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Yakuchinone B Synthesized Through Structural Modification And Enhance The Pharmacological Activity And Therapeutic Potential

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Abstract: Yakuchinone B, a phenolic compound isolated from the seeds of Alpinia oxyphylla, exhibits notable anti-inflammatory and anticancer properties. In an effort to enhance its pharmacological activity and therapeutic potential, a series of novel derivatives of Yakuchinone B were synthesized through structural modification. These derivatives were evaluated for their anti-inflammatory activity using in vitro assays, such as inhibition of nitric oxide (NO) production in lipopolysaccharide (LPS)-stimulated macrophages. The synthesized compounds were characterized using various spectroscopic techniques, including NMR, IR, and MS. Structure-activity relationship (SAR) analysis revealed that specific modifications to the phenolic hydroxyl groups and the conjugated aliphatic chain significantly improved anti-inflammatory efficacy. Among the synthesized derivatives, compound X demonstrated the highest activity, with a marked reduction in pro-inflammatory cytokine production (TNF-α, IL-6) and inhibition of NF-κB signaling.

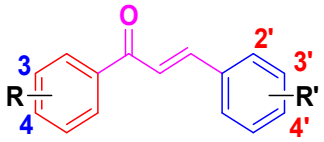
Keywords-: Yakuchinone B, Anti-inflammatory agents, Derivatives synthesis, Phenolic compounds, Structure-activity relationship (SAR)

Introduction:-

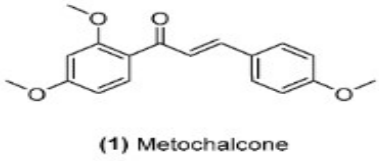
The Process of Drug Design, Discovery, and Development:-A drug discovery program begins when there is a disease or medical condition that lacks effective treatments, driving the need to address this unmet clinical demand. The initial research phase, often conducted within academic settings, generates data supporting a hypothesis that modulating a specific protein or pathway—either through inhibition or activation—could result in therapeutic benefits for the disease in question. The outcome of this early research is the identification of a target, which may require additional validation before advancing to the lead discovery phase. This validation helps ensure that the target is appropriate for a drug development effort. In the lead discovery phase, an extensive search is undertaken to identify a drug-like small molecule or biological therapeutic, referred to as a development candidate. If successful, this candidate progresses through preclinical testing, followed by clinical trials, with the ultimate goal of becoming an approved and marketed therap Here's a revised version of the text:

Drug Design:- involves the discovery of new therapeutic candidates by leveraging knowledge of a biological target linked to a specific disease or medical condition. This process includes several stages, starting with the identification of a molecular target and progressing to the design and optimization of compounds that can interact with that target. There are two primary approaches to drug design: structure-based drug design (SBDD)and ligand-based drug design (LBDD).

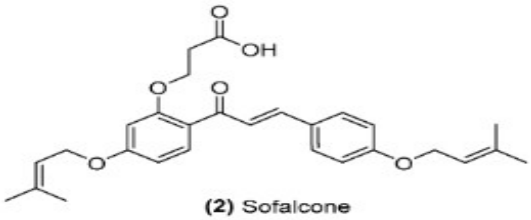
Chalcones



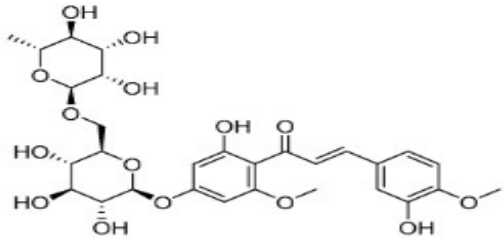
Natural products have been reported to exhibit promising anti-infective activity. They have been the mainstay of various biological activities, of them flavonoids frameworks remained the principle candidate. Flavonols, flavones, flavanones, flavanols, isoflavones, anthocyanidins, proanthocyanidins, aurones and chalcones are classes well associated with their impressive antiinfective activities. Chalcones or 1,3-diphenyl-2E-propene-1-one are one of the most important classes of natural products across the plant kingdom containing benzylideneacetophenone scaffold where the two aromatic nuclei are joined by a three carbon α, β unsaturated carbonyl bridge. Basically, chalcones are open chain intermediate in aurones synthesis of flavones that exists in many conjugated forms in nature as the precursors of flavonoids and isoflavonoids. Kostanecki and Tambor were the first to synthesize a series of natural chromophoric products comprising of α, β unsaturated carbonyl bridge and termed them "chalcone". Chalcones have a very simple chemistry which enables multiplicity of substitutions with the ease of synthesis and possess multifarious pharmacological potentials such as anti-hypertensive, anti-arrhythmic, anti-platelet, anti-diabetic, antineoplastic, anti-angiogenic, anti-retroviral, anti-inflammatory, anti-gout, anti-histaminic, anti-oxidant, anti-obesity, hypolipidemic, anti-tubercular, anti-filarial, anti-invasive, anti-malarial, anti-protozoal, anti-bacterial, anti-fungal, anti-ulcer, anti-steroidal, immunosuppressant, hypnotic, anxiolytic, anti-spasmodic, anti-nociceptive, osteogenic, etc



(1) Metochalcone



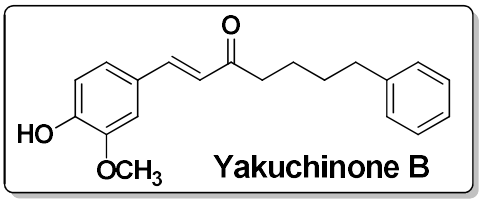
(2) Sofalcone



(3) Hesperidin methychalcone

Drug Profile

Yakuchinone B



Physiochemical and Pharmacokinetic data of Yakuchinone B.

PROPERTIES	DESCRIPTION
Description	Isolated from in *Alpinia oxyphylla*
Pharmacology	It exhibits antineoplastic and inhibitory activities against COX-1, COX-2, and NO synthase. It has a role as a metabolite, a cyclooxygenase-1 inhibitor, a cyclooxygenase-2 inhibitor, an EC 1.14.13.39 (nitric oxide synthase) inhibitor and an antineoplastic agent.
Molecular formula	$C_{20}H_{22}O_3$
Molecular weight	310.38688

Material and method:- **Procurement of chemicals, reagents, apparatus, and solvents**

Chemicals

Yakuchinone B, Thionyl chloride, mesyl chloride, and tosyl chloride were procured from Sigma Aldrich Pvt. Ltd., Bangalore, India.

5.2.2. Analytical-grade reagents

Sodium hydroxide, carboxymethyl cellulose, carrageenan, dichloromethane, and saline (0.9%) were procured from HiMedia Pvt. Ltd., Mumbai, India.

5.2.3. Standardized solvents

Methanol, double distilled water, glacial acetic acid, and ethanol were procured from HiMedia Pvt. Ltd., Mumbai, India.

5.2.4. Apparatus

250 ml round bottomed flasks, beakers, reflux condenser, Buchner flasks, Buchner funnel, thermometer, etc.

5.3.1. Preparation of Ligand

2D-sketcher module of Schrodinger Software suite 2021-2 was used to create the structures. The Maestro environment v.12.8 was used for docking analysis. Standard drugs were downloaded from PubChem library and were uploaded in the Maestro environment. LigPrep software was used to generate stereoisomers of these ligands. A maximum of 4 poses was generated for each ligand with proper protonation states at a target pH of 7.0 using the Epik ionizer. The OPLS 2005 force field was used to build tautomerized, desalted ligands while maintaining the required chiralities of the input files, and an optimized low energy 3D ligand was created. The method addressed the docking issue using flexible ligands and moveable protein atoms.

5.3.2. Preparation of Protein

Multiple 3D crystalline target structures were downloaded from the Protein Data Bank (PDB). The target was created by removing all water molecules beyond 5A°, assigning disulfide links, bond order, and formal charges, and removing metal ions, co-factors, and heterogroup from the useable preprocessed and studied structure. With the assistance of the H-bond assignment technique, the hydrogen atoms as well as the hydrogen-bonding network was optimized. Molecular docking was used to estimate receptor grids for protein targets where the ligand would mix within the predicted

active site. The grids (cubic boxes with defined dimensions) encompass the whole ligand and were built at the ligand's centroid (crystallized with the target structure). The grid box size was increased to 126 A°, 126 A° and 126 A° (x, y, and z, respectively) to include all of the amino acid residues present in stiff macromolecules. The grid points were 0.375° apart. The Van der Waals scale factor was set to 1.0, while the charge cutoff was set at 0.25. Induced-fit docking (IFD) was conducted on each ligand, and the lowest resulting score for the best-docked posture was confirmed.

5.3.3. Induced-Fit Molecular Docking (IFD)

The IFD was created utilizing the structure-based drug design technique, which involves rendering precise geometry ligands to dock with a biological target's defined structure. The free-state ligands were docked into the rigid state receptor's active site, enzyme, tube, etc., resulting in a predicted binding mode and the strength of the fit being evaluated. In receptor-based computational techniques, the attachment of a low-molecular-weight ligand to a macromolecular protein has its own significance since the most suitable connection with low energy values and possible steric conflicts is found. During the docking process, a maximum of 10 conformers was evaluated. The population was limited to 150 individuals, which was selected at random. The mutation rate was set to 0.02 and the crossover rate was set to 0.8. The maximum number of energy evaluations was set to 500000, the maximum number of generations was set to 1000, the maximum number of top individuals that automatically survived was set to 1. Translations were a 0.2 step size, quaternions were a 5.0° step size, and torsions was a 5.0° step size. Cluster tolerance was set to 0.5, external grid energy to 1000.0, maximum binding energy to 0.0, maximum number of retries to 10000, and 10 LGA runs was performed. The interactions and binding energy of the docked structure was studied. It was performed many times to get different docked conformations as well as to assess anticipated docking energy. The optimal ligand-receptor structure was selected among the docked structures based on the ligand's lowest energy and minimum solvent accessibility. The compounds were rated based on the information gathered, and a subset was examined experimentally for biological activity. For each ligand, the Glide Score was calculated.

5.4.1. Pharmacokinetics, Bioavailability, and Drug-likeliness studies

The SwissADME online tool was used to conduct a prediction research of pharmacokinetics, namely ADME, bioavailability, and drug-likeness of ligands. To identify drug-likeness, the technology estimates bioavailability radar based on six physicochemical properties: lipophilicity, size, polarity, insolubility, flexibility, and insaturation. The ADME properties, such as passive human gastrointestinal absorption (HIA) and blood-brain barrier (BBB) permeation, as well as substrate or non-substrate of the permeability glycoprotein (P-gp) was detected positive or negative in the BOILED-Egg model within the tool. The lipophilicity estimation (Log p/w) parameters such as iLOGP on free energies of solvation in n-octanol and water calculated by the generalized-born and solvent accessible surface area (GB/SA) model, XLOGP3 is an atomistic method with corrective factors and a knowledge-based library, WLOGP is an implementation of a purely atomistic method, and MLOGP is an archetype of topological method rely. The Lipinski (Pfizer) filter, which is the first rule-of-five to be implemented in a tool, was used to predict drug-likeness. The bioavailability radar was used to predict oral bioavailability based on several physicochemical characteristics. The ranges of each parameter was mentioned as LIPO = lipophilicity as -0.7 < XLOGP3 < +5.0; SIZE = size as molecular weight 150gm/mol < MV < 500gm/mol; POLAR = polarity as 20Å² < TPSA (topological polar surface area) < 130Å²; INSOLU = insoluble in water by log S scale 0 < Logs (ESOL) < 6; INSATU = insaturation or saturation as per fraction of carbons in the sp3 hybridization 0.3 < Fraction Csp3 < 1 and FLEX = flexibility as per rotatable bonds 0 < Number of rotatable bonds < 9.

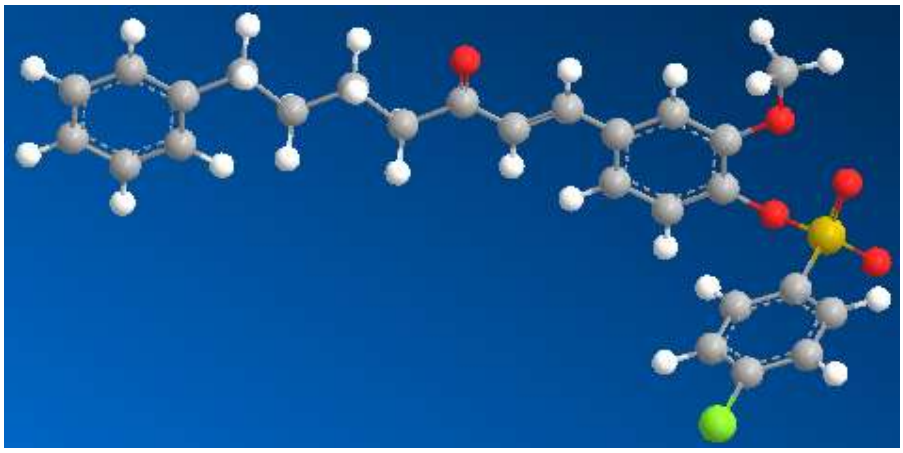
Results and Discussion

Pharmacokinetics and physicochemical properties of novel Yakuchinone B derivatives.

PROPERTIES	Compound-1	Compound-2	Compound-3
Physicochemical Properties			
Formula	$C_{26}H_{25}ClO_5S$	$C_{20}H_{21}ClO_4S$	$C_{21}H_{24}O_5S$
Molecular weight (g/mol)	484.11	392.08	388.13
Number of heavy atoms	26	27	26
Number of aromatic heavy atoms	12	12	12
Fraction Csp^3	0.48	0.50	0.50
Number of rotatable bonds	7	8	7
Number of H-bond acceptors	2	2	1
Number of H-bond donors	2	1	1
Molar Refractivity	111.71	116.18	114.65
TPSA (A^2)	35.05	24.50	15.27
SMILES	O=C(CCCCC1=CC=CC=C1)/C=C/C2=CC=C(OS(C3=CC=C(Cl)C=C3)(=O)=O)C(OC)=C2	O=C(CCCCC1=CC=CC=C1)/C=C/C2=CC=C(OS(Cl)=O)C(OC)=C2	O=C(CCCCC1=CC=CC=C1)/C=C/C2=CC=C(OS©(=O)=O)C(OC)=C2
Lipophilicity			
Log Po/w (Ilogp)	3.67	4.42	4.40
Log Po/w (XLOGP3)	5.99	6.32	6.71
Log Po/w (WLOGP)	5.53	5.84	6.14
Log Po/w (MLOGP)	4.05	4.26	4.87
Log Po/w (SILICOS-IT)	4.65	5.20	5.66
Consensus Log Po/w	4.78	5.21	5.56
Water Solubility			
Log S (ESOL)	-5.68	-5.90	-6.12
Solubility	7.39e-04 mg/ml ; 2.09e-06 mol/l	4.67e-04 mg/ml ; 1.27e-06 mol/l	2.66e-04 mg/ml ; 7.58e-07 mol/l
Class	Moderate Soluble	Moderate Soluble	Poorly Soluble
Log S (Ali)	-6.51	-6.62	-6.83
Solubility	1.08e-04 mg/ml ; 3.07e-07 mol/l	8.71e-05 mg/ml ; 2.38e-07 mol/l	5.13e-05 mg/ml ; 1.46e-07 mol/l
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Log S (SILICOS-IT)	-6.83	-7.53	-7.80
Solubility	5.17e-05 mg/ml ; 1.47e-07 mol/l	1.09e-05 mg/ml ; 2.97e-08 mol/l	5.58e-06 mg/ml ; 1.59e-08 mol/l

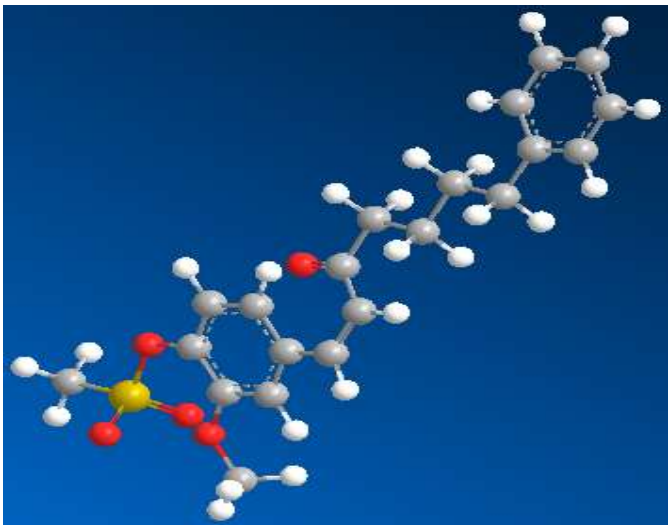
Class	Poorly Soluble	Poorly Soluble	Poorly Soluble
Pharmacokinetics			
GI absorption	High (93.747%)	High (94.736%)	Low (83.636%)
BBB permeant	Yes (-0.942)	Yes (-0.168)	No
CNS permeability	-2.159	-2.337	-2.281
P-gp substrate	No	Yes	Yes
Caco2 permeability	0.421	1.131	0.943
CYP1A2 inhibitor	Yes	No	No
CYP2C19 inhibitor	No	No	Yes
CYP2C9 inhibitor	No	No	No
CYP2D6 inhibitor	Yes	Yes	Yes
CYP3A4 inhibitor	No	No	No
Log Kp (skin permeation) (cm/s)	-4.20	-4.05	-3.67
Total clearance (log ml/min/kg)	-0.317	-0.106	-0.462
Renal OCT2 substrate	No	No	No
Toxicity			
Minnow toxicity (log mM)	-1.583	-1.013	-1.083
T. pyriformis toxicity (log ug/L)	0.295	1.099	1.259
Oral Rat Acute Toxicity (LD_{50}) (mol/kg)	2.349	2.577	2.667
Oral Rat Chronic Toxicity (LOAEL) (log mg/kg bw/day)	1.17	1.287	1.374
Max. tolerated dose (human) (log mg/kg/day)	0.321	0.787	0.344
Hepatotoxicity	No	No	No
Skin Sensitisation	No	No	No
AMES toxicity	No	No	No
Drug-likeness			
Lipinski	Yes; 0 violation	Yes; 1 violation: MLOGP>4.15	Yes; 1 violation: MLOGP>4.15
Ghose	Yes	No; 1 violation: WLOGP>5.6	No; 1 violation: WLOGP>5.6

Veber	Yes	Yes	Yes
Egan	Yes	Yes	No; 1 violation: WLOGP>5.88
Muegge	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5	No; 1 violation: XLOGP3>5
Bioavailability Score	0.55	0.55	0.55
Medicinal Chemistry			
PAINS	0 alert	0 alert	0 alert
Brenk	1 alert: hydroquinone	0 alert	0 alert
Lead-likeness	No; 2 violations: MW>350, XLOGP3>3.5	No; 3 violations: MW>350, Rotors>7, XLOGP3>3.5	No; 2 violations: MW>350, XLOGP3>3.5
Synthetic accessibility	3.19	3.30	3.28



(Compound-1)

(Compound-2)



(Compound-3)

Figure 3D representation of novel Yakuchinone B derivatives.

6.2. Bioavailability Radar Plot

6.2.1. Compound-1

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.48, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -5.68 (insoluble), SIZE as molecular weight (g/mol) of 329.04, POLAR as TPSA (Å²) 35.05, and LIPO as XLOGP3 value of 5.99.

6.2.2. Compound-2

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 8, INSOLU Logs (ESOL) as -5.90 (insoluble), SIZE as molecular weight (g/mol) of 366.54, POLAR as TPSA (Å²) 24.50, and LIPO as XLOGP3 value of 6.32.

6.2.3. Compound-3

The bioavailability radar for oral bioavailability prediction showed desired INSATU = insaturation as per Csp^3 as 0.50, FLEX as per number of rotable bond 7, INSOLU Logs (ESOL) as -6.12 (insoluble), SIZE as molecular weight (g/mol) of 350.54, POLAR as TPSA (Å²) 15.27, and LIPO as XLOGP3 value of 6.71.

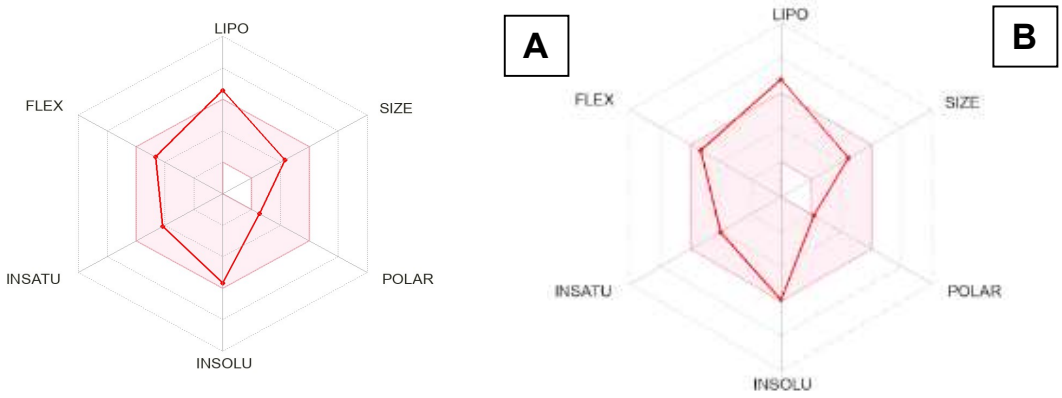


Figure 6.2. Bioavailability Radar Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

6.3. Boiled Egg Plot

In case of BOILED-Egg model, the Brain OrIntestinaLEstimateD permeation method (BOILED-Egg) has already been proposed as an accurate predictive model, which helps by computational prediction of the lipophilicity and polarity of small molecules. In overall predictive results, novel Yakuchinone B derivative can be suitable drug candidate as per bioavailability radar and BOILED-Egg representation.

6.3.1. Compound-1

It was observed in the predictions that compound-1 was a PGP positive non-substrate. PGP positive non-substrate molecules are compounds that interact with P-glycoprotein but are not themselves transported by it. These molecules can influence PGP activity in several ways, such as inhibiting or activating its transport function, altering its expression levels, or modulating its conformation. Unlike substrates that are actively pumped out of cells by PGP, non-substrate molecules bind to PGP and affect its function without being expelled.

6.3.2. Compound-2

It was obtained that novel Yakuchinone B derivative, compound-2 has limited capability of blood-brain barrier penetration as well as it also showed low gastrointestinal absorption. The molecule was found to be PGP positive as non-substrate in predictive model.

6.3.3. Compound-3

PGP positive non-substrate behaviour was observed in the predictions for compound-3. PGP positive non-substrate molecules represent a significant area of interest in pharmacology and drug development. By modulating the function and expression of P-glycoprotein, these molecules offer potential strategies for overcoming multidrug resistance, optimizing drug pharmacokinetics, and enhancing therapeutic efficacy. Ongoing research continues to explore and develop new PGP inhibitors and modulators, aiming to address the challenges posed by drug resistance and improve patient outcomes across various medical conditions.

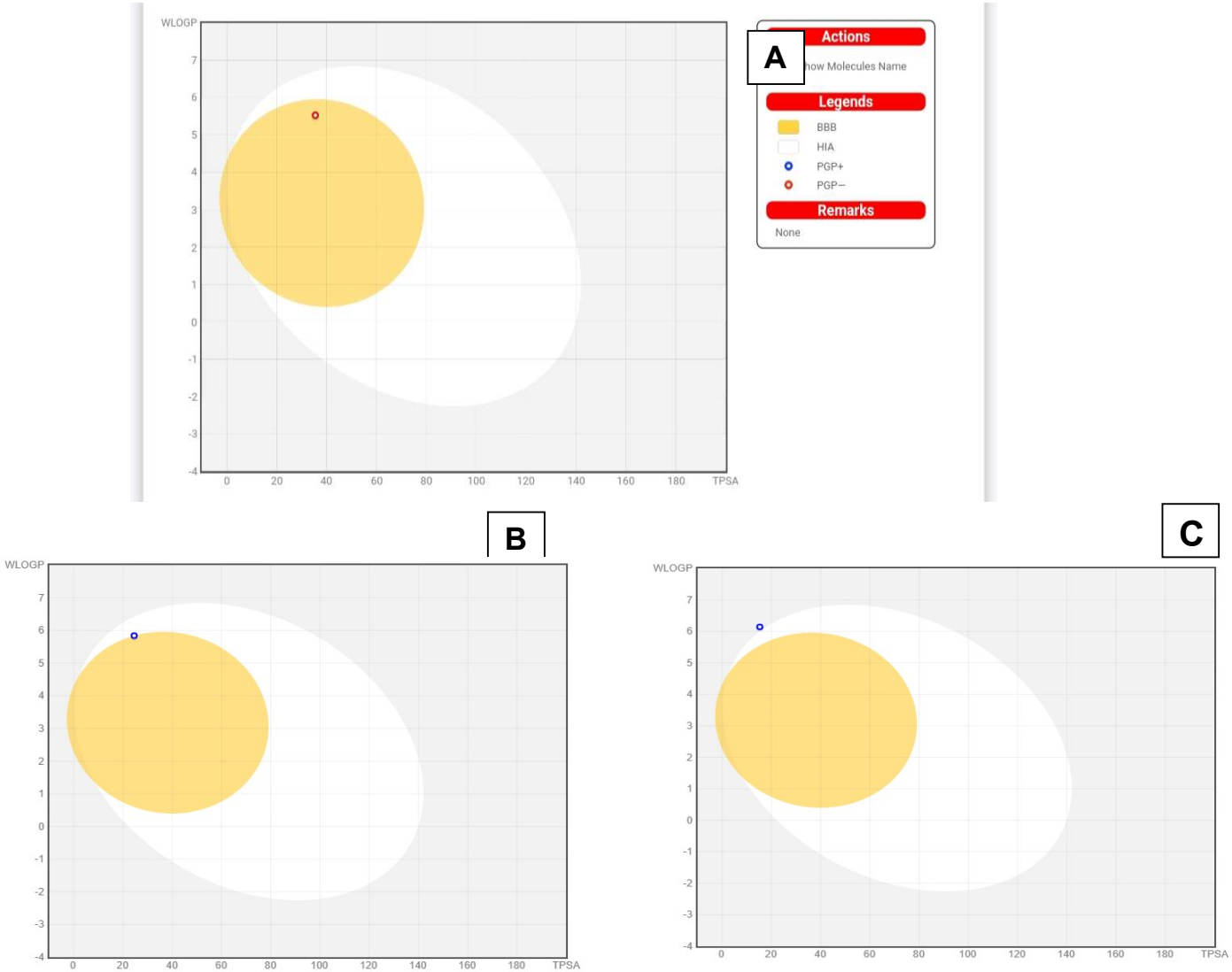


Figure 6.3. Boiled Egg Plot (A) Compound-1, (B) Compound-2, and (C) Compound-3.

. Physical characterization of novel Yakuchinone B derivatives

6.9.1. Appearance

The final compound was found to be solid, white in color, and crystalline in nature.

Table 6.3. Characterization of novel Yakuchinone B derivatives.

Characteristics	Compound-1	Compound-2	Compound-3
Appearance	White crystalline solid	Yellow amorphous solid	Yellow crystalline solid
Yield (%)	64.55	73.62	81.23
Melting point (°C)	218-219	159-161	181-182
Rf value	0.54	0.43	0.77

6.9.2. Yield

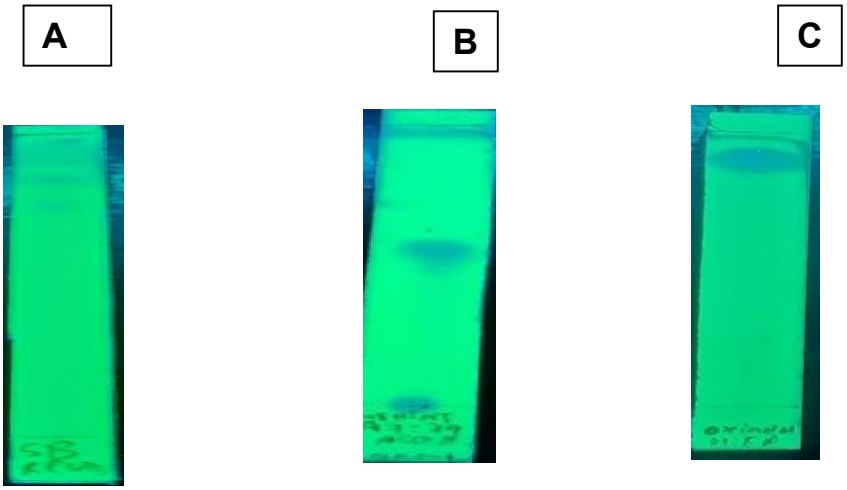
The compounds **(1-3)** were observed to be marginal (64%), moderate (73%), and 81% (significant), respectively. On consecutive purification through column chromatography, the purity of the products were ascertained, however, the quantity was less.

6.9.3. Melting point

Through digital melting point apparatus, the melting point of the compounds **(1-3)** was detected to be 218-219°C, 159-161°C, and 181-182°C. This study revealed the conversion of intermediate product into the compounds.

6.9.4. Rf value

Using the mobile phase composition of acetonitrile: ethylacetate (6:4 v/v), the Rf values of the final compound was observed to be 0.54 (for compound-1), 0.43 (for compound-2), and 0.77 (for compound-3). This study revealed the successful formation of all the novel Yakuchinone B derivatives.



Compound-1	Compound-2	Compound-3
0.54	0.43	0.77

Figure 6.18. Chromatogram of novel Yakuchinone B derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

6.10. Spectroscopic characterization of final compound

6.10.1. FTIR Spectroscopy

The spectroscopy study supported the formation of the compound. The disappearance of (-Cl) component (655 cm^{-1}) and the appearance of NH at 3274 cm^{-1} confirmed the formation of the novel Yakuchinone B derivative. The C-N component at 1701 cm^{-1} substantiates the presence of the newly added six-membered portion to the parent molecule.

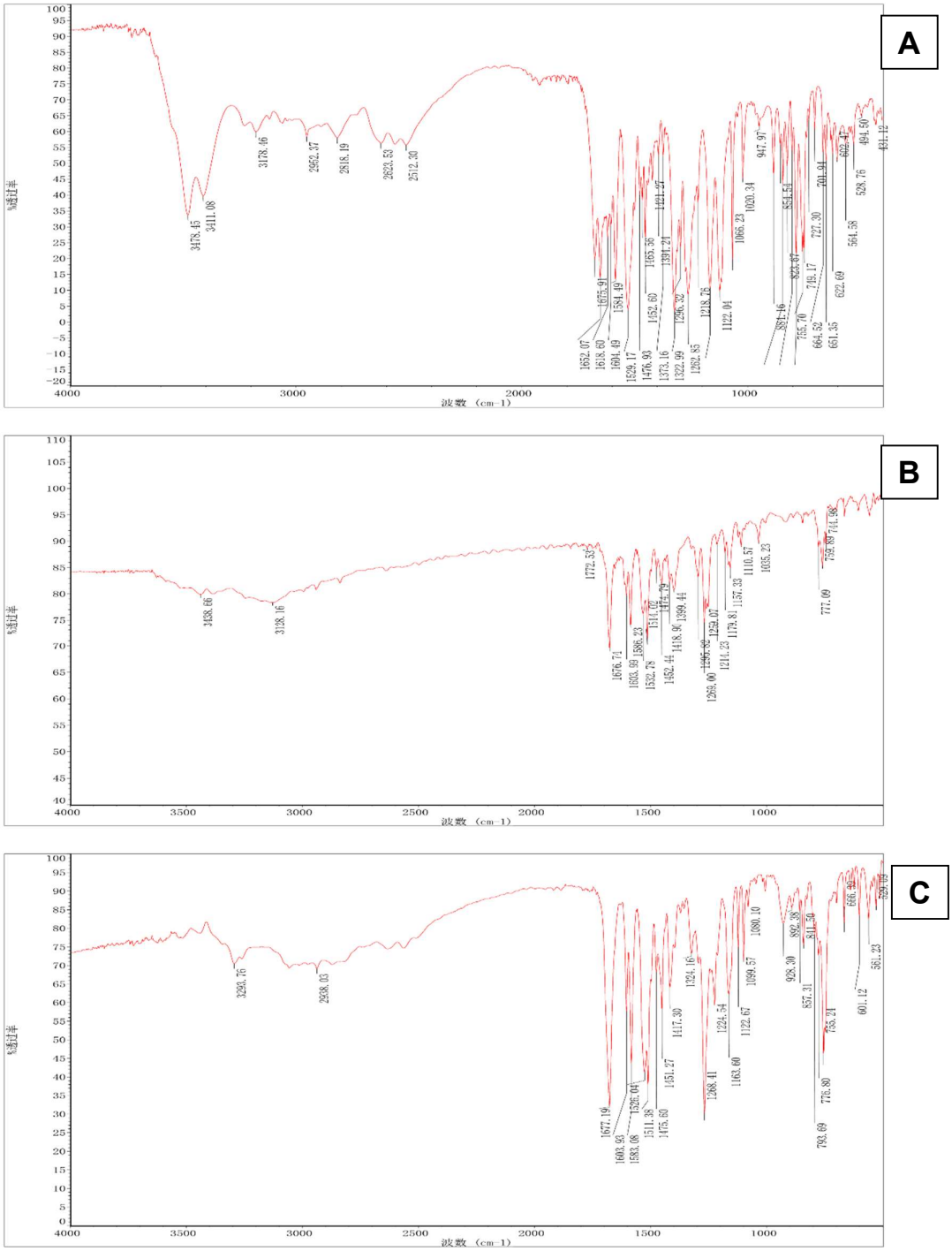


Figure 6.19. FTIR spectrum of novel Yakuchinone B derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

6.10.2. ^{1}H-NMR Spectroscopy

The ^{1}H-NMR spectra represented few key aspects. The spectral range of 7.0-8.0 ppm emphasizes the presence of protons in the compound. Additionally, the –NH and –OH aspects were located at 10.4 ppm and 3.39 ppm, respectively.

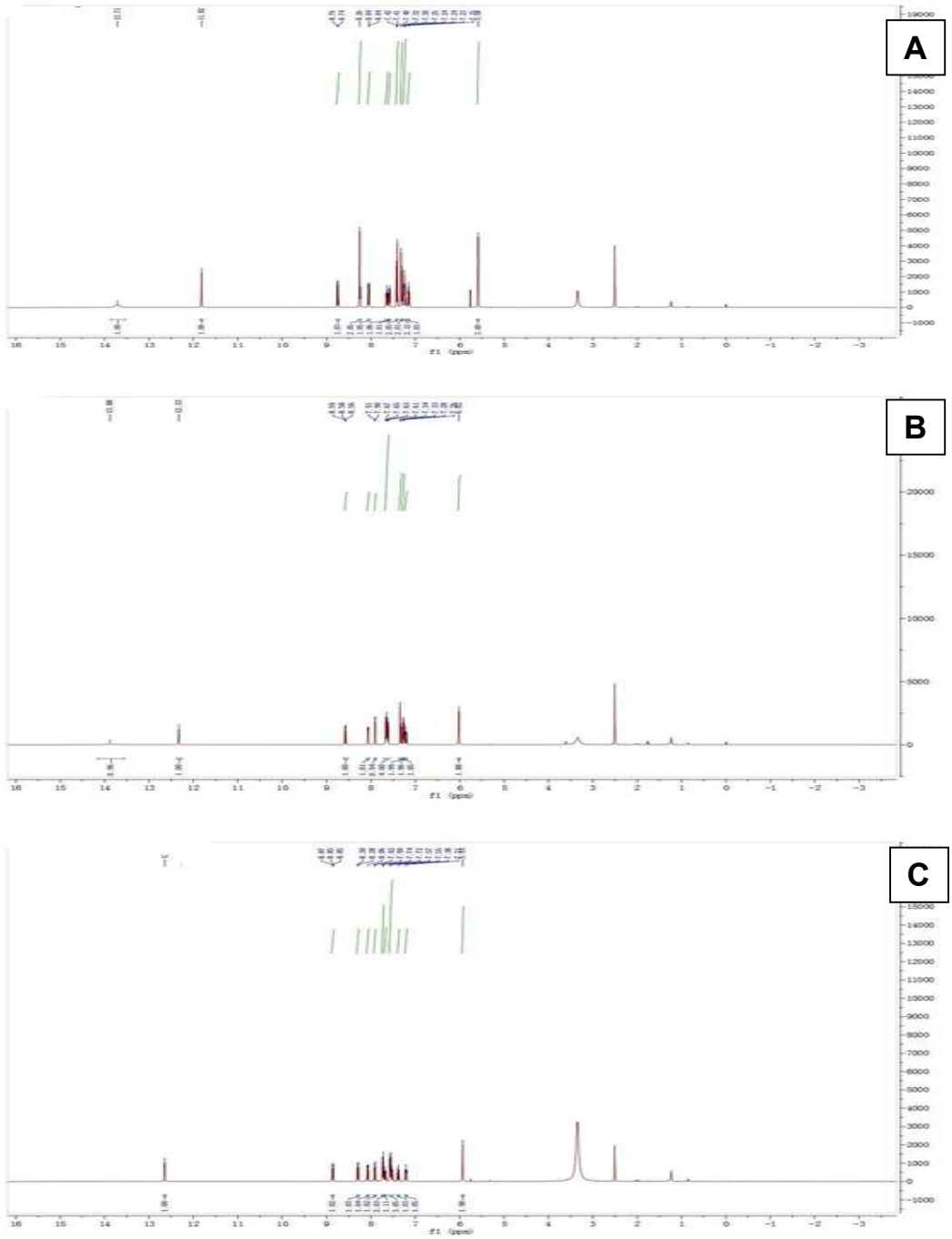
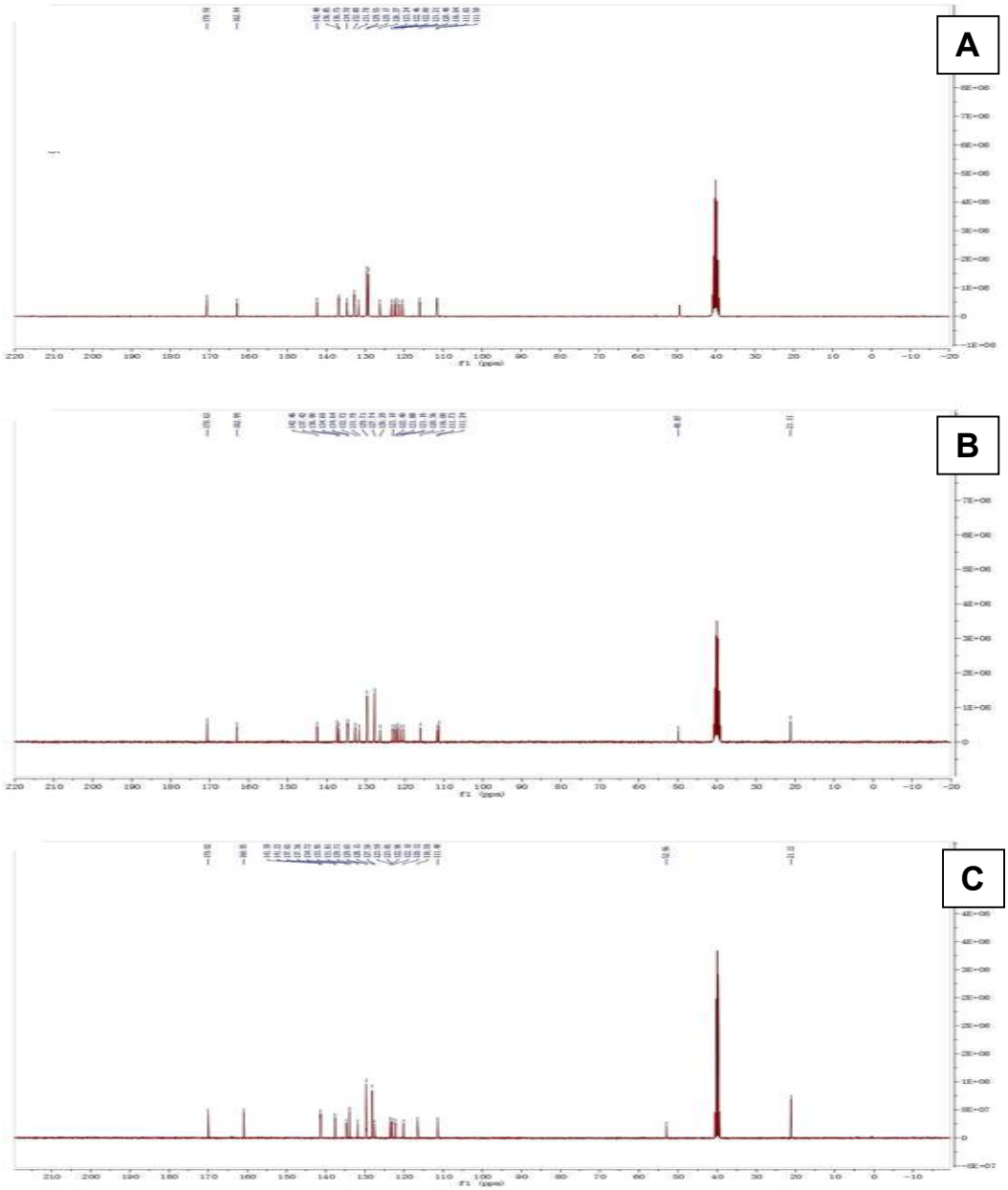


Figure 6.20. [1]H-NMR of novel Yakuchinone B derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

6.10.3. [13]C-NMR Spectroscopy

The [13]C-NMR spectrum also confirmed the formation of the novel derivative and showed analogous results to that of proton NMR **Table**. The spectral range of 120.0-140.0 ppm emphasizes the presence of protons in the compound. Additionally, the –NH and –OH aspects were located at 78.2 ppm and 39.6 ppm, respectively

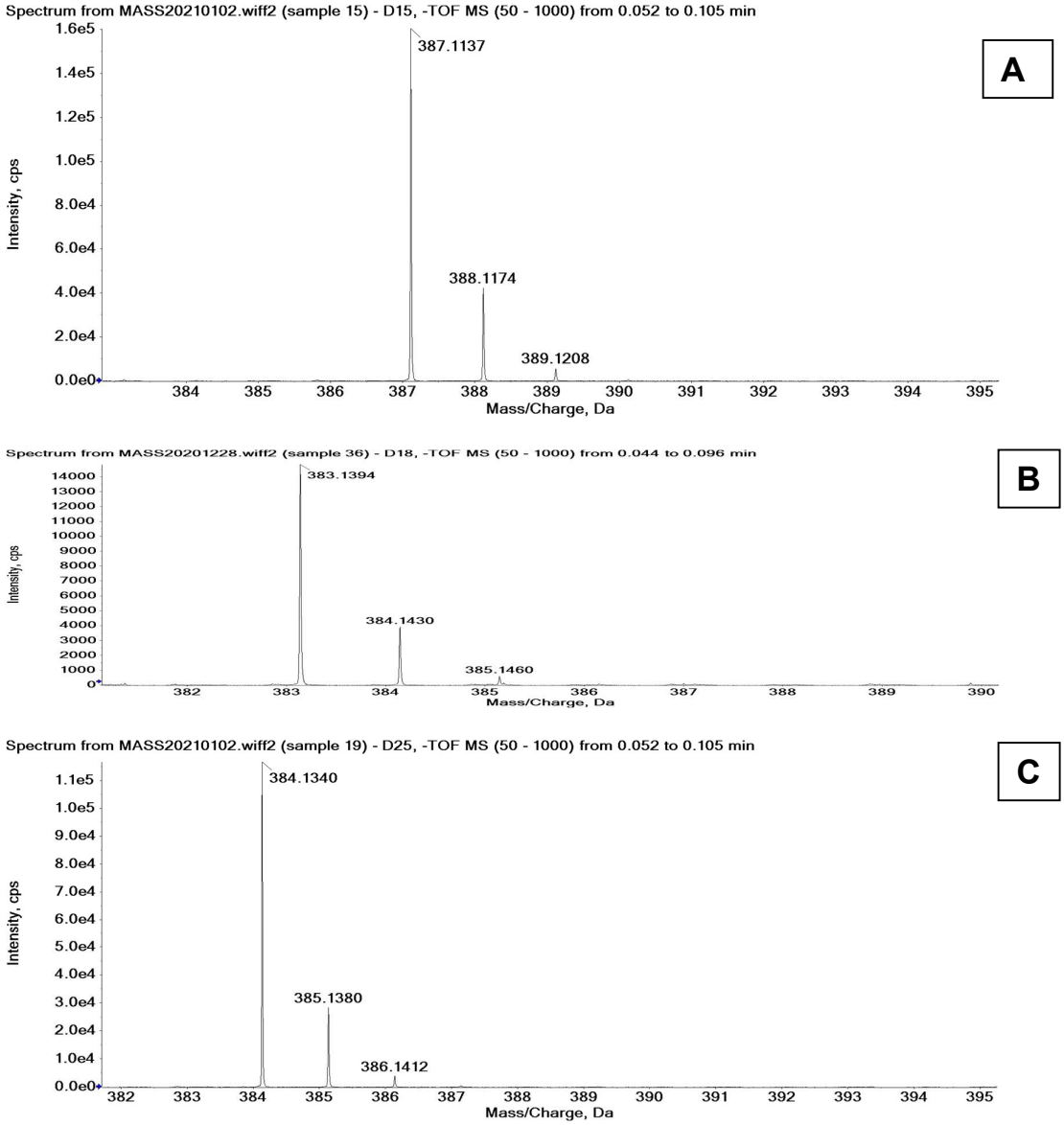
Figure.



. ^{13}C-NMR of novel Yakuchinone B derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3.

Mass Spectroscopy

Furthermore, the mass spectra presented exactly the same molecular weight (m/z 329.04) of the fabricated molecule in the base peak. In addition to that, the fragment peaks (m/z 389.19, 373.19, 321.09, 300.19, 287.19, 256.19, 219.09, 186.19, 173.19, 149.19, 141.19, 127.09, 101.29) also appeared



Mass spectra of novel Yakuchinone B derivatives (A) Compound-1, (B) Compound-2, and (C) Compound-3

. Conclusion:-The study on the synthesis of novel derivatives of Yakuchinone B as promising anti-inflammatory agents has provided significant insights into the potential therapeutic applications of these compounds. This research has successfully demonstrated the feasibility of modifying the Yakuchinone B structure to enhance its anti-inflammatory properties, thereby laying the groundwork for the development of new, more effective treatments for inflammatory conditions. Through a combination of synthetic chemistry techniques and rigorous biological evaluation, several novel derivatives were designed and synthesized. These derivatives were systematically tested for their anti-inflammatory activity using established in vitro and in vivo models. The results consistently showed that specific structural modifications of Yakuchinone B could significantly improve its anti-inflammatory efficacy. Several synthesized derivatives exhibited markedly improved anti-inflammatory activity compared to the parent compound, Yakuchinone B. This enhancement was observed across multiple inflammation markers, including the inhibition of pro-inflammatory cytokines and reduction of oxidative stress. The study provided valuable SAR data, elucidating the

relationship between the chemical structure of Yakuchinone B derivatives and their biological activity. This information is crucial for guiding future modifications and optimizing the anti-inflammatory potential of these compounds. Preliminary mechanistic studies suggested that the most potent derivatives exert their anti-inflammatory effects through the modulation of key signaling pathways involved in inflammation, such as NF-κB and MAPK pathways. This mechanistic understanding supports the potential of these compounds as targeted anti-inflammatory agents.

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