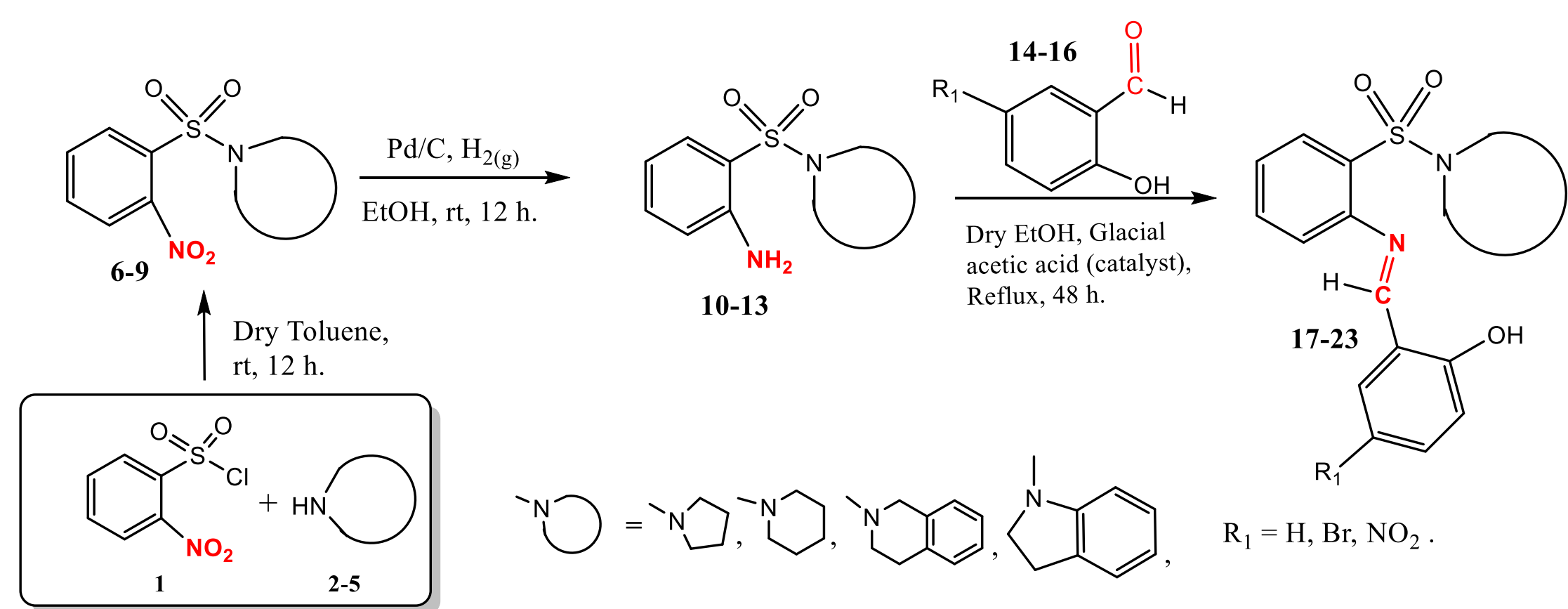


INTRODUCTION

Colon cancer, abnormal proliferation of colon cell, is a major global cause of cancer-related deaths¹, highlighting the urgent need for innovative treatments. Schiff bases, with their versatile chemical properties, are promising candidates for developing new anticancer agents. Sulphonamide-derived Schiff bases have garnered attention for their broad spectrum of applications, including corrosion inhibitors², antimicrobial³, antifungal⁴, and anticancer agents⁵. The aforementioned attributes of the sulphonamide Schiff bases are primarily relying on nitrogen, oxygen, and sulfur atoms present in the molecules⁶. This research project aims to synthesize and analyze aryl sulphonamide Schiff bases, with a focus on their crystal structures and in-silico evaluation for colon cancer treatment.

Graphical Abstract



Scheme 1 : Preparation of Potential Bioactive Sulphonamide Schiff Bases

Abstract

Aryl sulphonamide Schiff bases 17-23 were synthesized through the condensation reaction of *N*-cycloamino-2-sulphanilamides 10-13 with substituted salicylaldehydes 14-16. The precursors 10-13 were obtained from the catalytic hydrogenation of *N*-cycloamine-2-nitrobenzenesulphonamides 6-9 and these were prepared by the condensation of 2-nitrobenzenesulphonyl chloride 1 and cyclic amines 2-5 at room temperature in dry toluene. From the docking studies, many of the compounds showed significantly better anti-colon cancer activity as compared to the reference drugs investigated.

Keywords: Sulphonamide Schiff bases; catalytic hydrogenation; docking; anti-cancer activity.

Ligand's inhibitors against colon cancer cell line (5B6G)

Sulphonamide Schiff Bases as colon cancer inhibitors	Binding Affinity
5b6g_L7_uff_E=837.49 23	-7.6
5b6g_L6_uff_E=769.37 22	-7.3
5b6g_L5_uff_E=705.34 19	-7.0
5b6g_L2_uff_E=629.77 20	-6.7
5b6g_L3_uff_E=687.20 21	-6.5
5b6g_Capecitabine_uff_E=624.15	-6.4
5b6g_Trifluridine_E=282.80	-6.3
5b6g_L1_uff_E=665.88 17	-5.9
5b6g_L4_uff_E=681.92 18	-5.8
5b6g_5-Fluorouracil_uff_E=45.86	-4.3

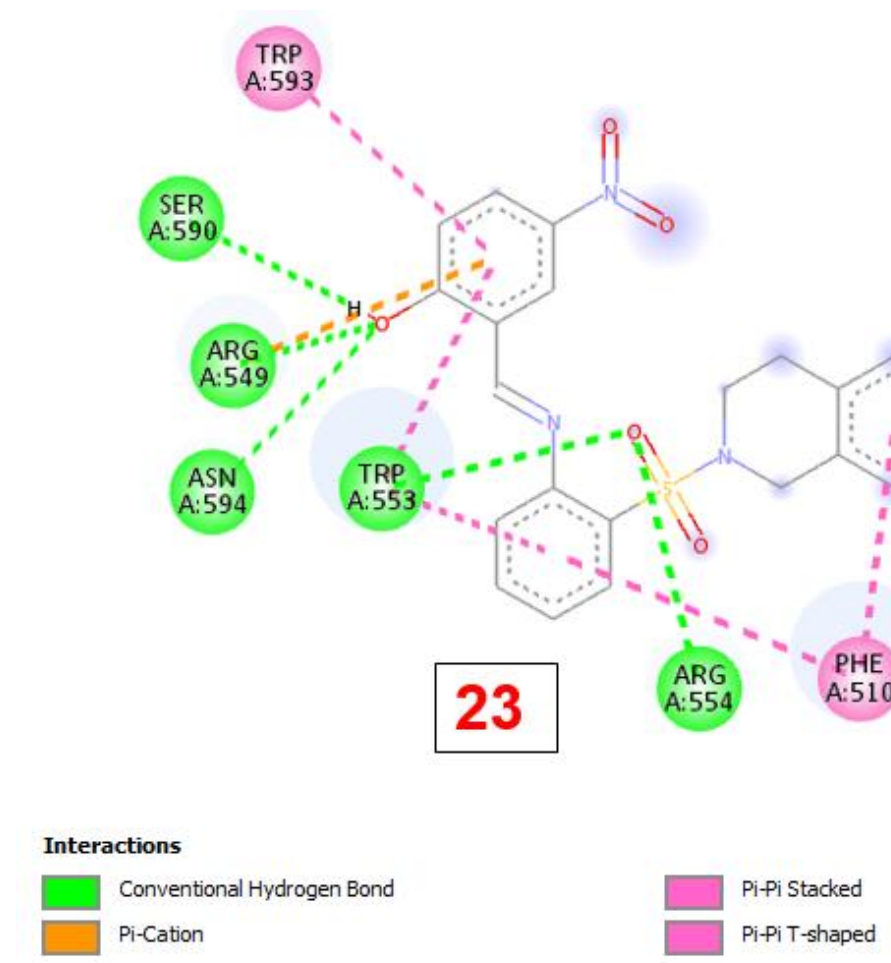


Figure 1: Inhibitory results of Ligands' Interaction with the colon cancer protein and that of 2D Structure of Ligand **23** with highest binding energy (-7.6 kcal / mol)

SYNTHESIS, CRYSTAL STRUCTURE AND *IN-SILICO* ANTICOLON CANCER STUDY OF ARYL SULFONAMIDE SCHIFF BASES

Sherif O. Kolade, Oluwafemi S. Aina, Olayinka T. Asekun, Idiris A. Olasupo, Adeniyi S. Ogunlaja and Oluwole B. Familoni*
Department of Chemistry, University of Lagos, Akoka, Lagos, Nigeria
 *familonio@unilag.edu.ng



Results and Discussion

Figure 2 (¹H NMR) showed 6 aromatic protons of compound **13** resonated downfield between δ 7.56-6.61 ppm. The singlet signal resonated at δ 5.03 ppm was assignable to the aromatic primary amine protons (**H16**) while the methylene protons

(**a**, **a'**, **i**, **i'** and **h**, **h'**) of isoquinoline occurred upfield as a singlet and triplets at δ 4.26, 3.36 ($J = 6.0$ Hz) and 2.96 ($J = 6.0$ Hz) ppm respectively. In **Figure 3**, phenolic and imine protons occurred at δ 13.47 and δ 8.37 ppm respectively. The disappearance of the singlet signal attributed to the amino protons, **H16** in the ¹H NMR spectrum of compound **23** with the requisite proximal carbon atom (**C7**) of the carbonyl of salicylaldehyde resonated downfield in ¹³C NMR spectrum of compound **23** (**Figure 5**) 162.47 ppm corroborated successful formation of imine carbon (**C=N**) of the potentially bioactive *N*¹-(2¹-hydroxyl-5¹-nitrobenzylidenyl)-*N*-1,3,4-trihydroisoquinolinyl-2-sulphanilamide **23**.

Docking studies of the synthesised compounds

Molecular docking studies (**Figure 1**) of all the synthesised compounds were performed using AutoDock vina 1.2.0. software. 5B6G (human adenomatous polyposis-colon cancer), 2XUS (breast cancer metastasis-suppressor 1) and 1GFZ (glycogen phosphorylase-lung cancer) cell lines were used to identify best anticancer target. Out of the seven synthesised sulphonamide Schiff bases (17-23) docked on the three cancer cell lines, five of them showed better activities against the colon cancer cell line than the three standard drugs (Capecitabine, Trifluridine and Fluorouracil) with compound **23** being the most potent. Many of the nitro sulphonamides (6-9) and amino sulphonamides (10-13) also displayed better inhibitory activity against colon cancer cell lines than the reference drugs. Interestingly, according to the *in-silico* study, compound **23** also showed good cytotoxic activity giving the percentage of Hepatotoxicity (inactive) 63 %, Carcinogenicity (inactive) 56 %, Immunotoxicity (inactive) 88%, Mutagenicity (active) 68% and Cytotoxicity (inactive) 75%.

Conclusion

The synthesis, crystallography, and computational studies of aryl sulphonamide Schiff bases represent a multidisciplinary approach to the development of potential anti-colon cancer agents. This research has the potential to make a significant contribution to the field of cancer therapeutics, ultimately benefiting patients suffering from colon cancer.

Finally, this research work agrees with the policy of the United Nation of Sustainable Development Goal (SDG) 3–“Good health and well-being.”

References

1. J. T. Wren, & J. B. Wardenburg, *Cell Host Microbe*, 2021, 29(10), 1480-1481.
2. C. K. Bhkakh, & J. S. Hadi, *Res. J. Chem. Sci.*, 2015, ISSN, 2231, 606X.
3. M. Krátký, M. Dzurková, J. Janoušek, K. Konečná, F. Trejtnar, J. Stolaříková, & J. Vinšová, *Mol.*, 2017, 22(9), 1573.
4. A. Hamad, Y. Chen, M. A. Khan, S. Jamshidi, N. Saeed, M. Clifford, ... & K. M. Rahman, *MicrobiologyOpen*, 2021, 10(4), e1218.
5. R. M. Elsamra, M. S. Masoud, & A. M. Ramadan, *Sci. Rep.*, 2022, 12(1), 20192.
6. S. Kumar, P. Sekar, & S. K. Raju, *IJCAAP*, 2023, 8(1), 10-21.

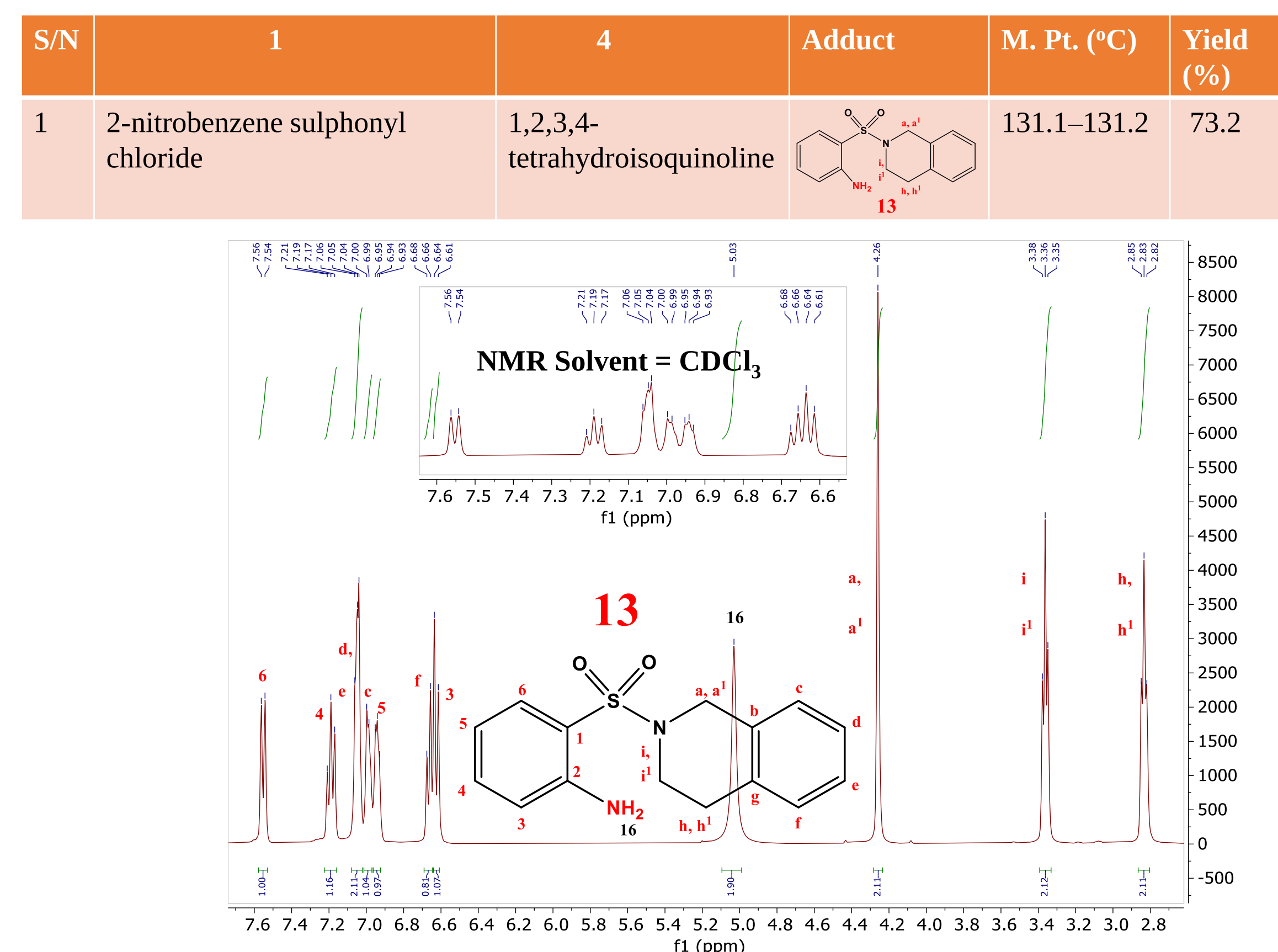


Figure 2: ¹H NMR spectrum of *N*-(1,3,4-trihydroisoquinolinyl)-2-sulphanilamide **13**

Table 2: Property of <i>N</i> ¹ -(2 ¹ -hydroxy-5 ¹ -nitrobenzylidenyl)- <i>N</i> -1,3,4-trihydroisoquinolinyl-2-sulphanilamide 23				
S/N	<i>N</i> -(1,3,4-trihydroisoquinolinyl)-2-sulphanilamide	<i>N</i> ¹ -(2 ¹ -hydroxy-5 ¹ -nitrobenzylidenyl)- <i>N</i> -1,3,4-trihydroisoquinolinyl-2-sulphanilamide 23	M. pt. (°C)	Yield (%)
1			168.5-168.7	87.3

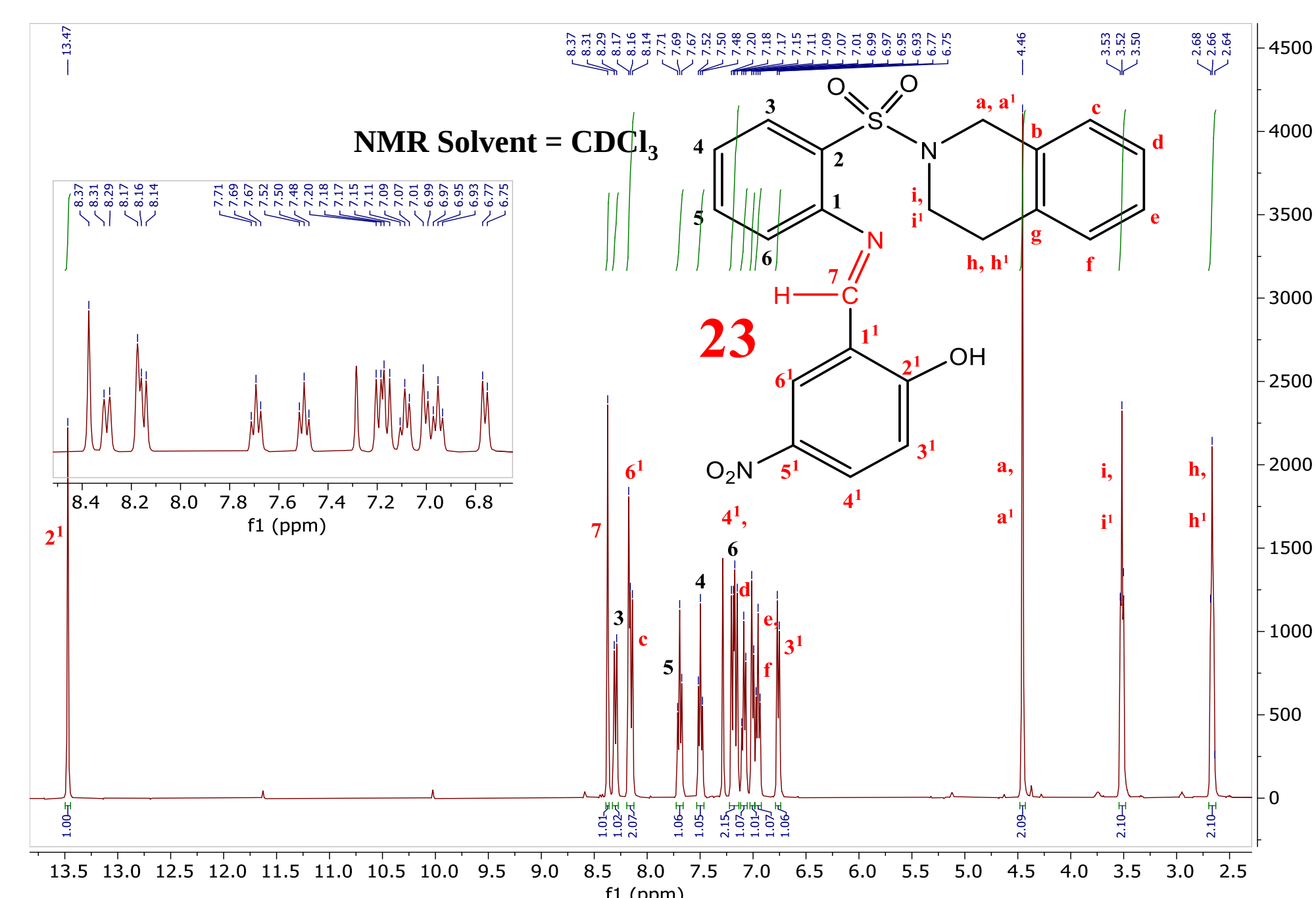


Figure 3: ¹H NMR spectrum of *N*¹-(2¹-hydroxy-5¹-nitrobenzylidenyl)-*N*-1,3,4-trihydroisoquinolinyl-2-sulphanilamide **23**

