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Facile Ambient Condition Synthesis and Characterisation of Bicyclic Amide Gallate via Galloyl Chloride Route

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ABSTRACT
Gallic acid and its derivatives (gallates) are biologically active molecules with potentials for therapeutic applications. They are also labile ligands for the synthesis of coordination compounds. The new gallate Ethyl-4-[(3,4,5-trihydroxybenzoyl) amino] benzoatewas synthesised via a mild condition, less strenuous route which involves room temperature reaction of ethyl-4-aminobenzoate with galloyl chloride. The galloyl chloride was obtained by the reaction of a solution of gallic acid in benzene with thionyl chloride using pyridine as a catalyst. The synthetic route afforded the gallate in good yield. The spectroscopy characterisation including FTIR, MS, ^{1}H, $^{13}C$and 2D NMR (COSY, HMQC and HMBC) was carried out.

I. INTRODUCTION

Gallates are esters, amides or salts of gallic acid, they have been reported to haveseveral chemical and biological applications. The gallic acid moiety consisting of the aromatic ring along withthree phenolic groups and a carbonyl group possess a wide array of biological activities such as antioxidant (Rasool et al., 2010), anti-inflammatory (Shranya et al., 2018, Toyama et al., 2022) antibacterial (Orlando et al, 2025), anticancer (Jiang et al., 2022, Huang et al., 2021), and antimicrobial (Shao et al., 2015, Kang et al., 2008) effects making them molecules with therapeutic potentials. Furthermore, many gallates have been reported as labile ligands (Rushi et al., 2018, Nidhi et al., 2018, Samy and Reham, 2022) for the synthesis of metal complexes. The lability of the gallate ligands stems from the presence of many hetero atoms with lone pairs of electrons which are used for coordination to the metal centre. In view of the many applications of gallates, the synthesis of new gallates will avail the scientific world with new molecules which can be harnessed to solve life's challenging problems.

Many synthetic routes to gallates have been documented. Some of the synthetic routes to gallate involves the direct coupling reaction between gallic acid an amine or alkanol using a coupling reagent such as N, N-diisopropyl carboiimide (DIC) and 4-dimethylaminopyridine. The associated challenge with this procedure is that it requires tedious workup to remove the urea generated during the process. Another approach is the reaction of gallic acid with thionyl chloride (or other chlorinating agents) resulting in the formation galloyl chloride which is coupled insitu with other reagent to yield the gallates (Alhazamet al., 2012).This approach works well with extremely anhydrous reagents since thionyl chloride readily reacts with water, also extensive separation is required to recover the gallate from the mixture of unreacted reagents. However, independent synthesis and isolation of galloyl chloride before reacting with another reagent to afford gallate is a facile and less strenuous synthetic route. It requires no coupling reagent, less separation and purification and give high yield. The galloyl chloride can be synthesis by the reaction of 1:1 (mole) mixture of galloyl chloride in aprotic solvent such as benzene with the addition of pyridine (a proton scavenger) (Human and Mills, 1946) and refluxing the result mixture at 70 ℃ for 2 hours.

Herein we report for the first timea facile ambient condition synthesis of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate, a bicyclic amide gallate via the reaction of galloyl chloride and ethyl-4-aminobenzoate. The synthesis and isolation of galloyl chloride is also reported. The gallate was also characterised by different

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spectroscopic techniques including ^{1}H and ^{13}C NMR and 2D NMR (DEPT, COSY, HMQC and HMBC). Mass spectrometry and FTIR were also used for the characterisation of the gallate.

II. MATERIALS AND METHODS

Gallic acid monohydrate (99%) used was a product of MolyChem, Mumbai, India. Thionyl chloride (98%), pyridine (99%), benzene (98%) and ethyl-4-aminobenzoate (99%) were purchased from Surechem Products Ltd, England. They reagents were used as purchased without further purification.

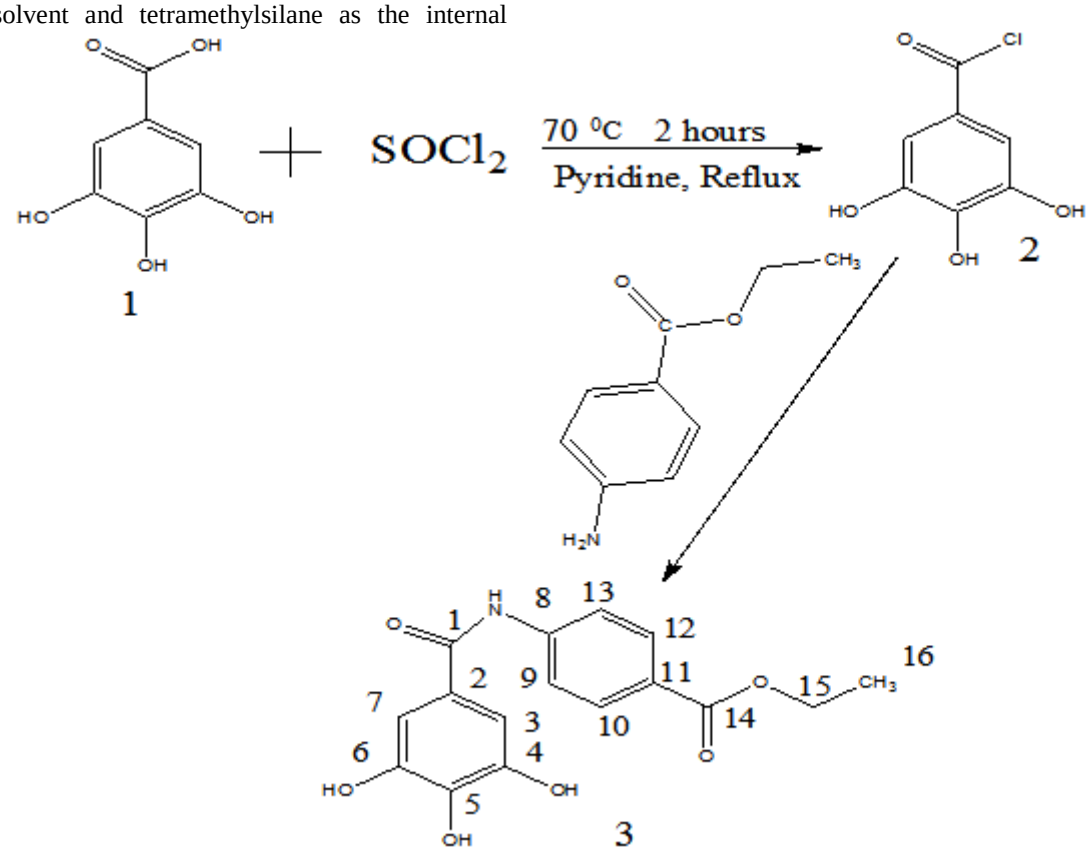
The melting point of the compound was determined using HANNA melting point determination equipment using capillary tube method without correction. The infrared spectrum of the compound was obtained using KBr pellets on a FTIR SHIMADZU spectrophotometer. Elemental composition of the gallate was determined using Vario MICRO elemental analyser. Nuclear magnetic resonance spectra (^{1}H, ^{13}C and DEPT 135, COSY, HMQC and HMBC) of the compound was recorded using Bruker AMX spectrophotometer at 500 MHz for ^{1}H and 125 MHz for ^{13}C respectively using deuterated DMSO as solvent and tetramethylsilane as the internal standard. The mass spectrum measured using a Thermo Scienctific HRMS (ESI) spectrometer.

Synthesis of 3,4,5-trihydroxybenzoyl chloride (Galloyl chloride)

Galloyl chloride was synthesis following the procedure reported by Human and Mills (1946). A solution containing 0.1mole (18.8g) of gallic acid monohydrate was dissolved in 100 cm^3 of benzene and 0.1 mole (7.33 cm^3) ofthionyl chloride ($SOCl_2$) added to it followed by adding 0.1 mole (8.16 cm^3) of pyridine. The resultant mixture was refluxed for 2 hours at 70 ℃. The precipitate formed was filtered and washed repeatedly with methanol and dried.

Synthesis of Ethyl-4-[(3,4, 5-trihydroxybenzoyl) amino] benzoate.

Methanolic solution containing 0.83g (5 mmols) of ethyl-4-aminobenzoate in 40 $cm^3$was reacted with 0.94g (5 mmols) of galloyl chloride in 40 cm^3 under reflux at 70 ℃ for 2 hours. A greenish-brown solution was formed which was left for 14 days. A brown precipitate formed was filtered and washed with water and dried in a desiccator.



Scheme 1: Synthetic route for the synthesis of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate.

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III. RESULTS AND DISCUSSION

Galloyl chloride ($C_7H_5ClO_4$) was synthesised via method stated above as a white powdery solid with a melting point of 142 ℃ in high yield of 93%. The synthesised galloyl chloride was used for the synthesis of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate. The elemental analysis (CHNO) ofgalloyl chloride ($C_7H_5ClO_4$) showed the calculated values for the composition by mass of carbon, hydrogen and oxygen to be in agreement with the experimentally determined values. The calculated values and the (found) in % are: C, 44.59 (44.70); H, 2.67 (2.61); O, 33.94 (33.78).

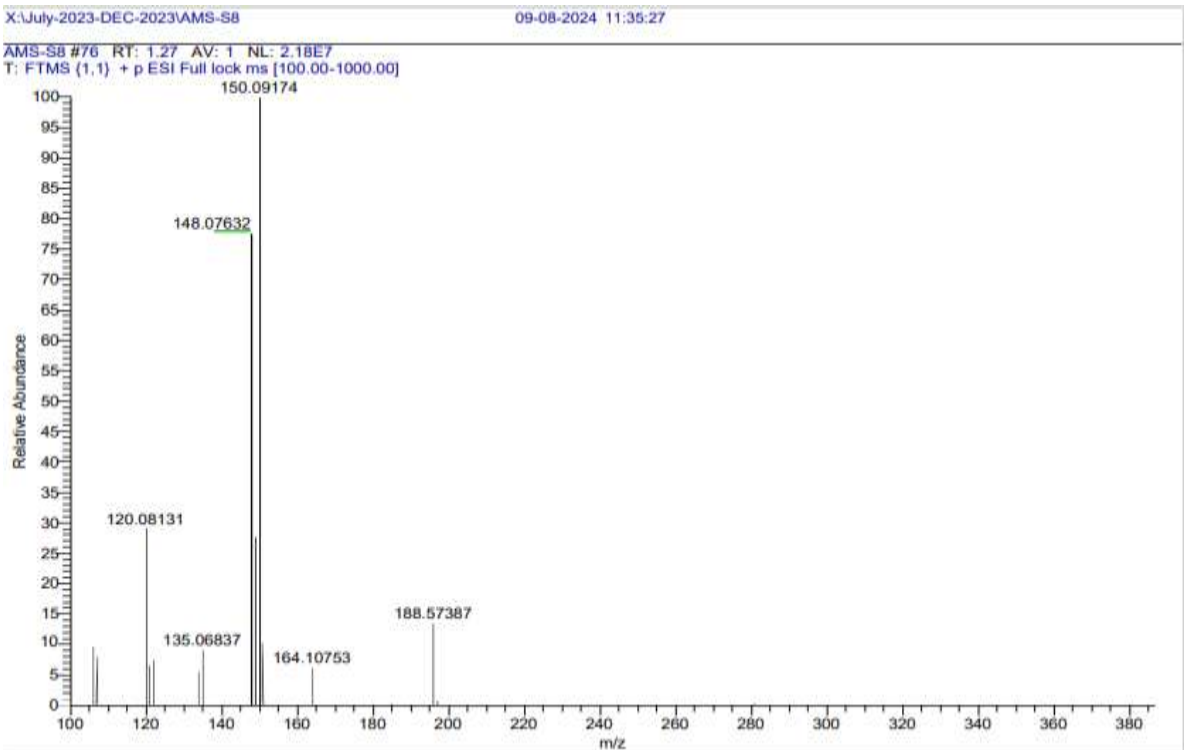

Figure 1: Mass Spectrum of Galloyl chloride

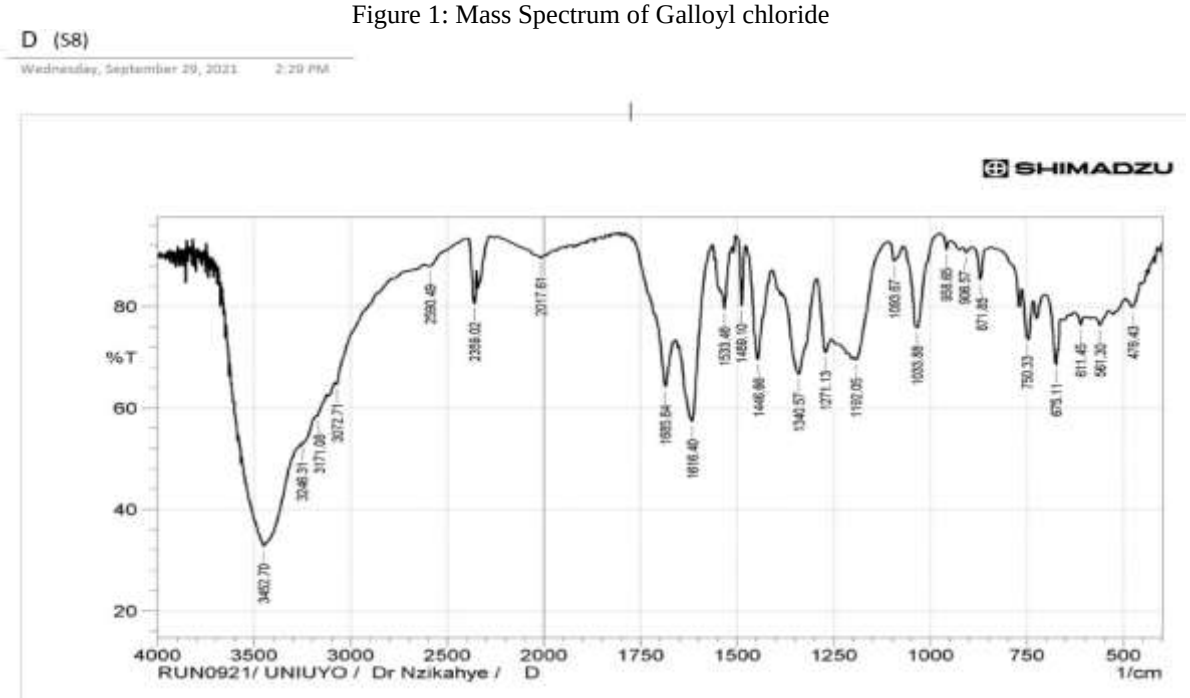

Figure 2: FTIR Spectrum of Galloyl chloride

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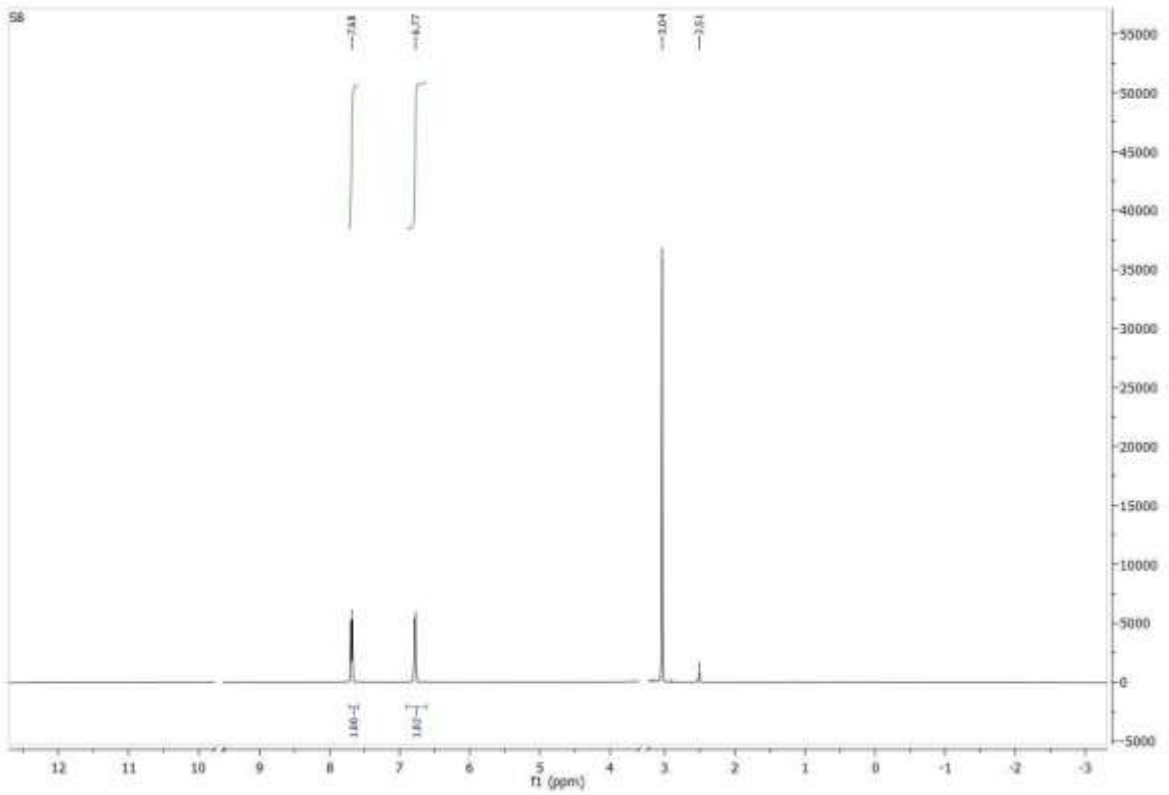

Figure 3: Proton NMR Spectrum of Galloyl chloride

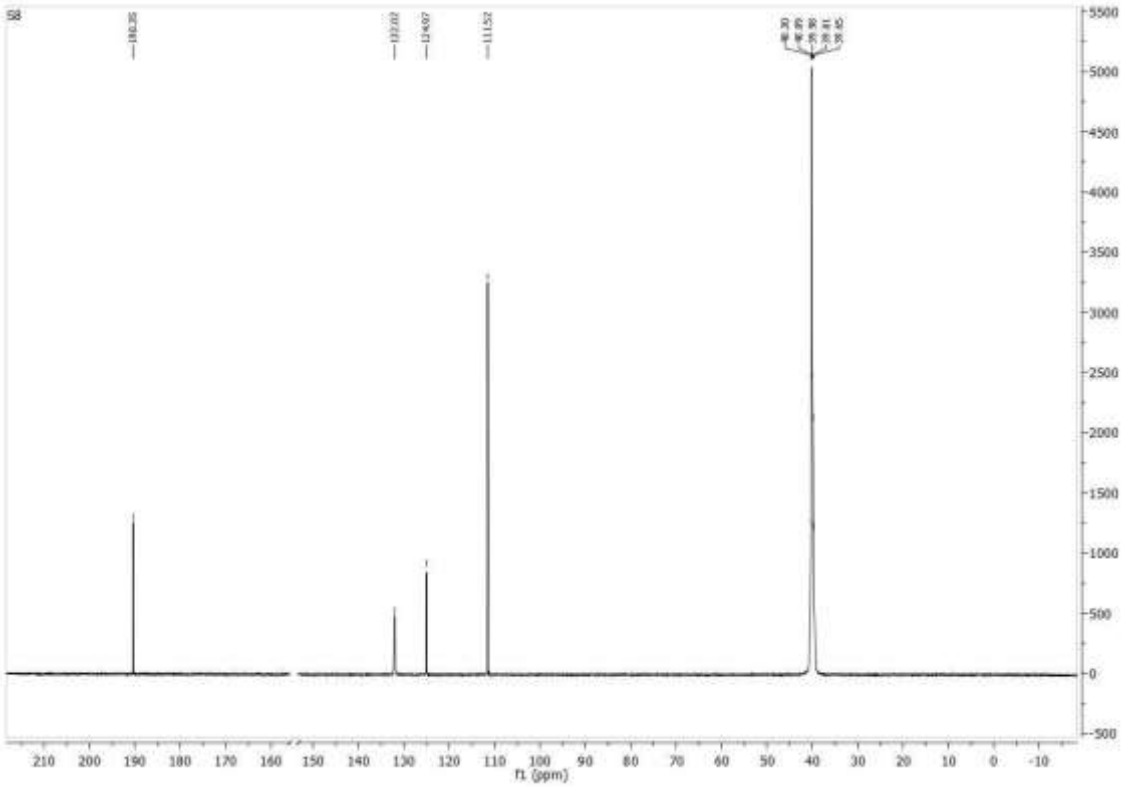

Figure 4: Caron-13 NMR Spectrum of Galloyl chloride

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The carbon-13 NMR (126 MHz, DMSO-d_6) showed five peaks; δ_c 190.35, 132.02, 124.97, 111.52. The deshielding signal at δ_c 190.35 was assigned to carbonyl carbon and δ_c111.52 was attributed to the aromatic carbons bonded to the phenolic groups. The two aromatic C-H aromatic carbons were assigned at δ_c124.97 while the ring carbon directly bonded to the carbonyl carbon was attributed to the δ_c 132.02, the solvent peak occurred at δ_c 39.98. The proton NMR result (500 MHz, DMSO-d_6) showed a peak δ_H 7.68 (1H, s) and δ_H 6.77 (1H, s) assigned to the two aromatic protons. The DMSO protons peak occurred as a singlet at δ_H3.04 while the δ_H2.51 peak iswater signal. The result of mass spectrometry of galloyl chloride confirmedthe molecular mass of the compound with the molecular ion peak is at 188.57 m/z. The FTIR spectra of galloyl chloride, showed absorptions at 3453 cm^{-1} assigned to O-H stretch phenol, 1686cm^{-1} assigned to C=O stretch acid chloride, 3246cm^{-1} assigned to C-H stretch aromatic, 1616cm^{-1} assigned C=C skeletal stretch phenyl, 1447cm^{-1} assigned to (O-H in plane bending, phenol), and 750 assigned to C-Cl stretch. The peaks at 3171 cm^{-1} and 3073cm^{-1} are likely due to the solvent.

Spectroscopic Characterisation ofEthyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

Ethy l-4-[(3, 4, 5-trihydroxybenzoyl) amino] benzoate was synthesised by the reaction of galloyl chloride and ethyl-4-aminobenzoate. The product has a melting point of 173 ℃ and was obtained in good yield of 81 %. The elemental analysis (CHNO) result of the compound with molecular formula $C_{16}H_{15}NO_6$ and molecular weight of 317.29 g/mol; reveals the calculated values and (found) percentage composition as: C 60.55 (60.87), H, 4.77 (4.89), N, 4.41 (4.37) and O, 30.25 (30.47) which are in good agreement. The molecular weight was confirmed by the molecular ion peak at 317.90 m/z in the result of mass spectrometry

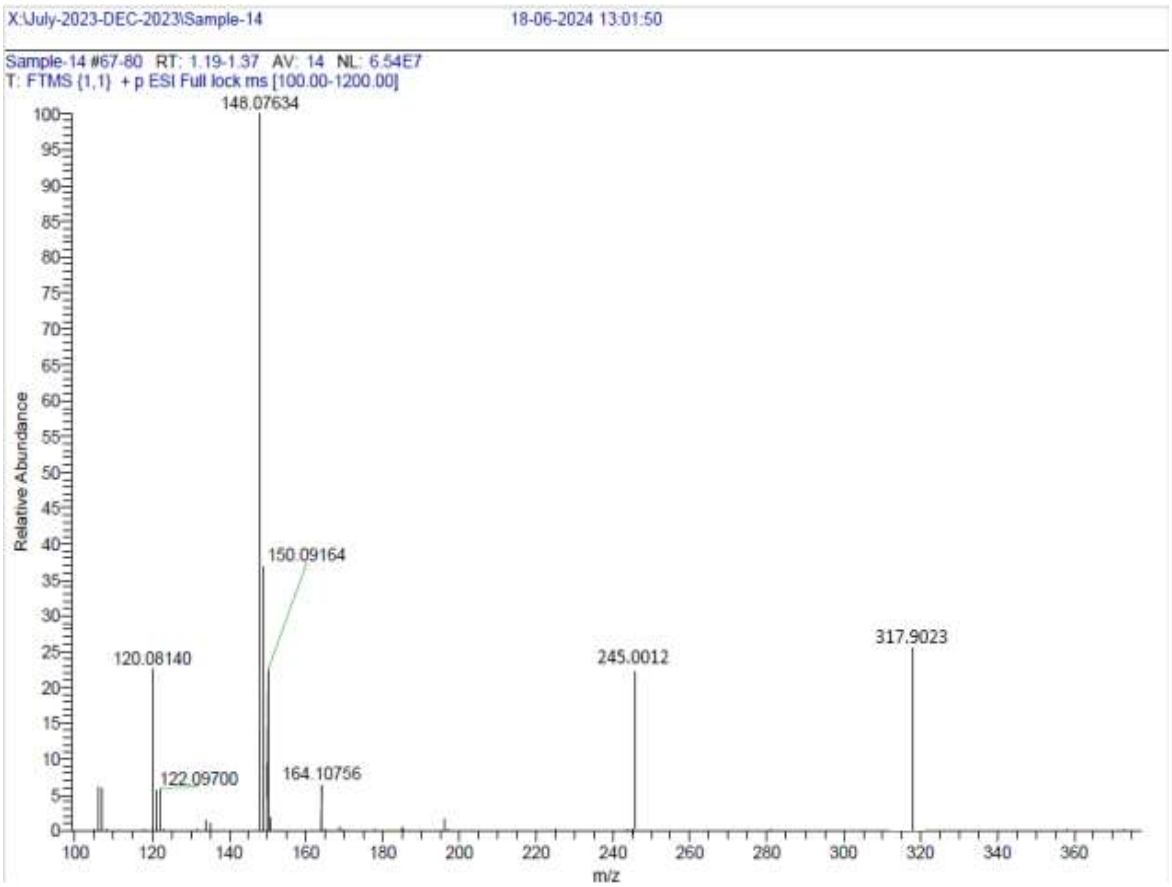

Figure 5: Mass Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

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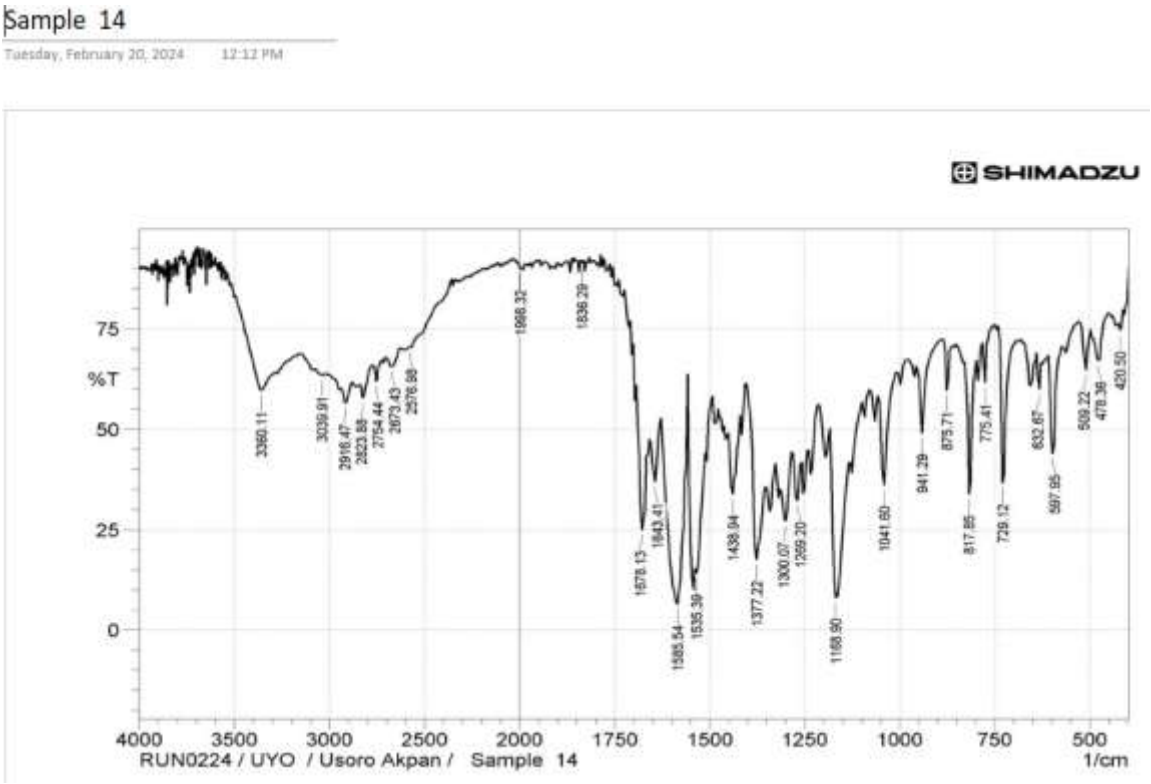

Figure 6: FTIR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

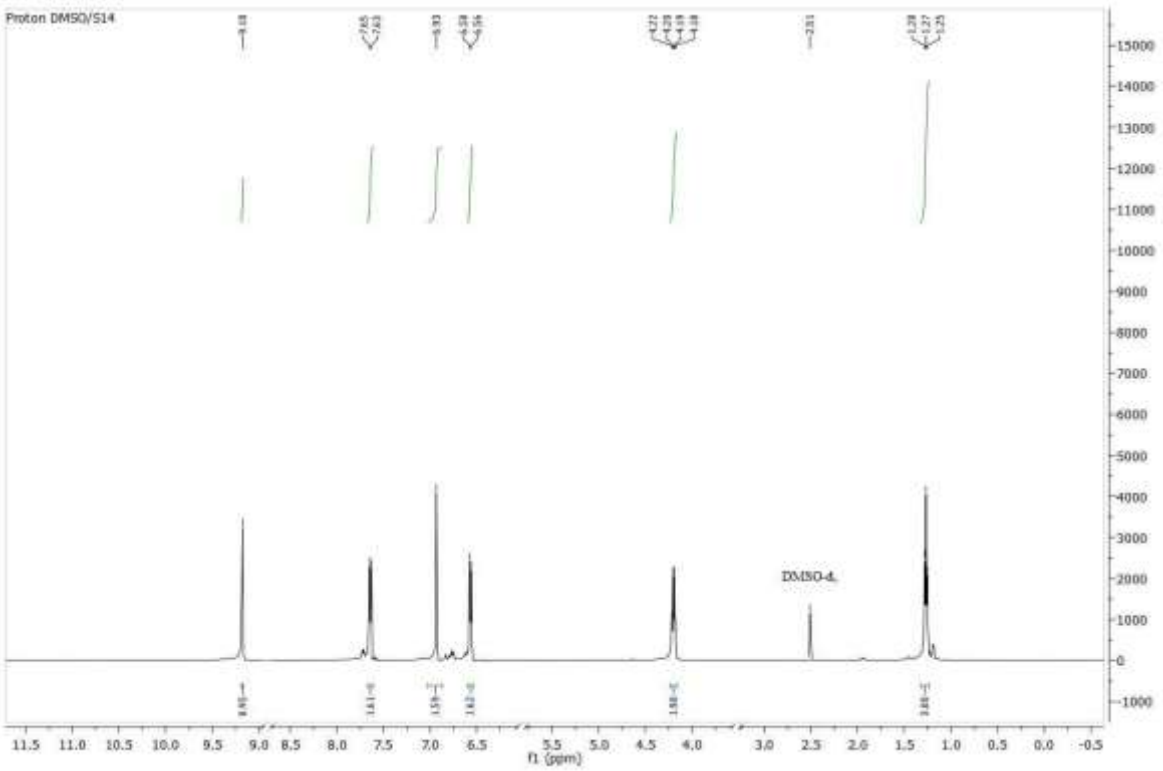

Figure 7: Proton NMR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

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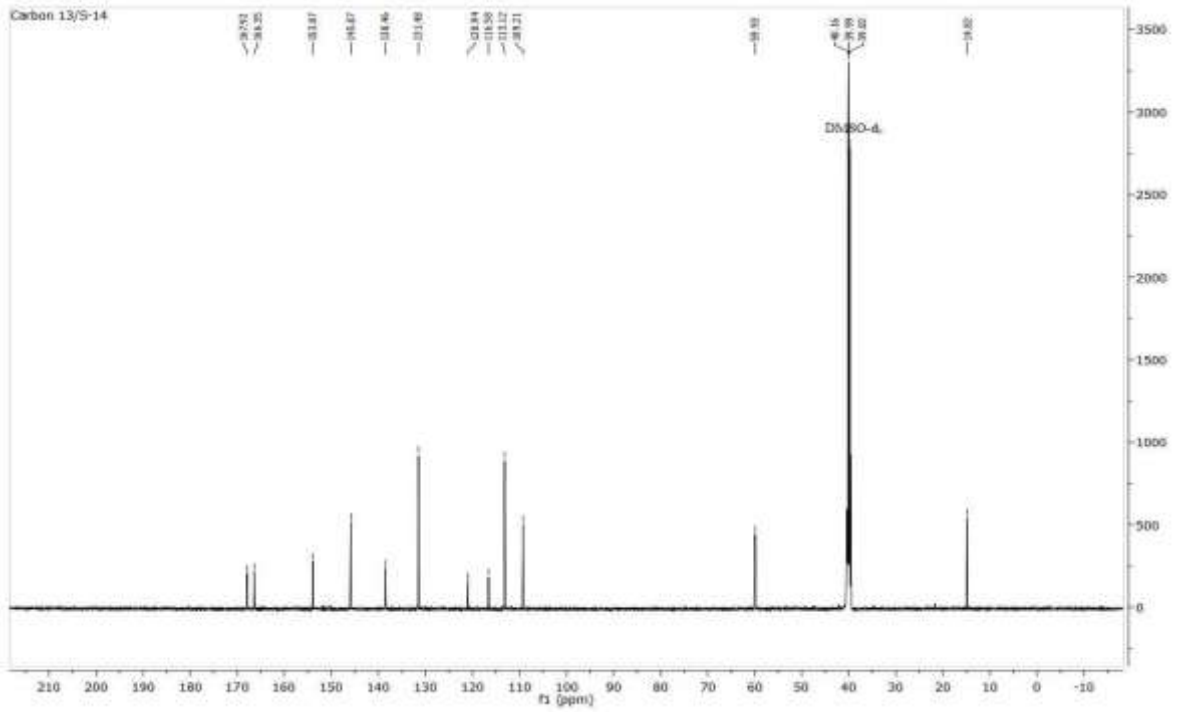

Figure 8: Carbon 13 NMR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

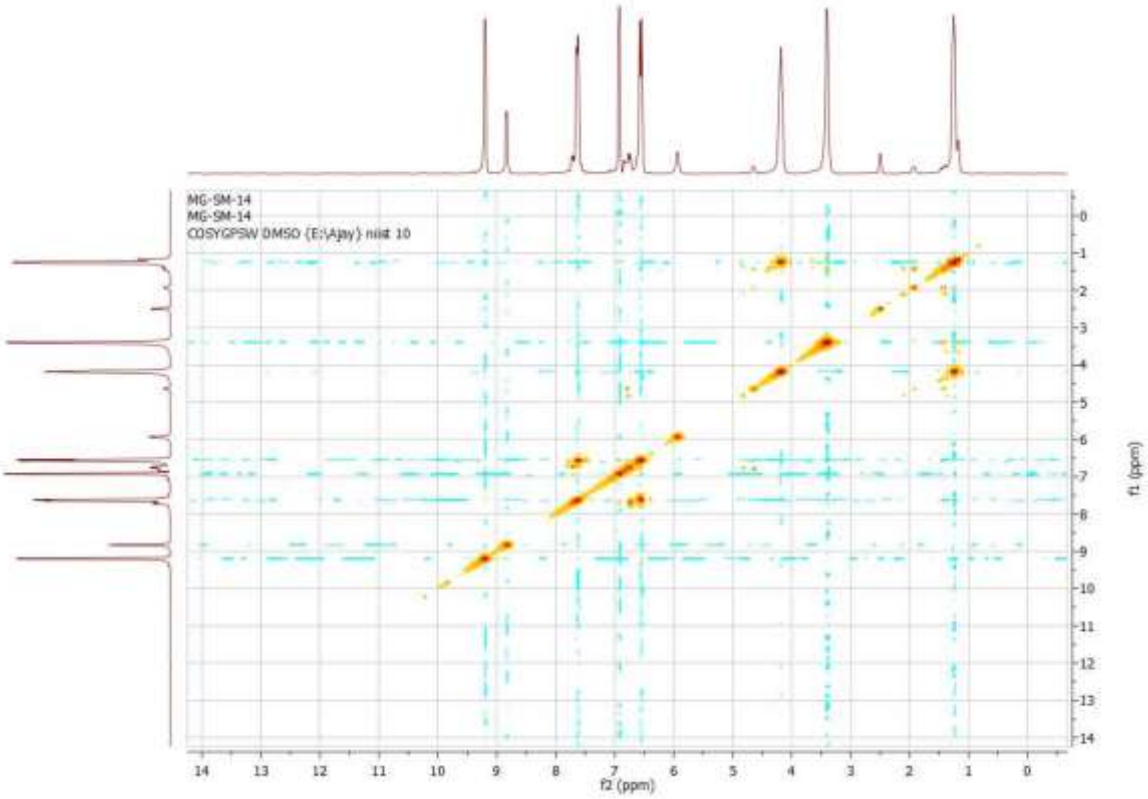

Figure 9: COSY NMR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

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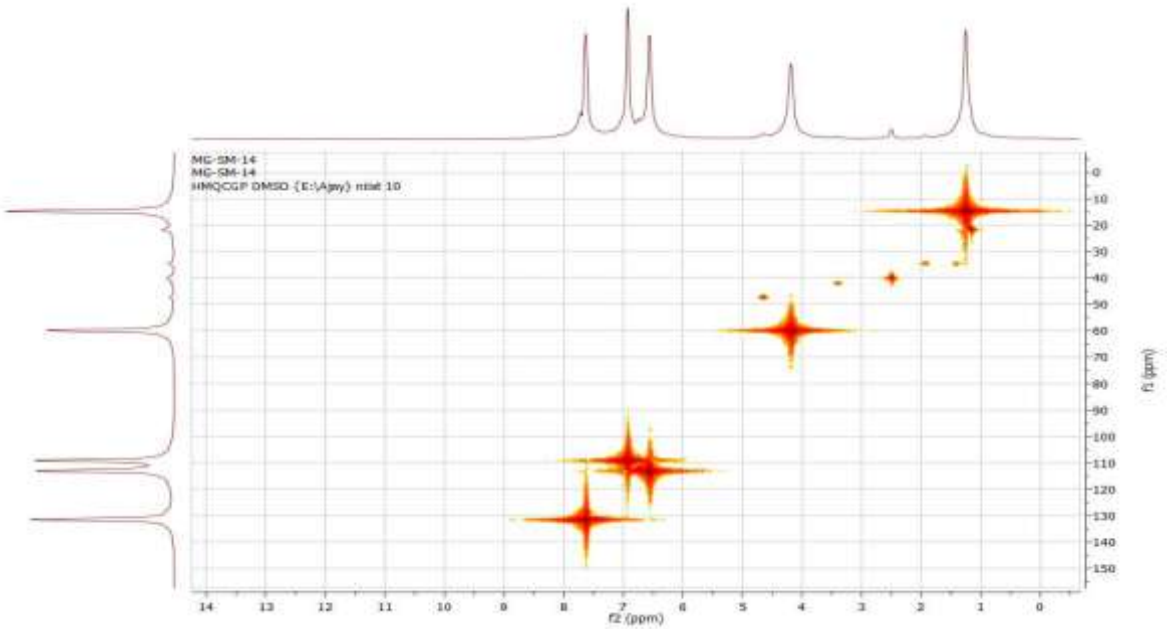

Figure 10: HMQC NMR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

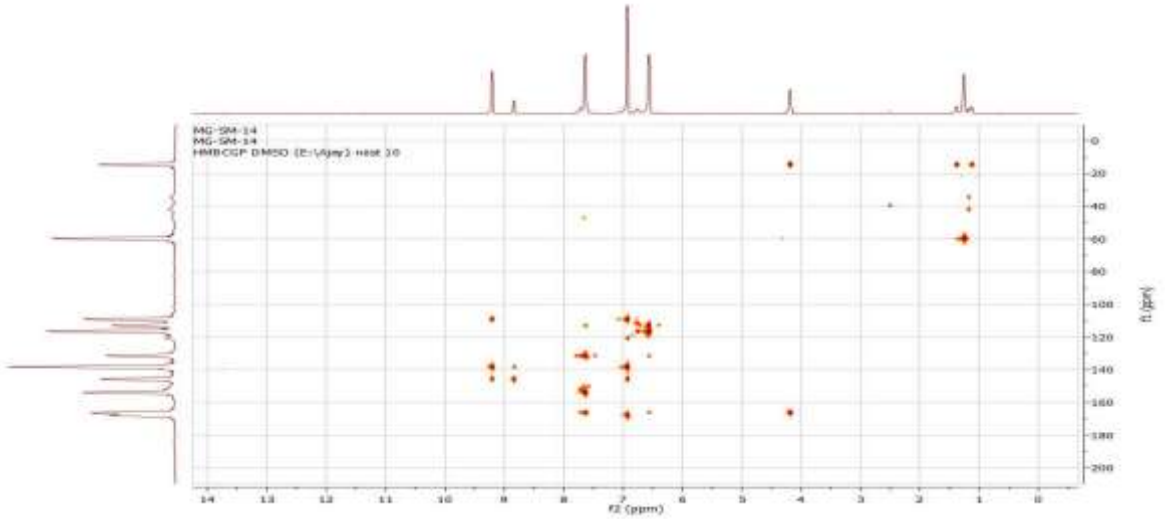

Figure 11: HMBC NMR Spectrum of Ethyl-4-[(3,4,5-trihydroxybenzoyl)amino]benzoate

The ^{1}H NMR (DMSO, δ (ppm)) spectrum of compound showed methyl signals at δ_H1.27 (3H, t, J=6.7 Hz), which was attributed to the protons at H-16. One deshielding proton signal at δ_H4.20 (2H, q, J=6.7 Hz) which was assigned to proton at H-15 and aromatic protons signal at δ_H6.57 (1H, d, J =7.8 Hz, H-12 and H-10), at the adjacent side, signal resonated at δ_H7.64 (1H, d, J=6.9 Hz, H-9 and H-13) was observed. A singlet signals resonated at δ_H6.93 (1H, s, H-3 and H-7) and highly deshielding proton resonated at δ_H9.18 (1H, s) was attributed to the proton bonded to nitrogen atom H-17. The ^{13}C NMR (125 MHz, DMSO, δ (ppm) showed 12 carbon signals, of which 4 carbon signals appearing in the same chemical environment resonated with high peak signals summing up to 16 carbon signals. The signal at 40.0 is the solvent (DMSO) peak. The carbon signals of the carbonyl carbon atoms resonated at δ_C 167.9 and aromatic δ_C 166.4, which were attributed to carbon atoms at C-1 and C-14 due to the deshielding effect of heteroatom, Nitrogen and Oxygen, while the aromatic carbon signals resonated between δ_C 153.8 to δ_C109.32. Carbon signals showing deshielding effect due to heteroatom was observed at δ_C 59.9 (C-15) while a methyl carbon (C-16) signal was observed at δ_C14.8. The DEPT 135 spectrum showed the presence of six aromatic C-H carbon atoms ranging from δ_C 131.50 to δ_C109.17, one CH_2 carbon atom assigned at δ_C59.95 (H-15) and one CH_3 carbon

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atom signalδ_C14.82 (H-16). The ^{1}H-^{1}H COSY showed a correlation between the methylene proton at δ_H4.20 (2H, q, J=6.7 Hz, H-15) with δ_H1.27 (3H, t, J=6.7 Hz, H-16) and the proton at δ_H6.57 (1H, d, J =7.8 Hz, H-12 and H-10) with δ_H7.64 (1H, d, J=6.9 Hz, H-9 and H-13). The ^{1}H-^{13}C HMQC spectrum indicated that sp^2 proton δ_H4.20 (2H, q, J=6.7 Hz) showed a direct bonding to δ_C 59.95 (C-15). The aromatic protons (H-3 and H-7) δ_H6.93 (1H, s) directly bonded to aromatic carbons (C-3 and C-7) δ_C 109.21 respectively. Also, aromatic protons (H-10 and H-12) δ_H6.57 (1H, s) is directly bonded to aromatic carbons (C-10 and C-12) δ_C 113.46 respectively and δ_H7.64 (1H, d, J = 8.2 Hz, H-9 and H-13 are correlated to Carbon (C-9 and C-13) δ_C 131.49 respectively. HMBC spectrum showed a correlation between the proton at δ_H6.93 (1H, s, H-3 and H-7) and the carbon atom at δ_C 167.9 (C-1). Also, the signals at δ_H1.27 (3H, t, J=6.7 Hz) showed correlation with carbon signal at δ_C 59.9 (C-15) and δ_H4.20 (2H, q, J=6.7 Hz) correlated with δ_C 14.8 (C-16) and δ_C166.4.

The FTIR spectra of the compound in KBr shows N-H stretch amide at 3360 cm^{-1}, O-H stretch phenol at 3040 cm^{-1},C=O stretch at 1678 cm^{-1}, C-H stretch aliphatic at 2824 cm^{-1} and 2754 cm^{-1}, C-H aromatic at 2917 cm^{-1}, C=C stretch aromatic at 1643 cm^{-1}, O-H in plane bending phenol at 1436 cm^{-1}, C-N stretch at 1269.26 cm^{-1}and C-H bending aromatic at 818cm^{-1}. Following the rule of three peaks for ester absorptions, peaks at 1678cm^{-1}, 1377 cm^{-1} and 1169 cm^{-1} were assigned to C=O stretch, C-C-O stretch and C-O-C stretch respectively of the ester moiety. The synthesis of compound was confirmed based on the above spectroscopic data.

IV. CONCLUSION

A novel bicyclic amide gallate: Ethyl-4-[(3, 4, 5-trihydroxybenzoyl) amino] benzoate was synthesis at room temperature and pressure by the direct reaction of galloyl chloride with ethyl-4-aminobenzoate. The synthesis and isolation of galloyl chloride was also achieved. This ambient condition synthesis of the gallate was facile and required minimum workup for the recovery of the product. The product was obtained in high yield with a short time duration.

REFERENCES

[1]. Arsianti, A.; Astuti, H., Simadibrata, D.M.; Adyasa, Z.M.; Amartya, D.; Bahtiar, A.; Tanimoto, H.; Kakiuchi, K. (2018). Synthesis and invitro antimalarial activity of alkyl esters of gallate as a growth inhibito of Plasmodium falciparum. Oriental Journal of Chemistry. 34: 665

[2]. Cai, W. and Qi, W. (2019). A kind of preparation of electronic grade gallic acid monooctyl ester. CN patent CN109438243A. 8 March 2019

[3]. Hanan A. A., Zainab Shakir Abdullah, Z. S. and Nahed Al-haidery, N. (2012). Synthesis, Characterization and Antioxidant Study of Some New Compounds of Gallic Acid Derivatives. International Journal of Chemistry and Applications. 4(3): 149-157

[4]. Huang, C.; Chang, Y., Wei, P., Hung, C.; Wang, W. (2021). Methyl gallate, gallic acid derived compounds, inhibit cell proliferation through increasing ROS production and apoptosis in hepatocellular carcinoma cells. PLOS One 16: 736-743

[5]. Human, J. P.E. and Mills, J. A. (1946). Action of thionyl chloride on carboxylic acids in the presence of pyridine. Nature 158: 877

[6]. Jiang, J.; Pei, J.; Zheng, Y.; Miao, Y.; Duan, B.; Huang, L. (2022). Gallic acid: A protective anticancer agent. Chinese Journal of Intergrative Medicine. 28: 661-671

[7]. Kang, M.; Oh, J.; Kang, I.; Hong, S.; Choi, C. (2008). Inhibitory effect of methyl gallate and gallic acid on oral bacteria. Journal of Microbiology 46: 744-750

[8]. Nidhi, G.; Ginni, K.; Romila, K.; Sharma, K.; Verma, P.S. (2018) Evaluation of chelating tendency of gallic acid as a detoxifying agent: an innovative approach. International Journal of Recent Scientific Research. 9(1) 23470-24474

[9]. Rasool, M.K.; Sabina, E.P; Ramya, S.R.; Preety, P. (2010). Hepatoprotective antioxidant effects of gallic acid in paracetamol-induced liver damage in mice. Journal of Pharmacy and Pharmacology. 62: 638-643

[10]. Rushi, L.; Shunpo, Y.; Hongtao, J. (2018). Study on metal complexes of gallates. Applied Chemical Engineering 1(1): 15-24

[11]. Samy, M. E. and Reham Z. H. (2022). Synthesis, spectroscopic characterisation, conductometric titration and investigation of potent activities of gallic acid complexes with Ca (11), Cu (II), Zn (III), Cr (III) and Se (IV) metal ions. Journal of Molecular Liquids. 358: 119196

[12]. Shao, D.; Li, J.; Tang, R.; Liu, L.; Shi, J.; Huang, Q.; Yang, H. (2015). Inhibition of gallic acid on the growth and biofilm formation of Escherichia Coliand Streptococcus mutans. Journal of food science 80: M1299-M1305

[13]. Sharanga, C.S.; Arun, K.G.; Vijaytha, V., Sabu, A.; Haeidas, M. (2018). Designing of enzyme inhibitors based on active site specificity: lessons from methyl gallate and its lipoxygenase inhibitory profile. Journal of Receptors and Signal Transduction. 38: 256-265

[14]. Sherin, L.; Shujaat, S.; Sohail, A.; Arif, F. (2018). Synthesis and biological evaluation of novel gallic acid analogues as potential antimicrobial agent. Croatica Chemica Acta. 91: 551-565

[15]. Toyama, M.H.; Rogero, A.; de Moraes, L.L.F.; Fernandes, G.A.; da Cruz Costa, C.R.; Belchor, M.N.; Carli, A.M.; de Oliveira, M.A. (2022). Gallic acid as a non-selective inhibitor of α/β-hydrolase fold enzymes involved in the inflammatory process. The two sides of the same coin. Pharmaceutics. 14: 368