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Synthesis of 1,4 Naphthoquinone Derivatives and their In-Silico Evaluations

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Abstract

In this study, we explored the arylation of 1,4-naphthoquinone with the help of Palladium acetate (Pd oAC). The synthesized compounds was characterized by using Proton NMR,and HR-Mass spectrometry and were subjected to molecular at this strategic position to evaluate its biological efficacy against anti-inflammation the parasitic target of the protein receptor 1W3R.The docking studies using the 1W3R protein structure to assess their binding affinities and interactions, comparing them to the clinically used drug, metronidazole. Results from the docking studies showed that the arylated 1,4-naphthoquinone derivatives exhibited stronger binding interactions at the active site of 1W3R than metronidazole, suggesting enhanced inhibition potential. Additionally, ADMET (absorption, distribution, metabolism, excretion, and toxicity) profiles were evaluated to assess the pharmacokinetics and safety of the compounds. The arylated derivatives displayed favorable ADMET properties, including good oral bioavailability and low toxicity, which further supports their potential as therapeutic agents. These findings suggest that second-position arylated 1,4-naphthoquinones may serve as promising leads for potential advantages over metronidazole. Further experimental validation and optimization of these compounds are recommended to fully harness their therapeutic potential.This research highlights the importance of scaffold functionalization in drug discovery and the potential of 1,4-naphthoquinone derivatives in developing new targeted Anti-inflammation therapies.

Keywords: 1,4-Naphthoquinone, antimalarial, Docking studies, etc.

1. Introduction

1.1 Quinone

Quinones are a family of chemical compounds distinguished by an aromatic ring with six members that have two replacements of ketone bodies. Quinones are often used as markers because they change physically, generally in terms of color, towards the conclusion of a chemical titration or around the equivalency point.**[1]** This means that, much as various dyes are used to colour different textiles, they are comparable to many other chemical markers that are now in use for indicating changes from acid to alkaline. Polyhydric phenols, polynuclear hydrocarbons, and aromatic amines may also be oxidised to produce quinones.**[2]** The quinhydrone electrode, which measures the hydrogen ion concentration of unknown solutions, is composed of equal parts p-benzoquinone and hydroquinone. Hydroquinone is often used in solutions for photographic development. Quinone Arrives as golden crystals with a strong, odd smell that is similar to chlorine. It dissolves somewhat in alkalis, water, alcohol, ether, and heated petroleum ether.**[3]** Quinone is usually converted to hydroquinone and is a strong oxidizing agent. In April 1993, it was categorized as a dangerous air pollutant under AB 2728 and as a federal hazardous air

pollutant. They are important for many biological activities, including oxidative reactions and electron transport.**[4]** The quinone derivatives are significant and widely used building blocks that serve as practical precursors for a variety of biological molecules, including those used in medicine and diagnostics**.** They may be present in a variety of useful chemicals and display specific biological functions.**[5]** Quinones have the potential to induce cytoprotection via the activation of detoxifying enzymes, alteration of the redox state, and anti-inflammatory effects. The underlying processes that underlie these impacts could be quite intricate.**[6]** Many oxidative enzymes and metal ions may simply oxidize hydroquinones to produce quinones, while more complex processes like P450-mediated first-stage hydroxylation events and subsequent two-electron oxidation can be used. Quinones serve as Michael acceptors and have the potential to impact biological processes by alkylating essential proteins and DNA. Together with their semiquinone radical anions, they may also engage in redox cycling, which generates reactive oxygen species (ROS) such as superoxide, hydrogen peroxide, and hydroxyl radicals. This makes them very redox-active. The generation of ROS has the potential to upset the redox equilibrium inside cells, which may cause macromolecules such as proteins, DNA, and lipids to oxidize. **[7,8]**

1.2 Naphthoquinones

Naphthalene-1,4-dione, or 1,4-dihydroxy naphthalene, are other names for 1,4-NQ, a chemical compound having the molecular formula $C_{10}H_6O_2$. It is a member of the quinones family of chemical compounds, distinguished by having two carbonyl groups in a conjugated ring structure.**[9]** Naphthalene is a bicyclic aromatic hydrocarbon that is the source of this chemical**.[10]** Because of their strong reactivity and well-developed techniques for chemical modification, the class of compounds known as naphthoquinones is attractive for the deep development of new molecules with high biological activity.

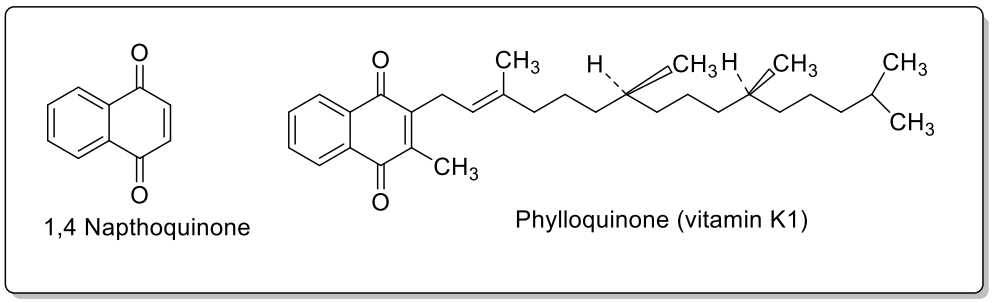


Fig.No.1 Example of Naphoquinone and it drug example.

Over the last decade, a number of unique 1,4-Nq with diverse structural properties have been synthesised and extracted from natural sources. Research has shown that these chemicals, with their unique combination of cardioprotective, hepatoprotective, anti-ischemic, and neuroprotective effects, may be able to help prevent neurodegenerative illnesses. **[11,12]** Additional research has been done on their anti-inflammatory, antibacterial, and anticancer properties;novel, unidentified intracellular molecular targets and methods of action have been found. Using current molecular imaging techniques, several of the compounds in this class may be used as biochemical probes and instruments for the non-invasive identification of sick regions in cells and tissues in myocardial infarction and neurodegenerative diseases. These days, a lot of these chemicals are utilised as drugs**. [13]** Many novel 1,4-naphthoquinone ring-containing moieties have been isolated from natural sources and synthesised, exhibiting a wide range of distinct structural properties**. [14]**

Tropical plants belonging to the Bignoniaceae family yielded the lapachol, along with its cyclic counterparts, α- and β-lapachone. Traditional Brazilian medicine used lapachol and its cyclic derivatives, α- and β-lapachone, we show in **Fig.No.2** as anti-inflammatory, antiseptic, antimalarial, antiparasitic, and anticancer medicines. **[15,16]**

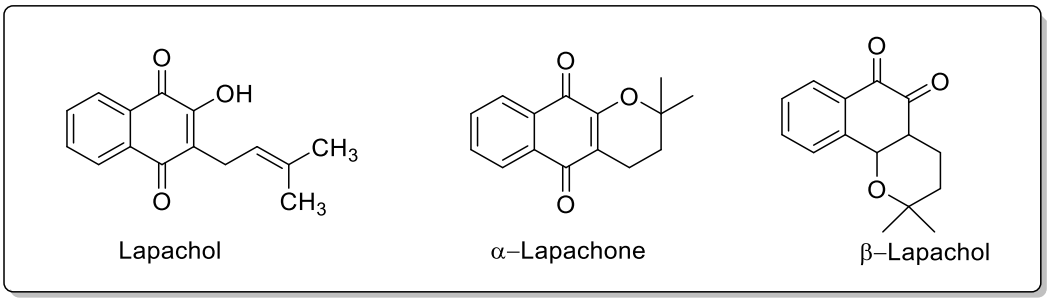


Fig.No.2 Example of Nq and its drug example.

It has been shown that these compounds possess special attributes including hepatoprotective, cardioprotective, anti-ischemic, and neuroprotective properties. They also seem to play a part in avoiding neurodegenerative illnesses. **[17]** The biological activities of 1,4-naphthoquinone ring-containing moieties, which may be produced chemically or naturally, are diverse and include cytotoxic, anti-cancer, antiviral, antifungal, antibacterial, and antiprotozoal properties. Thus, various biological reactions have been shown by their constituents, such as anti-inflammatory, anti-allergic, anti-bacterial, anti-fungal, anti-thrombotic, antiplatelet, antiviral, and anti-ringworm properties. Show in **Fig. 3 . [18,19,20]** Because of their structural traits and biological activity, these molecules are referred to as desirable structures in medicinal chemistry. Scientists are particularly interested in the 1,4-nq ring-containing moieties because of their potential medicinal benefits.**[21]**

2. Materials and methods.

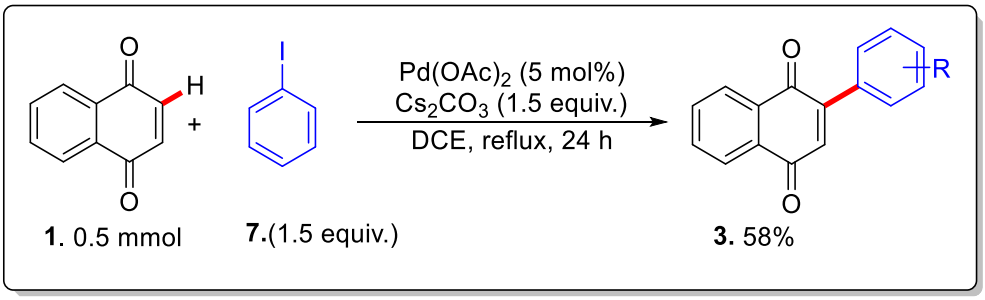
Material:

- TLC plates **(**Silica Gel 60 F254, Merck, Germany**)**
- All chemicals are bought from Sigma Aldrich, Tokyo Chemical Industries **(**TCI**)**, & Avra chemicals are used as such**.**
- All ^{1}H NMR spectra were recorded in Bruker spectrophotometer AMX**-**400 **(**400 MHz**)**,
- We utilized Autodock Vina for the *in-silico* studies.

Method:

4.1.0 General procedure for arylation of the 1,4 Naphthoquinone.

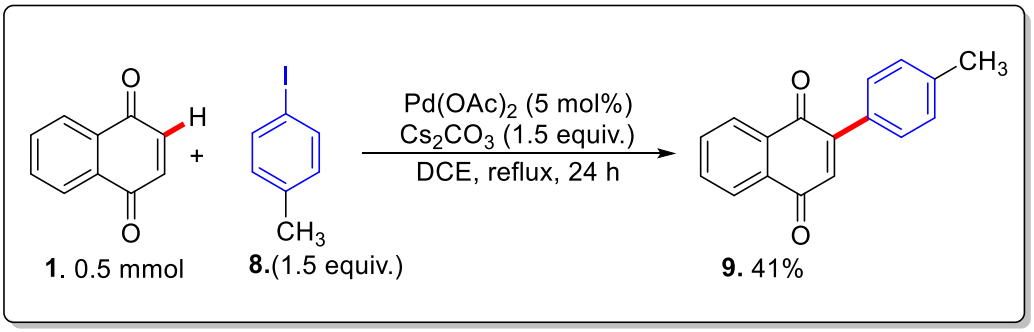
We take, 1,4 NQ (0.1 mmol), iodobenzene (1.5 equiv.), [Pd $(OAc)_2$] (5 mol%), Cs_2CO_3, and DCE (0.5 mL) were added screw cap reaction vial. The reaction mixture was refluxed at 80°C for 24 hours (Scheme 5). When it was finished, the reaction mixture was allowed to cool to rt. The solvent was then evaporated under reduced pressure, and the crude mixture was purified by column chromatography using an eluent of hexane/EtOAc and silica gel (230-400 mesh size).



Scheme 5: Pd catalyzed arylation of NQ

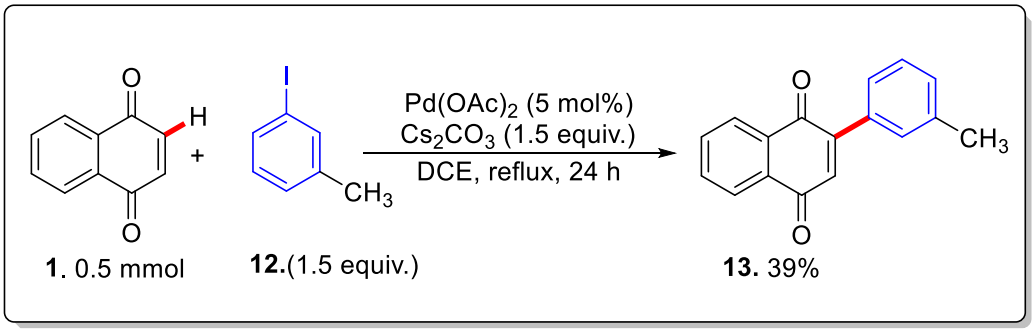
In below synthetic porocedure we follow the same above Procedure.The isolated yield are we mention below as the a table .

4.2.0 General procedure for synthesis of 2-(p-tolyl) naphthalene-1,4-dione.



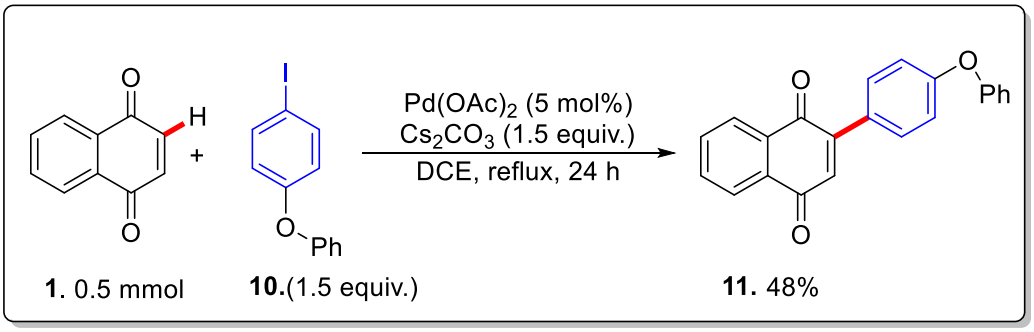
Scheme 6. Synthesis of 2-(p-tolyl)naphthalene-1,4-dione

4.3.0 General procedure for synthesis of 3-(m-tolyl)naphthalene-1,4-dione.



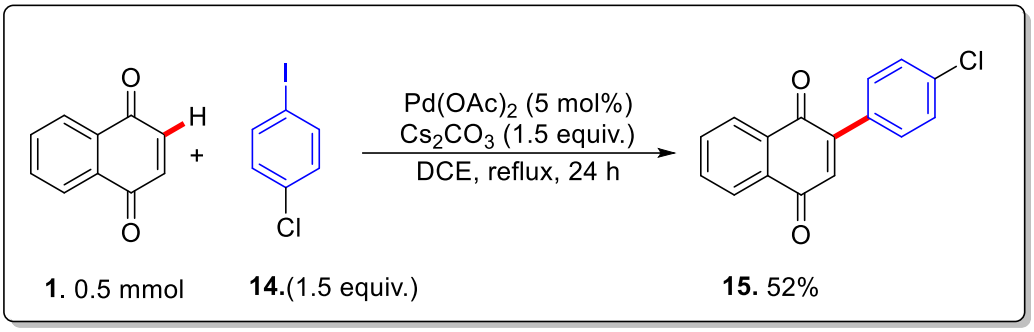
Scheme 7. For the synthesis of 3-(m-tolyl)naphthalene-1,4-dione

4.4.0 General procedure for synthesis of 2-(4-Phenoxyphenyl)naphthalene-1,4-dione.



Scheme 8. Synthesis of 2-(4-Phenoxyphenyl)naphthalene-1,4-dione.

4.5.0 General procedure for synthesis of 4-Chloronaphthalene-1,4-dione.



Scheme 9. Synthesis of 4-Chloronaphthalene-1,4-dione

We have successfully carried out Pd catalyzed arylation of NQ with the aryl iodide are get to desired yields.

3. RESULTS AND DISCUSSION

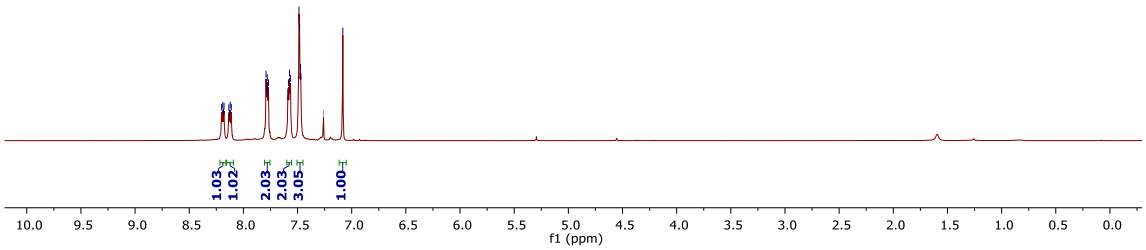
3.1. General procedure for the synthesis arylation of the 1,4 Naphthoquinone.

Following the general procedure for the arylation of the 1,4 Naphthoquinone, we have successfully synthesized diversely substituted iodobenzene (**Scheme 5**). Substitution of the "CH_3" group at the C3, C4 position of **9,13** gave the desired product in **41**% ,**39 %**yield respectively. Next, Phenoxy group at the C4 position of **11** gave the desired product **48**% yield. Halogen group substituted at the C4 position were also well tolerable and **52**% of yield was obtained. It is approximate isolated yield a not be a accurate. We obtain good yield.

3.2. Characterization data of arylated 1,4 Nq derivatives

2-Phenylnaphthalene-1,4-dione (**3**)**:** Off yellow solid, Yield = 81% Melting point: 92-94 ºC. ^{1}H NMR (400 MHz, $CDCl^3$-*d*) δ: 8.20 (m, 2H), 8.13-8.11 (m, 1H), 7.79 – 7.76 (m, 2H), 7.59-7.56 (m, 21H), 7.48 – 7.41 (m, 3H), 7.08 (s, 1H). HRMS (ESI-TOF) (m/z): $[M+H]^+$ Calcd. for $C_{16}H_{10}O_2$, 235.0754; found,235.0756.

^{1}H NMR (600 MHz)

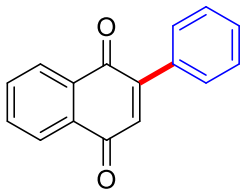


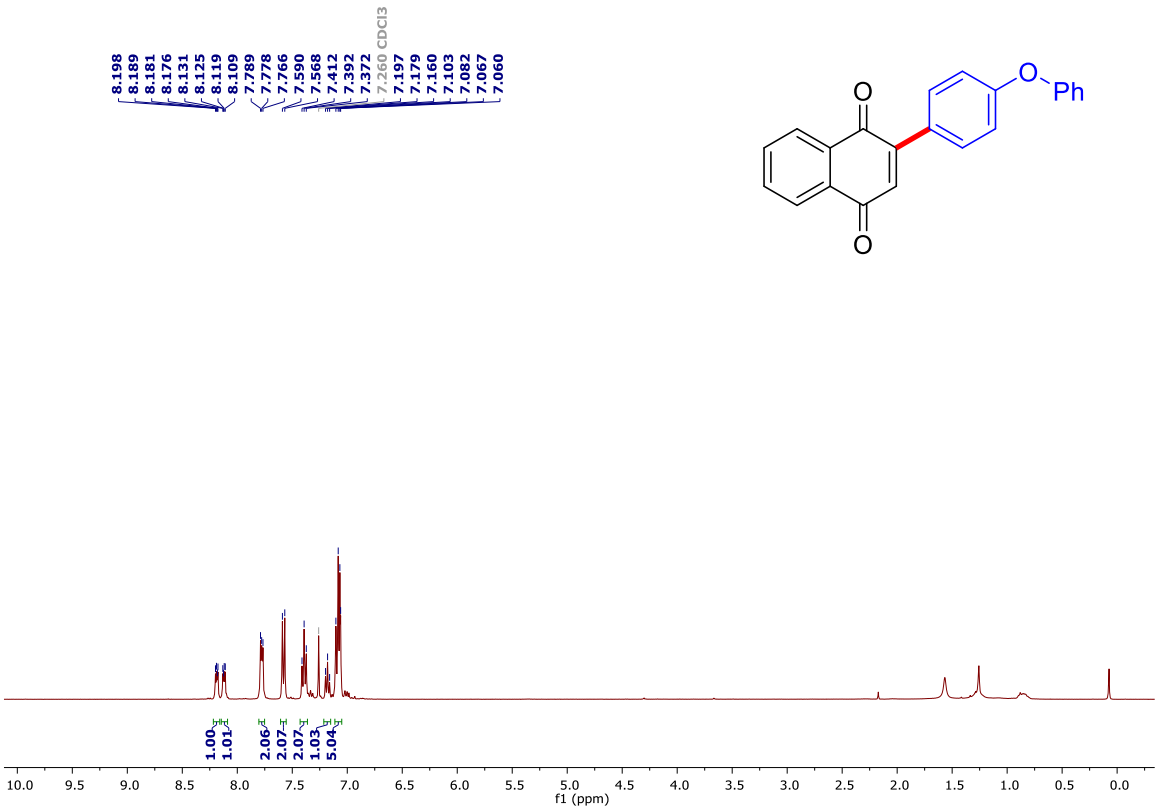
4-Methylnaphthalene-1,4-dione (**9**) Yellow, Yield =41% Melting Point:- 96-98 ºC. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calculated for $C_{17}H_{12}O_2^+$, 249.0910; found, 249.0917

3-Methylnaphthalene-1,4-dione (**13**) Yellow, Yield =39% Melting Point:- 96-98 ºC. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calculated for $C_{17}H_{12}O_2^+$, 249.0910; found, 249.0917

4-pheoxynaphthalene-1,4-dione (**11**): Orange, Yield=35%. 1H NMR (400 MHz, $CDCl_3$-d) δ: 8.19- 8.17 (m, 1H), 8.13-8.10 (m, 1H), 7.78 – 7.76 (m, 2H), 7.58 (d, J = 8.8 Hz, 2H), 7.39 (t, J = 8.0 Hz, 2H), 7.18 (t, J = 7.6 Hz, 1H), 7.10 – 7.06 (m, 5H).HRMS (ESI-TOF) (m/z): $[M+H]^+$ Calcd. for $C_{17}H_{12}O_3^+$, 327.1016; found, 327.1018.

^{1}H NMR (600 MHz)





4-Chloro naphthalene-1,4-dione (**15**) Light Yellow, Yield =52% Melting Point:- 94-96ºC. HRMS (ESI-TOF) (m/z): $[M+H]^+$ calculated for $C_{16}H_{10}O^+_2$, 269.0364; found, 269.0365

3.3. Molecular docking and its result

After the synthesis and characterization of arylated 1,4 Nq compounds such as Naphoquinone derivatives, compounds were investigated for molecular docking studies.

1. Screening for anti-inflammatory potential :

Five compounds with 1W3R were subjected to molecular docking experiments in order to assess their binding affinity and intricate molecular interactions. InstaDock, an automated molecular docking program that simplifies virtual screening with a single-click interface, was used to carry out the docking procedure [**23**]. QuickVina-W [**24**], a modified version of AutoDock Vina [**25**], which uses a blind search space for ligand docking and a hybrid scoring system (combining empirical and knowledge-based methodologies), was used to estimate binding affinities between the ligand and protein.
The following formula was used to get the inhibition constant (pKi), which was obtained from the ΔG parameter: [**26**].

$$\Delta G = RT(\text{Ln } Ki_{pred})$$
$$Ki_{pred} = e^{(\Delta G/RT)}$$
$$pKi = -\log(Ki_{pred})$$

3.3.2. Step involve in Docking Studies:

A. Protein Preparation:

The protein structure was retrieved from the pdb data bank in the form of 1W3R, which was prepared by using the protein preparation by.

B. Preparation of Ligand Structures:

The synthesized compounds were drawn in the sdf format by using ChemDraw 16.0 and a database was prepared for the virtual screening. The ligand database was prepared with the help of AutoDock LigPrep tool under default settings.

C. Grid Generation:

Next, the receptor grid was generated in the maestro software by specifying the internal ligand (metronidazole) inside the active pocket of the protein.

D. Running the Docking:

XP docking was performed for the synthesized ligand against the 1W3R protein within the active binding site.

Molecular Docking

In order to check the binding interaction of synthesized derivatives with the protein, we have performed the molecular docking by using Autodock Vina software (**27**). **Figure 27** shows nicely that the compounds can dock effectively into the binding pocket of protein (PDB ID-1W3R). The docking scores is -7.7, -8.8, -8.7, -9.1 and -9.2 of compounds **3, 13, 15, 9 and 11 Table 2**. The compounds **13, 9** and **11** showed higher docking affinity of –8.8, -9.1 and -9.2. The binding site analysis revealed that residues THR: 149, HIS:71, THR: 149 contribute the hydrogen bond interactions, residues SER:136 and ASP: 156 shows the van der Waals interaction, residues LEU:143, LEU:132, ILE: 152 and ARG: 159 shows the pi-pi staking with the phenyl ring of the ligands **13, 9** and **11**. According to the data above, compounds **13, 9** and **11** have much better tubulin receptor binding capabilities and may be successfully developed as lead structures for substantial anti-inflammatory action..

Ligands	**DOCKING SCORE (**kcal/mol)			
	1W3R	**2OYU**	**3LN1**	**3KK6**
3. *2-Phenyl Nq*	-7.7	-6.3	-5.5	-5.8
13. *3-Methyl Nq*	**-8.8**	-6.7	-7.0	6.5
15. *4-ChloroNq*	-8.7	-6.2	-6.9	-7.0
9. *4-Methyl Nq*	**-9.1**	-7.3	-7.5	-6.8
11.*4-phenoxy Nq*	**-9.2**	-8.1	-8.5	-8.7
Metronidazole (Ref.Molecules)	-6.6	-5.7	-6.6	-6.8

Table 2: Docking score of the synthesized ligands with respective proteins

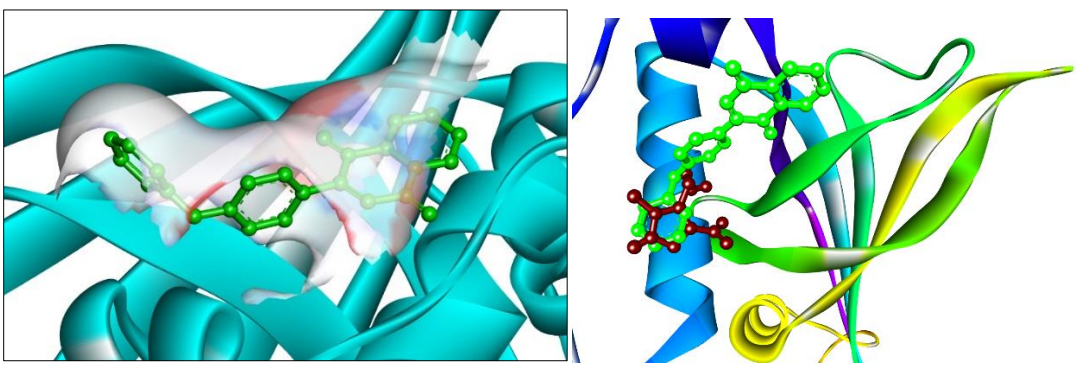


Fig. 23. Compound 11 (green colored) docked effectively into the binding pocket of protein.

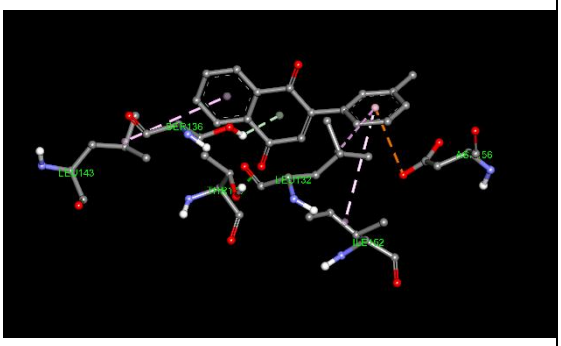
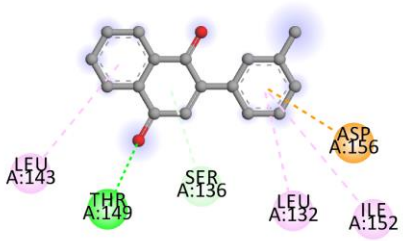
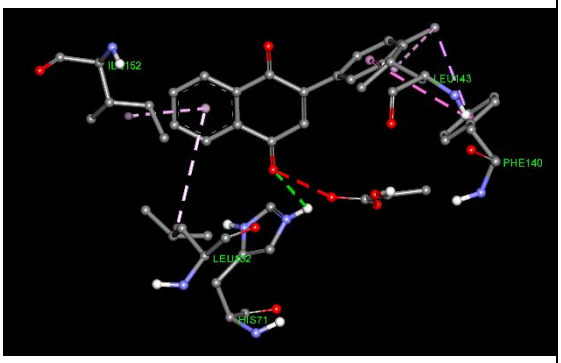
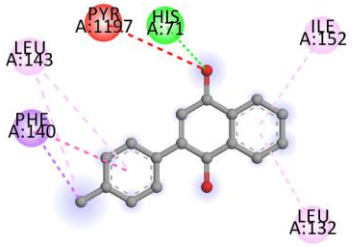
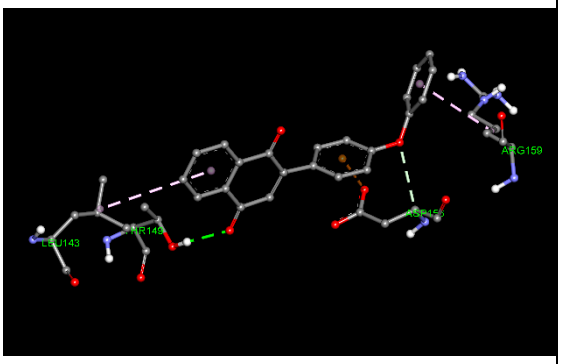
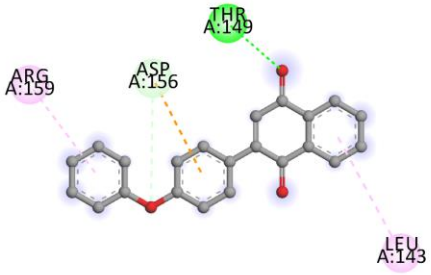
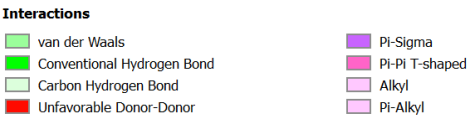
Ligand	3D Interaction	2D Interaction
13		
9		
11		
		

Table 3. Docking interaction of the ligands 13, 9 and 11 into the binding site of protein (PDB ID-1W3R)

ADME analysis

Few drug-like characteristics of the proposed ligands were revealed by in-silico analysis. Design ligands have molecular weights ranging from 220 to 330 Daltons. The donor-acceptor H bond values were determined to be within an acceptable range. The SwissADME [**28,29**] & ADMET 3.0 predictor's predicted values for these compounds' Log P, Log S molar refractivity, and total polar surface area (TPSA) were in good agreement with the most critical drug-likeness criterion. The 1–5 derivatives with high lipophilicity should display respectable GI absorption, even if these drugs showed adequate bioavailability

and a favorable hydrophilic–lipophilic balance. Because passively absorbed compounds with TPSA > 140 are believed to have limited oral bioavailability [**30**], the proposed ligands' TPSA ranged from 3 to 44. Every developed ligand complied with the PAINS warning and the Lipinski Rule of Five. Significant synthetic accessibility is shown by each of the proposed ligands. Table No. 3 displays the results of the Swiss ADME search engine.

These ligands' Bioavailability Radar diagram, which is shown in Fig. No. 25, demonstrates the characteristics necessary for a ligand to be drug-like. The yellow area represents the ideal range for each of the following properties: solubility: Log S ≤ 6; polarity: TPSA between 20 and 130 Å 2; lipophilicity: Log P between -0.7 and +5.0; size: MW between 150 and 500 g/mol; saturation: fraction of carbons in the SP3 hybridization ≥ 0.25; and flexibility: ≤ 9 rotatable bonds. It is anticipated that the ligands PM 1–8 would be lipophilic and have excellent bioavailability. It will absorb the most in the intestines.

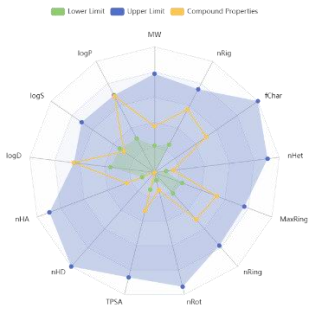
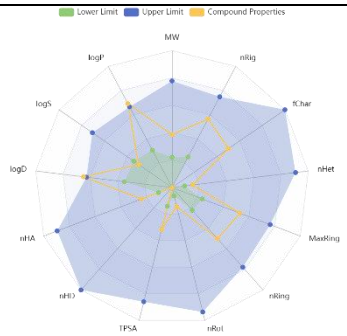
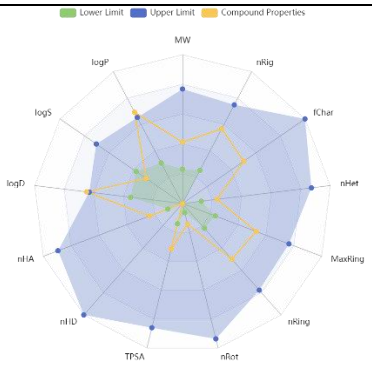
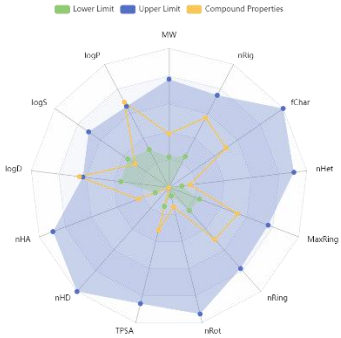
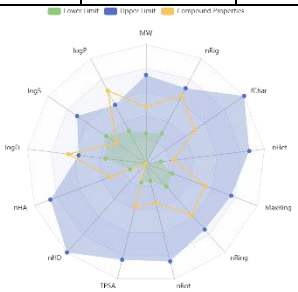
Ligand	Bioavailability radar graph	Ligand	Bioavailability radar graph
3		13	
15		9	
11			

Table no.4 Bioavailability radar graph of the ligands 3,13,15,9, & 11 (yellow area reflects the allowed values of drug-likeness properties of the molecule)

Ligands	MW	R Bond	HA	HD	TPSA	MR	W log P (lipophilicity)	ESOL log S	GI absorption	BBB permeant	Log Kp (cm/s)	Lipinski violations	Synthetic accessibility	PAINS
3. 2-Ph Nq	234.07	1	2	0	34.14	69.52	2.95	-3.90	High	Yes	-5.27	Accepted	2.86	1
13. 3 Meth Nq	248.08	1	2	0	34.14	74.49	3.227	-4.55	High	Yes	-5.10	Accepted	2.95	1
15. 4-Cl Nq	268.03	1	2	0	34.14	74.53	3.348	-5.123	High	Yes	-5.04	Accepted	2.83	1
9.4 Me Nq	248.08	1	2	0	34.14	74.49	3.287	-4.85	High	Yes	-5.10	Accepted	2.94	1
11.4phenox Nq	326.09	3	3	0	43.37	96.04	4.618	-5.67	High	Yes	-4.75	Accepted	3.11	1

Table 5. Physicochemical descriptors and ADME parameters

(MR = molar refractivity; TPSA = topological polar surface area; H-A = hydrogen bond-acceptor; H-D = hydrogen bond-donor; R bond = rotatable bond; PAINS stands for pan-assay interference structure; Log P for lipophilicity; Log S for water solubility; and Log Kp for permeability coefficient.)

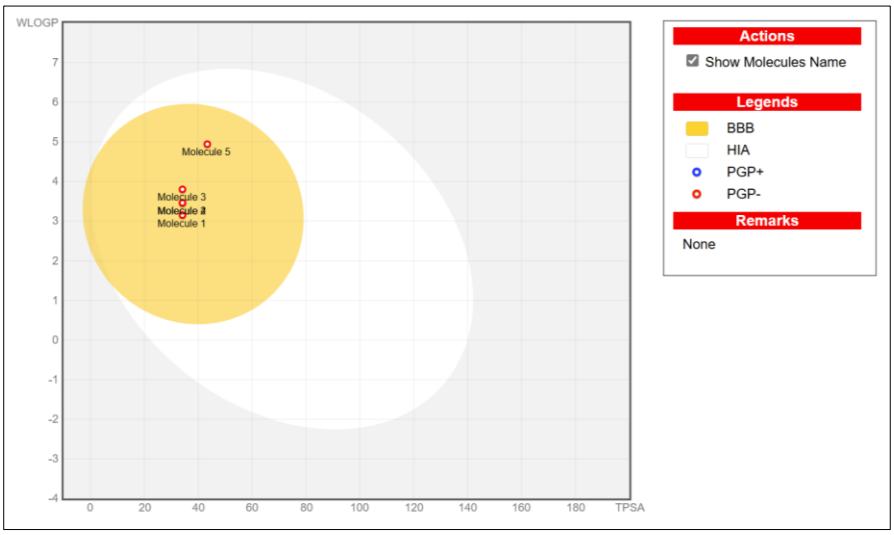


Fig. 24. ADME features of ligands predicting the distribution of specified ligands

Using a visual of a boiled egg, ADME features of ligands may be used to forecast small molecule penetration of the brain and gastrointestinal tract. BBB (Blood brain barrier) is denoted by the yellow color, while the gastrointestinal track is denoted by the color white. Predicting the distribution of specified ligands in various bodily compartments is another feature of SwissADME [**31**]. The outcome is shown in the boiled-egg graphic below. (**Fig No. 24**).

Overall, docking analysis gave three promising molecules (**13, 9** and **11**), which have good binding potential with the 1W3R protein. That is potent as an anti-inflammation NimA from D. radiodurans with Metronidazole. Further, these hits can be investigated for *in-vitro* and *in-vivo* activity to validate the computational results.

4. CONCLUSION

We have synthesized a library of *Nq* derivatives. Initially. The study began with the preparation of various Nq derivatives and their subsequent protection of *Nq* isolated product to form the desired *Nq* compounds. Characterization of the synthesized compounds was carried out using various spectroscopic techniques e.g.TLC, MS, NMR, etc. confirming the creation of the target Nq structures.

The docking results revealed several promising candidates with significant binding affinities, suggesting their potential efficacy as anti-inflammatory agents, and anticancer activity. Key interactions between the Nq scaffolds and amino acid residues of the 1W3R Metronidazole. active site were identified, contributing to a better understanding of the structure-activity relationships governing anti-inflammatory activity.

Shows nicely that the compounds can dock effectively into the binding pocket of protein (PDB ID-1W3R) NimA from D. radiodurans with Metronidazole and Pyruvate. The docking scores is -7.7, -8.8, -8.7, -9.1, and -9.2 of compounds **3,13,15,9, & 11** Table 2. The compounds 13, 9, and 11 showed higher docking affinity of –8.8, -9.1, and -9.2. The binding site analysis revealed that residues THR: 149, HIS:71, and THR: 149 contribute the hydrogen bond interactions, residues SER:136 and ASP: 156 show the van der Waals interaction, residues LEU:143, LEU:132, ILE: 152 and ARG: 159 shows the pi-pi staking with the phenyl ring of the ligands **13, 9** and **11**),. Predicting the distribution of specified ligands in various bodily compartments is another feature of SwissADME [88]. The outcome is shown in the boiled-egg graphic below.

In conclusion, we have successfully synthesized a library of Nq substrates. Moreover, the synthesized compounds were also inspected for ant-inflammatory potential via *in-silico* studies. Overall, docking analysis gave three promising molecules (**13, 9** and **11**), which have good binding potential with the **1W3R** protein.

In comparison to Metronidazole. and Naphoquinone derivatives have good binding potential with the **1W3R** protein better than Metronidazole.

5. FUTURE ASPECTS

It would be a great change towards allopathic medicines to counter and control the development. Moreover, the synthesized compounds were also inspected for ant-inflammatory potential via *in-silico* studies. Overall, docking analysis gave three promising molecules (**13, 9 and 11)**, which have good binding potential with the protein as compared to Metronidazole. It may also be refined that its production would be reasonable in terms of cost with relatively strong usefulness. It would be a great deal for stability of formulation as it comes from a natural source.

It suggests these hits can be investigated for *in-vitro* and *in-vivo* activity to validate the computational results

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