[165] B. Peterson, M. Weyers, J.H. Steenekamp, J.D. Steyn, C. Gouws, J.H. Hamman, Drug Bioavailability Enhancing Agents of Natural Origin (Bioenhancers) that Modulate Drug Membrane Permeation and Pre-Systemic Metabolism, *Pharmaceutics.* 11 (2019). <https://doi.org/10.3390/PHARMACEUTICS11010033>.

[166] M. Ravindra Babu, B. Sai Kumar, B. Ragini, A.B. Sravani, Emerging Diverse Medicinal Properties of Piperine: A Review, (n.d.).

[167] M. Ravindra Babu, B. Sai Kumar, B. Ragini, A.B. Sravani, Emerging Diverse Medicinal Properties of Piperine: A Review, (n.d.).

[168] G. Gutti, R. Kakarla, D. Kumar, M. Beohar, A. Ganeshpurkar, A. Kumar, S. Krishnamurthy, S.K. %J E.J. of M.C. Singh, Discovery of novel series of 2-substituted benzo [d] oxazol-5-amine derivatives as multi-target directed ligands for the treatment of Alzheimer's disease, 182 (2019) 111613. <https://doi.org/https://doi.org/10.1016/j.ejmech.2019.111613>.

[169] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules., *Sci Rep.* 7 (2017) 42717. <https://doi.org/10.1038/srep42717>.

[170] S.K. Seoul, bioinformatics and molecular design research center; 2004, PreADMET Program. Available from: URL: <Http://Preadmet.Bmdrc.Org>. (2004).

[171] J. Cheung, M.J. Rudolph, F. Burshteyn, M.S. Cassidy, E.N. Gary, J. Love, M.C. Franklin, J.J. Height, Structures of human acetylcholinesterase in complex with pharmacologically important ligands., *J Med Chem.* 55 (2012) 10282–10286. <https://doi.org/10.1021/jm300871x>.

[172] F. Nachon, E. Carletti, C. Ronco, M. Trovaslet, Y. Nicolet, L. Jean, P.-Y. Renard, Crystal structures of human cholinesterases in complex with huprine W and tacrine: elements of specificity for anti-Alzheimer's drugs targeting acetyl- and butyryl-cholinesterase., *Biochem J.* 453 (2013) 393–399. <https://doi.org/10.1042/BJ20130013>.

- [173] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne, The Protein Data Bank., *Nucleic Acids Res.* 28 (2000) 235–242. <https://doi.org/10.1093/nar/28.1.235>.
- [174] G.M. Morris, R. Huey, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility, *J Comput Chem.* 30 (2009) 2785–2791.
- [175] D.S. BiOVIA, Discovery Studio 2019. San Diego: Dassault Systèmes; 2019, (2021).
- [176] S. Release, 1: Maestro Desmond Interoperability Tools, Schrödinger: New York, NY, USA. (2020).
- [177] Y.P. Singh, G.N.V.C. Tej, A. Pandey, K. Priya, P. Pandey, G. Shankar, P.K. Nayak, G. Rai, A.G. Chittiboyina, R.J. %J E.J. of M.C. Doerksen, Design, synthesis and biological evaluation of novel naturally-inspired multifunctional molecules for the management of Alzheimer’s disease, 198 (2020) 112257. <https://doi.org/10.1016/j.ejmech.2020.112257>.
- [178] P. Sharma, A. Tripathi, P.N. Tripathi, S.K. Prajapati, A. Seth, M.K. Tripathi, P. Srivastava, V. Tiwari, S. Krishnamurthy, S.K. Shrivastava, Design and development of multitarget-directed N-Benzylpiperidine analogs as potential candidates for the treatment of Alzheimer’s disease., *Eur J Med Chem.* 167 (2019) 510–524. <https://doi.org/10.1016/j.ejmech.2019.02.030>.
- [179] D. Kumar, S.K. Gupta, A. Ganeshpurkar, G. Gutti, S. Krishnamurthy, G. Modi, S.K. Singh, Development of Piperazinediones as dual inhibitor for treatment of Alzheimer’s disease., *Eur J Med Chem.* 150 (2018) 87–101. <https://doi.org/10.1016/j.ejmech.2018.02.078>.
- [180] OECD, Test No. 423: Acute Oral toxicity - Acute Toxic Class Method, *Oecd Guideline for Testing of Chemicals.* (2002) 1–14. <https://doi.org/10.1787/9789264071001-EN>.
- [181] K. Ramakrishna, K. Srinivasan, S.S. Sharma, Chronic treatment of 4-phenylbutyric acid ameliorates cognitive impairment after focal cerebral ischemia/reperfusion injury in rats, *Indian J Physiol Pharmacol.* 64 (2021) 188–194.

- [182] A.H. Fischer, K.A. Jacobson, J. Rose, R. Zeller, Hematoxylin and eosin staining of tissue and cell sections., *CSH Protoc.* 2008 (2008) pdb.prot4986. <https://doi.org/10.1101/pdb.prot4986>.
- [183] G.L. ELLMAN, K.D. COURTNEY, V.J. ANDRES, R.M. FEATHER-STONE, A new and rapid colorimetric determination of acetylcholinesterase activity., *Biochem Pharmacol.* 7 (1961) 88–95. [https://doi.org/10.1016/0006-2952\(61\)90145-9](https://doi.org/10.1016/0006-2952(61)90145-9).
- [184] E. Mishra, M.K. Thakur, Alterations in hippocampal mitochondrial dynamics are associated with neurodegeneration and recognition memory decline in old male mice., *Biogerontology.* 23 (2022) 251–271. <https://doi.org/10.1007/s10522-022-09960-3>.
- [185] L. Di, E.H. Kerns, K. Fan, O.J. McConnell, G.T. Carter, High throughput artificial membrane permeability assay for blood–brain barrier, *Eur J Med Chem.* 38 (2003) 223–232. [https://doi.org/https://doi.org/10.1016/S0223-5234\(03\)00012-6](https://doi.org/https://doi.org/10.1016/S0223-5234(03)00012-6).
- [186] J. Cheung, M.J. Rudolph, F. Burshteyn, M.S. Cassidy, E.N. Gary, J. Love, M.C. Franklin, J.J. Height, Structures of human acetylcholinesterase in complex with pharmacologically important ligands, *J Med Chem.* 55 (2012) 10282–10286. <https://doi.org/10.1021/JM300871X>.
- [187] F. Nachon, E. Carletti, C. Ronco, M. Trovaslet, Y. Nicolet, L. Jean, P.Y. Renard, Crystal structures of human cholinesterases in complex with huprine W and tacrine: elements of specificity for anti-Alzheimer’s drugs targeting acetyl- and butyryl-cholinesterase, *Biochem J.* 453 (2013) 393–399. <https://doi.org/10.1042/BJ20130013>.
- [188] H.M. Berman, J. Westbrook, Z. Feng, G. Gilliland, T.N. Bhat, H. Weissig, I.N. Shindyalov, P.E. Bourne, The Protein Data Bank, *Nucleic Acids Res.* 28 (2000) 235–242. <https://doi.org/10.1093/NAR/28.1.235>.
- [189] D.S. BiOVIA, Discovery Studio 2019. San Diego: Dassault Systèmes; 2019, (2021).
- [190] G.M. Morris, H. Ruth, W. Lindstrom, M.F. Sanner, R.K. Belew, D.S. Goodsell, A.J. Olson, AutoDock4 and AutoDockTools4: Automated docking with selective receptor flexibility, *J Comput Chem.* 30 (2009) 2785–2791. <https://doi.org/10.1002/JCC.21256>.
- [191] S. Release, 1: Maestro Desmond Interoperability Tools, Schrödinger: New York, NY, USA. (2020).

- [192] A. Daina, O. Michielin, V. Zoete, SwissADME: a free web tool to evaluate pharmacokinetics, drug-likeness and medicinal chemistry friendliness of small molecules, *Sci Rep.* 7 (2017). <https://doi.org/10.1038/SREP42717>.
- [193] S.K. Seoul, bioinformatics and molecular design research center; 2004, PreADMET Program. Available from: URL: <Http://Preadmet.Bmdrc.Org>.
- [194] Y.P. Singh, G.N.V.C. Tej, A. Pandey, K. Priya, P. Pandey, G. Shankar, P.K. Nayak, G. Rai, A.G. Chittiboyina, R.J. Doerksen, S. Vishwakarma, G. Modi, Design, synthesis and biological evaluation of novel naturally-inspired multifunctional molecules for the management of Alzheimer's disease, *Eur J Med Chem.* 198 (2020). <https://doi.org/10.1016/J.EJMECH.2020.112257>.
- [195] G. Gutti, R. Kakarla, D. Kumar, M. Beohar, A. Ganeshpurkar, A. Kumar, S. Krishnamurthy, S.K. Singh, Discovery of novel series of 2-substituted benzo[d]oxazol-5-amine derivatives as multi-target directed ligands for the treatment of Alzheimer's disease, *Eur J Med Chem.* 182 (2019). <https://doi.org/10.1016/J.EJMECH.2019.111613>.
- [196] P. Sharma, A. Tripathi, P.N. Tripathi, S.K. Prajapati, A. Seth, M.K. Tripathi, P. Srivastava, V. Tiwari, S. Krishnamurthy, S.K. Shrivastava, Design and development of multitarget-directed N-Benzylpiperidine analogs as potential candidates for the treatment of Alzheimer's disease, *Eur J Med Chem.* 167 (2019) 510–524. <https://doi.org/10.1016/J.EJMECH.2019.02.030>.
- [197] D. Kumar, S.K. Gupta, A. Ganeshpurkar, G. Gutti, S. Krishnamurthy, G. Modi, S.K. Singh, Development of Piperazinediones as dual inhibitor for treatment of Alzheimer's disease, *Eur J Med Chem.* 150 (2018) 87–101. <https://doi.org/10.1016/J.EJMECH.2018.02.078>.
- [198] N.C. Inestrosa, J.P. Sagal, M. Colombres, Acetylcholinesterase interaction with Alzheimer amyloid beta, *Subcell Biochem.* 38 (2005) 299–317. https://doi.org/10.1007/0-387-23226-5_15.
- [199] T.P.C. Chieritto, S.P. Mantoani, C. Roca, C. Requena, V. Sebastian-Perez, W.O. Castillo, N.C.S. Moreira, C. Pérez, E.T. Sakamoto-Hojo, C.S. Takahashi, J. Jiménez-Barbero, F.J. Cañada, N.E. Campillo, A. Martinez, I. Carvalho, From dual binding site acetylcholinesterase inhibitors to allosteric modulators: A new avenue for disease-modifying

drugs in Alzheimer's disease, *Eur J Med Chem.* 139 (2017) 773–791. <https://doi.org/10.1016/J.EJMECH.2017.08.051>.

[200] OECD/OCDE 423 OECD GUIDELINE FOR TESTING OF CHEMICALS Acute Oral Toxicity-Acute Toxic Class Method INTRODUCTION, (2001).

[201] S. Majumdar, S. Krishnamurthy, In vivo toxicological evaluation of barium-doped bioactive glass in rats, *Ceram Int.* 48 (2022) 33288–33305. <https://doi.org/10.1016/J.CERAMINT.2022.07.272>.

[202] K. Ramakrishna, K. Srinivasan, S.S. Sharma, K. Ramakrishna, K. Srinivasan, S.S. Sharma, Chronic treatment of 4-phenylbutyric acid ameliorates cognitive impairment after focal cerebral ischemia/ reperfusion injury in rats, *Indian J Physiol Pharmacol.* 64 (2021) 188–194. https://doi.org/10.25259/IJPP_172_2020.

[203] A.H. Fischer, K.A. Jacobson, J. Rose, R. Zeller, Hematoxylin and eosin staining of tissue and cell sections, *Cold Spring Harb Protoc.* 3 (2008). <https://doi.org/10.1101/PDB.PROT4986>.

[204] G.L. Ellman, K.D. Courtney, V. Andres, R.M. Featherstone, A new and rapid colorimetric determination of acetylcholinesterase activity, *Biochem Pharmacol.* 7 (1961). [https://doi.org/10.1016/0006-2952\(61\)90145-9](https://doi.org/10.1016/0006-2952(61)90145-9).

[205] E. Mishra, M.K. Thakur, Alterations in hippocampal mitochondrial dynamics are associated with neurodegeneration and recognition memory decline in old male mice, *Biogerontology.* 23 (2022) 251–271. <https://doi.org/10.1007/S10522-022-09960-3>.

[206] S. Sharma, M. Kumar, O.S. Nayal, M.S. Thakur, V. Bhatt, N. Kumar, B. Singh, U. Sharma, Designing Vasicine-Derived Ligands and Their Application for Ruthenium-Catalyzed Transfer Hydrogenation Reactions in Water: Synthesis of Amines and Alcohols, *Wiley Online Library.* 5 (2016) 1471–1479. <https://doi.org/10.1002/ajoc.201600384>.

[207] J.M. Long, D.M. Holtzman, Alzheimer Disease: An Update on Pathobiology and Treatment Strategies, *Cell.* 179 (2019) 312–339. <https://doi.org/10.1016/J.CELL.2019.09.001>.

[208] P. Taylor, S. Lappi, Interaction of fluorescence probes with acetylcholinesterase. The site and specificity of propidium binding, *Biochemistry.* 14 (1975) 1989–1997. <https://doi.org/10.1021/BI00680A029>.

- [209] L. Di, E.H. Kerns, K. Fan, O.J. McConnell, G.T. Carter, High throughput artificial membrane permeability assay for blood-brain barrier, *Eur J Med Chem.* 38 (2003) 223–232. [https://doi.org/10.1016/S0223-5234\(03\)00012-6](https://doi.org/10.1016/S0223-5234(03)00012-6).
- [210] D.D. Allen, R. Caviedes, A.M. Cárdenas, T. Shimahara, J. Segura-Aguilar, P.A. Caviedes, Cell lines as in vitro models for drug screening and toxicity studies, *Drug Dev Ind Pharm.* 31 (2005) 757–768. <https://doi.org/10.1080/03639040500216246>.
- [211] U. Ebert, W. Kirch, Scopolamine model of dementia: electroencephalogram findings and cognitive performance, *Eur J Clin Invest.* 28 (1998) 944–949. <https://doi.org/10.1046/J.1365-2362.1998.00393.X>.
- [212] I. Klinkenberg, A. Blokland, The validity of scopolamine as a pharmacological model for cognitive impairment: a review of animal behavioral studies, *Neurosci Biobehav Rev.* 34 (2010) 1307–1350. <https://doi.org/10.1016/J.NEUBIOREV.2010.04.001>.
- [213] Q. Huang, C. Liao, F. Ge, J. Ao, T. Liu, Acetylcholine bidirectionally regulates learning and memory, *Journal of Neurorestoratology.* 10 (2022) 100002. <https://doi.org/10.1016/J.JNRT.2022.100002>.
- [214] R. Cukalevski, B. Boland, B. Frohm, E. Thulin, D. Walsh, S. Linse, Role of aromatic side chains in amyloid β -protein aggregation, *ACS Chem Neurosci.* 3 (2012) 1008–1016. <https://doi.org/10.1021/CN300073S>.
- [215] E.K. Perry, M. Johnson, J.M. Kerwin, M.A. Piggott, J.A. Court, P.J. Shaw, P.G. Ince, A. Brown, R.H. Perry, Convergent cholinergic activities in aging and Alzheimer’s disease, *Neurobiol Aging.* 13 (1992) 393–400. [https://doi.org/10.1016/0197-4580\(92\)90113-C](https://doi.org/10.1016/0197-4580(92)90113-C).
- [216] A. Nazem, R. Sankowski, M. Bacher, Y. Al-Abed, Rodent models of neuroinflammation for Alzheimer’s disease, *J Neuroinflammation.* 12 (2015). <https://doi.org/10.1186/S12974-015-0291-Y>.
- [217] K. Bhanukiran, R. Singh, G. T A, K. Ramakrishna, S.K. Singh, S. Krishnamurthy, A. Kumar, S. Hemalatha, Vasicinone, a pyrroloquinazoline alkaloid from *Adhatoda vasica* Nees enhances memory and cognition by inhibiting cholinesterases in Alzheimer’s disease, *Phytomedicine Plus.* 3 (2023) 100439. <https://doi.org/10.1016/J.PHYPLU.2023.100439>.

- [218] K. Bhanukiran, T.A. Gajendra, S. Krishnamurthy, S.K. Singh, S. Hemalatha, Discovery of multi-target directed 3-OH pyrrolidine derivatives through a semisynthetic approach from alkaloid vasicine for the treatment of Alzheimer's disease, *Eur J Med Chem.* 249 (2023) 115145. <https://doi.org/10.1016/J.EJMECH.2023.115145>.
- [219] A.K. Ghosh, N. Kumaragurubaran, L. Hong, S. Kulkarni, X. Xu, H.B. Miller, D. Srinivasa Reddy, V. Weerasena, R. Turner, W. Chang, G. Koelsch, J. Tang, Potent memapsin 2 (β -secretase) inhibitors: Design, synthesis, protein-ligand X-ray structure, and in vivo evaluation, *Bioorg Med Chem Lett.* 18 (2008) 1031–1036. <https://doi.org/10.1016/J.BMCL.2007.12.028>.
- [220] OECD/OCDE 423 OECD GUIDELINE FOR TESTING OF CHEMICALS Acute Oral Toxicity-Acute Toxic Class Method INTRODUCTION, (2001).
- [221] R.H. Zhang, H.Y. Guo, H. Deng, J. Li, Z.S. Quan, Piperazine skeleton in the structural modification of natural products: a review, *J Enzyme Inhib Med Chem.* 36 (2021) 1165. <https://doi.org/10.1080/14756366.2021.1931861>.
- [222] G.F. Chen, T.H. Xu, Y. Yan, Y.R. Zhou, Y. Jiang, K. Melcher, H.E. Xu, Amyloid beta: structure, biology and structure-based therapeutic development, *Acta Pharmacologica Sinica* 2017 38:9. 38 (2017) 1205–1235. <https://doi.org/10.1038/aps.2017.28>.
- [223] F. Peters, H. Salihoglu, E. Rodrigues, E. Herzog, T. Blume, S. Filser, M. Dorostkar, D.R. Shimshek, N. Brose, U. Neumann, J. Herms, BACE1 inhibition more effectively suppresses initiation than progression of β -amyloid pathology, *Acta Neuropathol.* 135 (2018) 695. <https://doi.org/10.1007/S00401-017-1804-9>.
- [224] G.S. Pahwa, U. Zutshi, C.K. Atal, Chronic toxicity studies with vasicine from *Adhatoda vasica* Nees. in rats and monkeys., *Indian J Exp Biol.* 25 (1987) 467–470.
- [225] R.L. Wakhloo, G. Kaul, O.P. Gupta, C.K. Atal, Safety of vasicine hydrochloride in human volunteers, *Indian J Pharmacol.* 13 (1980) 129.
- [226] J.M. Long, D.M. Holtzman, Alzheimer Disease: An Update on Pathobiology and Treatment Strategies., *Cell.* 179 (2019) 312–339. <https://doi.org/10.1016/j.cell.2019.09.001>.

- [227] R. Cukalevski, B. Boland, B. Frohm, E. Thulin, D. Walsh, S. Linse, Role of aromatic side chains in amyloid β -protein aggregation., *ACS Chem Neurosci.* 3 (2012) 1008–1016. <https://doi.org/10.1021/cn300073s>.
- [228] Y. Zhu, W. Liu, S. Qi, H. Wang, Y. Wang, G. Deng, Y. Zhang, S. Li, C. Ma, Y. Wang, X. Cheng, C. Wang, Stereoselective glucuronidation metabolism, pharmacokinetics, anti-amnesic pharmacodynamics, and toxic properties of vasicine enantiomers in vitro and in vivo, *European Journal of Pharmaceutical Sciences.* 123 (2018) 459–474. <https://doi.org/10.1016/j.ejps.2018.07.058>.
- [229] S.K. Ali, A.R. Hamed, M.M. Soltan, A.M. El-Halawany, U.M. Hegazy, A.A. Hussein, Kinetics and molecular docking of vasicine from *Adhatoda vasica*: An acetylcholinesterase inhibitor for Alzheimer's disease, *South African Journal of Botany.* 104 (2016) 118–124. <https://doi.org/10.1016/j.sajb.2015.09.021>.
- [230] S.K. Ali, A.R. Hamed, M.M. Soltan, A.M. El-Halawany, U.M. Hegazy, A.A. Hussein, Kinetics and molecular docking of vasicine from *Adhatoda vasica*: An acetylcholinesterase inhibitor for Alzheimer's disease, 104 (2016) 118–124. <https://doi.org/https://doi.org/10.1016/j.sajb.2015.09.021>.
- [231] W. Liu, X. Shi, Y. Yang, X. Cheng, Q. Liu, H. Han, B. Yang, C. He, Y. Wang, B. Jiang, In vitro and in vivo metabolism and inhibitory activities of vasicine, a potent acetylcholinesterase and butyrylcholinesterase inhibitor, 10 (2015) e0122366. <https://doi.org/https://doi.org/10.1371/journal.pone.0122366>.
- [232] J.M. Grange, N.J. Snell, Activity of bromhexine and ambroxol, semi-synthetic derivatives of vasicine from the Indian shrub *Adhatoda vasica*, against *Mycobacterium tuberculosis* in vitro., *J Ethnopharmacol.* 50 (1996) 49–53. [https://doi.org/10.1016/0378-8741\(95\)01331-8](https://doi.org/10.1016/0378-8741(95)01331-8).
- [233] A. Mishra, L.P. Chandravanshi, S.K. Trigun, S. Krishnamurthy, Ambroxol modulates 6-Hydroxydopamine-induced temporal reduction in Glucocerebrosidase (GCase) enzymatic activity and Parkinson's disease symptoms., *Biochem Pharmacol.* 155 (2018) 479–493. <https://doi.org/10.1016/j.bcp.2018.07.028>.

Appendices

HRLCMS chromatogram of DCM extract of Vasaka

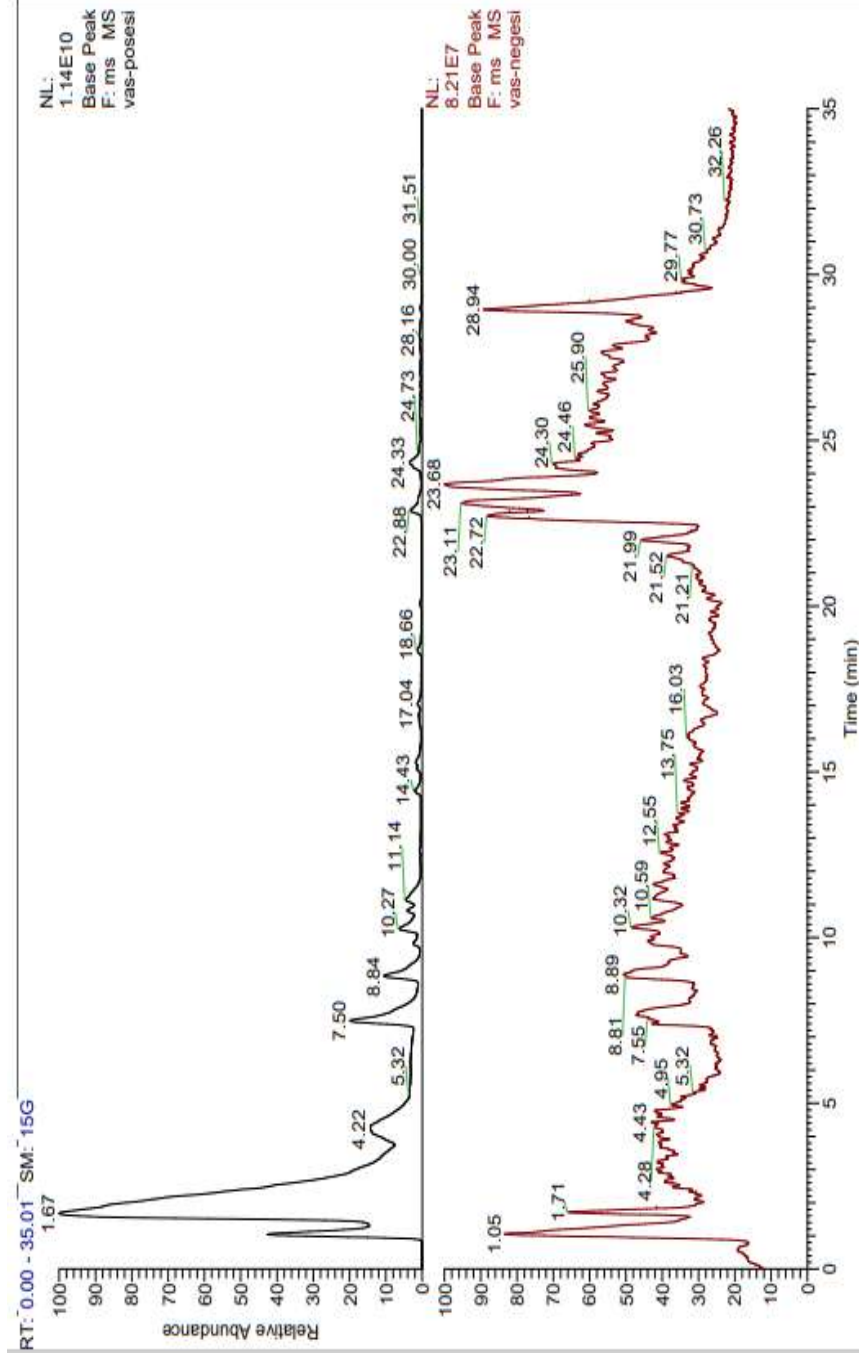


Figure 7.1. HRLCMS chromatogram of DCM extract of Vasaka

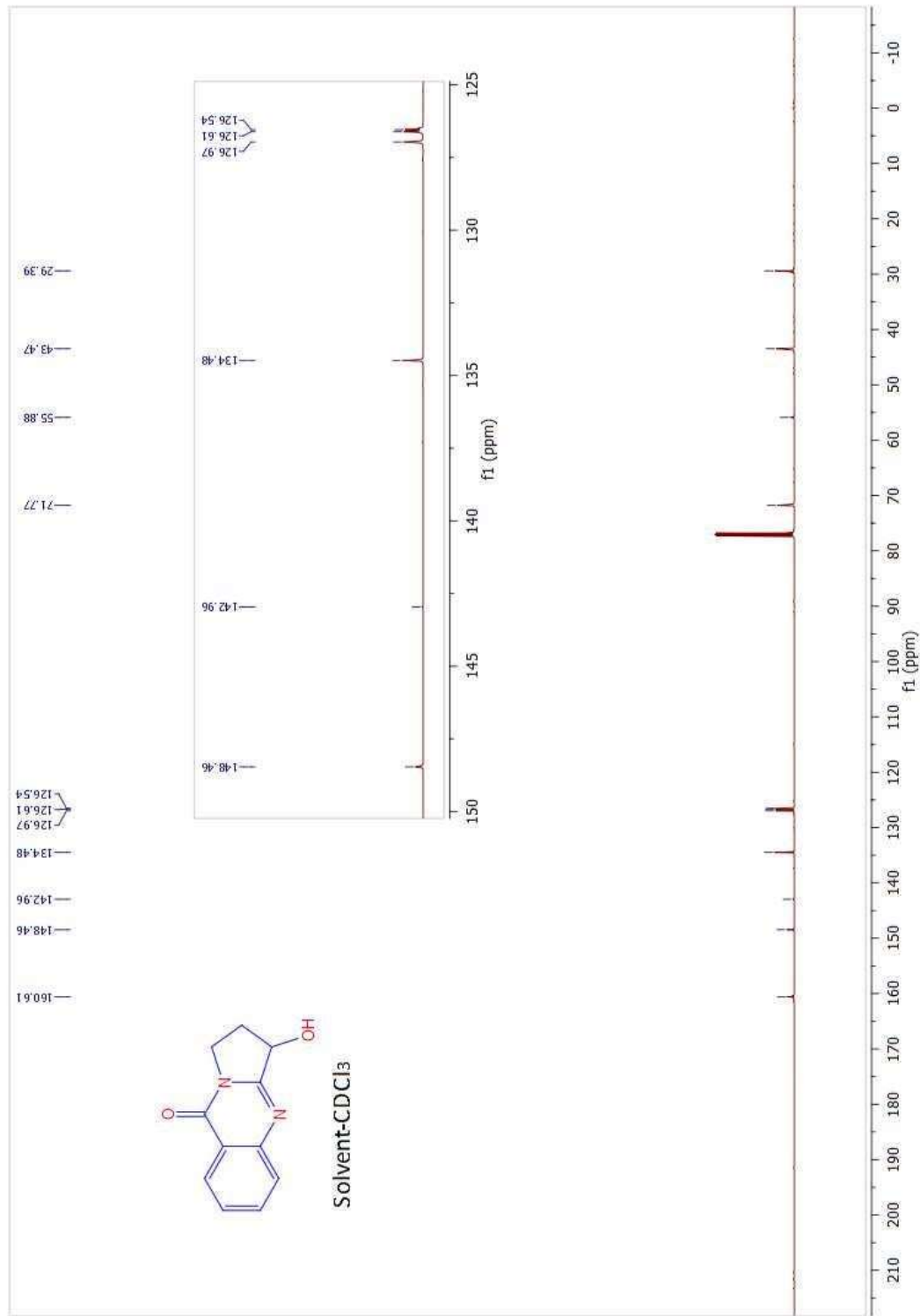


Figure 7.3. ¹³C NMR spectra of vasicinone (VAS), (125 MHz, CDCl₃)

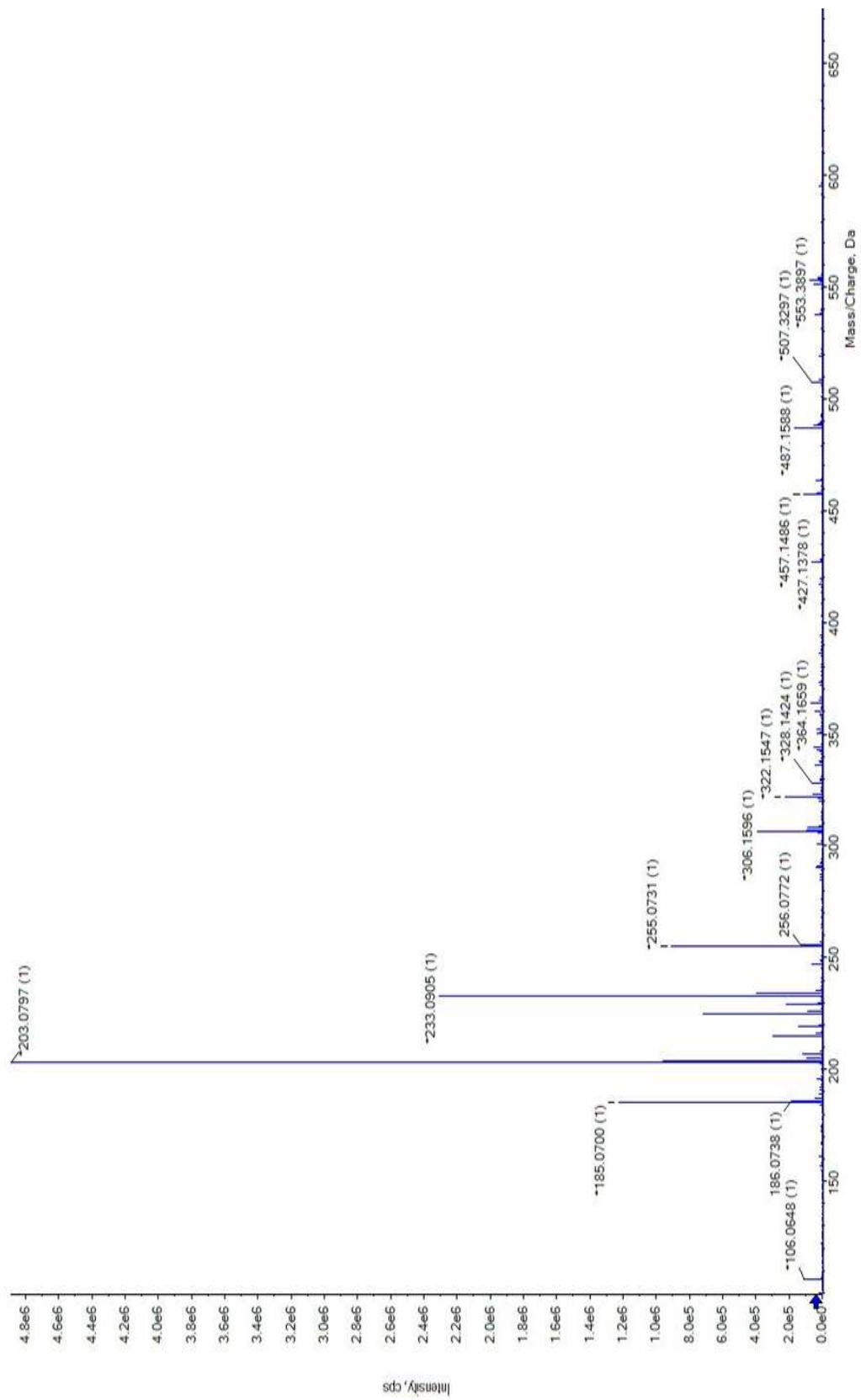


Figure 7.4. HRMS spectra of vasicinone (VAS)

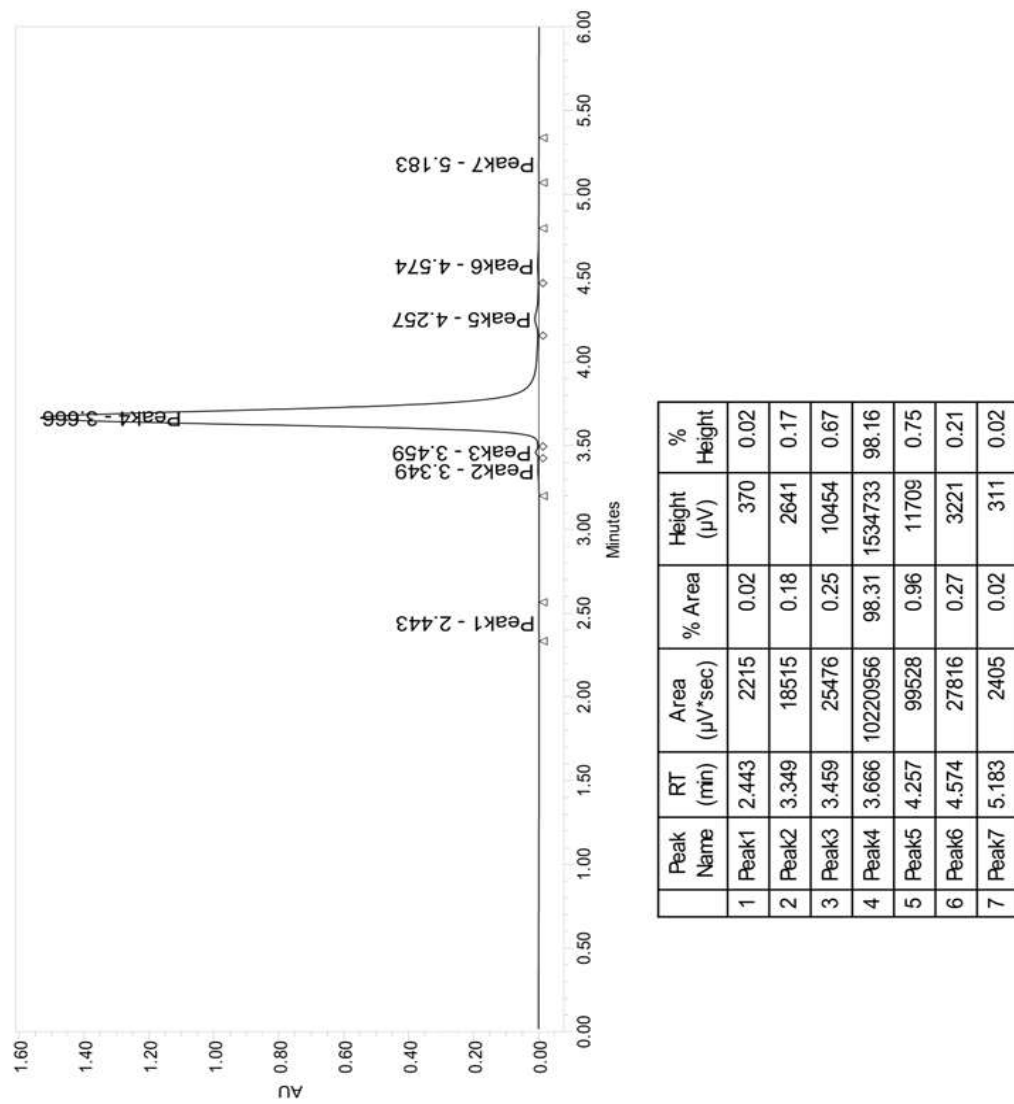


Figure 7.5. HPLC chromatogram of vasicinone (VAS).

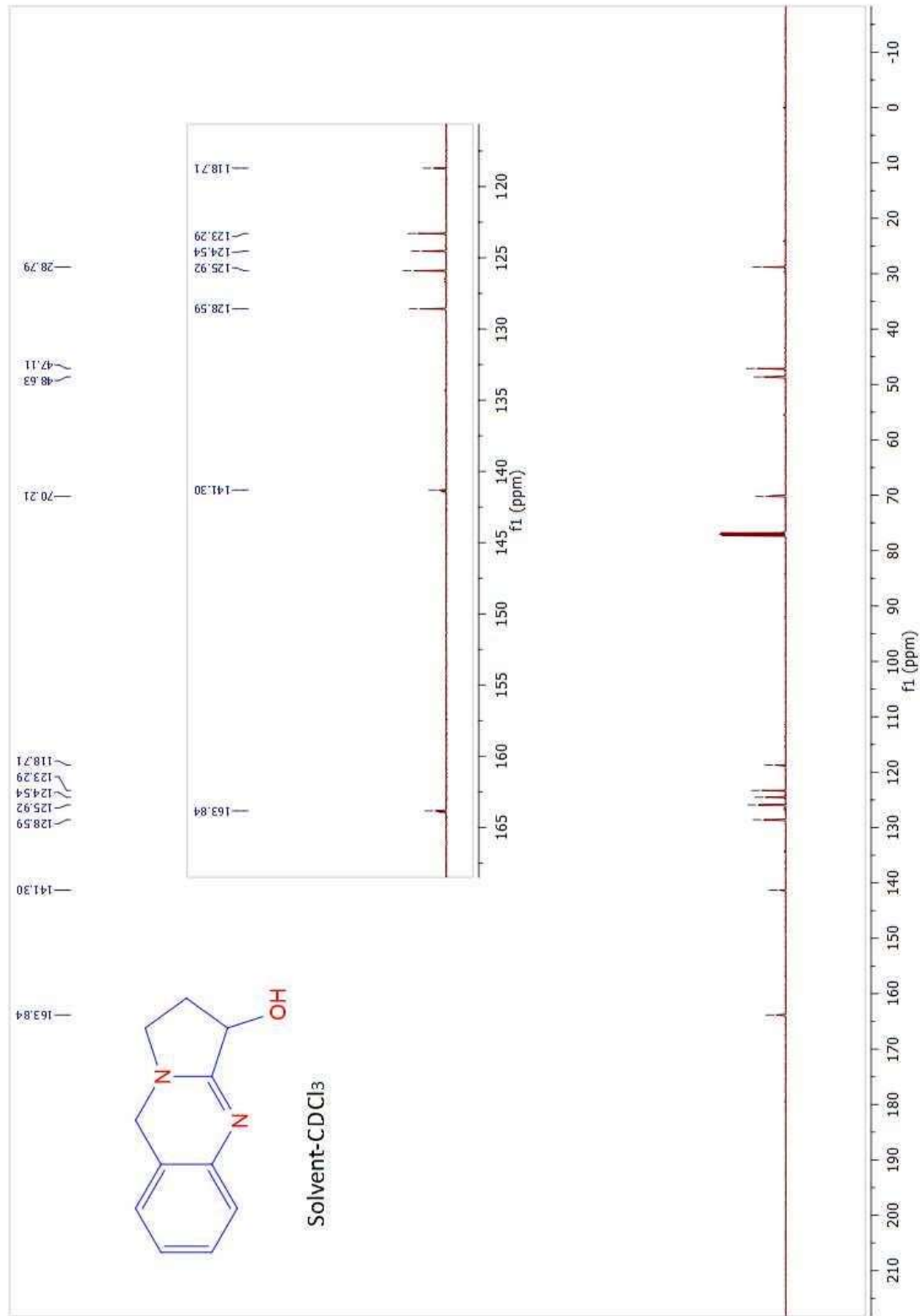


Figure 7.7. ^{13}C NMR spectra of vasicine (VA), (125 MHz, CDCl_3)

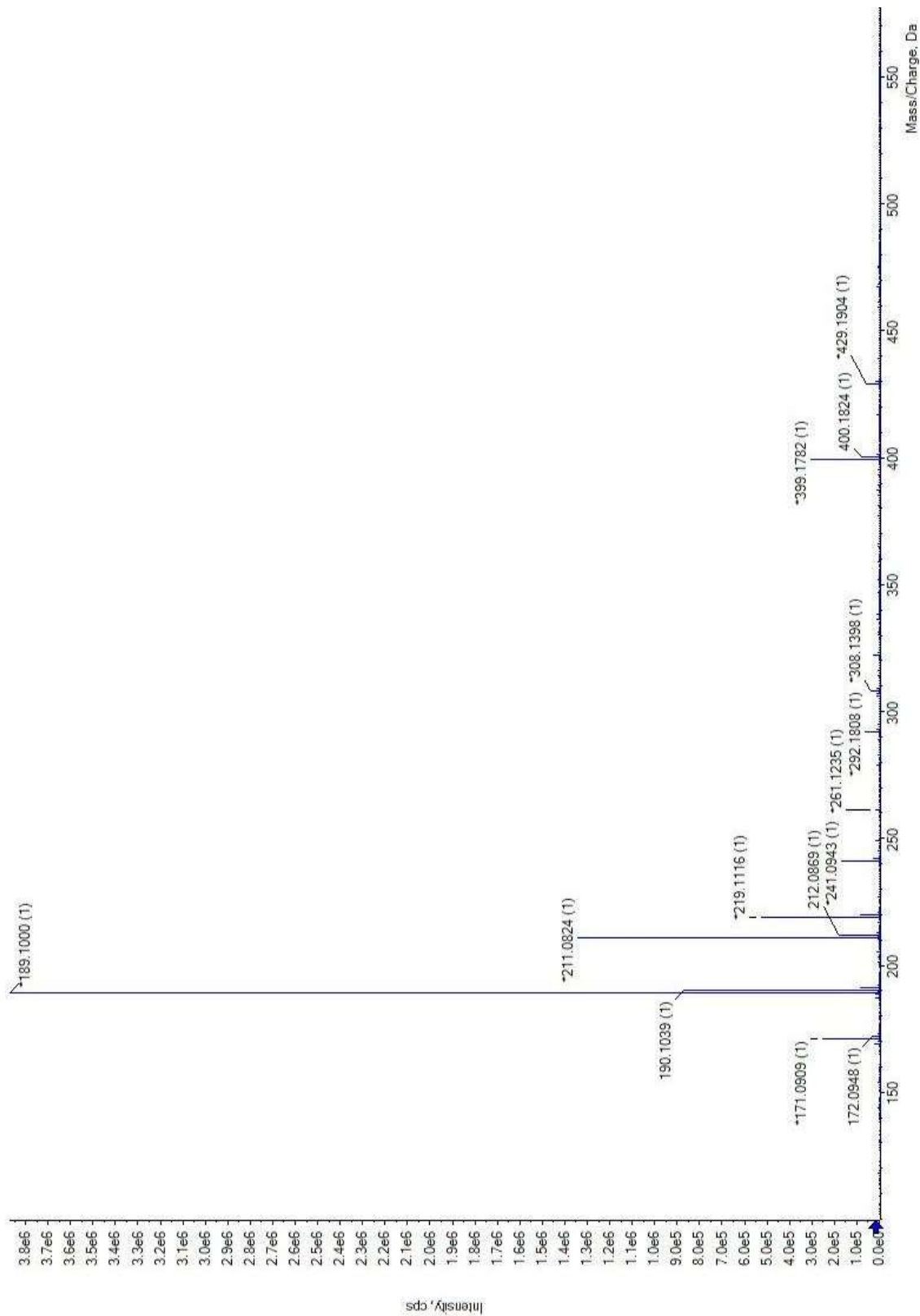


Figure 7.8. HRMS spectra of vasicine (VA)

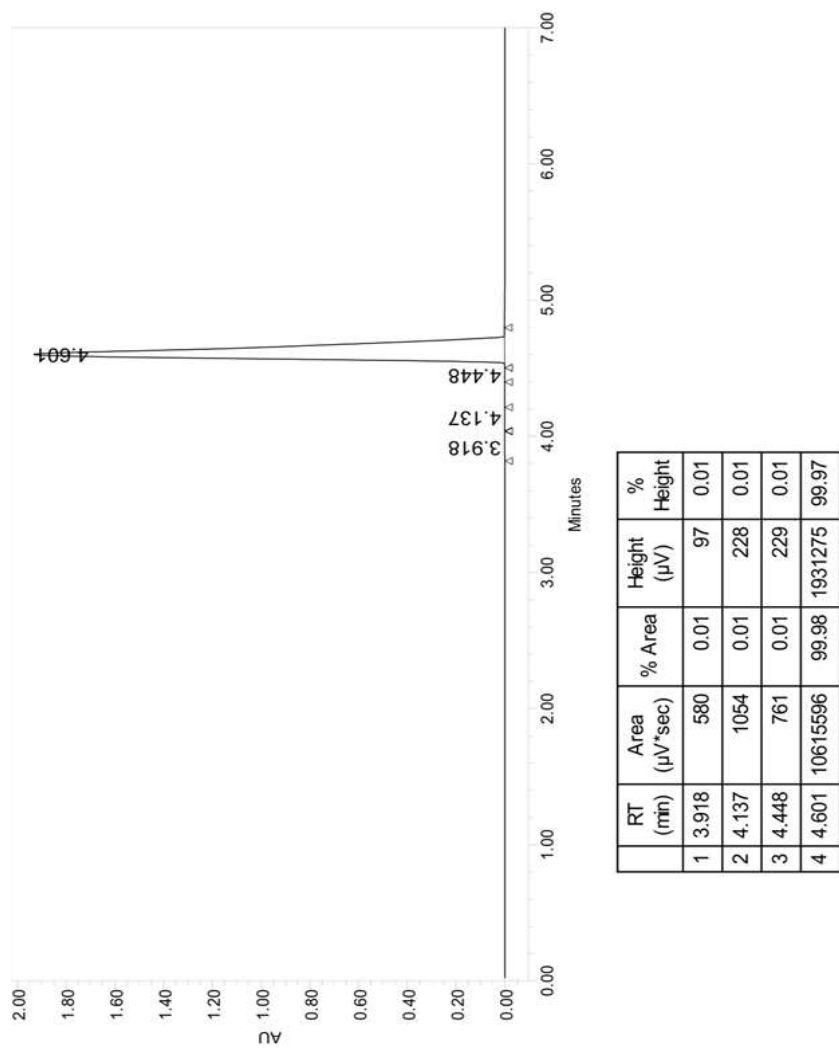


Figure 7.10. HPLC chromatogram of vasicine (VA).

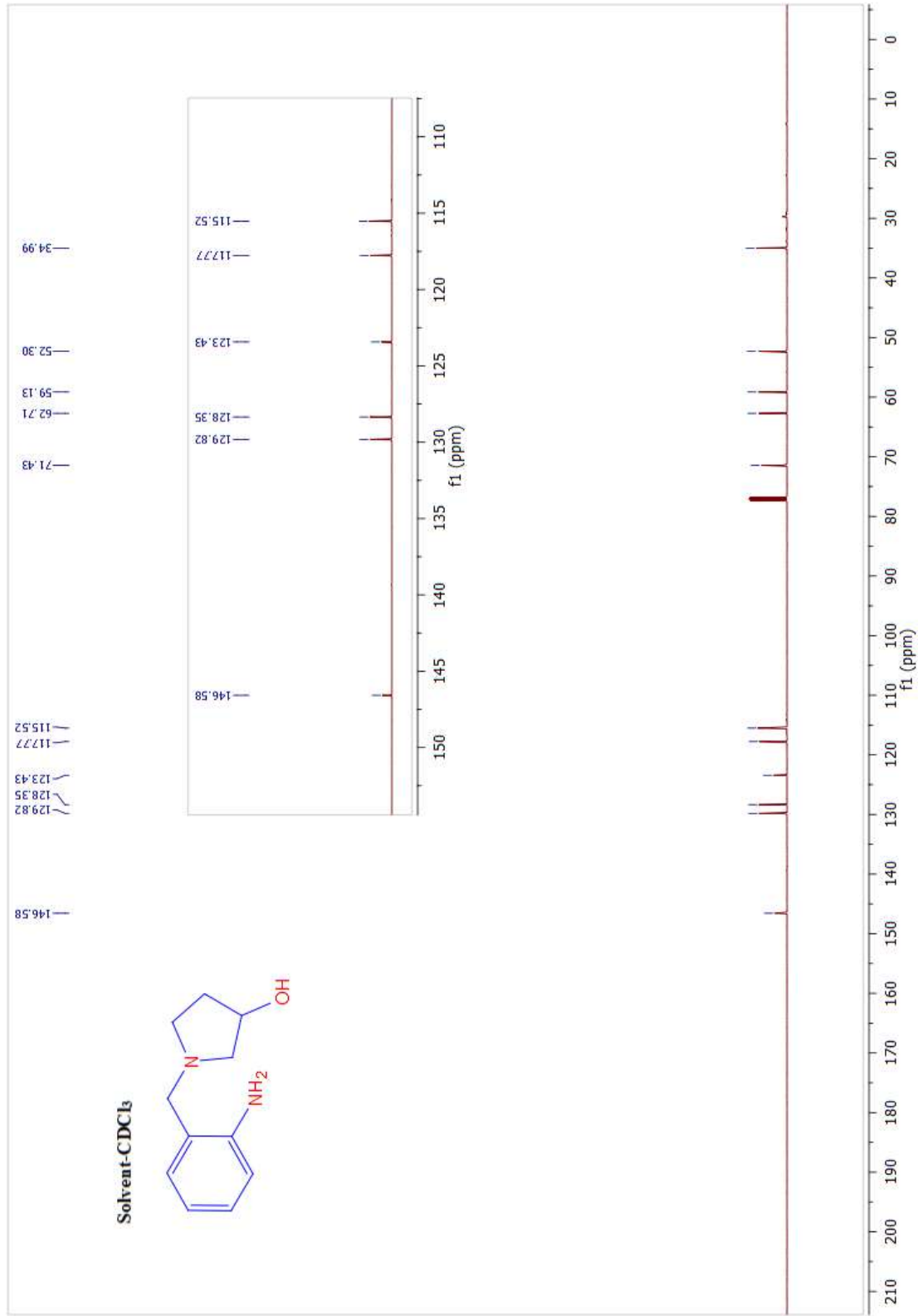


Figure 7.11. ¹³C NMR of compound VA0, (125 MHz, CDCl₃)

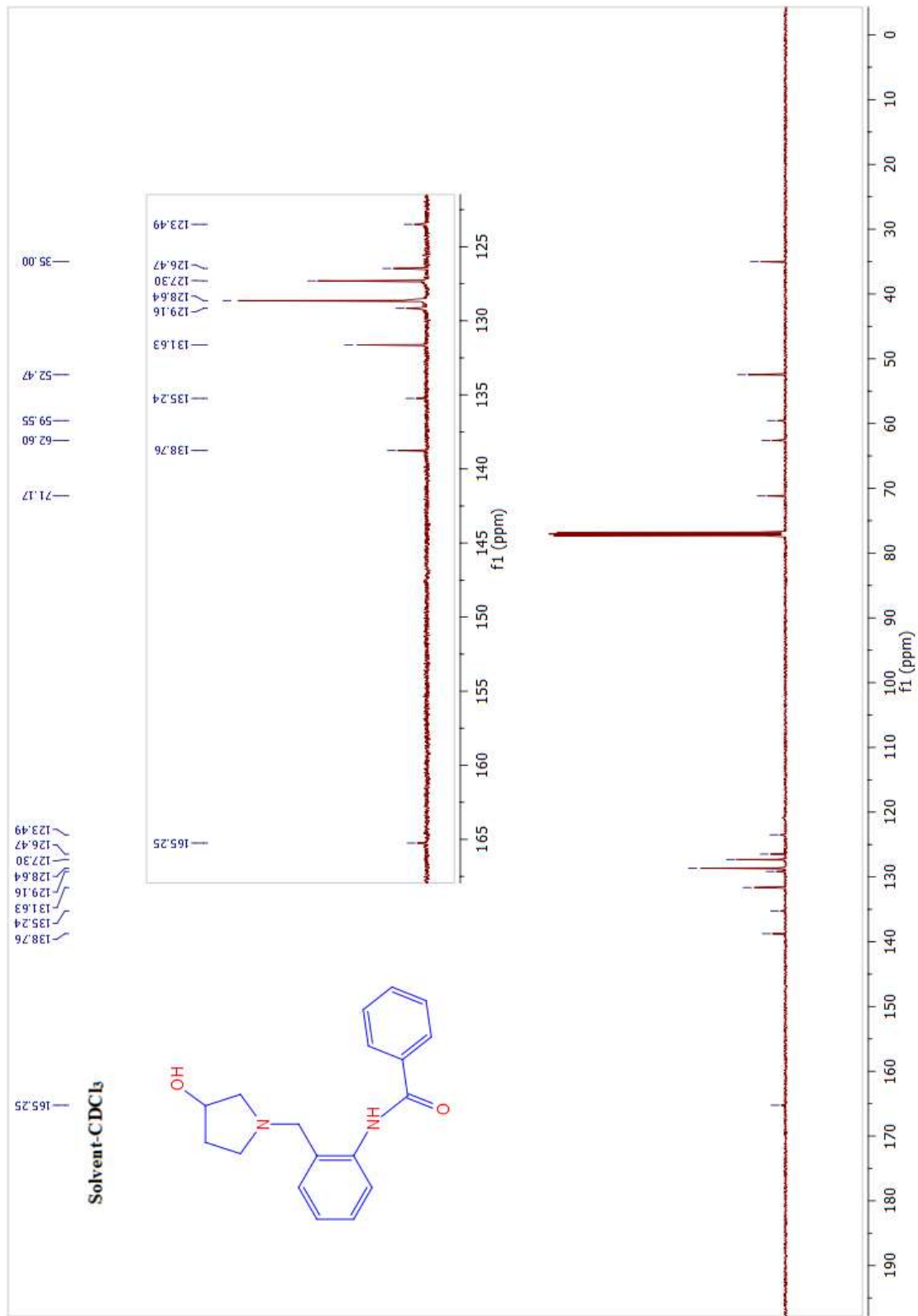


Figure 7.14. ¹³C NMR of compound VA01, (125 MHz, CDCl₃)

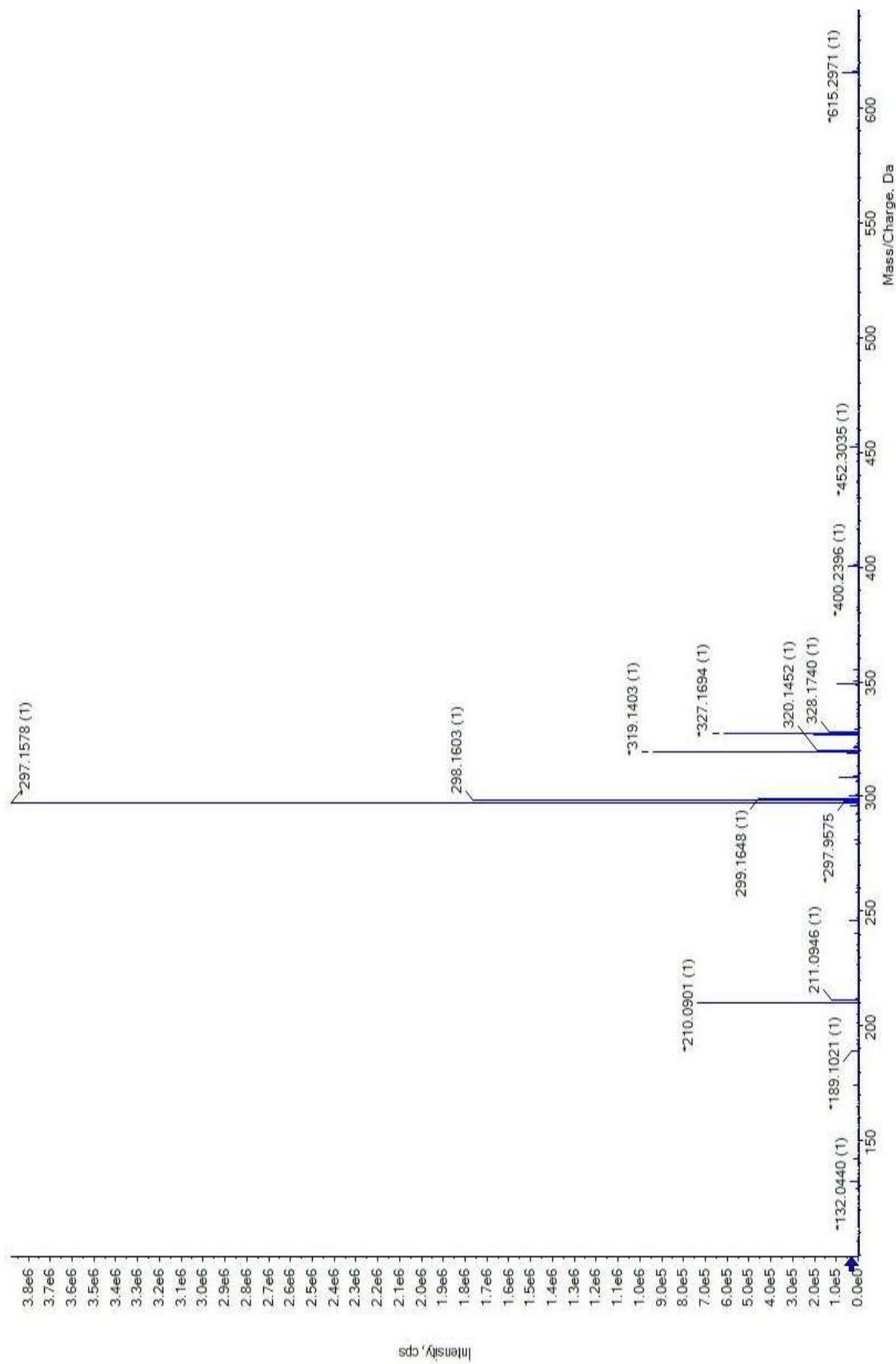


Figure 7.15. HRMS of compound VA01

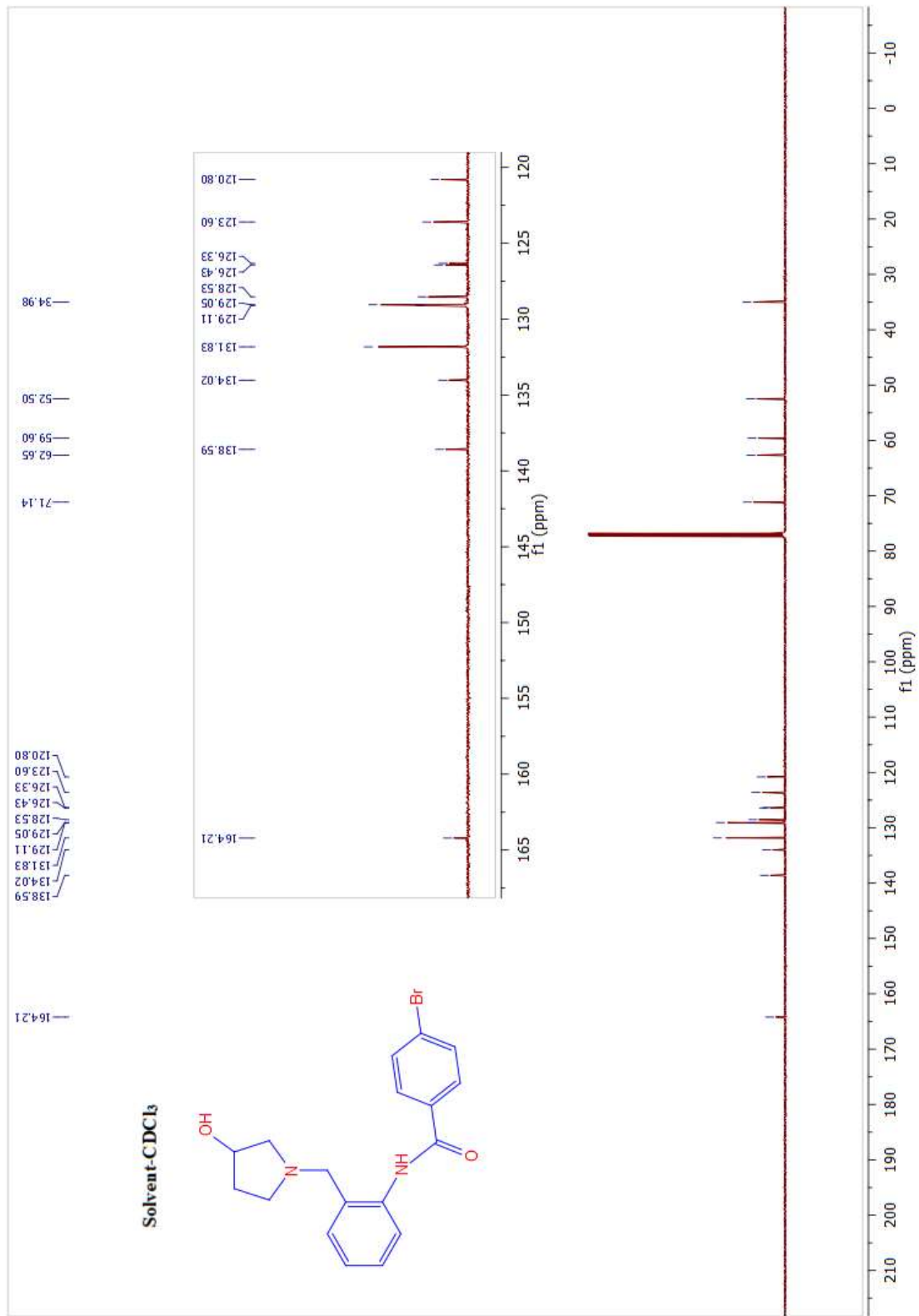


Figure 7.17. ¹³C NMR of compound VA10, (125 MHz, CDCl₃)

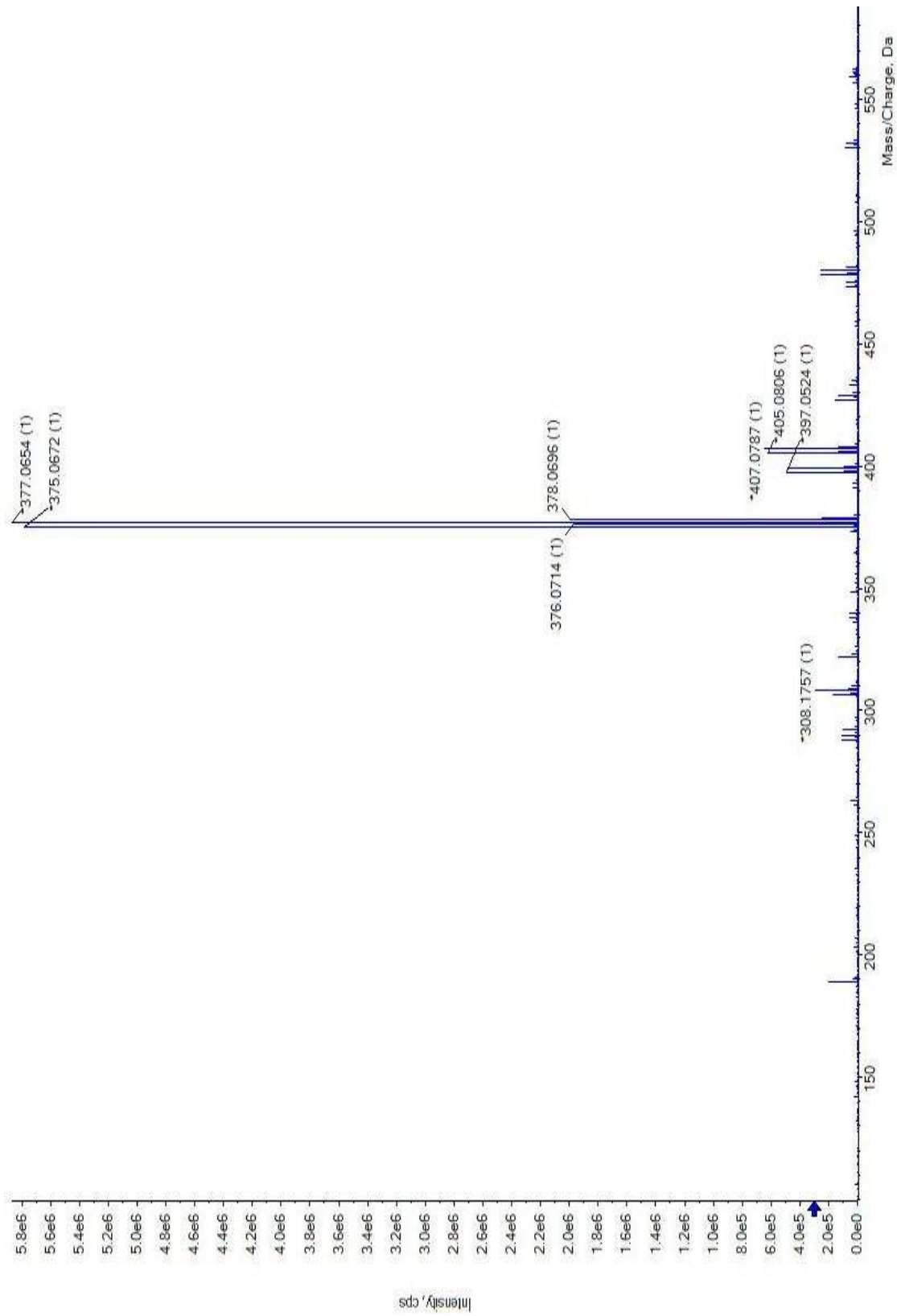


Figure 7.18. HRMS spectra of VA10

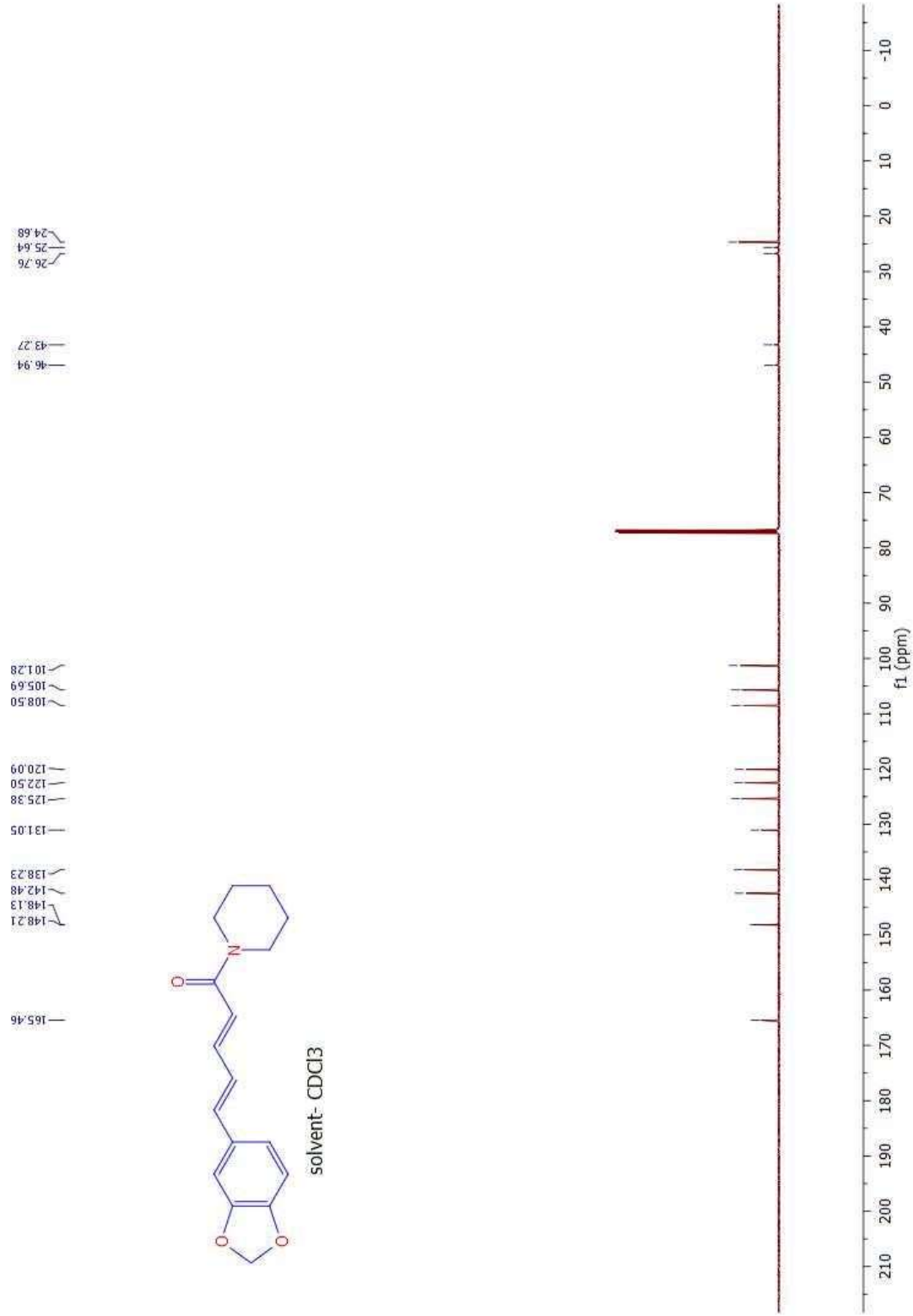


Figure 7.20. ¹³C NMR of compound PIP, (125 MHz, CDCl₃)

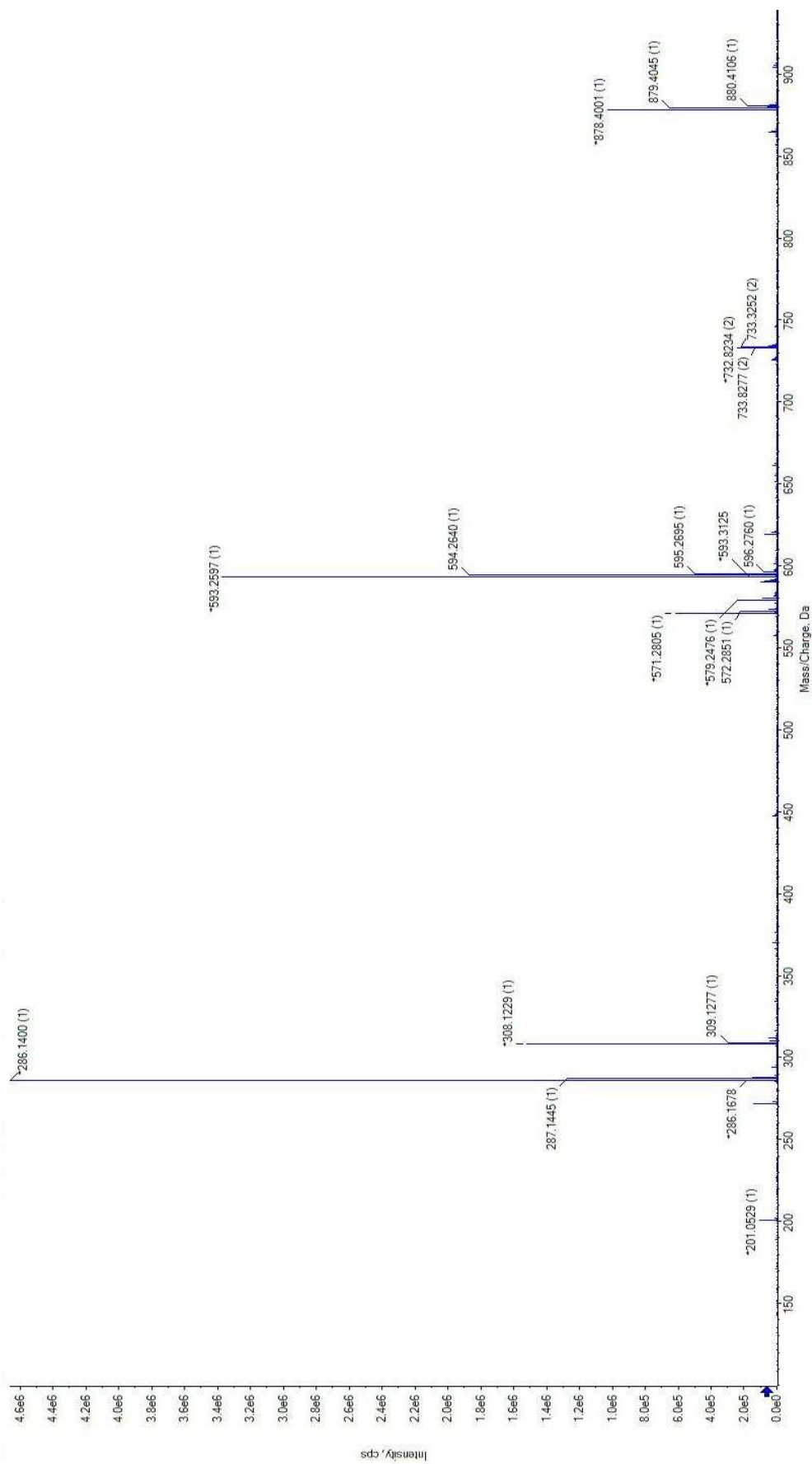


Figure 7.21. HRMS of compound PIP

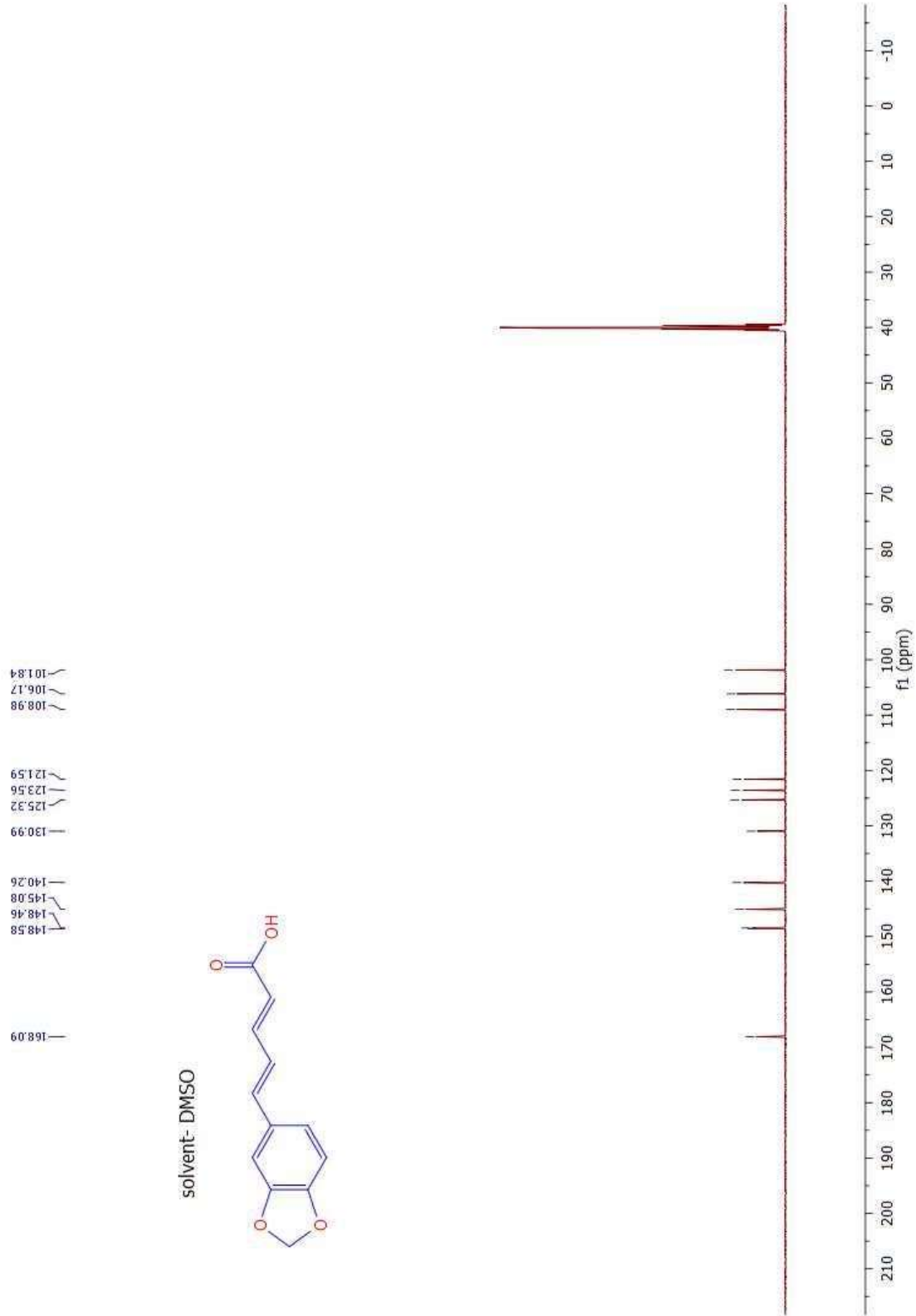


Figure 7.23. ¹³C NMR of compound PC, (125 MHz, DMSO)

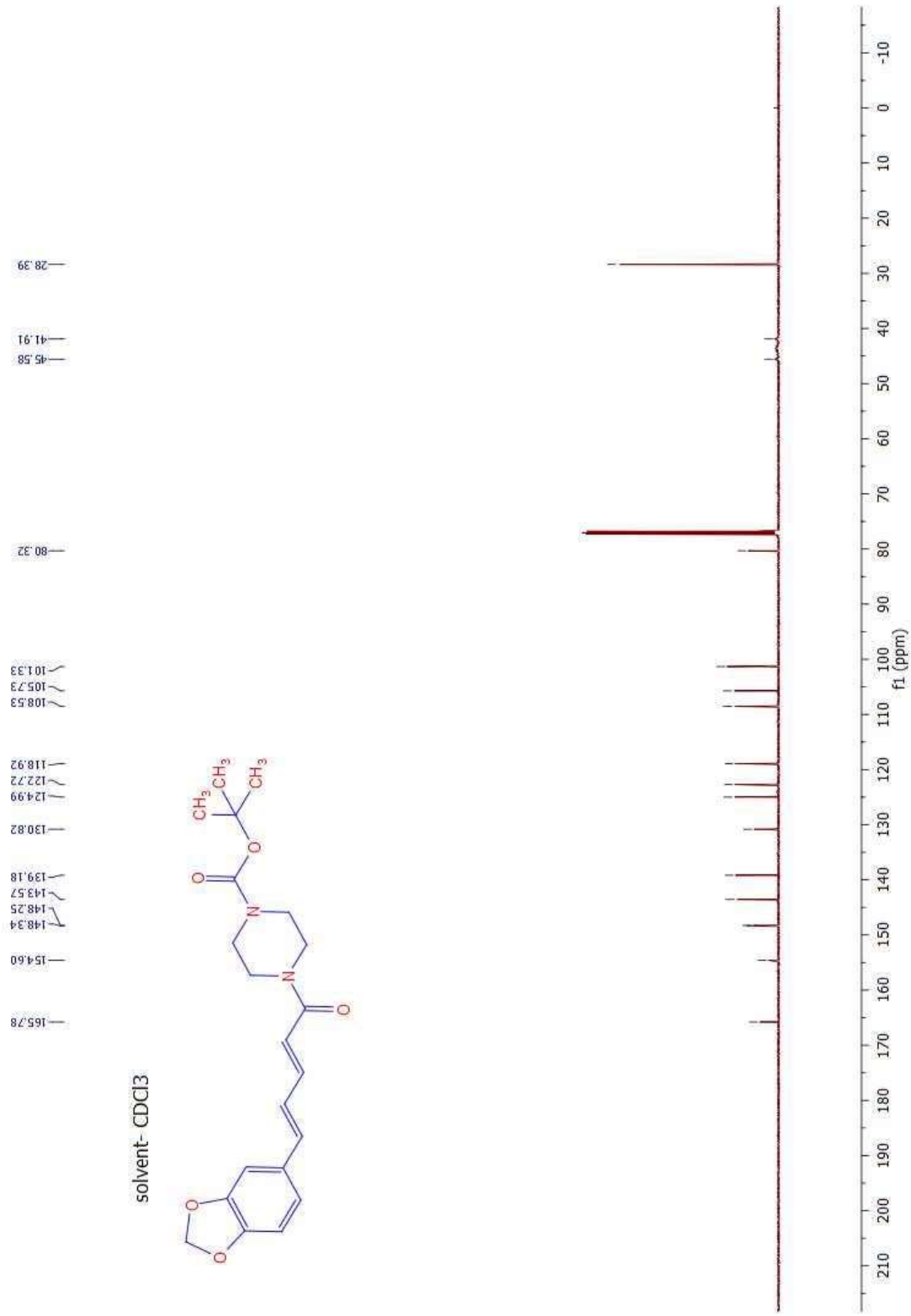


Figure 7.25. ¹³C NMR of compound PC08, (125 MHz, CDCl₃)

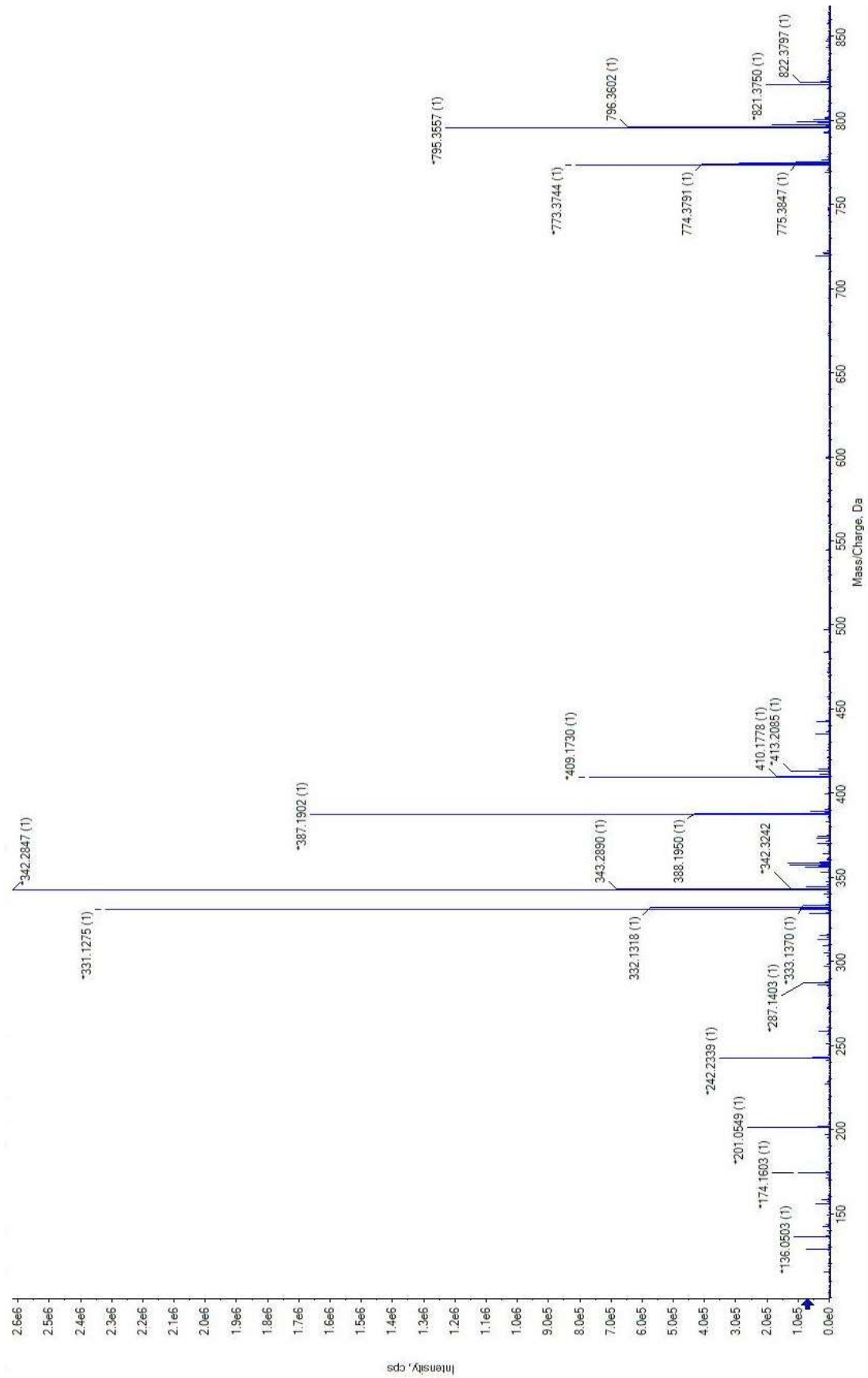


Figure 7.26. HRMS of compound PC08

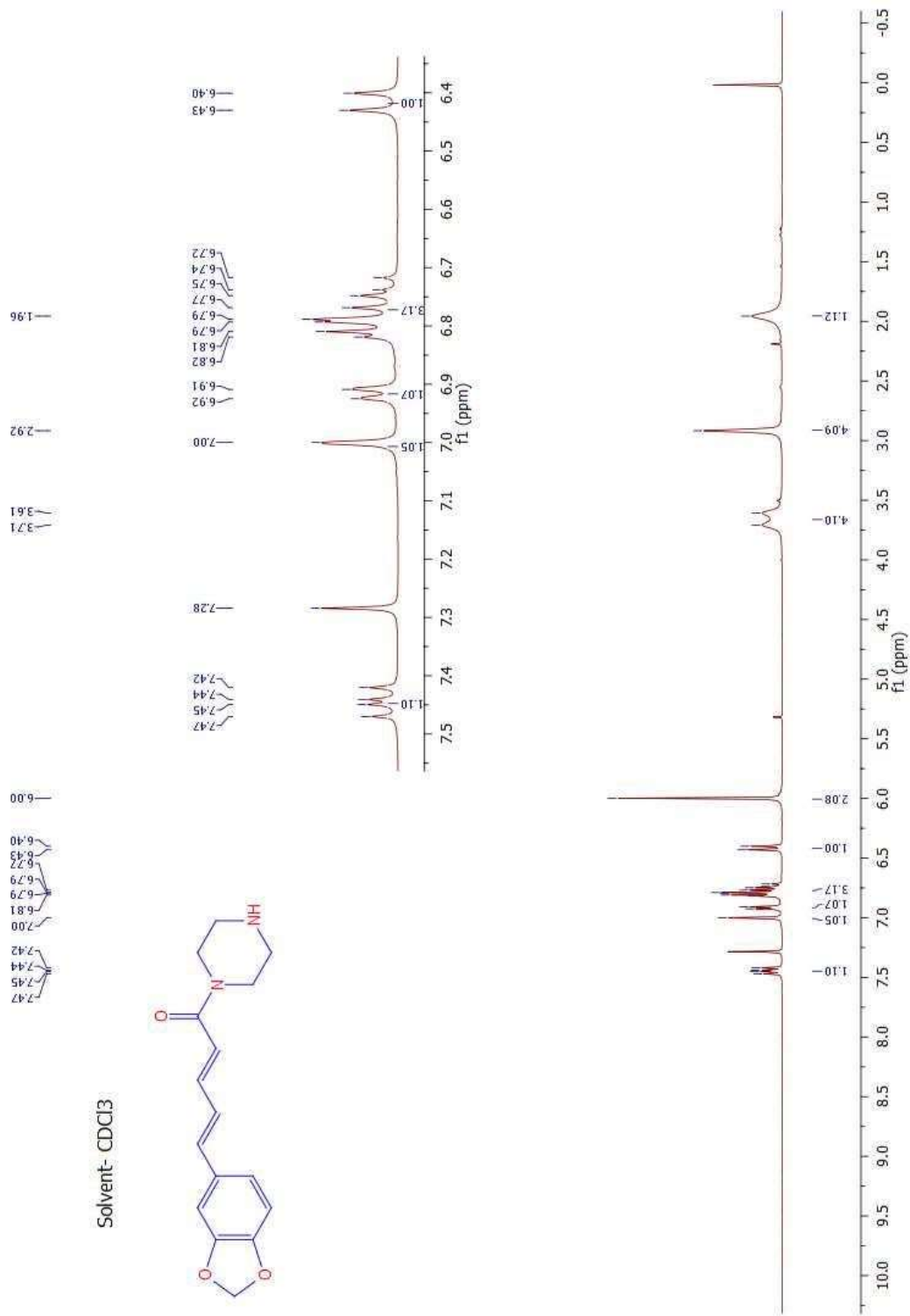


Figure 7.27. ¹H NMR of compound PC04, (500 MHz, CDCl₃)

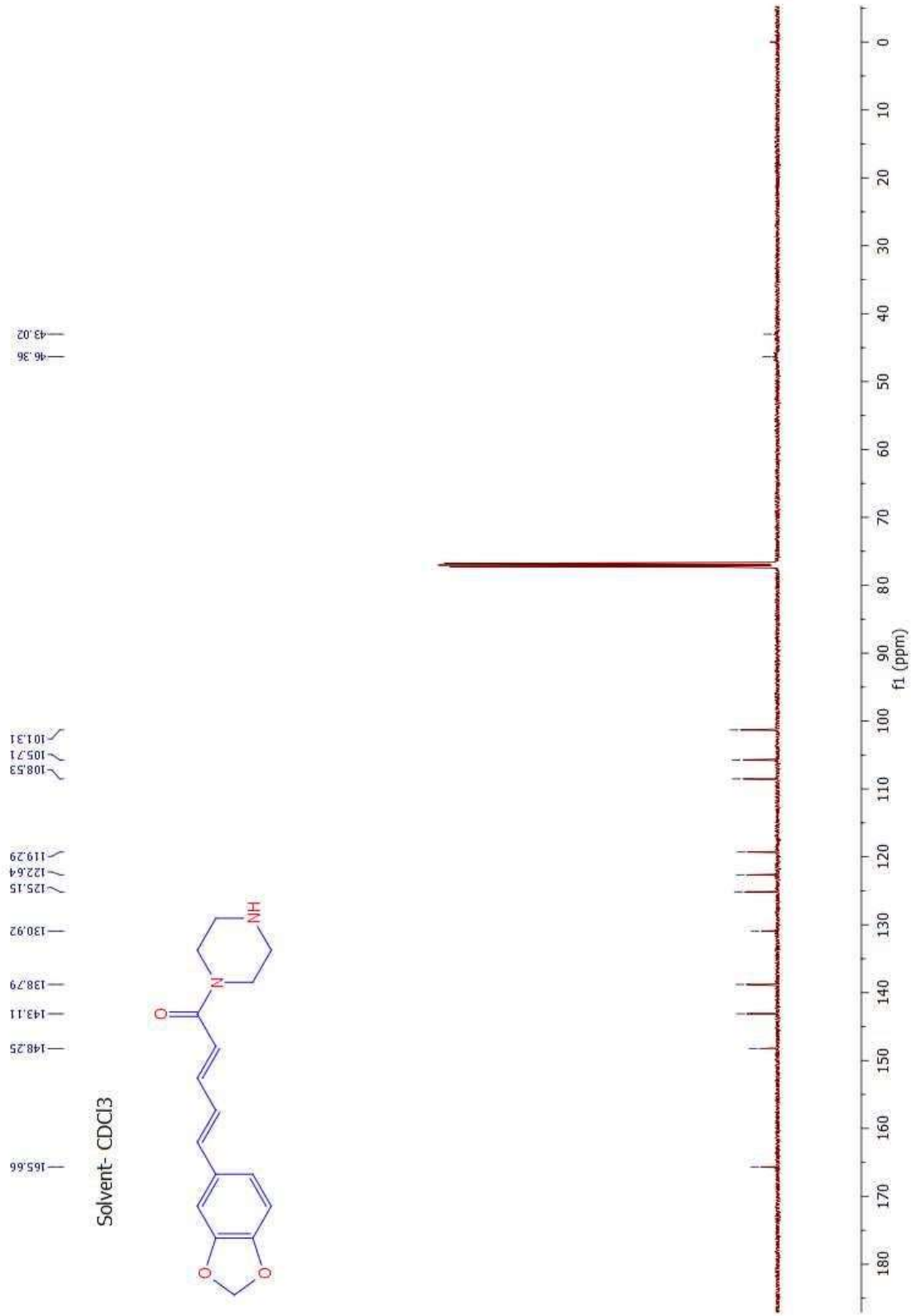


Figure 7.28. ¹³C NMR of compound PC04, (125 MHz, CDCl₃)

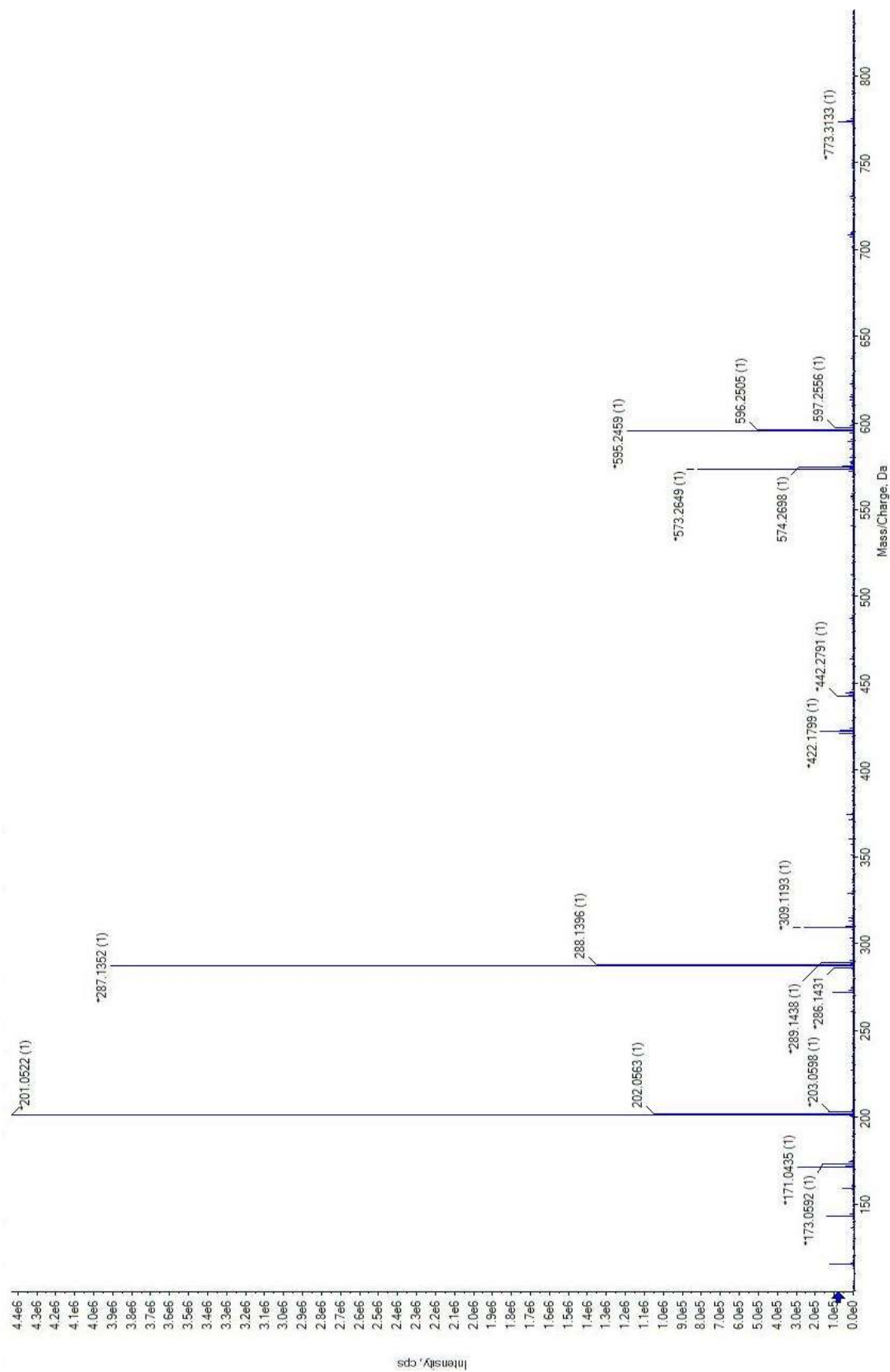


Figure 7.29. HRMS of compound PC04

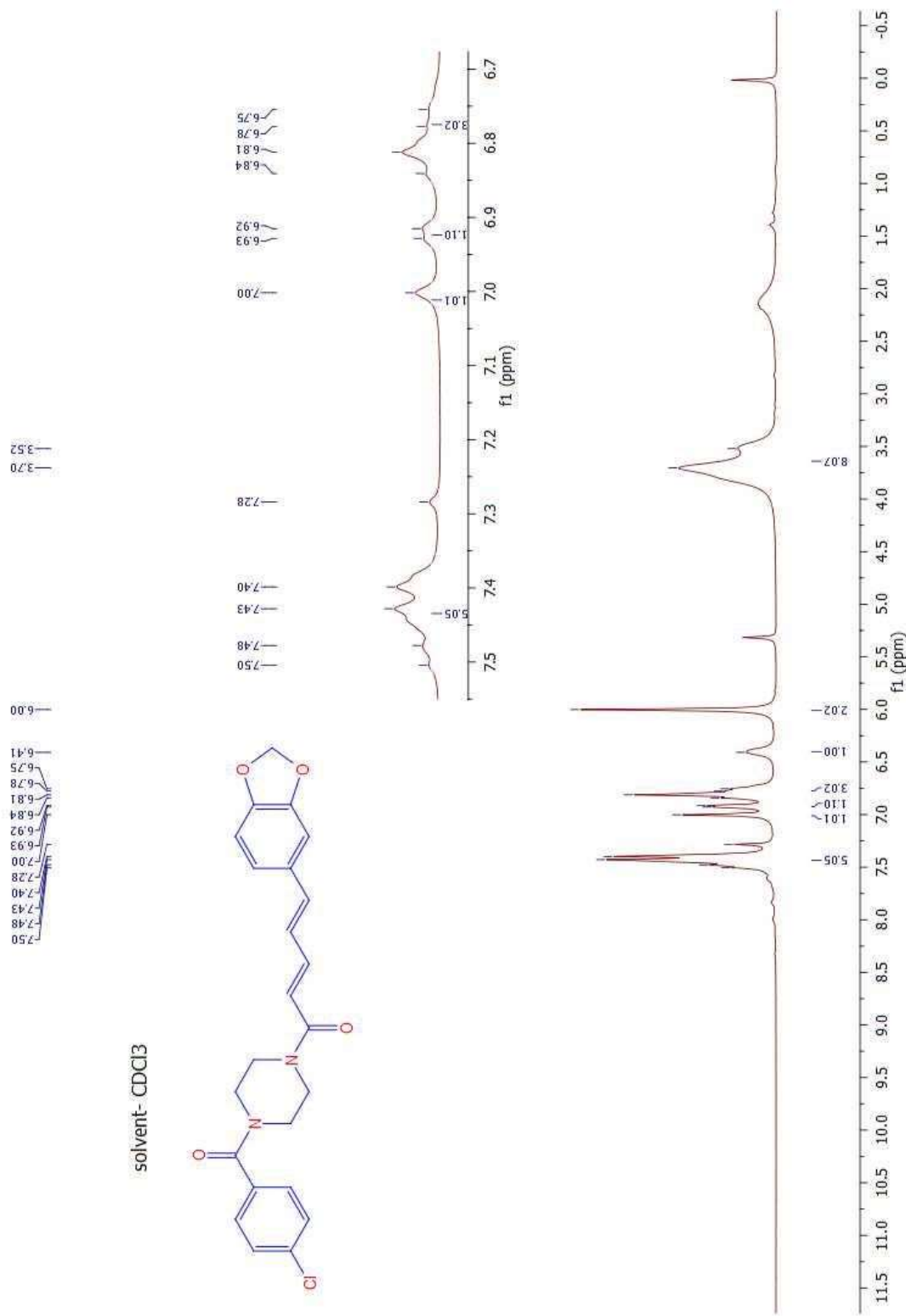


Figure 7.30. ¹H NMR of compound PD07, (500 MHz, CDCl₃)

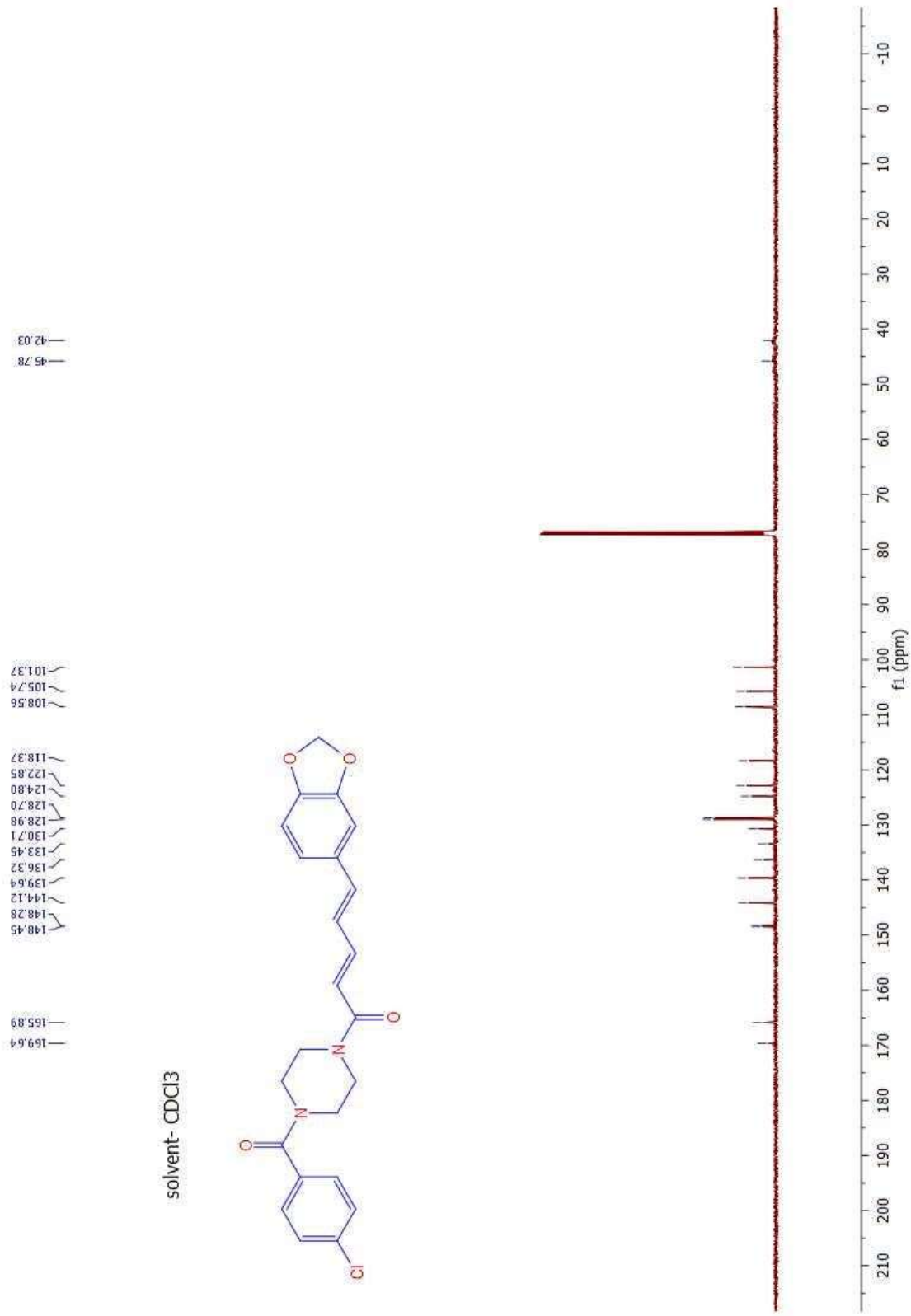


Figure 7.31. ¹³C NMR of compound PD07, (125 MHz, CDCl₃)

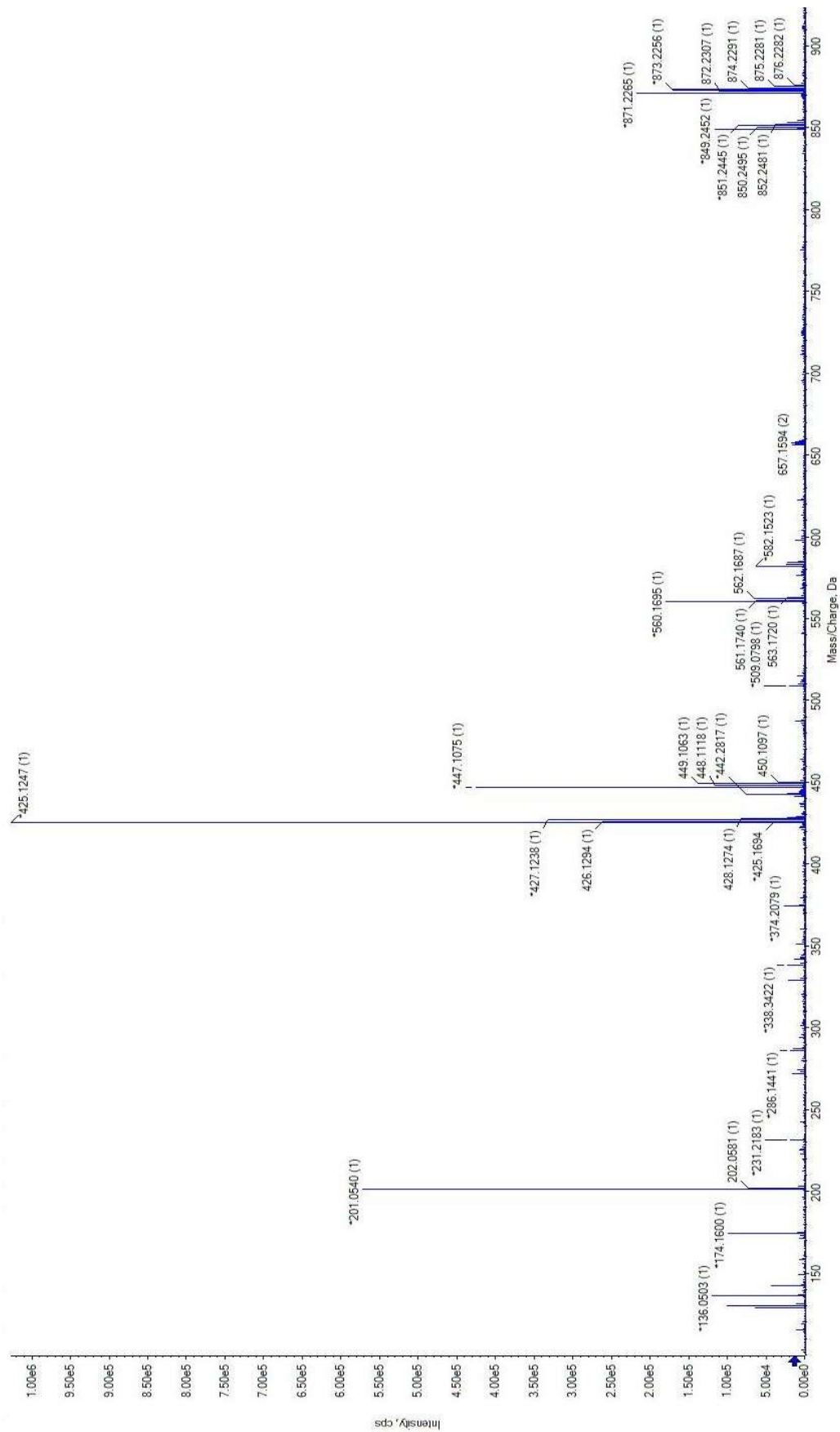


Figure 7.32. HRMS of compound PD07

List of publications

- **Bhanukiran, K.,** Singh, R., Gajendra, T.A., Ramakrishna, K., Singh, S.K., Krishnamurthy, S., Kumar, A. and Hemalatha, S., 2023. Vasicinone, a pyrroloquinazoline alkaloid from *Adhatoda vasica* Nees enhances memory and cognition by inhibiting cholinesterases in Alzheimer's disease. *Phytomedicine Plus*, 3(2), p.100439.
- **Bhanukiran, K.,** Gajendra, T.A., Krishnamurthy, S., Singh, S.K. and Hemalatha, S., 2023. Discovery of multi-target directed 3-OH pyrrolidine derivatives through a semisynthetic approach from alkaloid vasicine for the treatment of Alzheimer's disease. *European Journal of Medicinal Chemistry*, 249, p.115145. (IF- 7.088)
- **Bhanukiran, K.,** Singh, S.K., Singh, R., Kumar, A. and Hemalatha, S., 2023. Discovery of multi-target directed ligands from piperidine alkaloid piperine as a cap group for the management of Alzheimer's disease. *ACS Chemical Neuroscience*, 14(15) (IF-5.0)