Synthesis, Characterization, Molecular Docking, and Antioxidant Evaluation of Some Newer Triazole Derivatives

Aman Kumar[1,*], Shobhit Srivastava[2], Priyanka Singh Patel[3]

[1]Department of Pharmaceutical Chemistry, GCRG College of Pharmacy, Lucknow, Uttar Pradesh-226202, India

[2]Department of Pharmaceutical Chemistry, Goel Institute of Pharmacy & Sciences, Lucknow, Uttar Pradesh-226010, India

[3]Department of Pharmaceutics, GCRG College of Pharmacy, Lucknow, Uttar Pradesh-226202, India

[*]Corresponding Author: amangupta.agg@gmail.com

ABSTRACT

The synthesis of novel triazolic derivatives is of significant interest due to their potential therapeutic uses. Herein, we report the synthesis of seven novel triazolic derivatives through a two-step reaction process. The initial step involved the N-alkylation of 1, 2, 4-triazole **(1)** with ethyl 2-chloroacetate **(2)** in the presence of anhydrous potassium carbonate under reflux conditions, yielding ethyl 2-(1H-1, 2, 4-triazol-1-yl) acetate **(3)**. This intermediate was subsequently subjected to amidation with various substituted anilines **(A-G)** under reflux to afford the corresponding N-(substitutedphenyl)-2-(1H-1, 2, 4-triazol-1-yl) acetamides (4A-G). Characterisation of these compounds was carried out using ^{1}H-NMR, ESI-MS, and FT-IR. The ^{1}H-NMR spectra confirmed the presence of the expected chemical shifts, correlating with the aromatic protons and triazole moiety. ESI-MS provided molecular ion peaks consistent with the proposed molecular weights of the derivatives, while FT-IR spectra showed characteristic absorption bands corresponding to amide and ester functionalities, and the triazole ring.

The interactions of the synthesized derivatives to a target protein were evaluated by Molecular docking. Compounds 4D, 4E, and 4G exhibited the highest binding affinities with docking scores of -6.9, -6.2, and -6.4 kcal/mol, respectively. These results suggest strong interactions between these derivatives and the protein's active site, indicating potential biological activity. Furthermore, the antioxidant activity of the synthesized compounds assessed by scavenging activity assay. Compounds 4D, 4E, and 4G demonstrated significant antioxidant activity, correlating well with their docking scores. The scavenging activity percentages for these compounds were superior compared to the other derivatives, highlighting their potential as effective antioxidant agents.

In conclusion, the synthesis and characterisation of these novel triazolic derivatives provide valuable insights into their structure-activity relationships. The high docking scores and antioxidant activities of 4D, 4E, and 4G suggest compounds to serve as promising candidates for therapeutic advancement.

Keywords: Triazoles, Antioxidants, Molecular docking, Characterization, Oxidative stress.

INTRODUCTION

Recently, heterocyclic chemistry acknowledged as highly complex yet immensely rewarding area due to the prominence of heterocycles in chemistry. Heterocycles, predominantly present in biologically active pharmaceuticals, widely used in various industries. The remarkable ability to contain numerous substituents in main ring, coupled with distinct structural characteristics, has consistently drawn the attention of medicinal chemists in the quest to create new compounds. Thus, design of nitrogen-rich heterocycles has garnered significant interest in these years. Among these, triazoles stand out as particularly promising, exhibiting a wide array of properties. The growing importance of triazoles accelerated synthetic strategies.

The term "triazole", framed by Bladin (1885) to refer to a 5-membered ring system containing 3-nitrogen, C_3 H_3 N_3. Following its discovery, triazole chemistry evolved gradually, with significant acceleration due to the development of efficient synthetic methods and its interaction with biological systems. For instance, the identification of fungal-killing potential of azoles in 1944 paved way for creation of drugs such as posaconazole. Voriconazole and posaconazole are effective against fluconazole-resistant Candida strains, operating by inhibiting ergosterol formation and obstructing the CYP51.

Triazole rings can bind to the heme iron in CYP enzymes and form various weak interactions with biological receptors and enzymes, enhancing their medicinal value and making them significant in numerous scientific disciplines, including chemistry, agriculture, and pharmaceuticals. Triazole-based medications cover varied therapeutic areas, e.g., anticoagulant, antitubercular, antioxidant, anticancer treatments. However, the emergence of multidrug-resistant pathogens, particularly those resistant to triazole drugs, complicates treatment and worsens infection prognosis. Additionally, azole resistance has been observed in many strains. Triazole drugs also have various adverse effects, from mild issues like rash and diarrhea to severe conditions such as heart failure and Stevens–Johnson syndrome.

To combat these challenges, new triazole drugs development is crucial. Triazoles are characterized by their five-membered ring structure with two carbons, leading to formation of 2 significant isomers. In 1, 2, 4-triazoles, main compound is white powder highly soluble in water. The 2 tautomers, 1H- and 4H, rapidly convert into each other, with 1H, being more stable **[1]**.

Within the perplexing field of organic chemistry, the triazole moiety, with its lurking physicochemical properties, is a true conundrum; it is a model of molecular intricacy that has captivated the interest of academics and experts for years. Known for its characteristic triazolic ring structure, this archaic compound has become woven into the fabric of chemical discourse, displaying a power and delicacy that belies its powerful reactivity.

Its aromatic nature, which is a result of conjugated π-electron systems, gives it a resonance-stabilized behaviour and thermodynamic stability that attests to its enduring attraction. However, beneath this calm exterior lurks a whirlwind of chemical activity, as the component known as triazole performs a remarkable ballet of molecular changes?

It is an essential tool in the toolbox of synthetic chemists due to its inherent propensity towards azide-alkyne cycloaddition events, which can be catalyzed by a variety of metal complexes or even under mild temperature conditions. In fact, this esteemed moiety's flexible reactivity plays a major role in the synthesis of several heterocyclic scaffolds, from triazoles to triazolines.

Furthermore, the vagrant ability of the triazole to show a variety of pharmacological activities is a result of its protean nature, which is marked by minute variations in substitution patterns and electrical characteristics. From antimicrobials to antifungals, antiviral treatments to anticancer medications, the triazole moiety is a true wonder medicine, providing a powerful defense against a wide range of illnesses that affect people (Figure 1). In fact, the fact that it is blended into so many pharmaceutical medicines is proof of its significant existence in pharmaceuticals.

Reactivity, too, lies at the heart of the chemistry of triazoles, as these compounds engage in a rich tapestry of chemical transformations. The triazole ring, endowed with both nucleophilic and electrophilic character, serves as a nexus for a plethora of functional group interconversions and cascade reactions. From nucleophilic substitution to metal-catalyzed cross-coupling, from oxidative cyclization to radical-mediated processes, the triazole moiety stands as a veritable playground for the creative synthetic chemist **[2].**

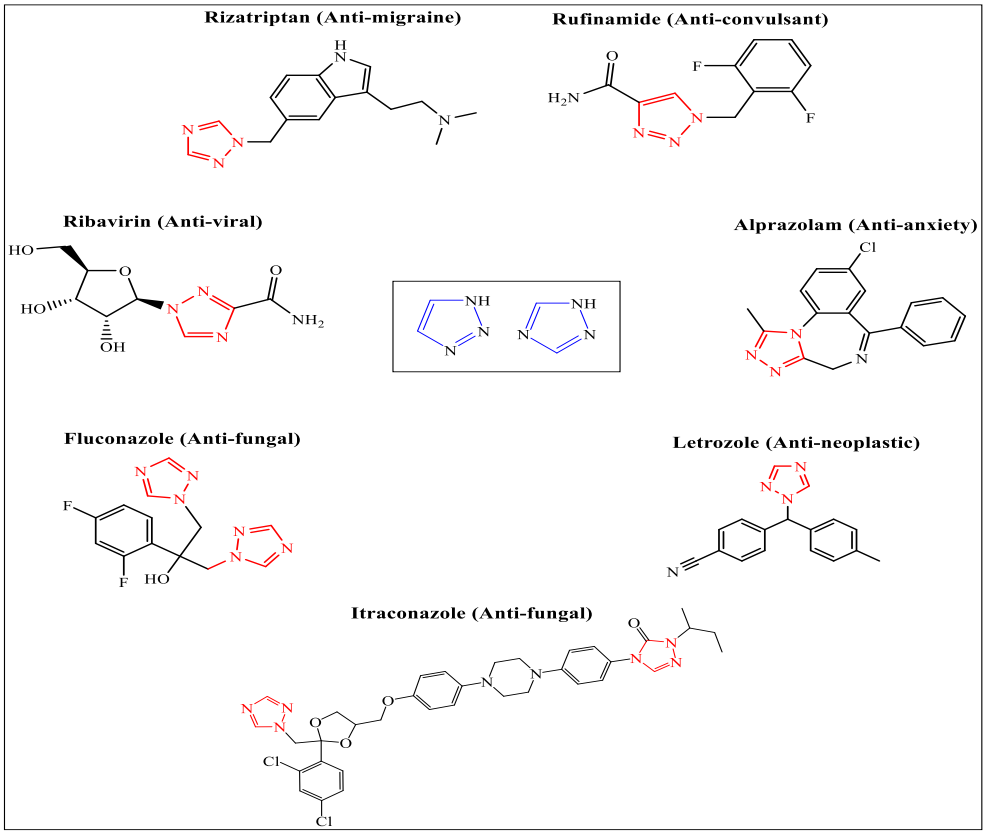


Figure 1. Triazole scaffold Biodiversity

Triazoles as Antioxidants

In the labyrinthine realm of biochemical research, the quest for potent antioxidants capable of safeguarding cellular integrity against the ravages of oxidative stress stands as a perennial pursuit. Amidst this fervent exploration, triazoles have emerged as intriguing candidates, offering a tantalizing glimpse into novel paradigms of antioxidant efficacy.

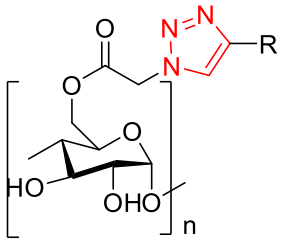
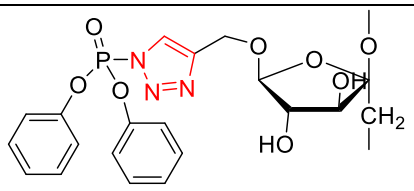
Delving deeper into the biochemical nuances of antioxidant action, we uncover the intricate kinetics of triazole-mediated redox modulation. Through a delicate dance of electron transfer reactions, triazoles intercept and neutralize ROS, halting propagation of oxidative damage and preserving integrity of cellular macromolecules. Yet, their efficacy extends beyond mere scavenging, as triazoles orchestrate a symphony of enzymatic reactions, bolstering the cellular antioxidant defense network and fortifying resilience against oxidative insult.

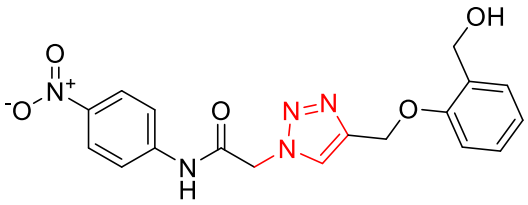
In the hallowed halls of translational medicine, the therapeutic potential of triazole antioxidants beckons with promise and possibility. Triazoles emerge as potent allies in our quest for health and longevity. Their capacity to traverse the blood-brain barrier and penetrate cellular membranes augurs well for the development of targeted therapies, offering a glimmer of hope amidst the spectre of chronic ailments and age-related decline.

Within the verdant embrace of nature's pharmacopoeia lies a treasure trove of triazole-containing compounds, each imbued with the potential to bestow vitality upon the human frame. From medicinal plants to marine organisms, these botanical and marine-derived marvels offer a rich tapestry of antioxidant diversity, providing inspiration for the synthesis of novel therapeutics. Through prudent exploration and strategic extraction, we unlock the transformative power of nature's bounty, harnessing the antioxidant potential of triazoles to enrich human health and well-being **[3].**

Recent researches involving triazole derivatives as Antioxidants

Table 1. Triazoles as Antioxidants

Compound Synthesized	Structure	References
Cationic 1,2,3triazole starch derivatives		**[4]**
1,2,3-triazole coupled Inulin derivatives		**[5]**

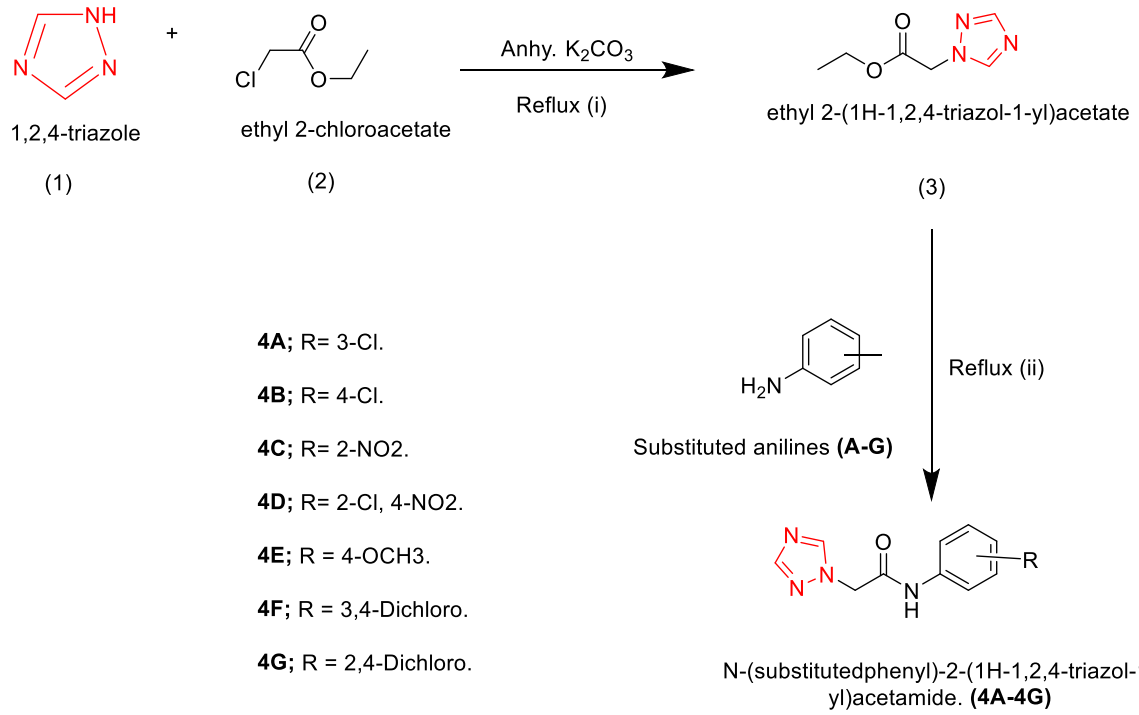
Amide-linked 1,4disubstituted 1,2,3triazole derivatives	 2 (4-((2-(hydroxymethyl)phenoxy)methyl)-1H 1,2,3 triazol-1 yl) N (4 nitrophenyl)acetamide	**[6]**

EXPERIMENTAL

Material and Methods

General synthesis procedure

The synthesis of desired triazole derivatives (4A-4G) was achieved through a two step reaction scheme shown in figure 2. The synthesized derivatives (4A-4G) were characterized by ^{1}H-NMR and FT-IR.



Reflux condition (i): Temperature 80-85 C; Time: 4-6 Hrs; Reflux Solvent: Dichloromethane;Crystallization with: Ethanol.

Reflux condition (ii): Temperature 80-85 C; Time: 4-6 Hrs; Reflux Solvent: Dichloromethane; Crystallization with: Ethanol.

Figure 2. Synthesis Scheme

Synthesis of ethyl 2-(1*H*-1, 2, 4-triazol-1-yl) acetate (3)

Mixture of 1*H*-1, 2, 4 -triazole **(1)** (0.1 mol) and ethyl 2-chloroacetate **(2)** (0.1 mol) in anhydrous K_2CO_3 (0.1 mol), dichloromethane (100 ml), heated and reflux with continuous stirring for 4-6 hrs. Until the reaction was completed. Reaction monitoring was done using TLC. After reaction completion, the reaction mixture shaken in separatory funnels to drain aqueous layer, retaining organic layer. The organic layer was further dried by adding a small amount of anhydrous sodium sulfate, followed by filtration under gravity and concentrating the organic layer. This concentrated organic layer was then crystallized from Ethanol (80%) to obtain the desired product **(3) [7].**

Synthesis of *N*-(substituted phenyl)-2-(1*H*-1, 2, 4-triazol-1-yl) acetamide derivatives (4_{A-G})

To magnetically stirred solution intermediate **3** (0.02 mol), substituted anilines **(A-G)** (0.02 mol), anhydrous K_2CO_3 (0.02 mol), dichloromethane (100 ml) added slowly. Reaction mixture was heated-refluxed with continuous stir (4-6 hrs) until reaction completed. Reaction checked using TLC. Once reaction gets completed, reaction mixture shaken in separatory funnels to drain aqueous layer, retaining organic layer. The organic layer was further dried by adding a small amount of anhydrous sodium sulfate, followed by filtration under gravity and concentrating the organic layer. This concentrated organic layer was then crystallized from Ethanol (80%) to obtain the desired product **(4A-4G) [7].**

Table 2. Characterization data of synthesized derivatives

Derivatives	**R**	**Appearance**	**% yield**	**Melting point (˚C)**	**FT-IR [KBr (ν_{max}/cm^{-1})]**	**^{1}H-NMR [300 MHz; D2O/ ppm]**
4A	3-Cl	Yellowish white solid	70	205-208	2930 (C-H Ar); 3402 (N-H); 1621 (C=O); 1393 (C-N); 768 (C-Cl).	6.13-7.50 (m, 5H, Ar-H); 4.20 (s, 1H, Ali-H); 4.43 (s, 1H, Ali-H); 8.09-8.12 (m, 1H, NH).
4B	4-Cl	Yellowish white solid	78	207-210	2930 (C-H Ar); 3405 (N-H); 1624 (C=O); 1391 (C-N); 769 (C-Cl).	7.13-7.67 (m, 6H, Ar-H); 4.31 (s, 2H, Ali-H); 8.09-8.11 (m, 1H, NH).
4C	2-NO_2	Creamy white solid	75	218-221	2927 (C-H Ar); 3402 (N-H); 1625 (C=O); 1391 (C-N); 1736 (NO_2).	6.60-7.71 (m, 6H, Ar-H); 4.31 (s, 2H, Ali-H); 8.09-8.11 (m, 1H, NH).

4D	2-Cl, 4-NO_2	White-creamy white solid	77	180-185	2929 (C-H Ar); 3396 (N-H); 1627 (C=O); 1393 (C-N); 771 (C-Cl).	6.18-7.99 (m, 5H, Ar-H); 4.31 (s, 2H, Ali-H); 7.99-8.01 (m, 1H, NH).
4E	4-OCH_3	Yellowish-white solid	70	230-235	2930 (C-H Ar); 3402 (N-H); 1621 (C=O); 1393 (C-N); 1201 (C-O).	7.13-7.71 (m, 5H, Ar-H); 4.31 (s, 2H, Ali-H); 2.50-3.41 (m, 3H, OCH_3); 8.09-8.11 (m, 1H, NH).
4F	3,4-Cl_2	White solid	65	250-254	2930 (C-H Ar); 3405 (N-H); 1624 (C=O); 1391 (C-N); 769 (C-Cl).	6.18-7.99 (m, 5H, Ar-H); 4.31 (s, 2H, Ali-H); 7.99-8.01 (m, 1H, NH).

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Table 2 (continued)

4G	2,4-Cl_2	White solid	66	255-258	2927 (C-H Ar); 3402 (N-H); 1625 (C=O); 1391 (C-N); 762 (C-Cl).	6.60-7.71 (m, 6H, Ar-H); 4.31 (s, 2H, Ali-H); 8.09-8.11 (m, 1H, NH).

Molecular Docking

Docking, performed via AutoDock Vina to investigate the binding interactions between a protein, identified by PDB ID 1AA4, and seven different triazole derivatives. The proteins 1AA4 was selected for this molecular docking study due to their critical roles in biological pathways relevant to oxidative stress and microbial defense. Protein 1AA4, a heme-containing enzyme, is involved in reducing oxygen to water, a crucial step in mitigating oxidative damage. Selection of these proteins provides a dual functional target to explore the combined antioxidant potential of the triazole derivatives.

The triazole derivatives are expected to bind within the active sites of these proteins, interacting through hydrogen bonding, hydrophobic interactions, and π-π stacking with key residues. With 1AA4, binding of the triazole derivatives may stabilize the enzyme-substrate complex, enhancing its antioxidant efficacy by facilitating the reduction of oxidative species.

Firstly, the structures of proteins (1AA4) acquired from Protein Data Bank. These structures were then prepared for docking by removing any co-crystallized ligands, water molecules, and non-essential ions. Hydrogen atoms were added to the proteins to correct protonation states at physiological pH. Additionally, any missing residues or atoms were added to ensure completeness of the structures. Next, triazole derivatives prepared for docking. 3D structures of these compounds, manually constructed using chemical drawing software (ChemDraw Ultra 8.0) **[8].**

The binding sites for docking were defined based on the available literature and visual inspection of the protein structures. Grid boxes were generated around the active sites to confine the docking search space. For each protein, grid box dimensions carefully set to cover entire active site while ensuring computational efficiency. With the proteins and ligands prepared, the docking simulations were conducted using AutoDock Vina. This software was chosen for its balance between accuracy and computational efficiency. Docking parameters were set to allow flexibility in the ligands while keeping the proteins rigid, reflecting a typical biological scenario. Multiple runs were performed to ensure thorough sampling of the conformational space and to increase the reliability of the results.

After docking, the resulting poses were scored and ranked based on their binding affinities. The top poses for each protein-ligand complex were selected for further analysis. PyMOL was used as visualization tool to inspect the interactions between the triazole derivatives and the active sites of 1AA4. Key interactions, including hydrogen bonds, hydrophobic contacts, and pi-pi stacking interactions, were identified and analyzed to understand the binding modes of the triazole derivatives. **[9].**
Receptor-Ligand Interaction in 2D & 3D has been tabulated under Result and Discussion section.

Antioxidant activity
Method used: DPPH scavenging method **[10].**
Procedure:
Antioxidant efficacy of the synthesized triazoles (4A-4G) was assessed using the DPPH assay method, the following detailed procedure was followed, taking Ascorbic acid as standard. The concentrations for assay prepared at 20, 40, 80, 100, and 200 µg/ml. DPPH (4 mg) mixed in methanol (40 ml). Solution subsequently poured in volumetric flask diluting to 100 ml with methanol. The resulting DPPH soln., then incubated in dark environment for 30 minutes. 100 µl of each concentration of the triazole derivatives and ascorbic acid were added to separate wells or cuvettes. Then 100 µl DPPH soln., also poured into all wells, making final volume 200 µl per well. A control wells or cuvettes containing 100 µl of methanol and 100 µl of DPPH solution was also prepared. These wells or cuvettes then darkly incubated at 25˚C for 30 min for reaction to occur. Absorbance of all well/cuvettes was assessed at 517 nm by spectrophotometer. Scavenging activity (%) was calculated using following equation.

$$Scavenging\ activity\ (\%) = \frac{A_{control} - A_{sample}}{A_{control}} \times 100$$

RESULTS AND DISCUSSION

Synthesis of Triazolic Derivatives

The fabrication path for triazolic derivatives involved the initial formation of first intermediate (3) throughN-alkylating 1,2,4-triazole (1) with ethyl 2-chloroacetate (2) under reflux conditions in ubiety of anhydrous K_2CO_3. This was subsequently subjected to amidation with various substituted anilines (A-G), forming seven distinct N-(substitutedphenyl)-2-(1H-1,2,4-triazol-1-yl) acetamides (4A-G). Reactions proceeded efficiently, with yields ranging from moderate to high.

Characterization of Compounds

The synthesized derivatives, outlined by ^{1}H-NMR, and FT-IR. The ^{1}H-NMR outcomes confirmed the realness of characteristic chemical shifts corresponding to the aromatic protons and the triazole moiety, while FT-IR spectra exhibited distinct absorption bands for amide and ester functionalities, as well as the triazole ring. ^{1}H-NMR and FT-IR data of the synthesized compounds have been attached in appendices I & II.

Molecular Docking Studies

Docking studies, conducted gauging the degree of interaction of the synthesized derivatives onto the intended protein. Compounds 4D, 4E, and 4G demonstrated the highest docking scores of -6.9, -6.2, and -6.4, respectively. These results suggest a strong interaction between the triazolic derivatives and the protein active site, indicative of potential biological activity.

Table 3. Receptor-Ligand Interaction in 2D & 3D.

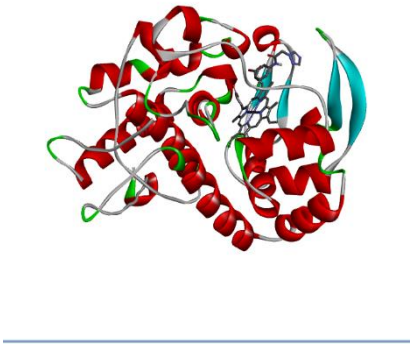
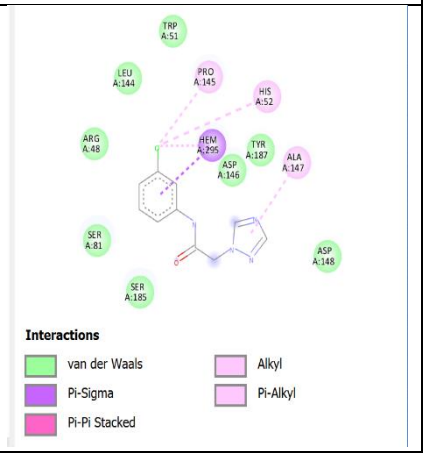
Ligand	Docking Score	Receptor-Ligand Interaction (3D)	Receptor-Ligand Interaction (2D)
4A	-6.0		

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Table 3 (continued)

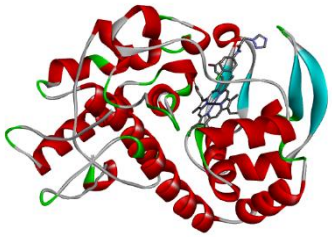
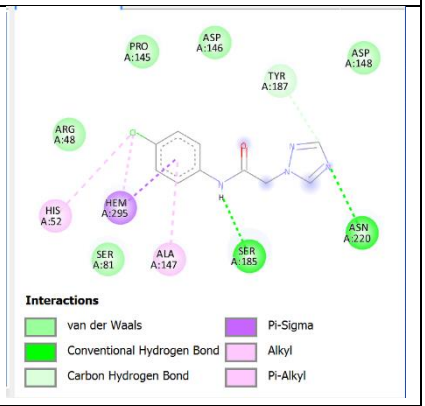
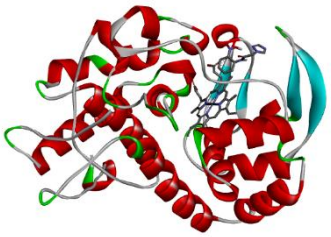
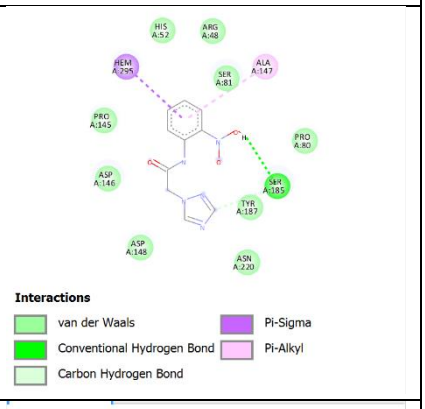
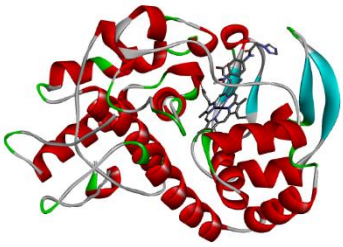
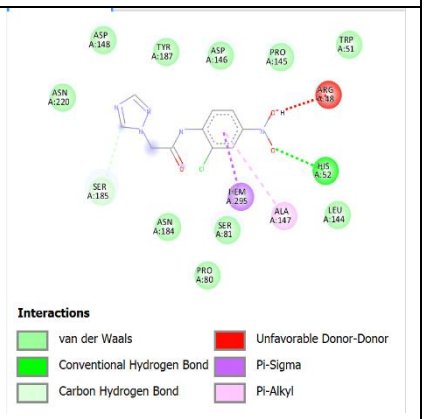
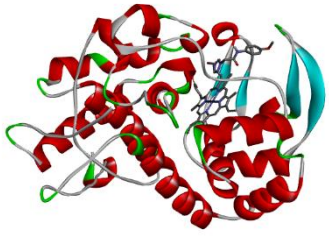
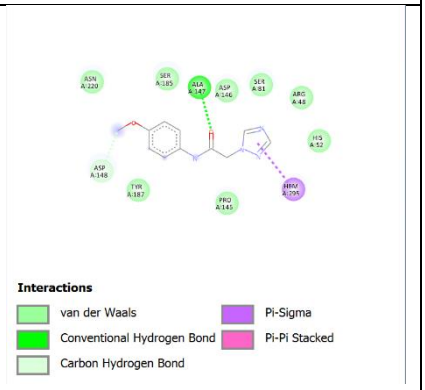
Ligand	Docking Score	Receptor-Ligand Interaction (3D)	Receptor-Ligand Interaction (2D)
4B	-5.9		
4C	-6.0		
4D	-6.9		
4E	-6.2		

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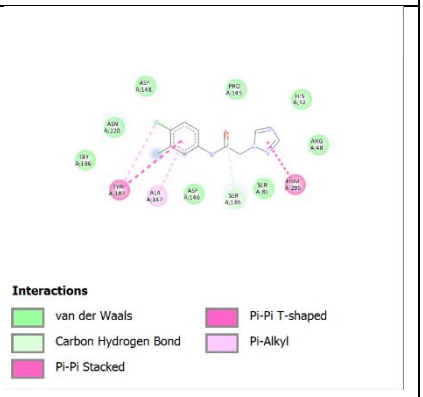
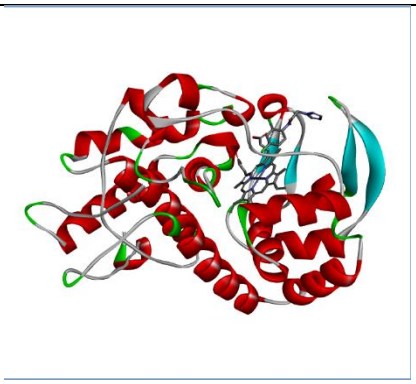
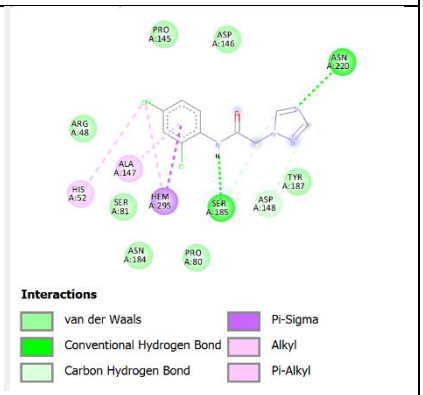
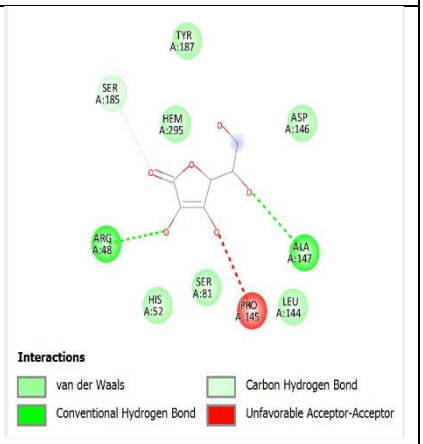
Table 3 (continued)

Ligand	Docking Score	Receptor-Ligand Interaction (3D)	Receptor-Ligand Interaction (2D)
4F	-6.0		
4G	-6.4		
Ascorbic acid (Standard)	-5.7		

Antioxidant Activity

Oxidant-diminishing efficacy of derivatives, evaluated by DPPH scavenging assay. Compounds 4D, 4E, and 4G exhibited significant antioxidant activity, correlating with their high docking scores. The scavenging activity percentages for these derivatives were notably higher than those of the other synthesized compounds, underscoring their potential as effective antioxidant agents.

Table 4. Receptor-Ligand Interaction in 2D & 3D.

Concentration (µg/ml)	Scavenging Activity (%)							
	Ascorbic acid	4A	4B	4C	4D	4E	4F	4G
20	35.71	14.28	13.23	13.33	30.55	29	19.71	24.65
40	60	20.2	29.41	25.33	37.5	40.57	28.16	35.61
80	80	30	41.17	41.33	45.83	52.17	38.02	47.94
100	87.14	41.42	51.47	50.66	59.72	60.86	54.92	57.53
200	94.28	50	63.23	69.33	70.83	69.56	69.01	72.6

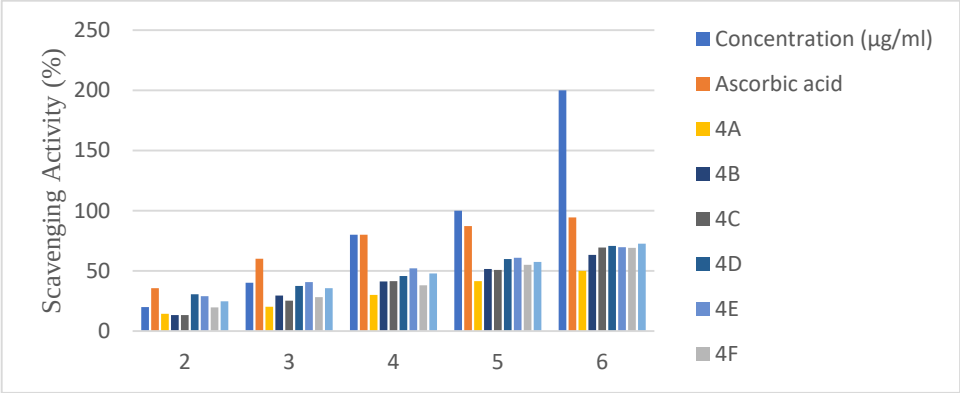


Figure 3. Graphical Representation-Antioxidant efficacy

CONCLUSION

The synthesis of seven novel triazolic derivatives was successfully accomplished through a straightforward two-step reaction sequence. Aniline ring substituents served a critical part influencing biological activity of derivatives. EWGs e.g., nitro (NO_2), chloro (Cl) in 4D and 4G, as well as the electron-donating methoxy (OCH_3) group in 4E, enhanced the binding affinities to the target protein, as reflected in their superior docking scores. Additionally, the antioxidant activity results indicate that these substituents contribute positively to the radical scavenging ability of the compounds. The strong correlation between docking scores and antioxidant activity suggests that these derivatives imply prospective for future expansion as therapeutic agents.

Concluding, the synthesized triazolic derivatives, particularly 4D, 4E, and 4G, exhibit potent biological activities. Such outcomes reveal insightful information into structure-activity relationships of triazole-based compounds and lay up possibilities for flourishing of new drugs of enhanced efficacy. Alongside in vivo and in vitro inquiry is warranted fully explore its therapeutic potential.

APPENDIX I

FT-IR Data(4A-4G)

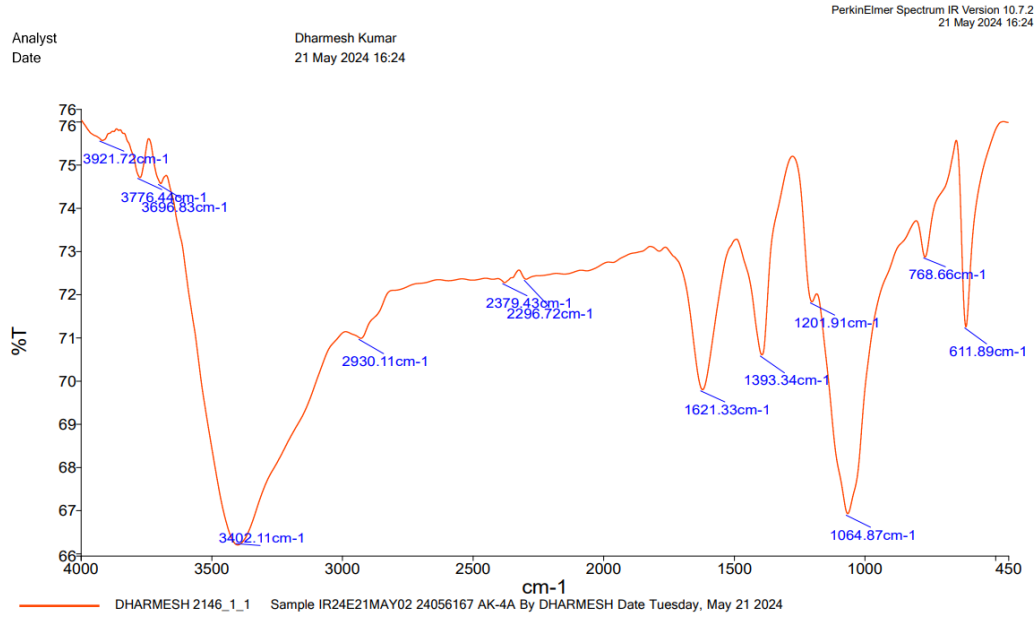


Figure 1. FT-IR (4A)

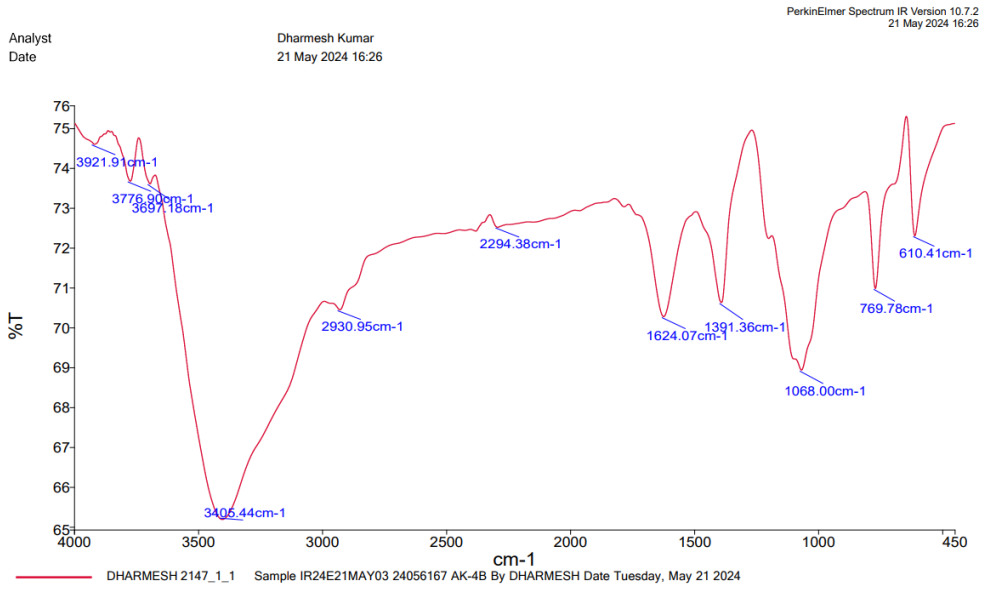


Figure 2. FT-IR (4B)

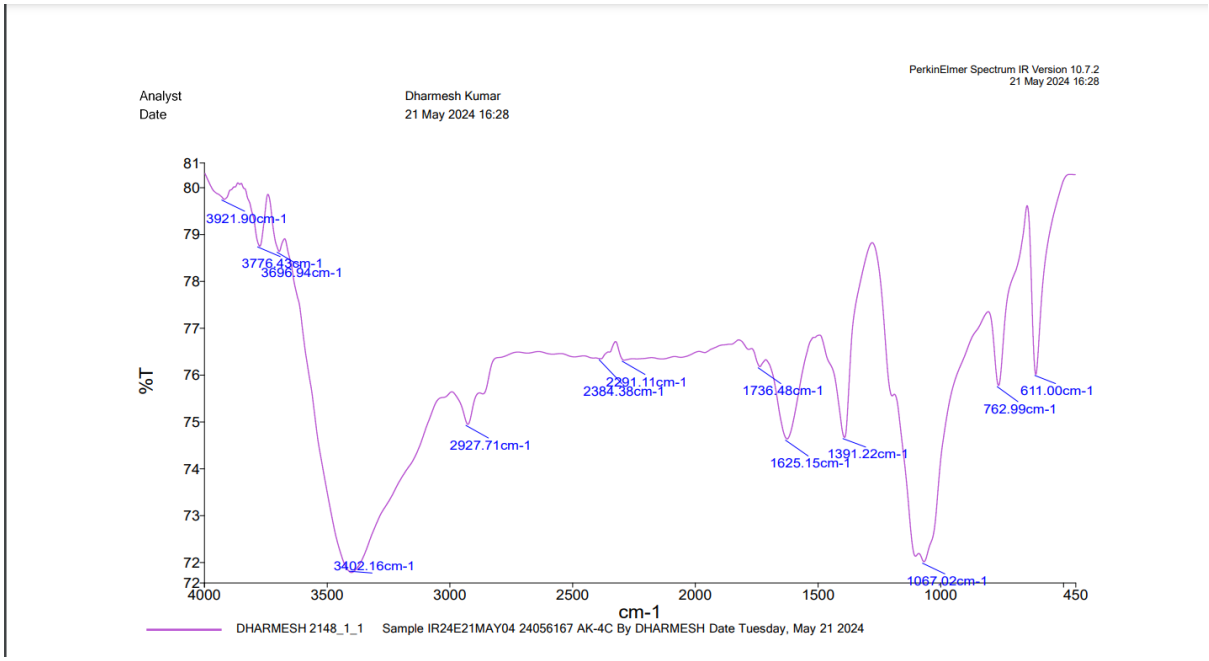


Figure 3. FT-IR (4C)

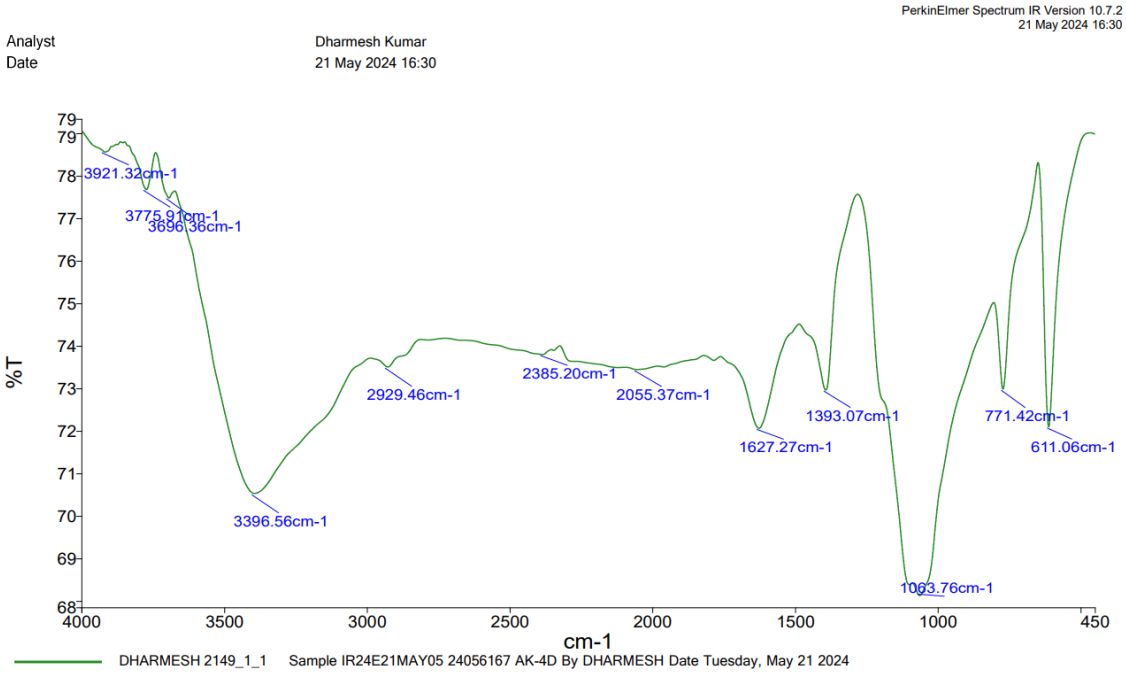


Figure 4. FT-IR (4D)

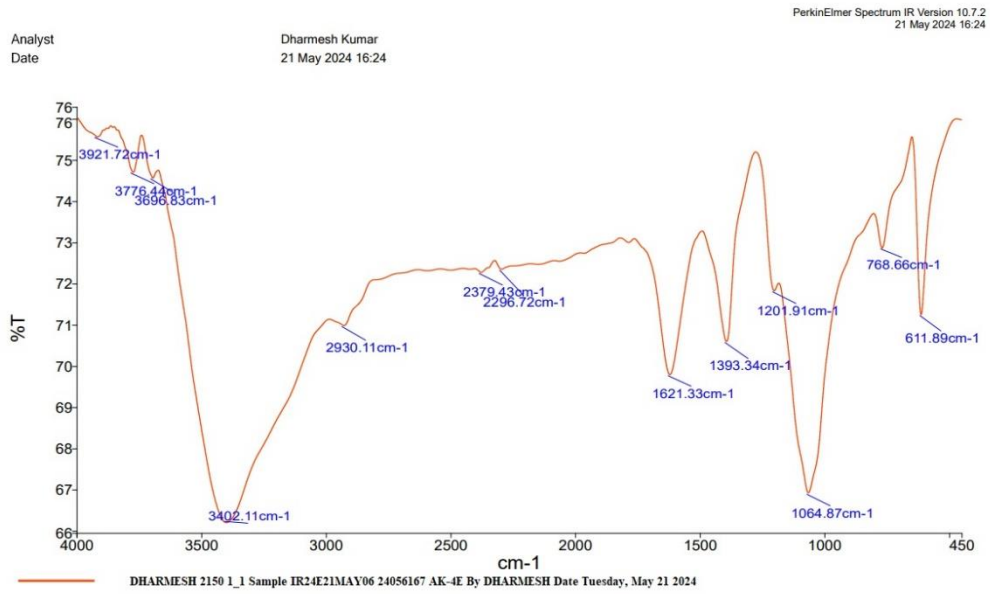


Figure 5. FT-IR (4E)

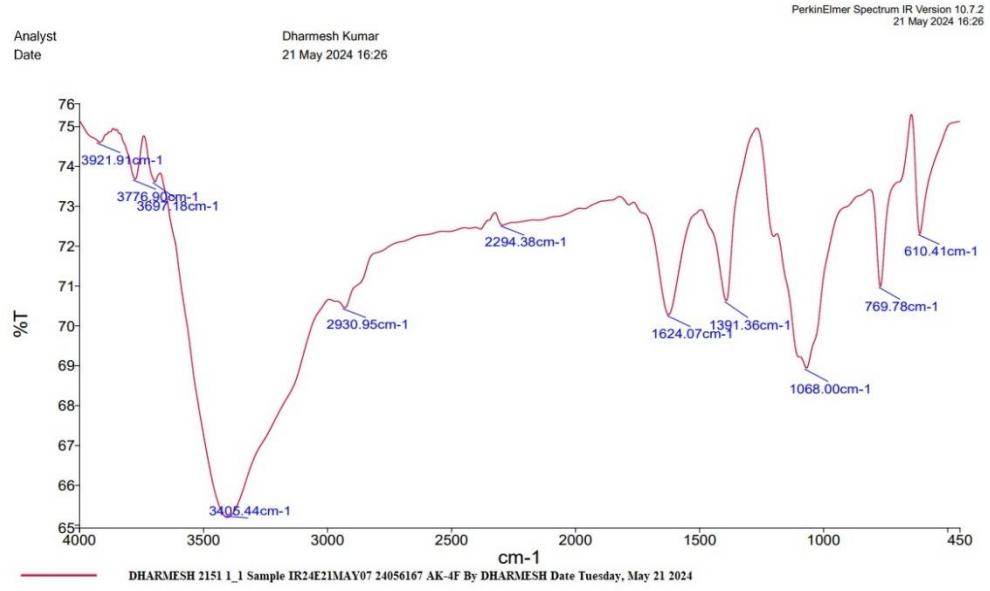


Figure 6. FT-IR (4F)

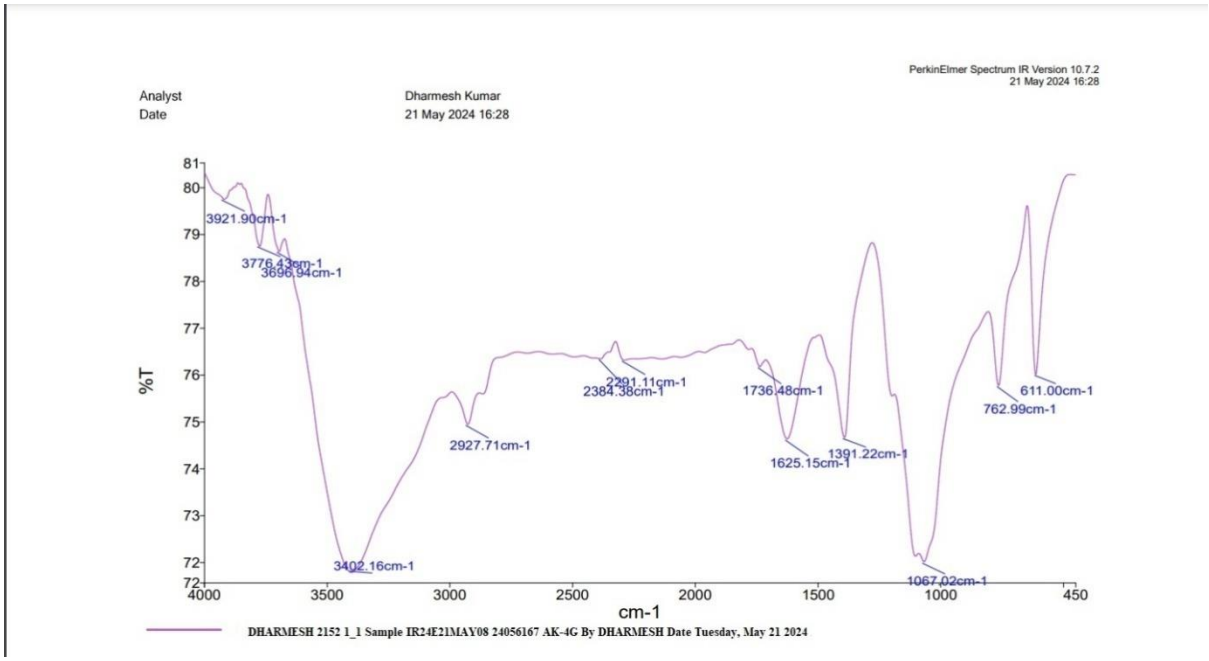


Figure 7. FT-IR (4G)

APPENDIX II

^{1}H-NMR Data (4A-4G)

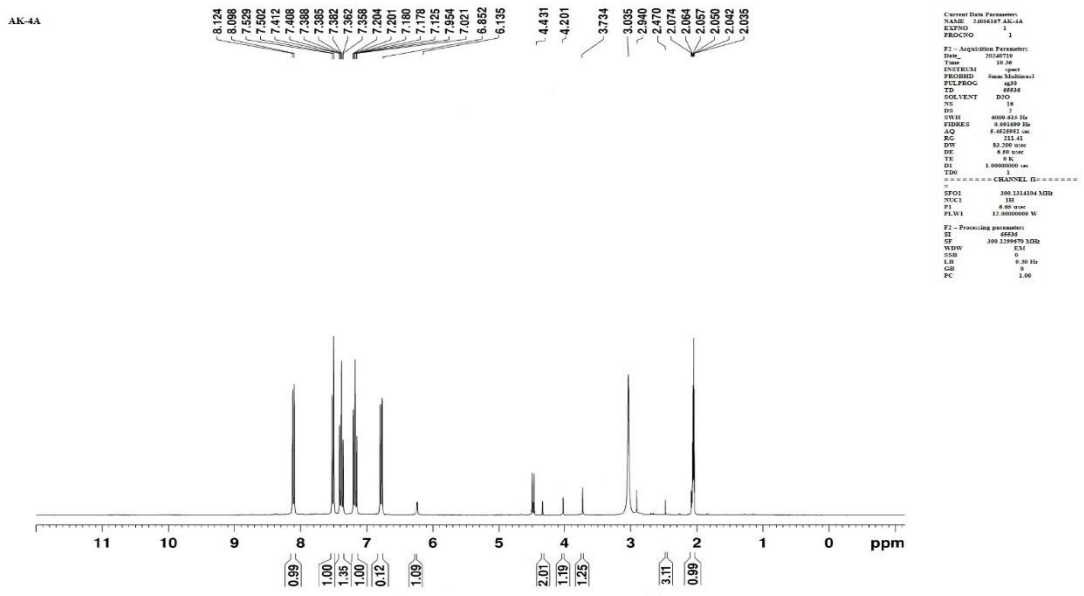


Figure 1. ^{1}H-NMR (4A)

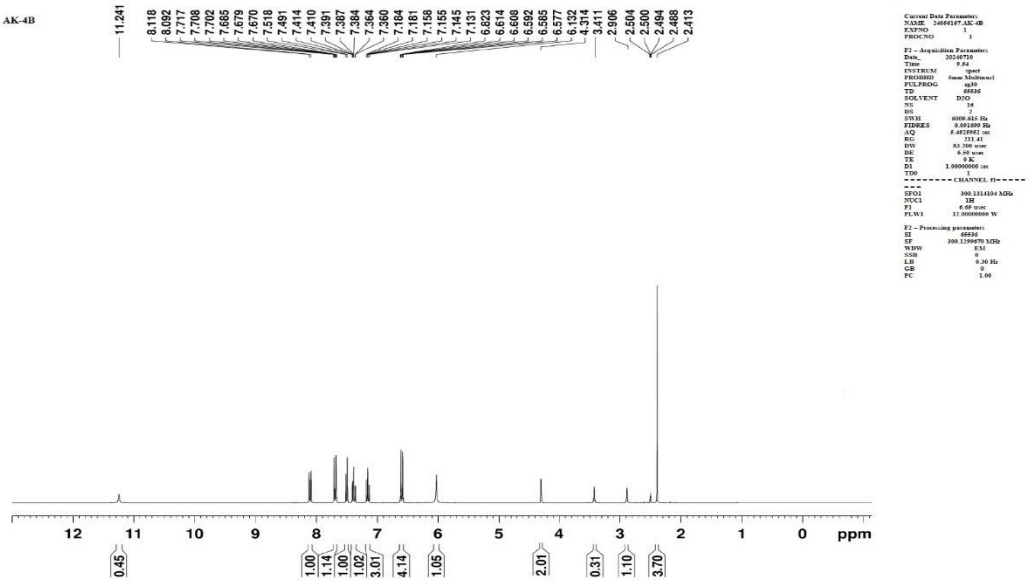


Figure 2. ^{1}H-NMR (4B)

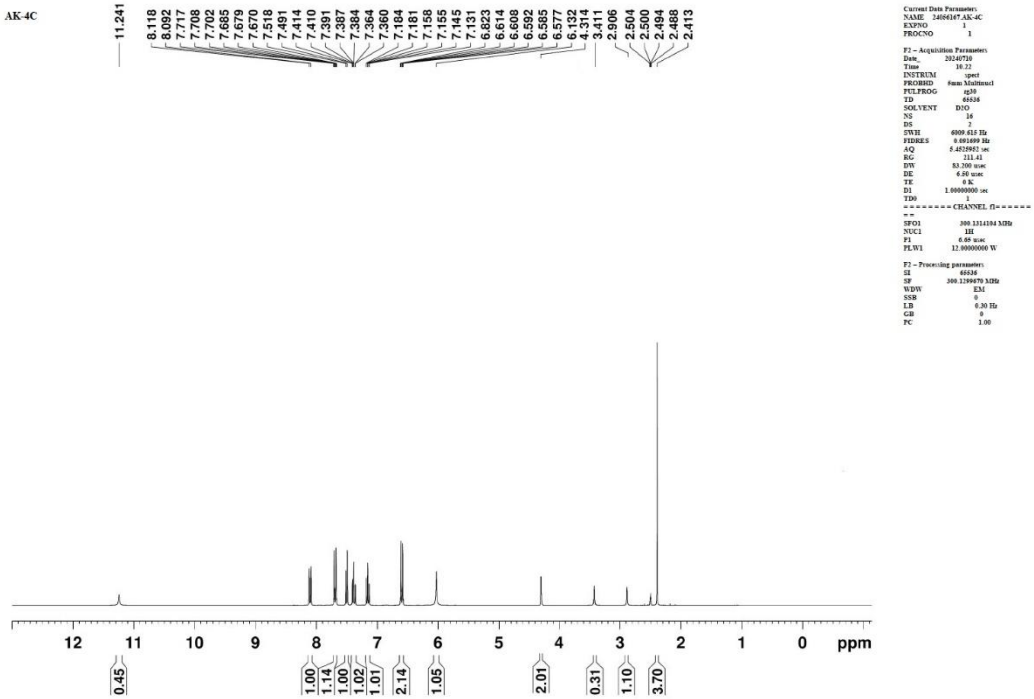


Figure 3. ^{1}H-NMR (4C)

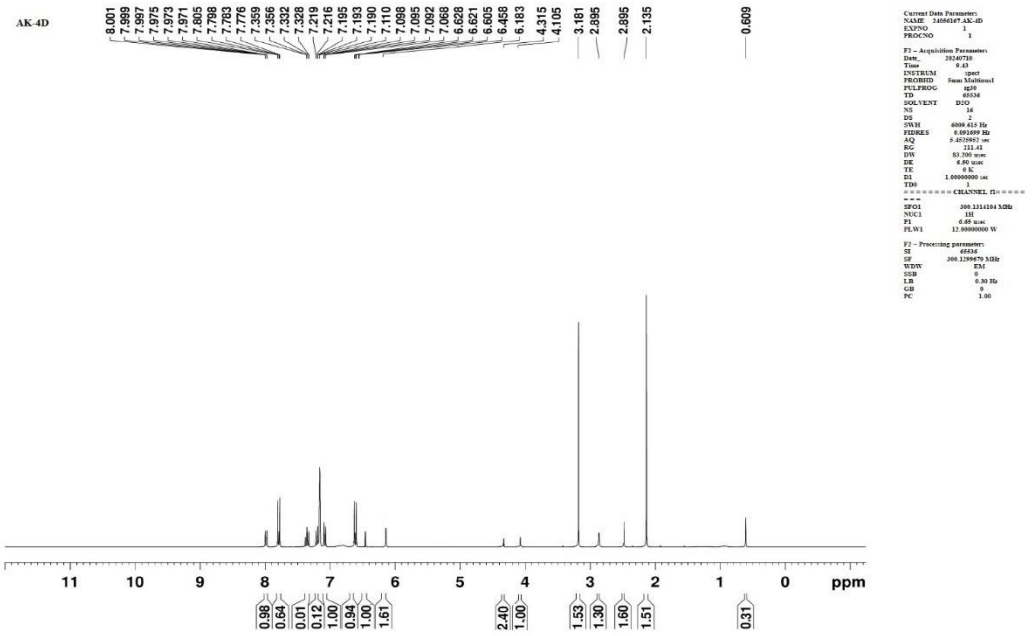


Figure 4. ^{1}H-NMR (4D)

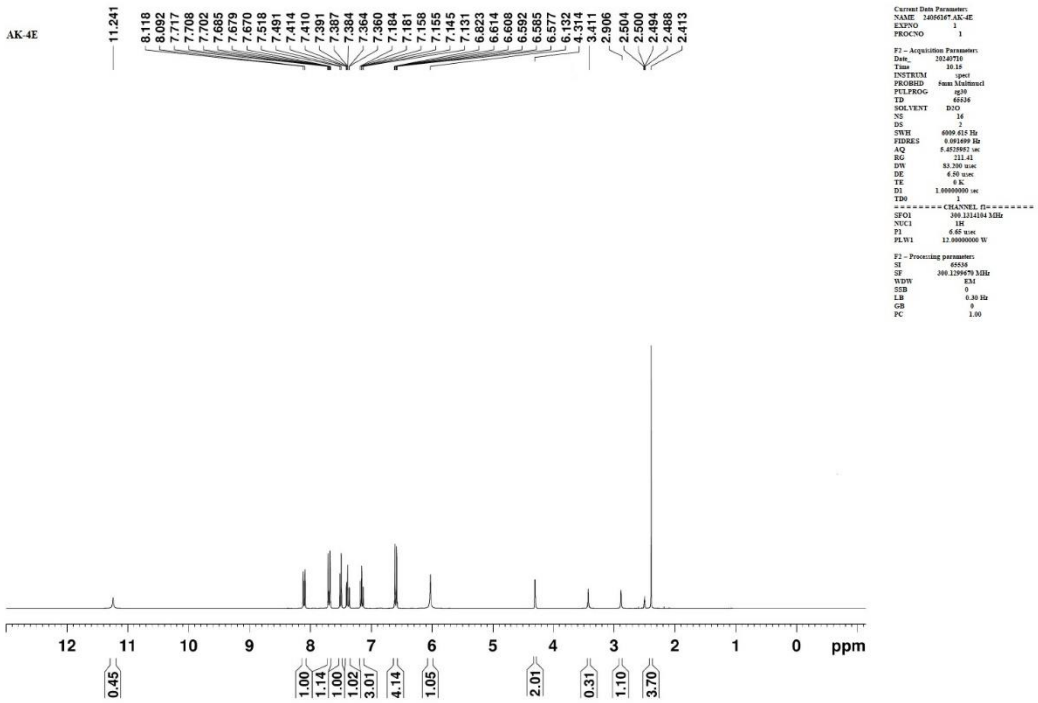


Figure 5. ^{1}H-NMR (4E)

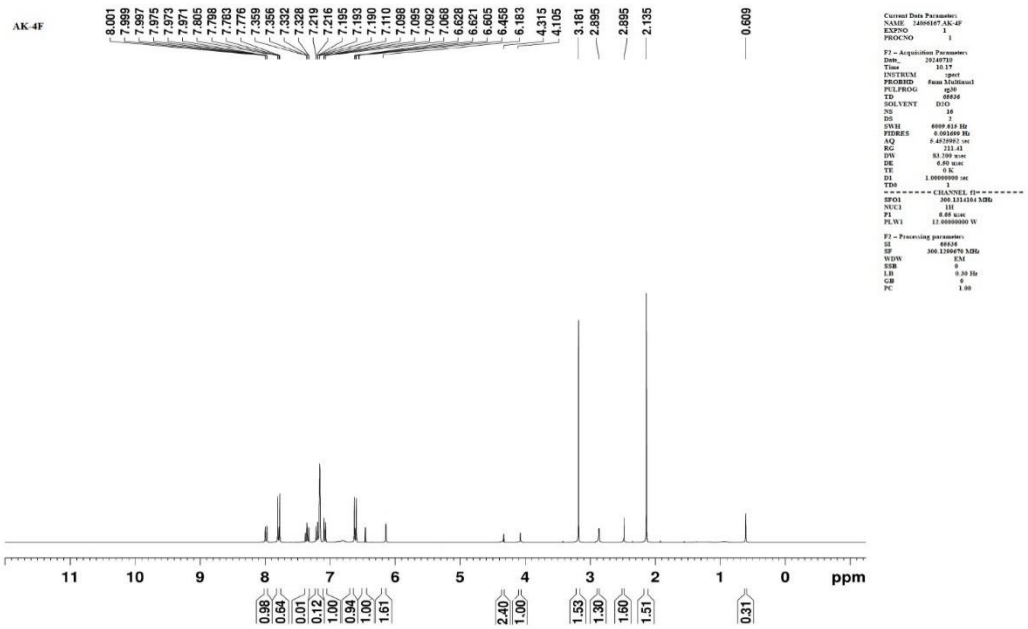


Figure 6. ^{1}H-NMR (4F)

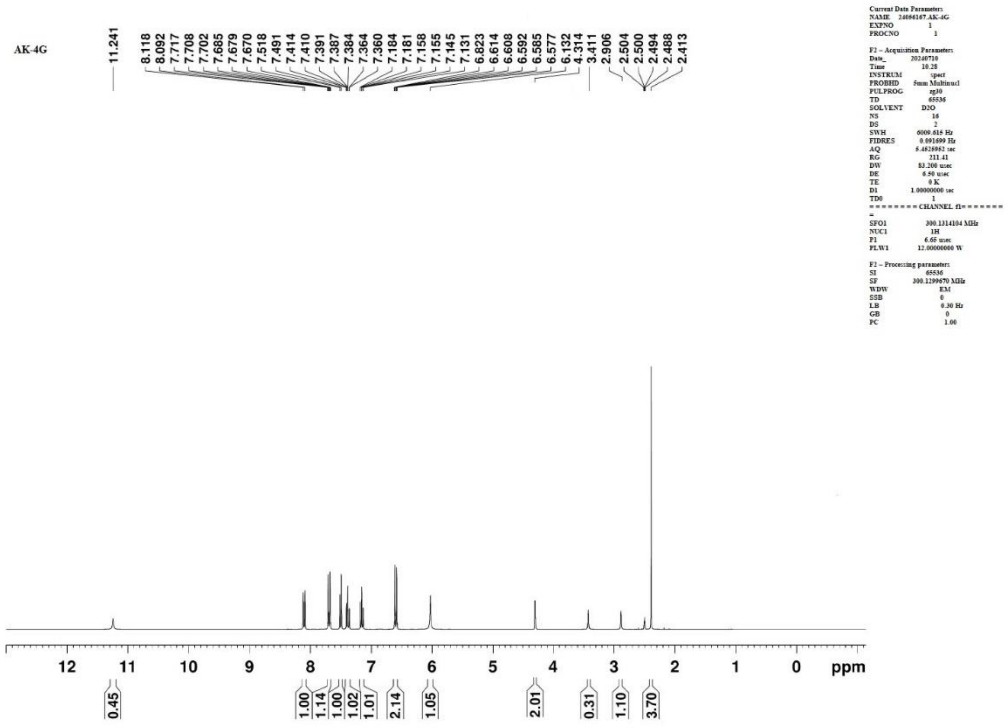


Figure 7. ^{1}H-NMR (4G)

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Conflict of Interest
Authors declare no conflict of interest

Ethical approval
Not applicable

Informed consent
Not applicable

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