RESEARCH ARTICLE

Pharmacokinetic and pharmacodynamic profiling of compounds similar to paracetamol from zinc database: an *in silico* analysis [version 1; peer review: awaiting peer review]

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Abstract

Introduction: Paracetamol is the most used drug for the management of pain and as an antipyretic through its mechanism of action on Cox 1,2 and 3 receptors. Paracetamol is a lipid-soluble molecule that can pass through the Blood Brain Barrier. Paracetamol has been formulated differently to ensure the optimal onset and duration of action as both analgesic and as antipyretic. Paracetamol overdose is associated with major side effects such as liver damage through its metabolite N-acetyl-p-benzoquinone Imine.
Methods: This study generated zinc compounds that are similar in structure to Paracetamol through Ligand-based virtual screening. Molecular docking of these compounds to Cox 1, 2, and 3 receptors followed through Structure-based virtual screening. Compounds with better docking scores to these receptors were analyzed for pharmacokinetics and toxicity profiles.
Results: ZINC01714506; 0.986; ZINC01714507; 0.986; and ZINC00394165; 0.987 showed the highest docking scores to cox 3 receptor with probability scores of -6.7kcal/mol, -6.4 and -6.2 kcal/ mol as compared to Paracetamol with -5.3kcal/mol. ZINC01714507; 0.986; ZINC01714506; 0.986; and ZINC00394165; 0.987; showed higher docking scores to Cox 2 with docking scores of -8.3kcal.mol, -8.1kcal/mole and -8.0 kcal/mol compared to paracetamol with -6.6kcal/mol. ZINC00394165; 0.987; ZINC00406627; 0.980; and ZINC01714506; 0.986; showed highest docking scores to Cox-1 than paracetamol with scores of -7.7kcal/mol, -7.6 and-7.6kcal/mol. ZINC01714506; 0.986 was predicted the safest with oral LD50 of 2000mg/kg as compared to paracetamol's 338mg/kg. ZINC00294715; 0.980, ZINC01747085; 0.985, ZINC00394165; 0.987, ZINC00406627; 0.980, ZINC01557001; 0.987 and ZINC19281575; 0.992 were predicted hepatoactive. ZINC00294715; 0.980; ZINC01557001; 0.987; and ZINC19281575; 0.992; lack Blood Brain Barrier permeation. All compounds showed high GIT absorption and all conform to Lipinski's rule of five.

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Conclusion: ZINC01557001; 0.987; ZINC01714506; 0.986; ZINC34120167; 0.994; ZINC00394165; 0.987, ZINC01714507; 0.986; and ZINC01747085; 0.985; are promising in drug discovery for new analgesic and antipyretic drugs, based on better docking scores and better oral LD50

Keywords
Cyclooxygenase, molecular docking, paracetamol, pharmacokinetics, toxicity

This article is included in the Cheminformatics gateway.

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Introduction

Globally, chronic pain affects about 1.9 billion people with the most prominent pain being tension type headaches (Fayaz *et al.*, 2016). In UK, 13%-50% of adults suffer from chronic pain (Mills *et al.*, 2019). In sub-Saharan Africa Prevalence of Pain in seropositive patients is 59-89% (Mills *et al.*, 2019) in Kenya, Uganda, and South Africa. 87.5% of cancer patients in South Africa and Uganda documented cancer-related pain (Wang *et al.*, 2019). In Kenya, studies have shown that patients often pass on due to pain-related conditions (Nchako *et al.*, 2018). Pain assessment in Paediatric patients is negligible and there is limited data supporting this (Rothemeyer & Enslin, 2016) in Sub-Saharan Africa.

Most outpatient cases suffer from chronic pain which is of more than one type of pain (Buhck *et al.*, 2022) and the cost of pain management exceeds greatly the costs from cancer, diabetes and cancer management. 67% of patients with chronic pain suffer from comorbid maniac disorder (Annagür *et al.*, 2014). Different types of pain exist and they include.

Neuropathic pain that includes Diabetic neuropathy pain, post-herpetic neuralgia and central pain associated with CVA, Nociceptive pain associated with injuries to the tissues and include bruises, burns or sprains, Inflammatory pain associated with RA or infection Psychogenic pain such as headaches or abdominal pain and Mechanical pain associated with metastatic malignancies.

Most used drug for pain and fever management. Both over-the-counter and prescription is Paracetamol (Freo *et al.*, 2021). Paracetamol's action involves both antipyretic and analgesic. Paracetamol has very little anti-inflammatory effects as compared to NSAIDs such as ibuprofen. Guidelines have so far recommended Paracetamol as a drug of choice in pain management (Freo *et al.*, 2021). Paracetamol has good efficacy since its formulations are broad and range from rapid dissolving formulations to suppositories. Paracetamol has opioid-sparing effects and this is helpful in mitigating opioid-induced side effects.

Acetaminophen binds to Cox 3, Cox 2, and Cox 1 enzymes leading to the inhibition of the synthesis of prostaglandins such as prostaglandin E (Ayoub, 2021). Acetaminophen blocks the peripheral generation of the pain impulse and by blocking prostaglandin production in the CNS. Paracetamol also exerts its effect by affecting endocannabinoid, serotonergic, inhibition of voltage-gated calcium channels, and inhibition of T-type calcium channels (Przybyła *et al.*, 2020).

Despite the admirable effects of paracetamol, its side effects when overdosed are detrimental. Paracetamols have long been used in alleviating pain in pregnancy however, studies have linked delay in the neurological development of infants to the use of paracetamol during pregnancy (Bauer *et al.*, 2021). Other effects reported are reproductive, urology system as well as genital disorders. Pregnant mothers are required to take paracetamol cautiously and they should alert the pharmacist or their physician.

Acetaminophen metabolism by the liver to generate NAPQI that causes acetylation and formation of covalent bonds with liver proteins causing liver damage, which can lead to hepatic failure (Mazaleuskaya *et al.*, 2015).

Acetaminophen (N-acetyl-p-aminophenol, APAP) is metabolized in the liver to its prodrug phenacetin through O-dealkylation which is hepatotoxic and carcinogenic. Acetaminophen is as well metabolized in the body to glucuronide conjugate as well as sulphate conjugates in the body indicated as PAP-gluc and APAP-sulphate respectively. In overdose, about 5% of acetaminophen is oxidized to NAPQI which binds covalently to sulfhydryl groups in the liver causing liver necrosis and eventually hepatotoxicity (PharmGKB, n.d.) (Figure 1).

This study determined similar zinc compounds to Paracetamol. The compounds were docked to Cox 1, 2, and 3 enzymes, and the docking scores were compared to that of Paracetamol. Compounds with better docking scores than paracetamol were highlighted and pharmacokinetics and toxicity profiles were analyzed.

Objectives

I. To identify zinc compounds similar to paracetamol.

II. To identify compounds with better docking scores than paracetamol.

III. To identify the pharmacokinetics properties of compounds with better docking scores than paracetamol.

IV. To identify toxicity profiles of the compounds with better docking scores than paracetamol

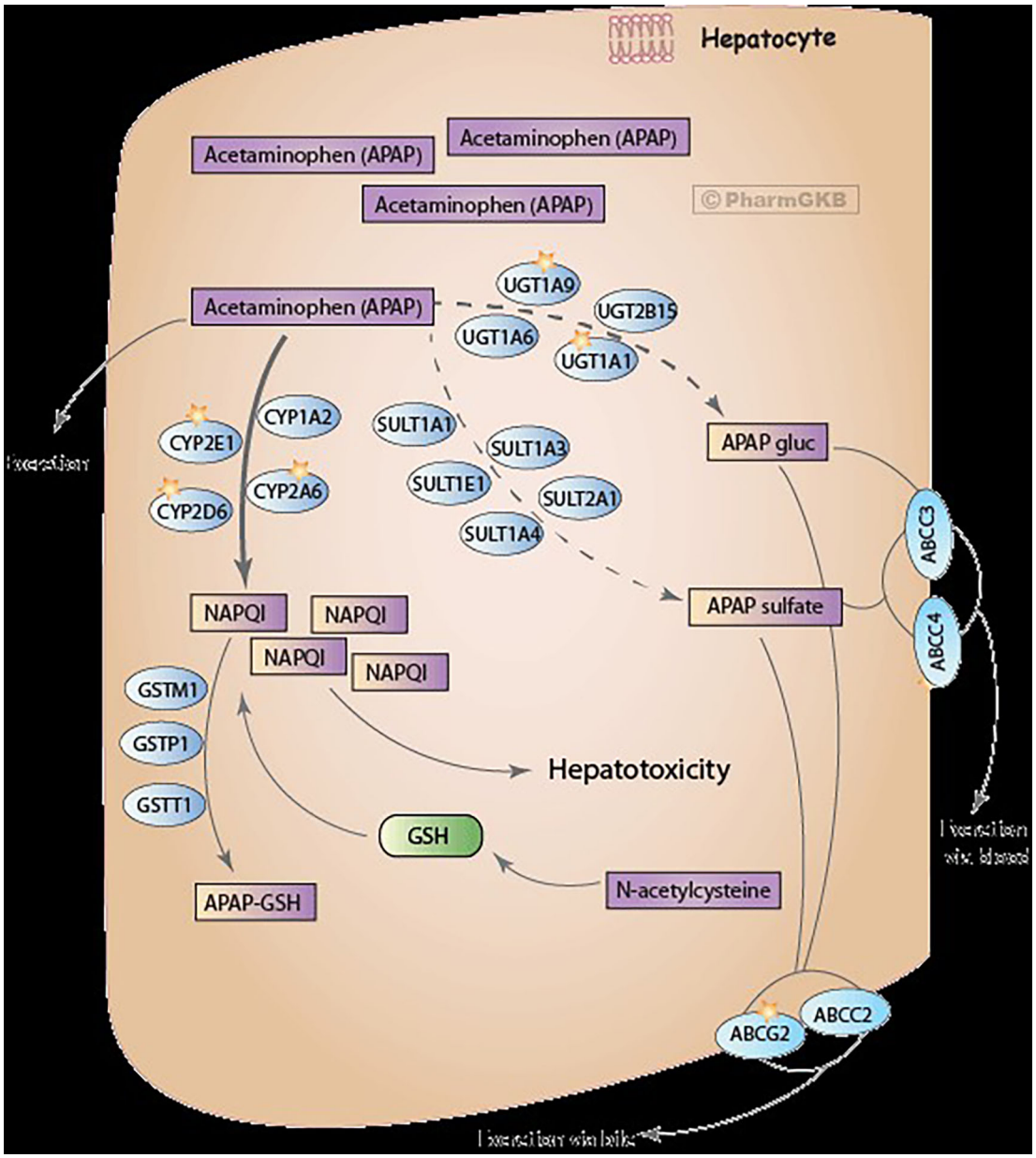

Figure 1. Diagrammatic mechanism of Acetaminophen induced hepatotoxicity (https://www.pharmgkb.org/pathway/PA166117881/pathway). *Note:* Has been reproduced with permission from, PharmGKB summary: pathways of acetaminophen metabolism at the therapeutic versus toxic doses by Mazaleuskaya *et al.* (2015).

Methods

Paracetamol was searched through PubChem (RRID:SCR_004284) and canonical smiles were copied and pasted to SwissSimilarity (*http://www.swisssimilarity.ch/index.php*). Paracetamol was used as a query to generate compounds with similar structures using the Zinc database. Similar compounds were generated using Ligand-based Virtual screening. The generated compounds that had a similarity score to Paracetamol above 80% were randomly selected and 20 compounds were sampled in total.

Cyclooxygenase 1, 2, and 3 were downloaded from Protein Data Bank (RRID:SCR_012820) using unique PDB codes that are 5F19,6Y3C and 1EJF. Preparations for these receptors were done using Chimera (RRID: SCR_004097) where all non-standard residues were eliminated. Ligands were prepared for docking first by auto-optimization to make the ligands be at the minimum energy using Avogadro (RRID: SCR_011958) (Eberhardt *et al.*, 2021). The optimized compounds were further minimized by the addition of hydrogen and charges using Chimera (RRID:SCR_004097).

Molecular docking of compounds to cyclooxygenase 1, 2 and 3 was done using Chimera (RRID: SCR_004097) and Autodock vina (RRID: SCR_011958). Compounds that had better docking scores to Paracetamol were further analyzed through Biovia Discovery studio to determine the interactions between the binding sites of these receptors with the compound's pharmacophore.

Pharmacokinetics profiles of the promising compounds were analyzed using SwissADME online tool (*http://www.swissadme.ch/*). Effects of the compounds on CYP enzymes were analyzed. The ability of these compounds to pass through Blood Brain Barrier was determined. Gastrointestinal absorption of compounds and their conformation with Lipinski rule of five was further analyzed.

Toxicity profiles of the compounds were analyzed using ProTox II (RRID:SCR_018506 webserver. Oral toxicities were determined using LD50. Organ toxicities were analyzed such as hepatoxicity. Immunotoxicity, carcinogenicity, and Tox 21 stress receptors were further analyzed.

Results

(Faith *et al.*, 2023)

(https://doi.org/10.7910/DVN/SO4CEH)

Paracetamol and Zinc compounds docking scores to Cox 3, 2, and 1

ZINC00294715; 0.980; ZINC00394165; 0.987, ZINC00406627; 0.980, ZINC01557001; 0.987, ZINC01714506; 0.986, ZINC01714507; 0.986, ZINC01747085; 0.985; ZINC19281575; 0.992, ZINC34120167; 0.994 and ZINC71451975; 0.975 showed higher binding to Cox 3 than paracetamol. These compounds were further analyzed for their toxicities as well as pharmacokinetic profiles (Table 1).

Table 1. Paracetamol and Zinc compounds docking scores to Cox 3, 2 and 1.

Serial no.	Similarity scores	compound	Binding to cox3 (1EJF)	Binding to cox2 (5F19)	Binding to cox1 (6Y3C)
1.		Paracetamol	-5.3	-6.6	-6.2
2.	98.00%	ZINC00294715; 0.980;	-5.5	-6.8	-6.1*
3.	98.70%	ZINC00394165; 0.987;	-6.2	-8	-7.7
4.	98.00%	ZINC00406627; 0.980;	-5.9	-6.6	-7.6
5.	99.40%	ZINC00874201; 0.994;	-5.2	-6.5	-4.9*
6.	98.70%	ZINC01557001; 0.987;	-5.7	-6.4	-6.5
7.	98.60%	ZINC01714506; 0.986;	-6.7	-8.1	-7.6
8.	98.60%	ZINC01714507; 0.986;	-6.4	-8.3	-6.8
9.	98.50%	ZINC01747085; 0.985;	-5.9	-7.3	-6.6
10.	98.20%	ZINC02568449; 0.982;	-5.2	-7.1	-6.4
11.	97.90%	ZINC04522243; 0.979;	-5.1	-6.7	-5.9
12.	98.60%	ZINC14982950; 0.986;	-5.2	-6.3	-6.4
13.	98.50%	ZINC18274777; 0.985;	-5.2	-6.9	-6.2
14.	97.50%	ZINC19093853; 0.975;	-5.3	-6.8	-6.6
15.	99.20%	ZINC19281575; 0.992;	-5.4	-6.6	-6.3
16.	98.10%	ZINC19898944; 0.981;	-5.0	-6.4	-6.5
17.	99.40%	ZINC34120167; 0.994;	-5.5	-6.3	-6.6
18.	99.10%	ZINC39650276; 0.991;	-5.1	-5	-5.5*
19.	99.40%	ZINC41699382; 0.994;	-5.1	-6.3	-5.6*
20.	98.20%	ZINC41723295; 0.982;	-5.2	-7.1	-6.8
21.	97.50%	ZINC71451975; 0.975;	-5.4	-6.3	-6.3

*Compounds with lower docking scores to Cox 1 than paracetamol.

ZINC00874201; 0.994; ZINC01557001; 0.987; ZINC14982950; 0.986; ZINC19898944; 0.981; ZINC34120167; 0.994; ZINC39650276; 0.991; ZINC41699382; 0.994; and ZINC71451975; 0.975; showed lower docking scores to Cox II than Paracetamol.

ZINC00294715; 0.980; has a higher binding score to Cox 3 and Cox 2 than paracetamol. The zinc compound also showed a lower docking score to Cox 1 therefore, its pharmacokinetic properties were analyzed by using SwissADME online tool (Table 1).

Paracetamol and ZINC00294715; 0.980; showed high GIT absorption and lack of Cytochrome inhibition. They lack inhibition of CYP1A2, CYP3A4, CYP2C9, and CYP2C19. They are not substrates to P-glycoprotein. Paracetamol showed BBB permeation while ZINC00294715; 0.980; showed a lack of BBB permeation. They both showed no violation of Lipinski's rule of five.

Toxicity profiles

Oral toxicity

ZINC01714506; 0.986 had the highest oral LD50 of 2000 mg/kg as compared to Paracetamol which had an oral LD50 of 338 mg/kg. ZINC01557001; 0.987; and ZINC34120167; 0.994; had similar oral LD50 of 1100 mg/kg. None of the compounds had lower LD50 than Paracetamol and these compounds, are, therefore, safer than paracetamol when taken orally (Table 2).

Table 2. Oral toxicity of Paracetamol and Zinc compounds.

Compound name	Oral LD50 (mg/kg)	Toxicity class	% Prediction accuracy
Paracetamol	338	IV	100
ZINC00294715; 0.980;	690	IV	69.26
ZINC01747085; 0.985;	1030	IV	100
ZINC00394165; 0.987;	338	IV	72.9
ZINC00406627; 0.980;	565	IV	69.26
ZINC01557001; 0.987;	1100	IV	70.97
ZINC01714506; 0.986;	2000	IV	72.9
ZINC01714507; 0.986;	500	IV	70.97
ZINC19281575; 0.992;	700	IV	69.26
ZINC34120167; 0.994;	1100	IV	70.97
ZINC71451975; 0.975;	600	IV	69.26

Organ toxicity

ZINC01714506; 0.986, ZINC01714507; 0.986; ZINC34120167; 0.994; and ZINC71451975; 0.975; were considered inactive in causing hepatotoxicity as compared to Paracetamol that was predicted Hepatoactive. None of the compounds were predicted immunoactive (Table 3).

Table 3. Organ toxicity of Paracetamol and Zinc compounds.

Compound	Hepatotoxicity	Probability	Immunotoxicity	Probability
Paracetamol	A	0.74	I	0.99
ZINC00294715; 0.980;	A	0.71	I	0.99
ZINC01747085; 0.985;	A	0.65	I	0.98
ZINC00394165; 0.987;	A	0.68	I	0.89
ZINC00406627; 0.980;	A	0.65	I	0.87
ZINC01557001; 0.987;	A	0.62	I	0.99

Table 3. *Continued*

Compound	Hepatotoxicity	Probability	Immunotoxicity	Probability
ZINC01714506; 0.986;	I	0.56	I	0.87
ZINC01714507; 0.986;	I	0.6	I	0.98
ZINC19281575; 0.992;	A	0.58	I	0.99
ZINC34120167; 0.994;	I	0.5	I	0.85
ZINC71451975; 0.975;	I	0.83	I	0.87

Key: I=Inactive, A=Active.

Carcinogenic, mutagenic, and cytogenic toxicity (Table 4)

Table 4. Carcinogenic, Mutagenic, and cytogenic toxicity profiles of Paracetamol and zinc compounds.

Compound	carc	P	Mut	P	cyt	P
Paracetamol	I	0.51	I	0.9	I	0.82
ZINC00294715; 0.980;	I	0.62	I	0.91	I	0.81
ZINC01747085; 0.985;	A	0.52	I	0.57	I	0.81
ZINC00394165; 0.987;	A	0.54	A	0.98	I	0.8
ZINC00406627; 0.980;	A	0.53	A	0.79	I	0.8
ZINC01557001; 0.987;	I	0.51	I	0.71	I	0.67
ZINC01714506; 0.986;	I	0.61	A	0.62	I	0.72
ZINC01714507; 0.986;	I	0.6	A	0.61	I	0.73
ZINC19281575; 0.992;	I	0.58	I	0.68	I	0.68
ZINC34120167; 0.994;	I	0.58	I	0.59	I	0.54
ZINC71451975; 0.975;	I	0.61	A	0.59	I	0.65

Key: Carc=Carcinogenicity, Mut=Mutagenicity, Cyt=Cytotoxicity, I=Inactive, A=Active.

Tox 21 toxicity (Table 5)

Table 5. Tox 21 Nuclear receptor signaling pathway toxicity prediction.

Compounds	Ahr	P
Paracetamol	I	0.9
ZINC01747085; 0.985;	A	0.55
ZINC00394165; 0.987;	A	0.72
ZINC00406627; 0.980;	A	0.81
ZINC01557001; 0.987;	A	0.59
ZINC71451975; 0.975;	A	0.56
	ER	**P**
Paracetamol	I	0.94
ZINC00394165; 0.987;	A	0.57
ZINC00406627; 0.980;	A	0.67
	MMP	**P**
Paracetamol	I	0.96
ZINC00406627; 0.980;	A	0.74
ZINC00394165; 0.987;	A	0.67

Key: A=Active, I=inactive, AhR=Aryl hydrocarbon Receptor=probability, ER= Estrogen receptor, MMP= Mitochondrial Membrane Potential.

Pharmacokinetic properties (Table 6)

Table 6. Pharmacokinetic properties.

Compound	BBB Penetration
Paracetamol	Yes
ZINC00294715; 0.980;	No
ZINC01557001; 0.987;	No
ZINC19281575; 0.992;	No
Compound	**CYP1A2 inhibition**
Paracetamol	No
ZINC00394165; 0.987;	Yes
ZINC01714506; 0.986;	Yes
ZINC01714507; 0.986;	Yes

Post-Docking analysis

Binding sites for Paracetamol and its zinc compounds

Paracetamol's pharmacophore binds at Cox 1 receptor by van der Waals forces as well as by conventional hydrogen bonding. Additional bonding in cox-2 is involved which is amide pi stacking as well as pi bonds with alkyl groups. ZINC01557001; 0.987; pharmacophore bonded with Cox-1 binding sites using van der Waals forces, donor–donor bonds as well as pi-alkyl bonding. ZINC01557001; 0.987; pharmacophore bonded with Cox 2 bindings sites using additional conventional hydrogen bonds as well as pi-sigma bonds. ZINC34120167; 0.994 pharmacophore bonded with Cox-1 using carbon–hydrogen bonding, pi-alkyl bonding, and van der Waals forces. ZINC34120167; 0.994 bonding in Cox-2 involved additional conventional hydrogen bonds (Figure 2).

Discussion

Paracetamol has been hypothesized to inhibit the production of prostaglandin E_2 primarily in the brain and has weaker effects on tissues at the periphery of the body (Ayoub & Flower, 2019). Prostaglandin E_2 is involved in the generation of hypothermia which is often more dependent on the Cox-2 enzyme than Cox-1. Paracetamol-induced hypothermia is, therefore, majorly due to the inhibition of Cox-2. Cox-3 enzyme is a variant of Cox-1 produced through modifications on mRNA sequence (Ayoub & Flower, 2019).

The analgesic action of Paracetamol has been linked to the inhibition of central Cox due to its lipid solubility as well as unionized at the physiological state and prevention of the production of peripheral prostaglandins (Ayoub, 2021). Paracetamol has also been researched to inhibit connectivity of brain regions such as grey matter and this is mediated by its metabolite, *N*-(4-hydroxyphenyl)-5*Z*,8*Z*,11*Z*,14*Z*-eicosatetraenamide (Barrière *et al.*, 2020).

ZINC01714506; 0.986; was predicted to have the highest binding score to Cox-3 as compared to Paracetamol. ZINC01714507; 0.986 showed the highest docking score -8.3 kj/mol for cox 2 receptor as compared to paracetamol.

Paracetamol and ZINC00394165; 0.987 showed LD50 of 338 mg/kg making these compounds to be most lethal than the rest of the compounds. ZINC01714507; 0.986 was predicted to have LD50 of 500 mg/kg, ZINC00406627; 0.980 showed LD50 of 565 mg/kg, ZINC71451975; 0.975 was predicted to having LD50 of 600 mg/kg and ZINC19281575; 0.992 showed LD50 of 700 mg/kg. ZINC01747085; 0.985 was predicted to have LD50 of 1030 mg/kg. ZINC01557001; 0.987, and ZINC34120167; 0.994 showed LD50 of 1100 mg/kg. ZINC01714506; 0.986 showed LD50 of 2000 mg/kg and therefore, was considered the safest than the rest of the zinc compounds. ZINC01714506; 0.986 had the highest Oral LD50 of 2000 mg/kg as compared to Paracetamol oral LD50 of 338 mg/kg. ZINC01557001; 0.987; and ZINC34120167; 0.994; had similar oral LD50 of 1100 mg/kg and therefore, they are relatively safe compounds.

Paracetamol and its zinc compounds ZINC00294715; 0.980, ZINC01747085; 0.985, ZINC00394165; 0.987, ZINC00406627; 0.980, ZINC01557001; 0.987 and ZINC19281575; 0.992 were predicted to be active in causing hepatotoxicity with the probability of 0.74, 0.71, 0.65, 0.68, 0.65, 0.62 and 0.58 respectively. Paracetamol hepatotoxicity profile has been studied widely and the results from this study conform to the studies done by other researchers (Rotundo & Pyrsopoulos, 2020).

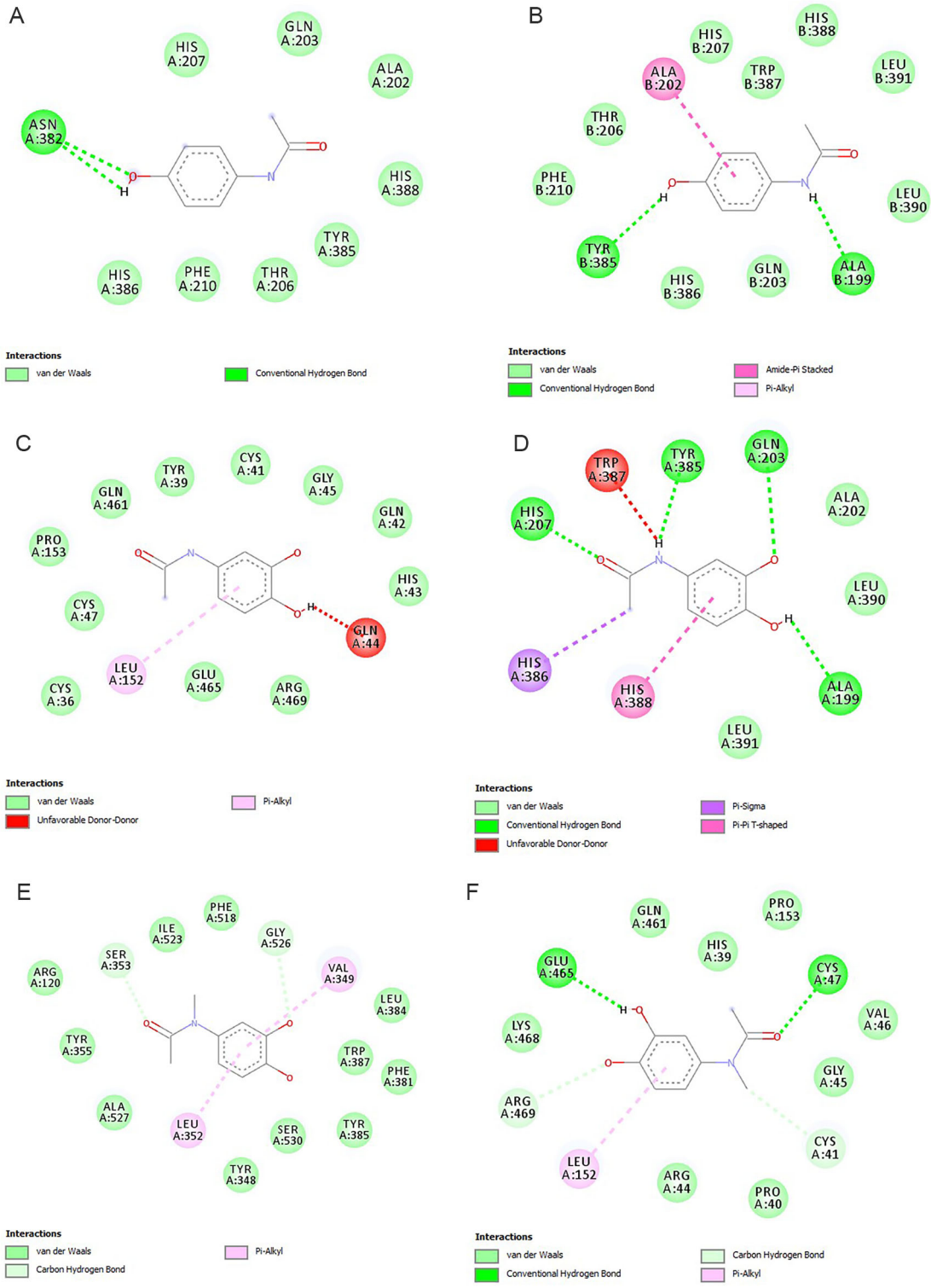

Figure 2. Paracetamol and zinc compounds 2D-interactions with receptors. *Note:* Drawn using BIOVIA discovery studio visualizer 21.1.0.0.

Three zinc compounds were predicted carcinogenic. These compounds are ZINC01747085; 0.985; ZINC00394165; 0.987; and ZINC00406627; 0.980; with probability scores of 0.52, 0.54, and 0.53 respectively. ZINC00394165; 0.987; ZINC00406627; 0.980; ZINC01714506; 0.986; and ZINC01714507; 0.986 were predicted active in causing mutagenicity with probability scores of 0.98, 0.79, 0.62 and 0.61 respectively.

Aryl hydrocarbon receptor is associated with metabolism and in causing toxic effects through the metabolism of compounds such as xenobiotics, tryptophan-based compounds, microorganism derived compounds amongst other effects. Aryl hydrocarbon receptor mediates cell cycle processes in the cells, metabolism, and reproduction and mediates immune reactions. Ahr is also associated with skin regulation by regulating oxidative stress as well as toxins from the environment and other sources (Napolitano *et al.*, 2021). ZINC01747085; 0.985; ZINC00394165; 0.987; ZINC00406627; 0.980; ZINC01557001; 0.987; and ZINC71451975; 0.975; were predicted active for Ahr receptor with the probability scores of 0.84,0.55,0.72,0.81 and 0.59 respectively. Paracetamol was predicted inactive for the Ahr receptor. ZINC00394165; 0.987; and ZINC00406627; 0.980; were also predicted active for ER with probability scores of 0.57 and 0.67 respectively. ZINC00406627; 0.980; and ZINC00394165; 0.987; were predicted active for MMP with probability scores of 0.67 and 0.74 respectively which has an important role in oxidative stress and in acute Kidney injury (Su *et al.*, 2022).

ZINC00294715; 0.980; ZINC01557001; 0.987; and ZINC19281575; 0.992; were predicted to lack Blood Brain Barrier permeation as compared to paracetamol and therefore, their use as antipyretics could be limited without further chemical modifications to enhance lipid solubility. ZINC00394165; 0.987, ZINC01714506; 0.986; and ZINC01714507; 0.986 were predicted to inhibit CYP1A2 with ZINC01714507; 0.986 with capacity to inhibit CYP 2C9. All compounds were predicted to have high GIT absorption and all conformed to Lipinski's rule of five.

Conclusion

The aims of the study were achieved. Compounds with better docking scores to Cox 1, 2, and 3, pharmacokinetics as well as toxicity profiles were highlighted. 16 compounds showed higher docking scores to Cox 1 than paracetamol and therefore, they are promising in the development of new analgesic compounds. Nine out of 20 compounds had better docking scores to Cox -2 than paracetamol and therefore, they could be analyzed further as hypothermic compounds. ZINC01714506; 0.986; ZINC01714507; 0.986; and ZINC00394165; 0.987 showed the highest docking scores to cox 3 receptors with probability scores of -6.7kcal/mol, -6.4 and -6.2 kcal/mol. ZINC01714506; 0.986 was predicted to be the safest although it showed CYP1A2 inhibition compared to paracetamol and its zinc compounds.

In summary, the following compounds ZINC01557001; 0.987; ZINC01714506; 0.986; ZINC34120167; 0.994; ZINC00394165; 0.987, ZINC01714507; 0.986; and ZINC01747085; 0.985; are promising in drug discovery for new analgesic and antipyretic drugs, based on better docking scores and better oral LD50. Although these compounds are promising they have unwanted predicted activities such as ZINC01557001; 0.987; and ZINC01747085; 0.985 were, however, predicted hepatoactive. ZINC01747085; 0.985; was predicted carcinogenic. ZINC01714506; 0.986 was predicted mutagenic.

Recommendations

1. Quantitative structure-activity relationship of ZINC01557001; 0.987; ZINC01714506; 0.986; ZINC34120167; 0.994; ZINC00394165; 0.987, ZINC01714507; 0.986; and ZINC01747085; 0.985; should be done in order to modify these compounds for better aqueous and lipid solubility and improve on oral toxicities, and decrease side effects associated with Cox 1 as well as untoward effects such as carcinogenic and effects of Ahr receptor.

2. In silico studies of ZINC01557001; 0.987; ZINC01714506; 0.986; ZINC34120167; 0.994; ZINC00394165; 0.987, ZINC01714507; 0.986; and ZINC01747085; 0.985; are as well recommended.

Data availability

Harvard Dataverse: Underlying data for *In silico analysis of Paracetamol.* DOI: https://doi.org/10.7910/DVN/SO4CEH (Faith *et al.*, 2023).

This project contains the following underlying data:

- Post-docking analysis
- Docking scores of compounds
- ADME profiles of the compounds
- Toxicity profile of the compounds

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