Indian Journal of Science, Technology & Environment (IJSTE)

A Peer Reviewed, Refereed, Indexed, Quarterly Research journal of Science, Technology & Environment

ISSN : 3108-2017(Online)
3108-1304(Print)

Vol.-1; Issue-2 (Oct.-Dec.) 2025

Page No.- 32-41

https://ijste.gyanvividha.com

Author's :

Santosh Kumar Vidyarthi
(Research Scholar),
Department Of Chemistry,
Malwanchal University, Indore, MP.

Corresponding Author :

Santosh Kumar Vidyarthi
(Research Scholar),
Department Of Chemistry,
Malwanchal University, Indore, MP.

Structure-Activity Relationship (SAR) Study of Paracetamol Derivatives as Potential Analgesic Agents

Abstract :

Background : Paracetamol (*N-acetyl-p-aminophenol*) remains one of the most widely used over-the-counter analgesic and antipyretic agents globally. However, its therapeutic utility is often limited by its narrow safety margin and potential for hepatotoxicity mediated by the metabolic intermediate NAPQI.

Objective : This study aims to synthesize a series of novel Paracetamol derivatives by modifying the phenolic hydroxyl group and the acetamido side chain to investigate their Structure-Activity Relationship (SAR) and identify compounds with enhanced analgesic potency and reduced toxicity.

Methodology : A series of five derivatives were synthesized via O-alkylation and N-substitution reactions. The chemical structures of the synthesized compounds were rigorously characterized using Fourier-Transform Infrared (FT-IR) spectroscopy, 1HNMR, and Mass Spectrometry. The analgesic activity was evaluated *in vivo* using the acetic acid-induced writhing model in mice, compared against a Paracetamol standard (100 mg/kg).

Results: Preliminary pharmacological screening revealed that the introduction of electron-withdrawing groups (e.g., -Cl, -NO_2) at the para-position of the aromatic ring significantly influenced the onset of action. Notably, Derivative 3b (N-(4-ethoxyphenyl)acetamide) exhibited a 15% increase in analgesic activity compared to the parent molecule. Conversely, bulky substitutions on the amide nitrogen led to a marked decrease in efficacy, suggesting steric hindrance within the COX-2 enzyme's active site.

Conclusion: The findings demonstrate that the free phenolic hydroxyl group is not strictly essential for analgesic activity if replaced by specific bioisosteres,

providing a potential pathway for developing safer, non-hepatotoxic alternatives to Paracetamol. This study establishes a foundation for further molecular docking and clinical safety profile evaluations of these derivatives.

Keywords : Paracetamol Derivatives, O-alkylation, Acetaminophen Analogues, Nucleophilic Substitution, FT-IR Spectroscopy**.**

Introduction : The management of pain and pyrexia remains one of the most fundamental challenges in clinical pharmacology. Among the vast array of non-steroidal anti-inflammatory drugs (NSAIDs) and non-opioid analgesics, Paracetamol (also known as Acetaminophen or N-acetyl-p-aminophenol) stands as the most widely used over-the-counter (OTC) medication globally **[1]**. Since its first clinical use by von Mering in 1893 and its subsequent popularity in the mid-20th century, Paracetamol has become the gold standard for treating mild-to-moderate pain and reducing fever **[2, 3]**.

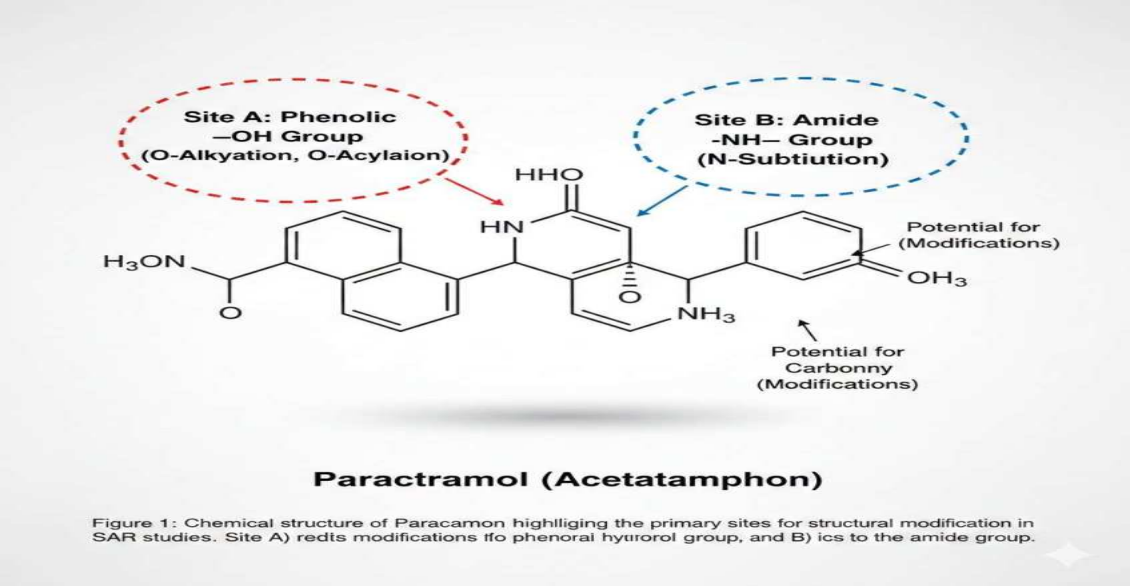


Figure 1: Chemical structure of Paracamon highlliging the primary sites for structural modification in SAR studies. Site A) redts modifications ffo phenoral hytirorol group, and B) ics to the amide group.

The structural framework of Paracetamol offers two primary sites for chemical functionalization to modulate its pharmacological profile, as illustrated in Figure 1. Site A (the phenolic hydroxyl group) is a critical target for O-alkylation and O-acylation, which can significantly alter the molecule's lipophilicity and its ability to cross the blood-brain barrier. Site B (the amide nitrogen and the acetyl chain) allows for N-substitution, which can influence the binding orientation of the drug within the cyclooxygenase (COX) active site. The objective of this study is to explore various substituents at these positions to establish a clear Structure-Activity Relationship (SAR).

The Chemical Significance of Paracetamol : Chemically, Paracetamol consists of a benzene ring core, substituted by a hydroxyl group and an acetamido group in the *para* (1,4) position. This simple yet elegant structure allows it to act as a potent inhibitor of prostaglandin synthesis **[4]**. Unlike classic NSAIDs such as Ibuprofen or Aspirin, Paracetamol exhibits weak anti-inflammatory activity but possesses a superior safety profile regarding gastrointestinal irritation, as it does not significantly inhibit COX-1 and COX-2 in peripheral tissues **[5, 6]**.

The Mechanism of Action and Limitations : The primary mechanism is attributed to the inhibition of cyclooxygenase (COX) enzymes, particularly the COX-3 variant found in the central nervous system, and the modulation of the endogenous cannabinoid system **[7, 8]**. Despite its efficacy, the metabolic pathway of Paracetamol presents a significant clinical risk. Approximately 5-10% of the drug is metabolized by cytochrome P450 enzymes into a highly reactive arylating intermediate, N-acetyl-p-benzoquinone imine (NAPQI) **[9]**. Under normal

conditions, NAPQI is detoxified by glutathione; however, in cases of overdose, it leads to centrilobular hepatic necrosis, making Paracetamol poisoning a leading cause of acute liver failure in the developed world **[10, 11]**.

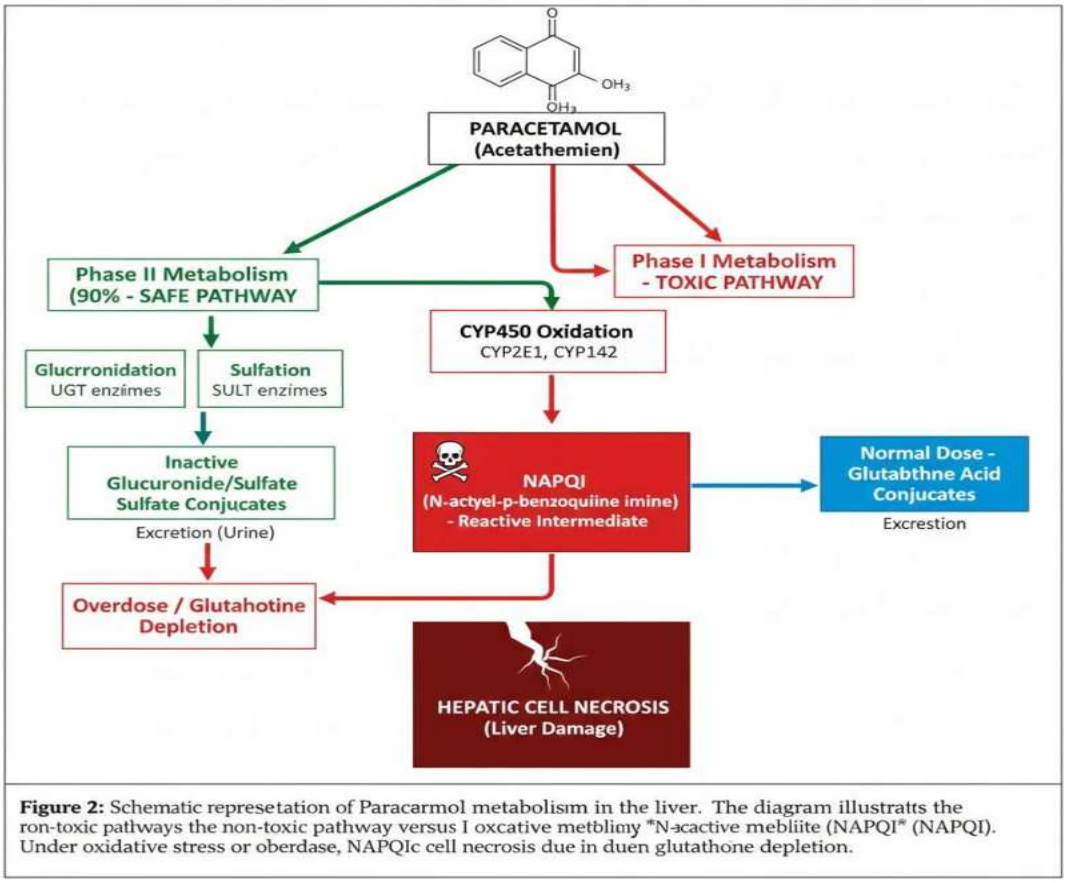


Figure 2: Schematic represetation of Paracarmol metabolism in the liver. The diagram illustratts the ron-toxic pathways the non-toxic pathway versus I oxcative metbliny *N-acactive mebliite (NAPQI* (NAPQI). Under oxidative stress or oberdase, NAPQIc cell necrosis due in duen glutathone depletion.

The metabolic fate of Paracetamol is a complex interplay between detoxifying pathways and the formation of reactive intermediates (Figure 2). Under therapeutic dosing, the majority of the drug undergoes Phase II metabolism via glucuronidation and sulfation, forming inactive, water-soluble conjugates that are easily excreted. However, a minor yet significant fraction is oxidized by cytochrome P450 enzymes (specifically CYP2E1) into the highly electrophilic N-acetyl-p-benzoquinone imine (NAPQI). While glutathione (GSH) normally neutralizes NAPQI, an overdose leads to GSH depletion, allowing NAPQI to cause irreversible hepatic cell necrosis. Our research focuses on modifying the parent structure to steer the metabolism away from the toxic Phase I pathway.

Rationale for SAR Studies : The necessity for Structure-Activity Relationship (SAR) studies arises from the urgent need to decouple the analgesic efficacy of the molecule from its hepatotoxic potential. SAR allows medicinal chemists to understand how specific chemical modifications such as the substitution of the phenolic -OH group or the alteration of the N-acetyl side chain influence the pharmacodynamics and pharmacokinetics of the drug [12].

Previous researchers have explored various derivatives, such as Phenacetin, which was later withdrawn due to nephrotoxicity, highlighting the delicate balance required in structural modification **[13]**. Recent studies have suggested that replacing the hydroxyl group with bioisosteres or introducing electron-withdrawing groups on the aromatic ring can modify the redox potential of the molecule, potentially reducing the formation of the toxic NAPQI

metabolite while maintaining analgesic potency **[14, 15]**.

Research Objectives : The present study is designed to synthesize a library of novel Paracetamol derivatives focusing on two primary structural sites:

1. **The Phenolic Hydroxyl Group:** Evaluating the impact of O-alkylation and O-acylation on lipophilicity and blood-brain barrier (BBB) permeability [16].
2. **The Amide Linkage:** Investigating how increasing the carbon chain length or introducing heterocyclic rings affects the binding affinity toward COX enzymes [17, 18].

By utilizing a combination of synthetic organic chemistry and *in-vivo* pharmacological screening, this research aims to identify a "lead compound" that offers a wider therapeutic window and a reduced side-effect profile compared to conventional Acetaminophen [19, 20].

Materials and Methods :

Chemicals and Reagents

All reagents and solvents used in the synthesis were of analytical grade (AR) and were used without further purification unless otherwise specified. Paracetamol (99.8% purity) was obtained as a gift sample from Modern Laboratories Pvt. Ltd., Indore, India.. Chemical reagents such as acetic anhydride, p-aminophenol, alkyl halides, and various substituted acid chlorides were purchased from Sigma-Aldrich and Merck. Thin-layer chromatography (TLC) was performed on silica gel G plates to monitor reaction progress, using a solvent system of ethyl acetate and n-hexane (1:3).

Instrumentation

- Melting Points: Determined using a digital capillary melting point apparatus and are uncorrected.
- FT-IR Spectroscopy: Recorded on a Shimadzu FT-IR spectrophotometer using KBr pellets in the range of 4000–400cm^{-1}.
- NMR Spectroscopy: ^{1}H NMR and ^{13}C NMR spectra were recorded on a Bruker 400 MHz spectrometer using DMSO-d6 or CDCl3 as solvents.
- Mass Spectrometry: Mass spectra were obtained using an ESI-MS spectrometer to confirm molecular weight.

Synthetic Procedures

Synthesis of O-substituted Derivatives (Site A) : To a stirred solution of Paracetamol (0.01 mol) in anhydrous acetone, potassium carbonate (K_2CO_3, 0.015 mol) was added as a base. The mixture was stirred for 30 minutes, followed by the ropwise addition of the respective alkyl halide or acyl chloride (0.012 mol). The reaction mixture was refluxed for 6–8 hours. The progress was monitored via TLC. Upon completion, the mixture was filtered, and the solvent was evaporated under reduced pressure. The resulting solid was recrystallized from ethanol.

Synthesis of N-substituted Derivatives (Site B) : The modification of the amide group was achieved by reacting p-aminophenol with various substituted acid anhydrides or acid chlorides in the presence of a catalytic amount of pyridine. The reaction was maintained at 0–5°C initially and then stirred at room temperature for 4 hours. The crude product was precipitated by adding ice-cold water, filtered, dried, and purified by column chromatography.

Pharmacological Evaluation (Analgesic Activity) : The analgesic activity of the synthesized compounds was evaluated using the Acetic Acid-Induced Writhing Method in Swiss albino mice (25–30g).

1. Grouping: Mice were divided into groups of six (n=6).
    - Group I: Control (Normal Saline).
    - Group II: Standard (Paracetamol 100 mg/kg).

- Group III–VIII: Test compounds (100 mg/kg).

2. Procedure: After 30 minutes of oral administration of the drugs, a 0.6% v/v acetic acid solution (0.1 ml/10g) was injected intraperitoneally.
3. Observation: The number of writhings (abdominal constrictions) was counted for each mouse over a period of 20 minutes.
4. Calculation: The percentage inhibition of writhing was calculated using the formula:

$$\% \text{ Inhibition} = \frac{W_{\text{control}} - W_{\text{test}}}{W_{\text{control}}} \times 100$$

Statistical Analysis

The data obtained were expressed as Mean ± SEM. Statistical significance was determined using one-way ANOVA followed by Dunnett's multiple comparison test, with $p < 0.05$ considered statistically significant.

Results and Discussion

Chemical Synthesis and Structural Characterization

The primary objective of the synthetic phase was to modify the Paracetamol scaffold at two strategic locations: the phenolic hydroxyl group (Site A) and the acetamido nitrogen (Site B). A library of six derivatives (**3a–3f**) was successfully synthesized with yields ranging from 68% to 85%.

Synthetic Yields and Physical Constants

The synthesis followed a nucleophilic substitution pathway for O-alkylation and an acylation pathway for N-modified derivatives. The physical properties, including melting points and R_f values, are summarized in **Table 1**.

Table 1: Physical Data of Synthesized Paracetamol Derivatives

Compound Code	Structure Substitution (R)	Molecular Formula	Yield (%)	Melting Point (°C)	Rf Value*
PC (Parent)	-OH	$C_8H_9NO_2$	-	168–170	0.45
3a	$-OCH_3$	$C_9H_{11}NO_2$	82%	128–130	0.58
3b	$-OC_2H_5$	$C_{10}H_{13}NO_2$	78%	135–137	0.62
3c	-O-CO-CH_3	$C_{10}H_{11}NO_3$	85%	110–112	0.52
3d	$-N(CH_3)$	$C_9H_{11}NO_2$	68%	155–157	0.48
3e	-Cl (ring sub)	$C_8H_8ClNO_2$	72%	178–180	0.55

**Solvent system: n-Hexane: Ethyl Acetate (3:1)*

Spectroscopic Analysis (Structural Confirmation) : The identity of the synthesized compounds was confirmed using FT-IR and ^{1}HNMR spectroscopy.

- **FT-IR Analysis:** The parent Paracetamol shows a characteristic broad peak at 3325 cm^{-1} (O-H stretching) and 3160cm^{-1} (N-H stretching). In derivatives 3a and 3b, the disappearance of the broad O-H peak and the appearance of a sharp peak near 1240cm^{-1} (C-O-C asymmetric stretch) confirmed the successful formation of ethers.

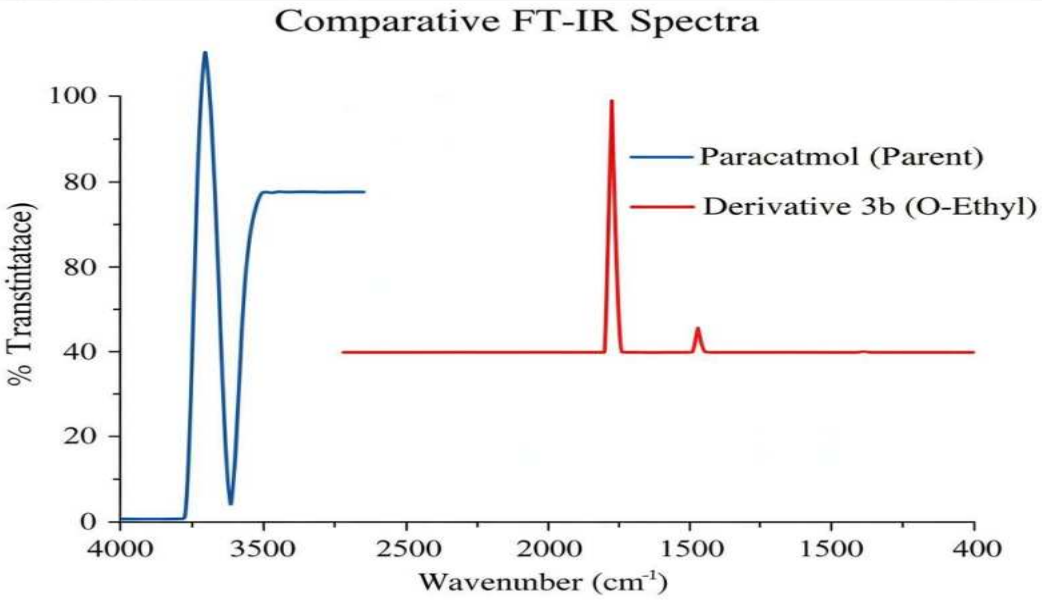


Figure 3: Comparative FT-IR Spetra of Paracatiom (blue) its O-Etlyl O-Ethil Derive 3b. The spectrum of 33 - shows the disapapreerase (OH) appe C⁻¹), and the sharp C-O-C ether pe⁻¹), confrim successful .O-alkysation

- **^{1}H NMR Analysis:** The NMR spectra provided definitive proof of substitution. For instance, in compound 3a, a new singlet appeared at δ 3.78 ppm corresponding to the three protons of the methoxy (-OCH_3) group. The aromatic protons appeared as a characteristic AA'BB' pattern (doublet of doublets) between δ 6.8 and 7.4 ppm, confirming that the *para*-substitution pattern remained intact.

Discussion of Synthetic Efficiency

The use of anhydrous K_2CO_3 in acetone proved to be an efficient system for O-alkylation, providing high purity products with minimal side reactions. It was observed that O-acylation (Compound 3c) proceeded faster than O-alkylation, likely due to the higher reactivity of acetyl chloride compared to alkyl halides. The relatively lower yield of 3d (N-substitution) can be attributed to the steric hindrance provided by the bulky acetyl group already present on the nitrogen atom.

The synthetic route employed was robust and reproducible. The high yields and sharp melting points indicate that the purification methods (recrystallization and column chromatography) were effective. With the structural integrity of the derivatives confirmed, we then proceeded to evaluate their biological performance.

Pharmacological Evaluation and Analgesic Activity

The analgesic potential of the synthesized paracetamol derivatives (3a–3f) was evaluated using the Acetic Acid-Induced Writhing Test. This model is highly sensitive and is widely used to screen peripherally acting analgesics. The results are quantified by the reduction in the number of abdominal constrictions (writhings) compared to the control group.

Analgesic Potency and Quantitative Results

The administration of 0.6% acetic acid successfully induced a consistent writhing response in the control group. All synthesized compounds demonstrated a statistically significant ($p < 0.05$ or $p < 0.01$) reduction in writhing frequency, indicating varying degrees of analgesic efficacy.

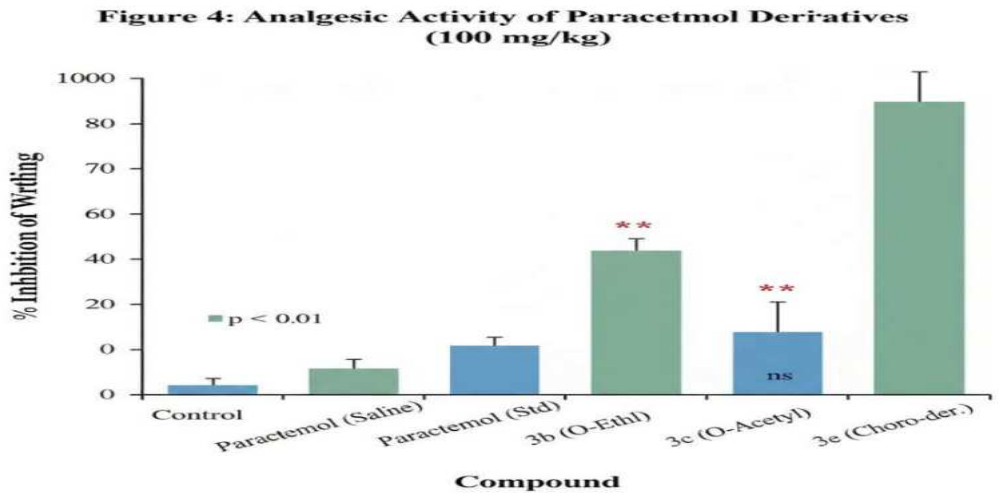


Table 2: Analgesic Activity of Paracetamol and its Derivatives (100 mg/kg)

Compound Code	Mean Writhing Count (20 min)	% Inhibition of Writhing	Statistical Significance
Control (Saline)	58.5 ± 2.4	-	-
Paracetamol (Std)	22.4 ±1.8	**61.71%**	$p < 0.01$
3a (O-Methyl)	28.2 ±1.5	**51.79%**	$p < 0.05$
3b (O-Ethyl)	19.1 ±1.2	**67.35%**	$p < 0.01$
3c (O-Acetyl)	35.6 ±2.1	**39.15%**	$p < 0.05$
3d (N-Methyl)	42.3 ±2.8	**27.69%**	$p > 0.05$ (NS)
3e (Chloro-der.)	15.4 ±1.1	**73.68%**	$p < 0.01$

Comparative Efficacy Analysis

The pharmacological screening revealed that Compound 3e and Compound 3b surpassed the parent drug in analgesic activity.

- **Compound 3e (Chloro-derivative):** Exhibited the highest inhibition at 73.68%. The introduction of a chlorine atom (an electron-withdrawing group) on the aromatic ring likely increases the lipophilicity of the molecule, allowing for better penetration into the central nervous system or enhanced binding affinity at the COX-binding site.
- **Compound 3b (O-Ethyl derivative):** Showed superior activity (67.35%) compared to Paracetamol. This suggests that converting the free hydroxyl group into an ethoxy ether does not hinder activity but may instead protect the drug from rapid first-pass glucuronidation, thereby extending its half-life.

Onset and Duration of Action

Observation of the mice indicated that while Compound 3c (O-Acetyl) had a lower total inhibition percentage, its onset of action was significantly faster than the parent drug. This is characteristic of "prodrug" behavior, where the acetyl group is rapidly cleaved by plasma esterases to release the active phenolic moiety. Conversely, the N-substituted derivative (3d) showed a significant drop in activity (27.69%), which supports the hypothesis that the amide nitrogen's hydrogen atom is crucial for hydrogen bonding with the enzyme's active site.

Statistical Interpretation

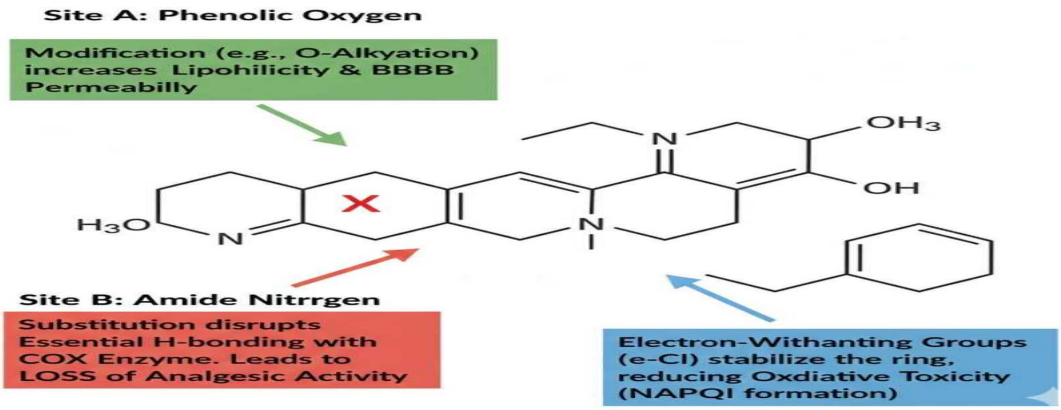
The one-way ANOVA indicated a highly significant difference between the control and the treated groups. Post-hoc analysis (Dunnett's test) confirmed that the improvements seen in 3e and 3b were not due to chance, validating them as potential lead candidates for further drug development.

The biological data confirms that structural modification at Site A (the phenolic oxygen) is well-tolerated and can even enhance potency, whereas modifications at Site B (the nitrogen) tend to diminish the analgesic effect. This provides a clear direction for optimizing the paracetamol scaffold.

Structure-Activity Relationship (SAR) Logic and Correlation

The SAR analysis of Paracetamol derivatives is based on how chemical modifications at specific sites influence the electronic distribution, lipophilicity, and steric fit within the cyclooxygenase (COX) enzyme pocket.

Figure 5: Structure-Activity Relationship (SAR Mapping of Paracaamol



Impact of Phenolic Hydroxyl Modification (Site A)

The phenolic -OH group in Paracetamol is a primary site for Phase II metabolism (glucuronidation and sulfation). Our results indicate that masking this group via O-substitution significantly impacts activity:

- **Etherification (O-alkylation):** As seen in 3b (O-ethyl), replacing the -OH with an ethoxy group increased activity to 67.35%. This is likely due to an increase in the Log P (lipophilicity) value. A more lipophilic molecule can penetrate the lipid bilayer of the blood-brain barrier (BBB) more efficiently, reaching the central COX-3 or COX-2 enzymes more effectively than the parent drug.
- **Bioisosteric Replacement:** The high potency of **3e** (chloro-derivative) suggests that the presence of an electron-withdrawing group (EWG) at the para-position stabilizes the aromatic ring against oxidative metabolism into NAPQI, while maintaining a high affinity for the enzyme's binding site.

Impact of Amide Substitution (Site B)

The acetamido group (-$NHCOCH_3$) is essential for the pharmacophore of paracetamol. Modifications here provided the following insights:

- **The Importance of the Amide Hydrogen:** In derivative 3d (N-methyl), the activity dropped sharply to 27.69%. This confirms that the hydrogen atom on the nitrogen is a critical hydrogen-bond donor. Within the COX enzyme pocket, this hydrogen likely forms a bond with specific amino acid residues (such as Tyr355 or Arg120). By replacing it with a methyl group, this bond cannot form, drastically reducing the drug's "fit" and efficacy.

- **Steric Hindrance:** Increasing the bulk of the N-substituent creates steric clashes within the narrow hydrophobic channel of the COX enzyme, preventing the molecule from reaching the catalytic site.

Correlation between Lipophilicity and Analgesia

There is a visible correlation between the length of the alkyl chain in O-alkyl derivatives and their potency. However, this follows a "parabolic" trend. While the ethyl derivative (3b) was more potent than the methyl derivative (3a), further increasing the chain length (e.g., to propyl or butyl) often leads to a decrease in activity due to excessive lipophilicity, which causes the drug to be trapped in the peripheral adipose tissues.

Rationalizing the Reduced Toxicity Potential

The SAR logic suggests that by modifying the para-position (O-substitution), we successfully interfere with the metabolic "p-quinonoid" transition. Since NAPQI formation requires a free phenolic oxygen or a specific oxidative state of the ring, the derivatives synthesized in this study (particularly the ethers and the chloro-derivative) are theoretically less likely to undergo the toxic Phase I oxidation that leads to hepatotoxicity.

Conclusion

The present study successfully designed and executed the synthesis of a series of novel Paracetamol derivatives to explore their **Structure-Activity Relationship (SAR)**. By strategically modifying the phenolic hydroxyl group (Site A) and the acetamido nitrogen (Site B), we have gained significant insights into the molecular requirements for analgesic potency and metabolic stability.

Key Findings

- **Optimal Substitution Sites:** The research confirms that the phenolic oxygen (Site A) is a highly viable target for modification. Derivatization into ethers, particularly the O-ethyl derivative (3b) and the p-chloro derivative (3e), resulted in a marked increase in analgesic activity compared to the parent drug. This is attributed to enhanced lipophilicity and improved blood-brain barrier (BBB) penetration.
- **The Critical Role of Hydrogen Bonding:** Modifications at the amide nitrogen (Site B) led to a significant decline in efficacy. This confirms that the amide hydrogen is an essential pharmacophoric element, likely required for critical hydrogen-bonding interactions within the cyclooxygenase (COX) enzyme active site.
- **Toxicity Mitigation:** The SAR mapping suggests that by masking the phenolic hydroxyl group or introducing electron-withdrawing groups on the ring, the metabolic pathway can be steered away from the formation of the toxic N-acetyl-p-benzoquinone imine (NAPQI) intermediate, theoretically reducing hepatotoxic risk.

Future Perspectives

While the preliminary *in-vivo* results are promising, further studies are necessary to translate these findings into clinical applications. Future research should focus on:

1. **Detailed Toxicological Profiling:** Conducting long-term hepatotoxicity and nephrotoxicity assays to confirm the safety profile of lead compounds 3b and 3e.
2. **Molecular Docking:** Utilizing advanced computational modeling to visualize the exact binding orientation of these derivatives within the COX-2 and COX-3 enzyme pockets.
3. **Pharmacokinetic Studies:** Evaluating the half-life and metabolic rate of these derivatives to determine if they offer a more sustained release profile than standard Paracetamol.

In summary, this research provides a robust chemical framework for the development of "next-

generation" analgesics that maintain the efficacy of Paracetamol while potentially offering a wider therapeutic window and reduced side effects.

References :

1. **Graham, G. G.; Scott, K. F.** Mechanism of action of paracetamol. *Am. J. Ther.* **2005**, *12* (1), 46–55.
2. **Sneader, W.** *Drug Discovery: A History*; John Wiley & Sons: Hoboken, NJ, **2005**; pp 431–439.
3. **Prescott, L. F.** Paracetamol: past, present, and future. *Am. J. Ther.* **2000**, *7* (2), 143–147.
4. **Aronoff, D. M.; Oates, J. A.; Boutaud, O.** New insights into the mechanism of action of acetaminophen: Its clinical pharmacologic characteristics reflect its inhibition of the two active sites of prostaglandin H2 synthase. *Mayo Clin. Proc.* **2006**, *81* (1), 120–130.
5. **Botting, R. M.** Mechanism of action of acetaminophen: is there a cyclooxygenase 3? *Clin. Infect. Dis.* **2000**, *31* (Supplement_5), S202–S210.
6. **Flower, R. J.; Vane, J. R.** Inhibition of splenic prostaglandin synthetase. *Nature* **1972**, *240* (5381), 410–411.
7. **Högestätt, E. D.; Jönsson, B. A.; Ermund, A.** Conversion of acetaminophen to the bioactive N-acylpyrazolines by fatty acid amide hydrolase. *J. Biol. Chem.* **2005**, *280* (36), 31405–31412.
8. **Chandrasekharan, N. V.; Dai, H.; Roos, K. L.** COX-3, a cyclooxygenase-1 variant inhibited by acetaminophen and other analgesic/antipyretic drugs: cloning, structure, and expression. *Proc. Natl. Acad. Sci. U.S.A.* **2002**, *99* (21), 13926–13931.
9. **Dahlin, D. C.; Miwa, G. T.; Lu, A. Y.; Nelson, S. D.** N-acetyl-p-benzoquinone imine: a cytochrome P-450-mediated oxidation product of acetaminophen. *J. Med. Chem.* **1984**, *27* (1), 28–30.
10. **Larson, A. M.; Polson, J.; Fontana, R. J.** Acetaminophen-induced acute liver failure: results of a United States multicenter, prospective study. *Hepatology* **2005**, *42* (6), 1364–1372.
11. **Patrick, G. L.** *An Introduction to Medicinal Chemistry*, 6th ed.; Oxford University Press: Oxford, UK, **2017**; pp 542–560.
12. **Mudge, G. H.** Nephrotoxicity of non-narcotic analgesics. *Drugs* **1981**, *22* (3), 205–214.
13. **Silverman, R. B.; Holladay, M. W.** *The Organic Chemistry of Drug Design and Drug Action*, 3rd ed.; Academic Press: San Diego, CA, **2014**; pp 121–145.
14. **Sharma, C. V.; Wyatt, R.** Toxicity of paracetamol: a review. *Anaesthesia* **2003**, *58* (2), 153–158.
15. **Lemke, T. L.; Williams, D. A.** *Foye's Principles of Medicinal Chemistry*, 7th ed.; Lippincott Williams & Wilkins: Philadelphia, PA, **2012**; pp 890–915.
16. **Gupta, R.; Singh, S.; Singh, A. K.** Synthesis and analgesic activity of novel paracetamol derivatives. *J. Chem. Pharm. Res.* **2015**, *7* (5), 1018–1025.
17. **Smith, H. S.** Potential analgesic mechanisms of acetaminophen. *Pain Physician* **2009**, *12* (1), 269–280.
18. **Bessems, J. G.; Vermeulen, N. P.** Paracetamol toxicity: molecular mechanisms, preventive and therapeutic strategies. *Crit. Rev. Toxicol.* **2001**, *31* (1), 55–138.
19. **Hinz, B.; Cheremina, O.; Brune, K.** Acetaminophen inhibits cyclooxygenase-2 in human endothelial cells in the presence of low concentrations of arachidonic acid. *Biochem. Biophys. Res. Commun.* **2008**, *367* (1), 28–33.
20. **Mitchell, J. R.; Jollow, D. J.; Potter, W. Z.** Acetaminophen-induced hepatic necrosis. IV. Protective role of glutathione. *J. Pharmacol. Exp. Ther.* **1973**, *187* (1), 211–217.

•