MALAYSIAN JOURNAL OF SCIENCE
MJS
ISSN 1394-3065

Regular Issue

Malaysian Journal of Science 43(1): 86-112 (March 2024) https://mjs.um.edu.my

SYNTHESIS AND BIOLOGICAL ACTIVITIES OF ACETAMINOPHEN AND IBUPROFEN METAL COMPLEXES OR DERIVATIVES: A REVIEW

Azni Izwati Hamdan[1a], Dike Dandari Sukmana[2a] and Norsyafikah Asyilla Nordin[3a]*

Abstract: We reviewed scientific literature on the synthesis of acetaminophen and ibuprofen, as well as their derivatives and biological properties. The synthesis of acetaminophen involves the acetylation of 4-aminophenol and acetic anhydride, while ibuprofen is synthesised by reacting isobutyl benzene and acetic anhydride in four continuous reaction stages, which are Friedel-Crafts acylation, carbonyl reduction, chloride substitution, and Grignard reaction. To obtain their derivatives, modifications have been made either by complexing the main structure of the drug compound with metal elements or adding certain desired moieties, such as thiourea, amide, ammonium, halogen, silicon, and 1,3,4-oxadiazole. Ibuprofen and acetaminophen have been recognised as effective painkillers and anti-inflammatories. Recently, their derivatives have been implicated in a variety of biological effects. The biological activities of acetaminophen and ibuprofen derivatives have been reported to exhibit urease inhibition and inflammatory inhibition, as well as inhibit the proliferation of breast cancer cells MCF-7. Overall, this review article describes the synthesis of acetaminophen and ibuprofen derivatives, complete with their biological activities such as antimicrobial, antifungal, anti-inflammatory, urease inhibitors, and anticancer.

Keywords: *Acetaminophen, ibuprofen, biological activity, chemical modification, comparative study*

1. Introduction

Human and diseases are inseparable. It is not an exaggeration to say that the plagues that happened over centuries are actually the humans' fault (Kiriiri et al., 2020). On the bright side, due to these phenomena, researchers have identified several ailments and listed a large range of herbal and other treatments. For instance, anaesthetic was one of the first synthetic chemicals ever made. This led to the development of synthetic organic chemistry, which led to the growth of the pharmaceutical industry (Hill & Rang, 2013). Pharmaceutical chemists are employed by the sector to design pharmaceuticals, perform drug research, and oversee quality assurance procedures. Nevertheless, issues with the efficacy and toxicity of medicinal drugs have impeded their success in clinical use, leading to the introduction of molecular/chemical modification. There exists a range of chemical modifications that can enhance various biological properties, including stability, cellular uptake, and potency (Corey, 2007). Drug designing can alter the chemical structure of the established drugs and integrate the principle of organic compounds, producing a tailored drug (Hughes et al., 2011). This approach establishes new research avenues and also introduces a novel compound with demonstrable therapeutic effect (Akhondzadeh, 2016).

There are many reasons on why therapeutic effect is important to the human body. For example, inflammation is common as it is adaptive immune response to infection. If left unchecked for a certain time, it may result in neurodegenerative disease or cancer (Dinarello, 2010). Therefore, anti-inflammatory drug is required. On the other hand, antimicrobial resistance is rapidly increasing, making infections from Gram-positive and Gram-negative pathogens difficult to almost impossible to treat (Collignon et al., 2016). Unsurprisingly, inappropriate prescription and poor antimicrobial control have also contributed to massive resistance issues (Reygaert, 2018). Another therapeutic effect is antiproliferative, which is used to inhibit cell growth on cells, especially tumours. This is an alternative approach in finding safe, effective, and stable drug modifications to treat or prevent cancer (AlKhalil et al., 2020).

Acetaminophen is known to have a mild antimicrobial activity due to the absence of enzyme that contributes to the mechanism of pain alleviation in microorganisms (Verma et al., 2020). Meanwhile, ibuprofen has low anticancer effects against several cancer cell lines (He et al., 2021; Pedro-Hernández et al., 2017) and does not inhibit urease by itself (Seraj et al., 2021). It is necessary to make structural modifications to increase drug potency and selectivity (Guo, 2012). Therefore, this review article documents, discusses, and compares the biological activities of the derivatives or metal complexes of acetaminophen and ibuprofen with their parent drugs, which can help researchers identify chemical modification variables. It also provides the understanding of the current state of knowledge in this area and identifies potential future explorations by understanding the factors (ligands, type and position of halogen, etc.) that affect biological activity.

Authors information:
[a]Faculty of Pharmacy, Universiti Sultan Zainal Abidin, Besut Campus, 22200, Besut, Terengganu, MALAYSIA. E-mail: azni64@gmail.com[1]; dikedandari1996@gmail.com[2]; asyillanordin@unisza.edu.my[3]
*Corresponding Author: asyillanordin@unisza.edu.my

Received: January 1, 2023
Accepted: May 12, 2023
Published: March 31, 2024

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

2. Acetaminophen

Acetaminophen (Figure 1), which is also known by the name paracetamol, is the non-prescription analgesic and antipyretic medication that is purchased in the greatest quantity worldwide. It has attracted interest as the first line of pharmacological therapy because it is more promising in terms of its safety profile compared to other treatment alternatives. A diverse variety of acute and chronic, severe symptoms are treated with acetaminophen (Ennis et al., 2016; Roberts et al., 2016).

Unlike non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin and ibuprofen, it has no anti-inflammatory properties due to weak inhibition of cyclooxygenase (COX) enzyme in the peripheral tissues (Ohashi & Kohno, 2020). Acetaminophen does not bind to the active site of COX-1 or COX-2 enzyme, but it rather reduces the activity pathway of COX that inhibits the synthesis of prostaglandin in the central nervous system, making it a prominent analgesic and antipyretic agent (Gerriets et al., 2023). However, due to its availability, acetaminophen may lead to overdose, which can cause hepatotoxic (Bateman et al., 2014; Caparrotta et al., 2018; Ramachandran & Jaeschke, 2019). As it is eradicated through various metabolic pathways, acetaminophen is metabolised by several cytochrome P450 enzymes to the potentially toxic, chemically reactive metabolite N-acetyl-p-benzoquinone imine (NAPQI), and a small portion of it is excreted through urine as unchanged drug (Mian et al., 2020). NAPQI causes toxic metabolites as it is covalently bonded to protein, thus contributing to liver failure (Ozawa et al., 2019).

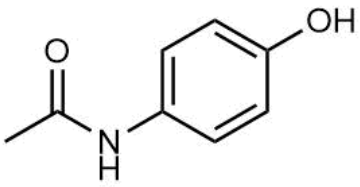
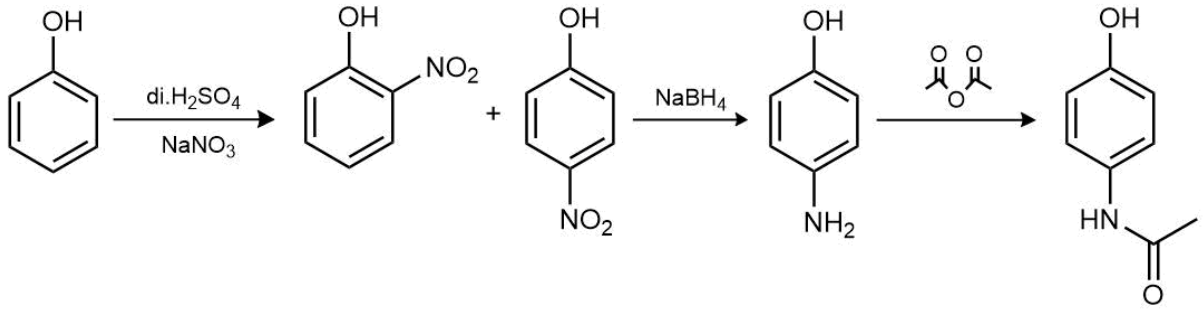


Figure 1. Structure of acetaminophen

Acetaminophen contains hydroxyl and amide functional groups. The incorporation of a hydroxyl group can make a molecule more lipophilic (Syahri et al., 2017), hence influencing its pharmacokinetic, pharmacodynamic, and toxicological profiles (Lobo, 2020).

Acetaminophen is synthesised in three stages, beginning with phenol with the addition of diluted sulphuric acid and sodium nitrate ($NaNO_3$), producing nitrophenol. Following that, sodium borohydride ($NaBH_4$) reduction is used to convert the nitro group on the para-substituted nitrophenol to an amine. Finally, acetic anhydride is reacted with the obtained para-aminophenol to produce acetaminophen via acetylation (Scheme 1) (Khosroshahi et al., 2016; Kingsley Ogemdi, 2019).



Scheme 1. Synthesis of acetaminophen

Acetaminophen with Metal Complexes

Metal complexes are important in drug design for coordination with metals (Amin et al., 2017), which are potent against cancer cells and can act as drug-resistant bacteria (Malik et al., 2018; Nandanwar & Kim, 2019). Metals seem to target a variety of different cellular processes, which results in the pleiotropic effect on bacterial cells (Turner, 2017). Complex metal (II) such as cobalt, nickel, copper, and zinc are potent against certain species of microorganisms, such as *Escherichia coli*, *Bacillus cereus*, and *Pseudomonas aeruginosa* (Damilola et al., 2019). These complex metals in the form of metal-based drugs possess modified pharmacological and toxicological potential. They form low molecular weight complexes which are more advantageous against numerous diseases (Rizzotto, 2012). There is a wide variety of modes of action for metal complexes, including ligand exchange or release, reactive oxygen species (ROS) production, coordination spheres, and redox activation, which can influence the kinetic and thermodynamic aspects of biological receptors (Malik et al., 2018; Zuegg et al., 2020). Metal complexes exert their effect by inhibition of cell membrane functions, arresting cell cycle, inhibiting enzymes, enhancing lipophilicity, etc. (Malik et al., 2018).

Antimicrobial Activity of Novel Metal Complexes of Piperaquine-Acetaminophen

Piperaquine (Figure 2) is a bisquinoline used in conjunction with dihydroartemisinin as a potential antimalarial agent (Assefa et al., 2021). It belongs to the 4-aminoquinoline group, a derivative of quinine (Ayipo et al., 2016), and is a highly lipophilic base that increases the oral bioavailability of drug when administered together with fat (Annerberg et al., 2011; Iseh et al., 2017). Although piperaquine derivatives are well-known for their antimalarial properties (Ma et al., 2019; Permala et al., 2017; Rasmussen et al., 2017), other derivatives also showed potential

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

in antibacterial (Ayipo et al., 2021) and antimicrobial studies (Ayipo et al., 2016).

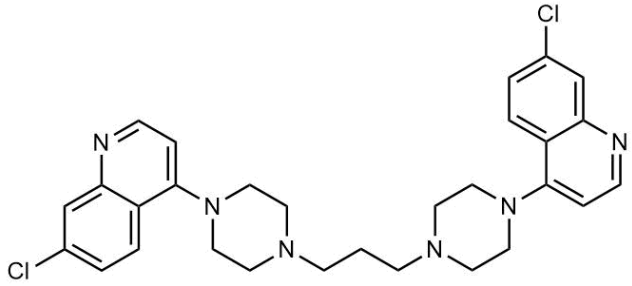


Figure 2. Structure of piperaquine

Although NSAIDs, like acetaminophen, have no antibiotic activity when used alone at therapeutic concentrations, they can enhance the inhibitory potential of antibiotics when co-administered with them. This joint administration can either impede bacterial growth or modify resistance mechanisms, resulting in more effective treatment (Singh et al., 2021). As metal complexes and piperaquine derivatives showed high potential in antimicrobial drugs, a metal-piperaquine-acetaminophen drug was investigated (Ayipo et al., 2016; Malik et al., 2018).

The procedure involved the combination of metal salt, piperaquine phosphate, and acetaminophen in a 1:1:1 mole ratio. The resulting mixed ligands were dissolved in a solution of 5% lactic acid and added to the previously prepared metal salt solutions in ethanol. 10% methanolic ammoniacal solution was added to maintain the pH of the mixture solution. The mixture was then refluxed for several hours and cooled in a refrigerator to facilitate the crystallisation of the metal. The resulting crystals were filtered, and the unwanted reactants and products were removed by washing them with diluted lactic acid and distilled water. The final products were then dried in a desiccator for several days. The same procedure was applied for all metal salts. The synthesised metal complexes piperaquine-acetaminophen (Figure 3) were evaluated for biological activity against *E. coli* and *S. aureus* (Ayipo et al., 2016).

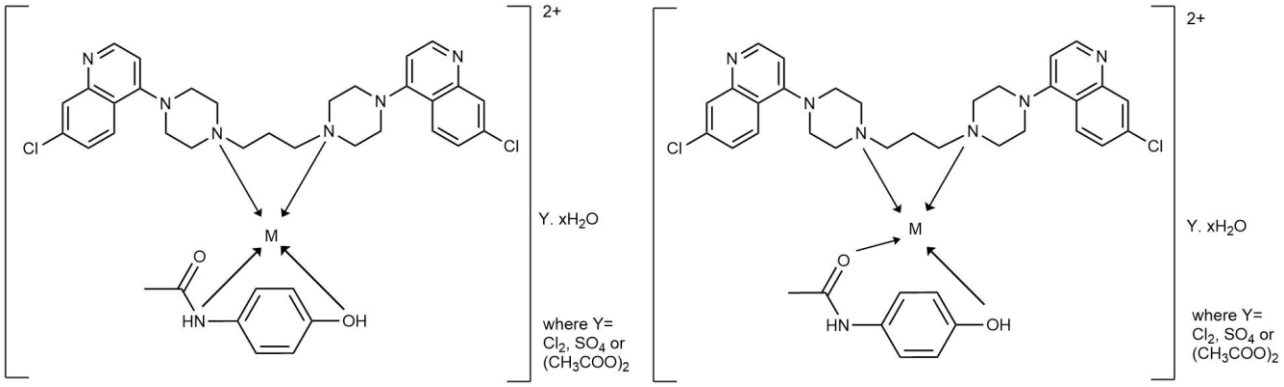


Figure 3. Proposed structures of metal complexes piperaquine-acetaminophen, where M = Fe(II), Cu(II), Zn(II), and Co(II)

Antimicrobial activities signify that piperaquine-acetaminophen metal complexes are stronger against Gram-positive bacteria (*S. aureus*) compared to the parent drug, acetaminophen. The result of the antimicrobial activities can be seen in Table 1.

Table 1. Antibacterial Activity of Acetaminophen, Piperaquine, and Their Metal Complexes

Compound / Complexes	Inhibition Zone (mm)
	S. aureus
$Cu(PQ)(Ac)Cl_2$	5.00
$Co(PQ)(Ac)(OAc)_2$	4.20
$Zn(PQ)(Ac)SO_4$	4.80
$Fe(PQ)(Ac)Cl_2$	5.20
Piperaquine (PQ)	3.55
Acetaminophen (Ac)	2.50

Among the piperaquine-acetaminophen metal complexes tested, Fe(II) showed the highest inhibition against *S. aureus* (5.20 mm), followed by Cu(II) (5.00 mm), Zn(II) (4.80 mm), and Co(II) (4.20 mm). The inhibition zone of piperaquine-acetaminophen against *S. aureus* increased significantly compared to the parent drug (Ayipo et al., 2016).

Chelation is effective in reducing the polarity of metal (II) complexes by sharing the metal's positive charge with ligand donor groups and delocalising the electron across aromatic rings. As a result, the metal atom's polarity weakens. It has increased the lipophilicity of the bacterial cell membrane, making it easier for it to get through the lipid layers of the bacterial membrane (Osowole et al., 2014). This shows that metal complexes of piperaquine and acetaminophen perform better against microorganisms than acetaminophen alone (Ayipo et al., 2016). Besides, heavy metals are known to be able to form secondary metabolites that can inhibit the growth of bacteria and are also toxic to organisms (Chudobova et al., 2015; Garza-Cervantes et al., 2017).

Antibacterial and Antifungal Activity of Cu(II) and Co(II) of Prednisolone-Acetaminophen

Prednisolone (Figure 4) is a synthetic cortisol glucocorticoid that works as analogue cortisol, a natural hormone that is produced by adrenal gland and used for many disease treatments

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

to suppress inflammations and various allergies (Straub & Cutolo, 2016). Prednisolone is also potentially a good anti-inflammatory agent as it can inhibit prostaglandin and leukotriene (Kumria et al., 2016; Santis & Saad, 2016; Motwani et al., 2018).

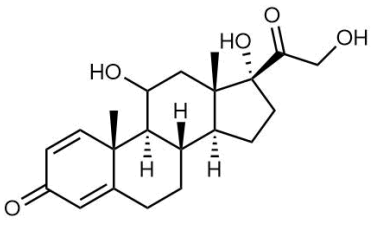


Figure 4. Structure of prednisolone

The synthesis of Co(II) and Cu(II) of prednisolone-acetaminophen used the same method (i.e., direct mixing). Prednisolone solution was prepared in distilled water-isopropyl alcohol medium and mixed in Cu(II) sulphate pentahydrate. The mixture was stirred for 1 h and then mixed with acetaminophen solution. The stirring continued for several hours. The mole ratio for metal salt, prednisolone, and acetaminophen was 1:1:1. The mixture was filtered and then washed using distilled water-isopropyl alcohol. The residue obtained was left to dry in a desiccator for several days and weighed. The process was repeated for Co(II) chloride (Damilola et al., 2019).

Gram-negative bacteria like *Xanthomonas axonopodis (A)*, *Streptococcus faecalis (B)*, *Pseudomonas aeruginosa (C)*, *Chromobacterium liusdium (D)*, and *Erwinia carotovora (E)* were used for antibacterial activity determination. The results showed that the inhibition zones of the synthesised drugs were higher compared to the parent paracetamol (Damilola et al., 2019). The results of the antibacterial activity are tabulated in Table 2.

Table 2. Antibacterial Activity of Acetaminophen, Prednisolone, Their Metal Complexes, and Streptomycin Sulphate

Compound/ Complexes	Zone of Inhibition (mm)				
	A	*B*	*C*	*D*	*E*
Cu(Pd)(Ac)(H_2O)	15.00	15.00	13.00	10.00	3.50
Co(Pd)(Ac)(H_2O)	20.00	19.00	17.00	17.50	18.50
Prednisolone (Pd)	10.00	1.00	6.00	3.50	0.00
Acetaminophen (Ac)	12.00	10.00	5.50	5.00	2.00
Streptomycin sulphate	27.00	31.00	31.00	33.00	22.00

The results showed that the metal complexes acetaminophen-prednisolone demonstrated higher inhibition against microbials, especially Co(Pd)(Ac)(H_2O). It gives an almost comparable value with the control when used against *E*. Although the results of the metal complexes of acetaminophen-prednisolone may not be as robust as the standard control (i.e., streptomycin sulphate), they still demonstrate satisfactory performance when compared with acetaminophen and prednisolone. The Co(II) and Cu(II) of prednisolone-acetaminophen showed more inhibition due to the antimicrobial mode of action. Different properties of metal ions gave higher activity of metal complexes due to chelation. This caused a decrease in the polarity of the metal ions by the overlapping of ligand orbitals and the partial sharing of the metal ion's positive charge with the donor group. Therefore, chelation facilitates complexes' penetration of lipid membranes and is more effective in inhibiting metal binding sites in bacterial enzymes (Al-Amiery et al., 2012).

Antimicrobial Activity of Mg(II) Complex of Acetaminophen

Mg(II) acetaminophen (Figure 5) was synthesised by the addition of $MgCl_2 \cdot 6H_2O$ to acetaminophen in distilled water and then heated for a few hours. It was left overnight to allow precipitation. The precipitate was filtered, washed, and allowed to dry for a few days. The final product was taken for the antimicrobial activity study by oral administration in rats (Paul et al., 2018). The microorganisms tested were *S. aureus*, *Bacillus subtilis*, *E. coli*, *Salmonella typhi*, *P. aeruginosa*, *Candida albicans*, and *Aspergillus niger* (Table 3).

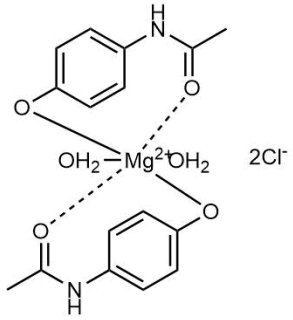


Figure 5. The proposed structure of Mg(II) acetaminophen

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Table 3. Antimicrobial Activity of Acetaminophen, Mg(II) Acetaminophen Complex, and Control

Organism Tested	Zone of Inhibition (mm) at Varying Concentrations (mg/mL)				
	Compound/ Complex	6.25	12.5	25	50
S. aureus	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	13.0	15.0	19.0
	Cp	20.0	25.0	30.0	38.0
B. subtilis	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	0.0	0.0	0.0
	Cp	25.0	28.0	32.0	39.0
E. coli	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	0.0	0.0	0.0
	Cp	19.0	22.0	25.0	30.0
S. typhi	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	0.0	12.0	15.0
	Cp	25.0	28.0	32.0	37.0
P. aeruginosa	Ac	0.0	0.0	15.0	18.0
	Mg(II)Ac	0.0	13.0	18.0	27.0
	Cp	16.0	18.0	21.0	25.0
C. albicans	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	0.0	0.0	0.0
	Fl	25.0	28.0	32.0	36.0
A. niger	Ac	0.0	0.0	0.0	0.0
	Mg(II)Ac	0.0	0.0	0.0	0.0
	Fl	13.0	15.0	20.0	25.0

Note:- Ac: Acetaminophen, Mg(II)Ac: Magnesium complex of acetaminophen, Cp: Ciprofloxacin, Fl: Fluconazole

The results showed that the parent drug (acetaminophen) did not inhibit bacterial growth at any concentration (6.25, 12.5, 25, and 50 mg/mL) except *P. aeruginosa* at 25 and 50 mg/mL (Paul et al., 2018). The antibacterial effects of acetaminophen have been reported to be negligible (Singh et al., 2021). However, the inhibition zones of *S. aureus*, *S. typhi*, and *P. aeruginosa* increased proportionally to the concentration of Mg(II) acetaminophen being administered (Paul et al., 2018). Although Mg(II) acetaminophen exhibits less potency than the standard control, it shows a noteworthy improvement in comparison to the isolated effects of acetaminophen. Tweedy's chelation hypothesis predicted that the polarity of the metal atom would decrease with chelation, mostly as a result of the metal's positive charge being partially shared with donor groups and perhaps resulting in electron delocalisation over the whole ring. This increased the lipophilic nature of the chelates, which made it more possible for them to penetrate through the lipid layers of the bacterial membrane (Al-Amiery et al., 2012).

Antimicrobial Activity of Metal Complexes of Acetaminophen-Ascorbic Acid

Ascorbic acid (Figure 6), commonly known as vitamin C or ascorbate, is made up of an enediol that is conjugated to the carbonyl group in the lactone ring. This enediol provides an electron for ascorbic acid's function as an antioxidant (Barba et al., 2014). It is a renowned water-soluble antioxidant that plays an essential part in several physiological processes in the human body (Attia et al., 2020). It can control the gastrointestinal absorption of iron ions and stabilise iron-binding protein, as well as post-translational hydroxylation of collagen, carnitine biosynthesis, and tyrosine metabolism (Golonka et al., 2017). Ascorbic acid is widely recognised as a strong antioxidant and free radical scavenger (Njus et al., 2020), but people do not seem aware of its other biological activities, such as anticancer (Shenoy et al., 2018), antitumor (Mata et al., 2016), antiviral (Biancatelli et al., 2020), and antimicrobial properties (Hernandez-Patlan et al., 2017; Sangcharoen et al., 2017; Verghese et al., 2018). As metal ions like cobalt, nickel, and zinc are known for their effectiveness against several diseases, the combination of analgesic-antioxidant drug metal complexes is being studied.

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

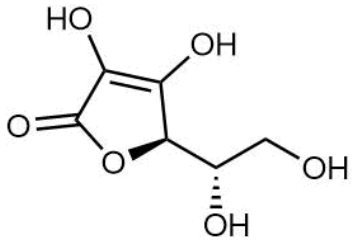


Figure 6. Structure of ascorbic acid

Acetaminophen-ascorbic acid metal complexes (Figure 7) are synthesised by the preparation of metal chlorides (Ni, Co, Fe, Cu) and metal sulphate (Zn) in aqueous solution. Then, acetaminophen and ascorbic acid were mixed in their appropriate solvent. The mixture was refluxed, and the resulting precipitate was filtered, solvent-washed, air-dried, and stored. The experiment was conducted in 3.0 and 5.0 mmol concentrations. The antimicrobial activity of acetaminophen, ascorbic acid, and acetaminophen-ascorbic acid metal complexes can be seen in Table 4.

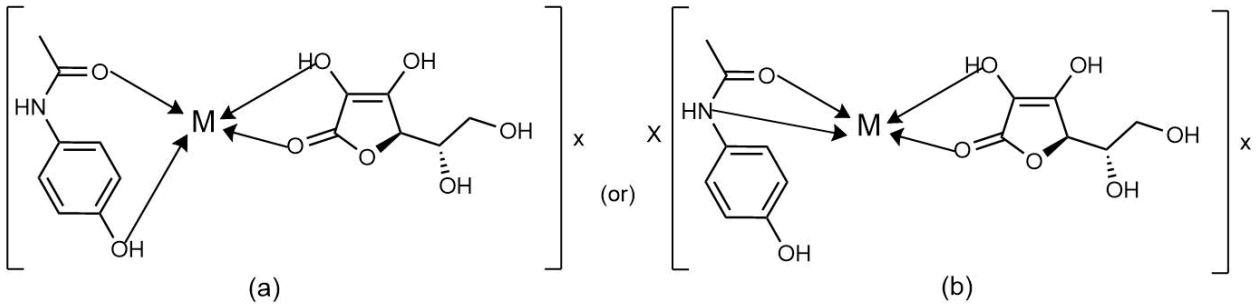


Figure 7. Proposed structures of acetaminophen-ascorbic acid metal complexes

Table 4. Antimicrobial Activity of Acetaminophen, Ascorbic Acid, and Acetaminophen-Ascorbic Acid Metal Complexes

Compound/ Complex	Inhibition Zones (mm)					
	Conc. (mmol)	A	B	C	D	E
$Co(Ac)(Asc)Cl_2$	3.0	5.0	0.0	2.0	3.0	2.0
	5.0	6.0	0.0	6.0	6.0	0.0
$Ni(Ac)(Asc)Cl_2$	3.0	14.0	9.0	5.0	10.0	2.0
	5.0	0.0	4.0	1.0	3.0	11.0
$Cu(Ac)(Asc)Cl_2$	3.0	2.0	6.0	4.0	0.0	0.0
	5.0	31.0	32.0	15.0	0.0	0.0
$Fe(Ac)(Asc)Cl_2$	3.0	1.0	0.0	3.0	0.0	0.0
	5.0	-	-	-	-	-
$Zn(Ac)(Asc)Cl_2$	3.0	7.0	0.0	10.0	0.0	0.0
	5.0	0.0	0.0	0.0	0.0	0.0
Acetaminophen (Ac)	3.0	2.0	4.0	5.0	3.0	9.0
	5.0	-	-	-	-	-
Ascorbic acid (Asc)	3.0	5.0	0.0	5.0	9.9	2.0
	5.0	-	-	-	-	-

Biological assays of the complexes were experimented on for 3 days against *Enterococcus faecalis (A)*, *S. aureus (B)*, *Clostridium difficile (C)*, *Klebsiella spp. (D)*, and *Helicobacter pylori (E)*. Different concentrations of complexes were found to give different results.

At 3.0 mmol, the acetaminophen-ascorbic acid metal complexes did not exhibit antimicrobial activity on the first day. Meanwhile, at a concentration of 5.0 mmol, acetaminophen-ascorbic acid with copper complex, $Cu(Par)(Asc)SO_4$ against *S. aureus* (32 mm) and acetaminophen-ascorbic acid with cobalt complex, $Co(Par)(Asc)SO_4$ against *H. pylori* (31 mm) showed the best antimicrobial activity. Both complexes showed higher inhibition compared to the parent acetaminophen itself. However, the complexes' inhibition decreased on the third day due to the reduction in the concentration of the drug (Babamale et al., 2016). This is due to the population of bacteria exposed to

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

an inadequate concentration of a specific drug as they can develop resistance to the drug (Kowalska-Krochmal & Dudek-Wicher, 2021).

3. Ibuprofen

Ibuprofen (2-(4-isobutylphenyl) propionic acid) (Figure 8) is a common over-the-counter drug used as an analgesic and antipyretic agent. It is consumed to inhibit COX, thus reducing the level of prostaglandin in the human body, which is used to treat inflammation or pain and can also be used as a fever reliever. It is usually used to treat headaches, menstrual cramps, minor injury, toothaches, and blood clotting, and to control blood pressure. The adverse effect of ibuprofen is likely due to frequent and widespread usage (Gomaa, 2018). Ibuprofen exerts its anti-inflammatory effect based on the inhibition of COXs in prostaglandin synthesis (Amir et al., 2016). It also has an antibacterial effect, especially on *E. coli*, which is a major pathogen causing urinary tract infection (Ahmed et al., 2016). The presence of carboxyl and aromatic groups in the molecular structure of ibuprofen has been reported to contribute to its biological properties (Martínez et al., 2017).

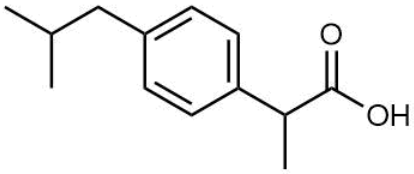
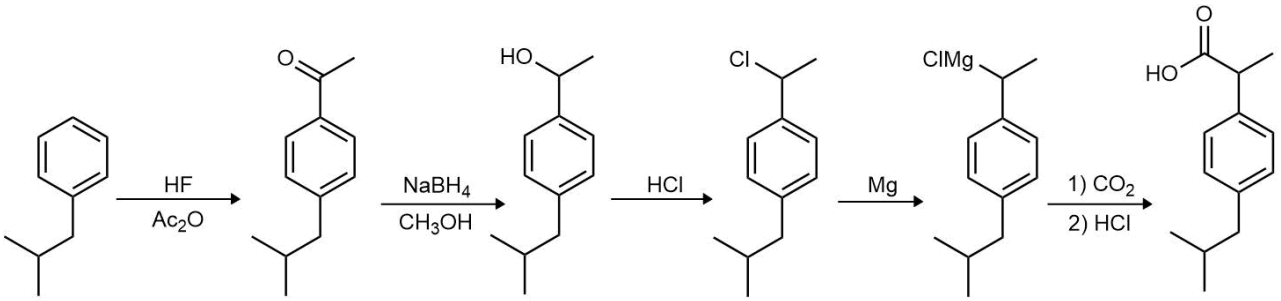


Figure 8. Structure of ibuprofen

The synthesis of ibuprofen can be accomplished using isobutyl benzene and acetic anhydride with four continuous reactions, which are Friedel-Craft acylation, carbonyl reduction, chloride substitution, and Grignard reaction (Kilburg & Tyler, 2017) (Scheme 2).



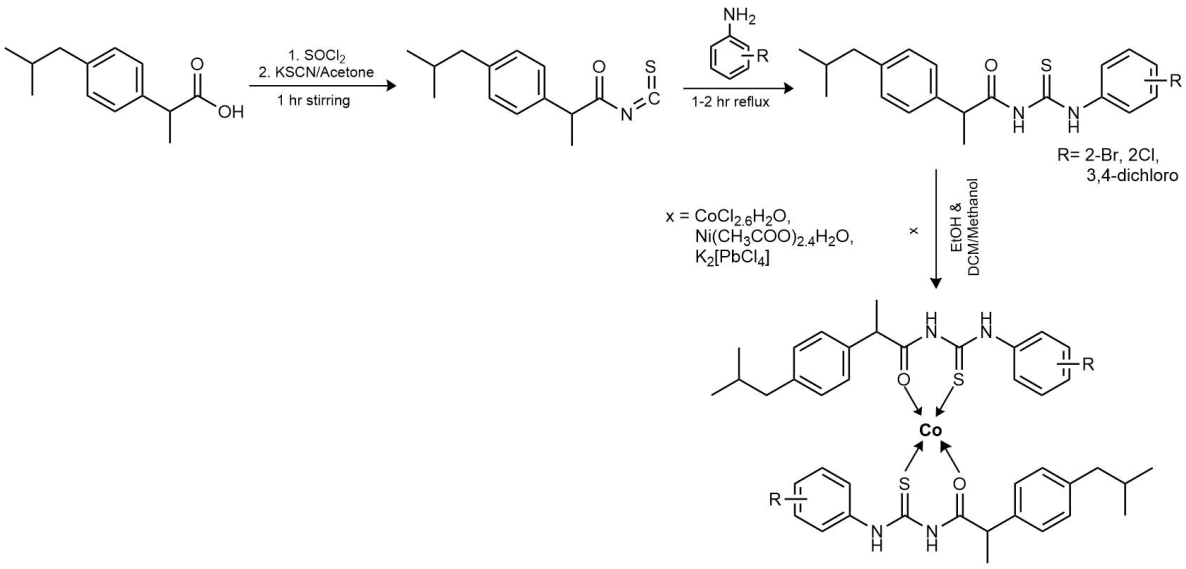
Scheme 2. Synthesis of ibuprofen

Urease Inhibition of Co(II) Complex of Ibuprofen-Thiourea Derivatives

Thiourea derivative is known for its biological activities, such as antimicrobial (Stratan et al., 2018; Vedavathi et al., 2017), antituberculosis (Stratan et al., 2018), and analgesic (Shoaib et al., 2017). It has a variety of uses outside of pharmaceuticals, including as a fungicide and herbicide, a growth inhibitor for plants, and as a substance used to control insect and insect-related growth (Shakeel, 2016). It has also been considered as a particularly good chelating agent for transition metal complexes by inhibiting enzymes due to their specific molecular architecture (Mumtaz et al., 2018). Urease is a nickel-based metalloenzyme that is present throughout the human body (Seraj et al., 2021). It catalysed the hydrolysis of urea to produce ammonia and carbon dioxide, which were subsequently protonated to produce ammonium (Rizvi et al., 2019). This assists in an increase of pH in the stomach. Urease enzyme can promote the growth of *H. pylori* that caused many pathological conditions including peptic ulcer, hepatic encephalopathy, and urinary stone formation, which answered the growing interest of urease inhibitor in the medicinal field in recent years (Kafarski & Talma, 2018; Mumtaz et al., 2018; Seraj et al., 2021).

Mumtaz et al. (2018) studied urease inhibition by introducing metal ligands into ibuprofen-thiourea. Ibuprofen-thiourea with halogen substitutes obtained were characterised and underwent reaction with metal complex (Figure 9) (Mumtaz et al., 2018). The synthesis of Co(II) complex of ibuprofen-thiourea is represented below (Scheme 3).

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)



Scheme 3. Synthesis of Co(II) complex of ibuprofen-thiourea

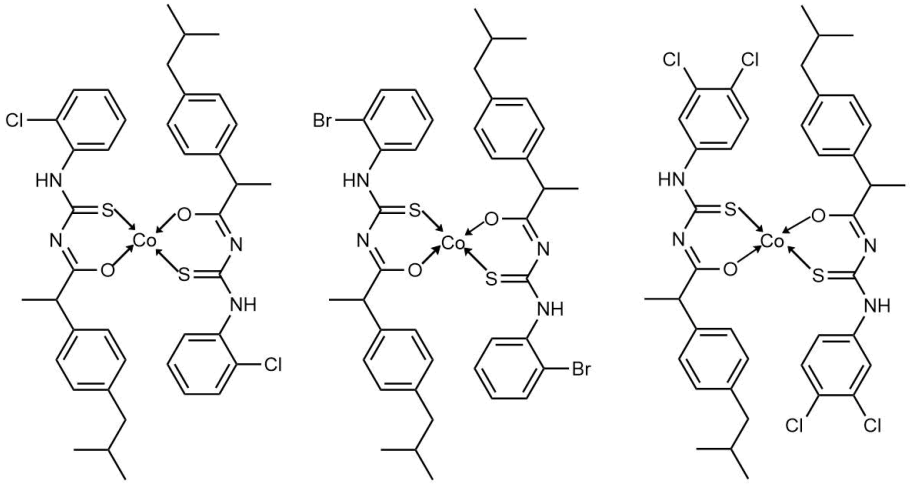


Figure 9. Proposed structure of Co(II) complex of ibuprofen-thiourea: (a) chloro substituent, (b) bromo substituent, and (c) dichloro substituent

Urease inhibition of ibuprofen-thiourea derivatives were compared with jack bean urease. The enzyme activity was determined by the amount of ammonia produced measured by the indophenol method and the absorbance was recorded (Mumtaz et al., 2018). The collected data indicated that ibuprofen was unable to inhibit urease enzyme. However, the incorporation of thiourea moiety into ibuprofen has increased the inhibition potency of enzyme activity (Seraj et al., 2021). Therefore, thiourea has been used as a standard for urease inhibition. Table 5 shows the results for urease inhibition of Co(II) complex of ibuprofen-thiourea.

Table 4. Urease Inhibition Activity of Co(II) Complex of Ibuprofen-Thiourea Derivatives

Compound	IC_{50} (µM) ± SEM
(a)	14.6 ± 3.3
(b)	32.9 ± 14.1
(c)	24.6 ± 7.45
Standard (thiourea)	21.1 ± 1.23
Ibuprofen	-

Ibuprofen-thiourea derivative with metal ligand bearing -Cl exhibited the most potent inhibition against urease enzyme. Ibuprofen-thiourea metal-containing bromine atom showed lower urease inhibition than -Cl (Mumtaz et al., 2018). Although both -Cl and -Br belong to the electron-withdrawing group (EWG),

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

-Cl is more electronegative and has smaller atomic size than -Br, which may affect the urease inhibitory activity (Rashid et al., 2020). Moreover, -Br exhibits inadequate inhibition of enzyme due to extended bulkiness of the compound, which resulted in longer and more labile bonds (metal ligand easily broken), thus unsuitable for drug candidates, whereas the presence of -Cl has altered the volume and shape of the compound, allowing for positioning in deep cavities of enzyme (Fejzagić et al., 2019). Compound (c) containing two -Cl at meta-para position showed a moderate result compared to the standard and compound (b). This shows that the position of halogens determines the inhibitory activity instead of the number of halogen present (Ashraf et al., 2019).

Antibacterial Activity of Metal Complexes with Isoniazid-Ibuprofen

Formerly, metal has been used as an antimicrobial agent that is highly beneficial in the medical field. Normal cell metabolism requires many metals, but higher concentrations may cause health risks. According to the oligodynamic effect, heavy metal can bind to thiol or amine moiety of cellular protein, leading to deactivation and precipitation of proteins. As proteins are strongly attracted to metal ions, it results in cellular concentration growth and cell death (Mittapally et al., 2018). As antibiotics are developed, the use of metals as antimicrobials is gradually being phased out. However, the emergence of several reports related to antibiotic resistance became a reason for the development of metals used as antibiotic conjugates (Hegde et al., 2021; Mittapally et al., 2018).

Isoniazid (Figure 10), also called isonicotinyl hydrazide (INH), is an antibiotic consisting of a pyridine ring with hydrazine moiety that has a narrow spectrum antimicrobial against *Mycobacterium tuberculosis* (Hegde et al., 2021).

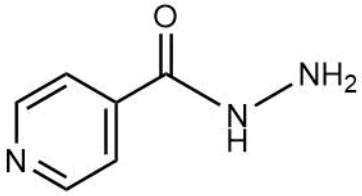


Figure 10. Structure of isoniazid

It is a pro-drug activated by KatG (a biological enzyme presents in mycobacteria) to generate isonicotinoyl radical. Nicotinamide adenine dinucleotide (NAD+) and this free radical interact to form a complex called NAD-INH, which functions as a competitive inhibitor of InhA. The inhibition interrupts the entire process of mycolic acid synthesis, which is responsible for the formation of mycobacterial cell wall. Furthermore, the inhibition process resulting in NADH accumulation and ATP burst that is toxic to the mycobacterial itself (Shetty & Dick, 2018; Hegde et al., 2021).

Isoniazid has been used as an antituberculosis agent for more than 6 decades until the emergence of resistance cases. Numerous researchers have established isoniazid derivatives to combat INH resistance using newly discovered mycobacterial targets and host-directed treatment (Torfs et al., 2019). The combination of isoniazid-pyrrole hybrid LL-3858 resulting in a promising compound for tuberculosis treatment (Hu et al., 2017). Isoniazid embedded with triazole moiety induces antitubercular and antimicrobial activities. Mixed isoniazid-ibuprofen metal complexes also showed antibacterial activities (Bamigboye et al., 2019).

The synthesis of isoniazid-ibuprofen metal complexes (Figure 11) started with isoniazid in methanol and ibuprofen in ethanol, which were mixed in metal chloride salts (Cu^{2+}, Zn^{2+}, Ni^{2+}, and Cd^{2+}) and dissolved in solvents. After being refluxed for a short period of time at a certain temperature, the mixture was cooled to room temperature, allowed to precipitate, filtered, and washed with a mixture of solvents. The product was dried in a desiccator and used in antibacterial screening against *E. coli*, *S. aureus*, and *P. aeruginosa* (Bamigboye et al., 2019).

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

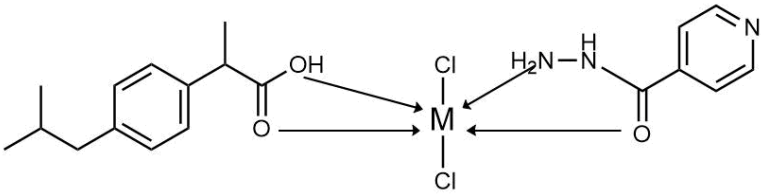


Figure 11. Proposed structure of isoniazid-ibuprofen metal

The antibacterial activity of metal complexes (Ni, Cu, Cd, and Co) isoniazid-ibuprofen compounds resulted in higher inhibition zones against *E. coli*, *S. aureus*, and *P. aeruginosa* compared to the parent ibuprofen. The results (Table 6) indicated that ibuprofen and isoniazid themselves did not inhibit bacteria at 20 and 40 µL/mL (except for isoniazid against *S. aureus* at 40 µL/mL) (Bamigboye et al., 2019).

Table 5. Antibacterial Activity of Complexes, Ibuprofen, and Isoniazid

Compound/Complexes	Inhibition Activity at 20 and 40 µL/mL Concentration					
	E. coli		*S. aureus*		*P. aeruginosa*	
	20.0	40.0	20.	40.0	20.0	40.0
Ni(Iso)(Ibu)Cl_2	11.0	14.0	8.0	12.0	8.0	13.0
Cu(Iso)(Ibu)Cl_2	4.0	16.0	5.0	24.0	14.0	19.0
Cd(Iso)(Ibu)Cl_2	22.0	29.0	13.0	14.0	13.0	16.0
Co(Iso)(Ibu)Cl_2	9.0	12.0	11.0	11.0	17.0	18.0
Isoniazid (Iso)	-	-	-	11	-	-
Ibuprofen (Ibu)	-	-	-	-	-	-

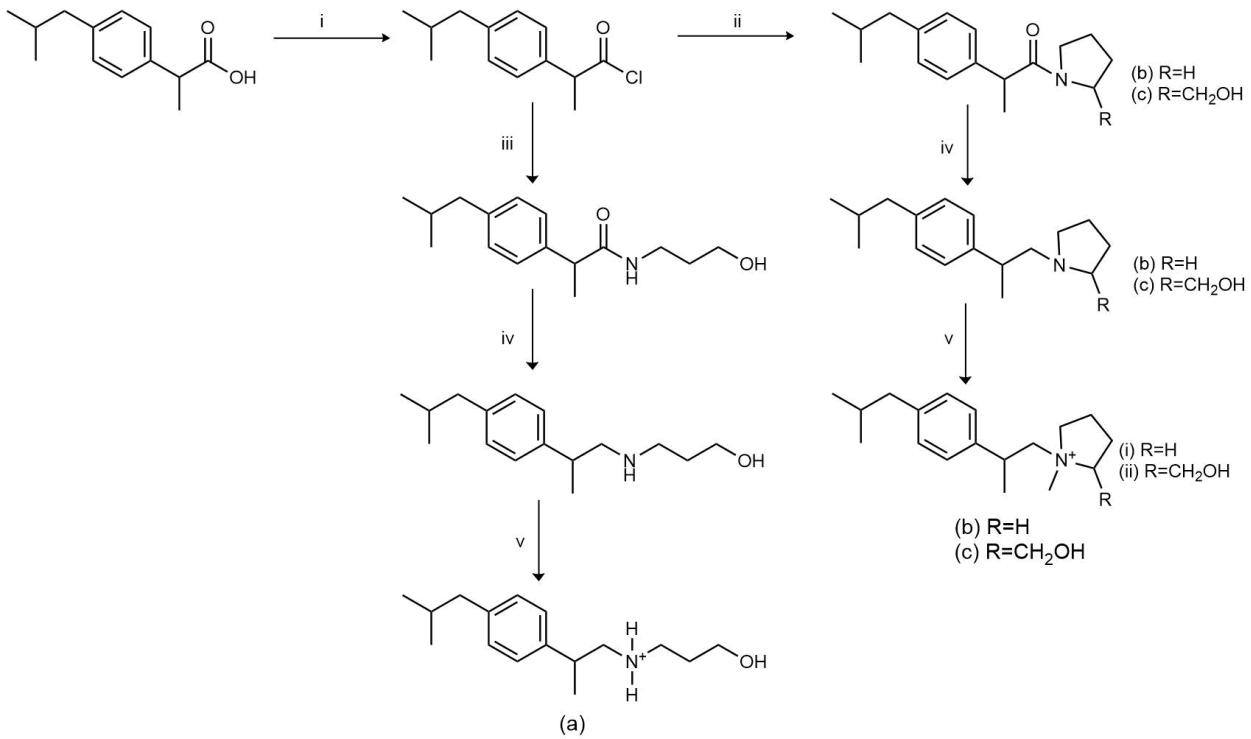
Meanwhile, the existence of metals in the complex enhanced the effectiveness of ligand to inhibit bacterial growth. This increasing antimicrobial activity can be linked to the chelation theory. Chelation usually results in ligand acting as a more effective bactericidal agent (Damilola et al., 2019). The donor atoms in the ligands partially share some of the positive charge of the metal, as in the complex, and may contribute to electron delocalisation in the chelate ring. This factor contributes to the lipophilicity of the central metal atom, which improves its hydrophobicity and solubility in lipids, allowing it to permeate through the lipid layer of bacterial membrane (Abd El-Halim et al., 2018).

Anti-Inflammatory and Ulcerogenic Activity of Ibuprofen Bearing Ammonium Moieties

Drugs containing carboxylic acid have an essential function in the medical treatment of pain and diseases. One of the roles is acting as a solubiliser to modulate lipophilicity and cell permeation (Badea & Radu, 2018). However, some claim that the damage caused by NSAIDs containing a carboxylic group (ibuprofen, aspirin) is more potent (Mehta et al., 2010). It has been questioned whether NSAIDs require the presence of carboxylic acid group. One of the test drugs is ibuprofen. The carboxylic acid-free group of ibuprofen can cause gastrointestinal (GI) toxicity (erosion or bleeding) due to its pharmacological mechanism that inhibits COX-1 and COX-2, thus decreasing the formation of prostaglandin and thromboxane systematically (Bhandari et al., 2008; Ullah et al., 2016).

The synthesis of ibuprofen bearing ammonium moieties is depicted below (Scheme 4).

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)



Scheme 4. Synthesis of ibuprofen bearing ammonium derivatives. Reagents and conditions: (i) oxalyl chloride, DCM, 25 °C, 3–12 h; (ii) pyrrolidine or L-proline, DCM, 25 °C, 3 h; (iii) 2-hydroxyethylamine, DCM, 25 °C, 3 h; (iv) $LiAlH_4$, THF, 25 °C for 3d, reflux (a) for 3 h; and (v) dry HCl, ether, N_2, 25 °C

The subsequent ammonium salt was taken for anti-inflammatory and ulcerogenic assay. Based on the in vitro results, compounds 2e, 3e(i), and 3e(ii) (Figure 12) gave the half-maximal inhibitory concentration (IC_{50}) values of 28.1, 22.2, and 20.7 µM, respectively, whereas celecoxib gave 0.02 µM. This indicates that these drug modifications are not as potent as celecoxib as the selective COX-2 inhibitor.

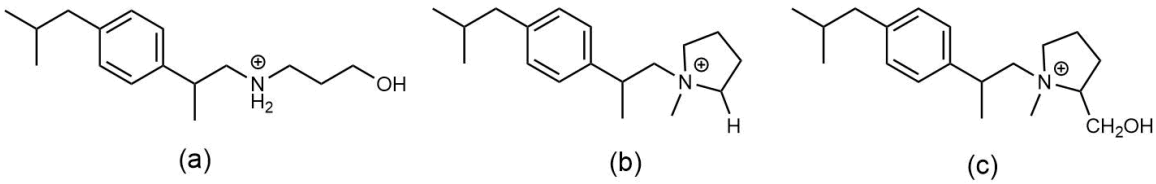


Figure 12. Structure of ibuprofen-ammonium derivatives

Meanwhile, in the findings of in vivo anti-inflammatory activity (Table 7), the compounds (a) and (b) had a statistically relevant anti-inflammatory impact in comparison to the control group, whereas compound (c) had no effect (Ullah et al., 2016). Drugs containing ammonium salts could improve solubility in body fluids (Ouellette & Rawn, 2018). The ammonium salts made from ibuprofen have shown that NSAIDs are not required to include carboxylic acid groups (Ullah et al., 2016). Nevertheless, further study needs to be done to increase the potency.

Table 6. COX-1 and COX-2 Inhibition of Ibuprofen Derivatives without Carboxylic Acid Group

Compounds	IC_{50} (µM)	
	COX-1	COX-2
(a)	>100	28.1
(b)	>100	22.2
(c)	>100	20.7
Celecoxib	>100	0.02

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Anti-Inflammatory and Anticancer Activity of Ibuprofen-Amide Derivatives

Studies found that amide derivatives of NSAIDs contributed to antitumor activity (Zhang et al., 2021). Compared to the parent NSAIDs itself, amide derivatives are said to be potent inhibitors of cell proliferation. A compound comprises amide linkage is said to be anticancer, antimicrobial, antinociceptive, and anti-inflammatory (Haider et al., 2018). It is well-known that heterocyclic compounds containing nitrogen are a valuable source of therapeutic agents (Figure 13) (Ansari et al., 2017).

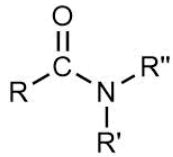
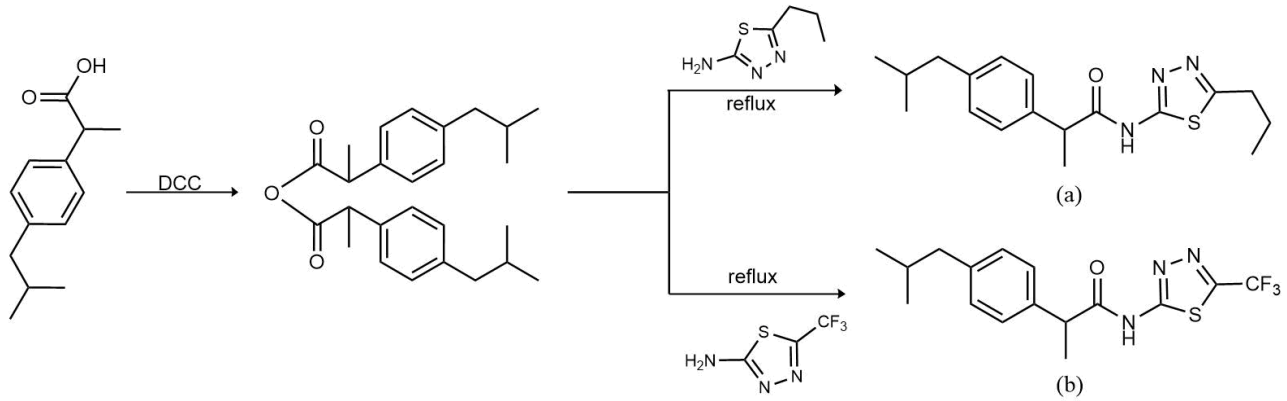


Figure 13. Structure of amide

Anti-Inflammatory Activity of with 1,3,4-Thiadiazolyl–Propanamide Ibuprofen Derivatives

Alkabodi et al. (2016) aimed to derive a potential ibuprofen-amide derivatives drug with selective COX-2 inhibition having a low ulcerogenic effect. The synthesis of the ibuprofen-amide derivatives is shown below (Scheme 5):



Scheme 5. Synthesis of ibuprofen-amide derivatives

The experiment continued with the anti-inflammatory activity test using the ovalbumin paw edema method of albino rats and ulcerogenic index screening, and the results obtained are as shown in Table 8 (Alkabodi et al., 2016).

Table 8. Percentage Inhibition of Paw Edema and Ulcer Index to Determine the Anti-Inflammatory Activity of Ibuprofen with 1,3,4-Thiadiazol Amide Derivatives

Compound	% Inhibition of Paw Edema	Ulcer Index
(a)	45.0	5.8
(b)	44.0	8.3
Diclofenac	41.0	-
Celecoxib	-	6.0
Indomethacin	-	17.0

The inhibition of compounds (a) and (b) resulted in a decent anti-inflammatory activity (45% and 44%, respectively) compared to the standard drug, diclofenac (41%) (Alkabodi et al., 2016). Meanwhile, the ulcerogenic screening showed that compounds (a) and (b) gave 5.8 and 8.3 ulcer index while celecoxib produced an ulcer index of 6.0. The activity of ibuprofen-amide derivatives was compared to diclofenac and celecoxib (selective COX-2 inhibitors). Overall, it was discovered that compound (a) gave better results in comparison to celecoxib. The difference between compound (a) and celecoxib is the presence of amide functional group (Alkabodi et al., 2016). Several studies found that the amide derivatives have increased the anti-inflammatory activity (Ahmadi et al., 2017; Narsinghani & Sharma, 2017).

Compounds (a) and (b) also consist of thiadiazol, which may contribute to COX-2 inhibition. Several studies on thiadiazol derivatives showed promising scaffolds for potent selective COX-2 inhibitors (Maddila et al., 2016; Ragab et al., 2017; Murahari et al., 2019).

The difference between these two compounds is the presence of ethyl in compound (a) and trifluoromethyl in compound (b). A study found that trifluoromethyl may affect the electrical properties of the target chemicals, and its lipophilicity can

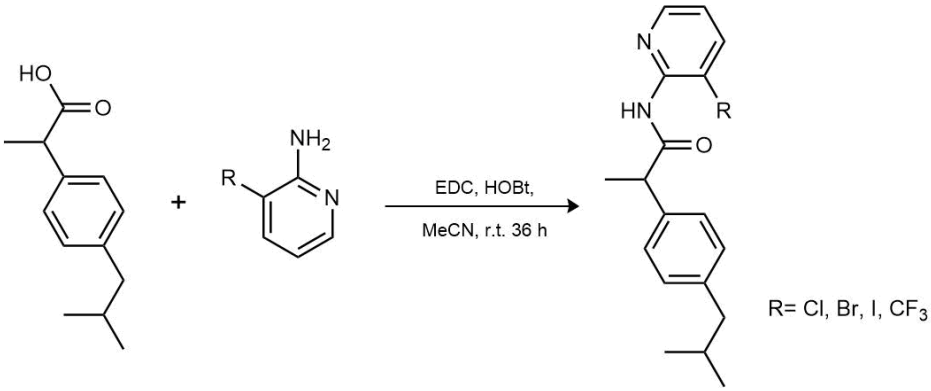
DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

promote membrane permeability (Cong et al., 2021). However, comparing compound (b) to non-selective COX inhibitor indomethacin, the GI side effects for compound (b) are less severe but not as efficient as a COX-2 inhibitor, celecoxib.

Hence, the presence of amide and 1,3,4-thiadiazol in ibuprofen-amide derivatives (compound (a)) has improved the anti-inflammatory effect on the edema paw of albino rats and gives better tolerance against the ulcerogenic of albino rats compared to celecoxib.

Anti-inflammatory Activity of Ibuprofen-Amide Derivatives as Dual FAAH/COX Inhibitor

Ibuprofen can initiate gastrointestinal toxicity after a long time of usage, and the pharmaceutical industry will design a new drug candidate with improved therapeutic properties compared to the parent drug (Mehta et al., 2010). The suppression of both COX-1 and COX-2 caused gastrointestinal damage. In order to overcome this phenomenon, the inhibition of fatty acid amide hydrolase (FAAH) alongside COX inhibitors is introduced (Deplano et al., 2019; Goodman et al., 2018). FAAH is a serine hydrolase that is important in controlling the endogenous level of anandamide, an endocannabinoid mediator with analgesic and tissue protective function, and works as a pain and inflammation reliever (Dainese et al., 2020; Deplano et al., 2019; Sasso et al., 2015; Scarpelli et al., 2016). A dual-action FAAH-COX inhibitor is reported to give useful therapeutic properties. The synthesis of ibuprofen-amide derivatives is shown below (Scheme 6).



Scheme 6. Synthesis of ibuprofen-amide derivatives

Figure 14 shows the proposed structure of ibuprofen-amide derivatives with different substituents (halogen and trifluoromethyl). The first endogenous ligand discovered to interact with cannabinoid receptors is *N*-arachidonoylethanolamine (AEA). FAAH enzyme breaks down AEA to arachidonic acid and ethanolamine in most rat tissues (Ahn et al., 2009; Marrs & Stella, 2009). The ibuprofen-amide derivatives were tested towards rat brain FAAH-catalysed hydrolysis of AEA. The inhibition of the ibuprofen-amide derivatives at IC_{50} was analysed (Table 9) (Deplano et al., 2020).

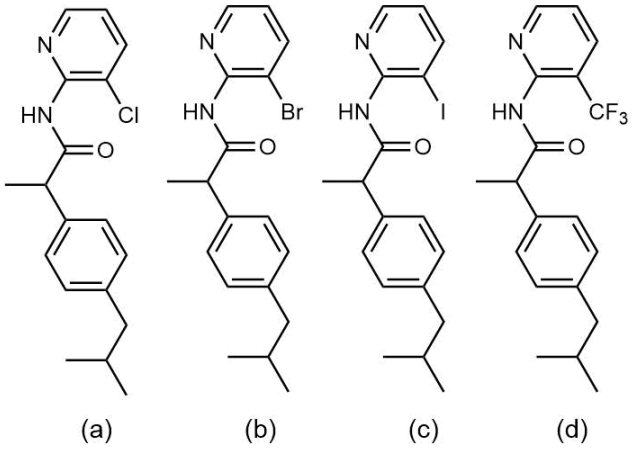


Figure 14. Structure of ibuprofen-amide derivatives (Cl, Br, I, CF_3)

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Table 9. IC_{50} Values for the Inhibition of Rat Brain FAAH Catalysed Hydrolysis of AEA by Ibuprofen-Amide Derivatives

Compound	IC_{50} (µM)
(a)	0.910
(b)	0.083
(c)	0.120
(d)	0.360
Ibuprofen	-

The presence of -Cl, -Br, and -I resulted in bulky compounds, which blocked the active sites or affected the permeability of cell membranes. Even though brominated compounds were said to be longer with a more labile bond, it allowed for easier incorporation into molecules (Fejzagić et al., 2019). This explains the highest potency of ibuprofen-amide derivatives starting with (b), which has -Br at 0.083 µM, followed by (c) with -I at 0.120 µM, (d) with $-CF_3$ at 0.360 µM, and lastly (a) with -Cl at 0.910 µM (Deplano et al., 2020). These results indicated the presence of halogen, which increased the potency of ibuprofen-amide derivatives as FAAH inhibitors but still retained its ability as a selective COX-2 inhibitor. The presence of EWG such as halogen and trifluoromethyl gives higher activity compared to ibuprofen itself.

Anticancer Activity of Dexibuprofen-Amide Derivatives

Anhydrous benzene is present when a reaction took place between thionyl chloride and dexibuprofen, producing the corresponding acid chloride. In the second stage, the dexibuprofen acid chloride underwent condensation with substituted amines in the presence of dry acetone to obtain the required dexibuprofen-amides (a–d). After being synthesised, each dexibuprofen-amide derivative was subjected to flash chromatography to achieve purity and their structures were validated using spectroscopic data.

The dexibuprofen amides with halogen substituted on aromatic moieties improved the antitumor activities. These compounds (Figure 15) were evaluated against breast carcinoma cells (MCF-7).

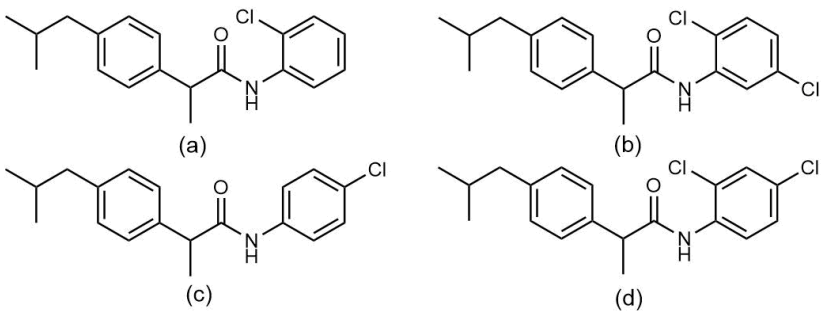


Figure 15. Structure of dexibuprofen-amide derivatives with different positions of chloro-halogen: (a) 2-Cl, (b) 2,5-dichloro, (c) 4-choro, and (d) 2,4-dichloro

Compound (a) with 2-chloro, (b) with 2,5-dichloro, (c) 4-chloro, and (d) 2,4-dichloro substituted gave excellent IC_{50} results for MCF-7 (Table 10). Both compounds (a) and (b) exhibited excellent outcomes against the cancer cells, but neither compound was cytotoxic to normal breast cells.

Table 10. Cytotoxic Activity against MCF-7 Cell Line by the Synthesised Dexibuprofen Amides, Erlotinib, and Doxorubicin

Compounds	IC_{50} (µM/mL)
	MCF-7
(a)	0.03 ± 0.004
(b)	0.01 ± 0.002
(c)	6.57 ± 1.54
(d)	1.02 ± 0.15
Erlotinib	0.02 ± 0.003
Doxorubicin	0.04 ± 0.006

For compounds (a) and (b), the chloro substituent at the ortho-position of the phenyl ring is crucial to the anticancer activity of these derivatives. Under these circumstances, the chlorine substituents' steric and/or electronic actions caused localised electronic attraction or repulsion, as well as steric interference with any nearby amino acids of the target proteins. (Fang et al., 2019). Compound (c) with a para-chloro substituent has reduced the cytotoxicity. Due to the increasing number of chloro-substituents, compound (d) demonstrated the least inhibition. It can be concluded that the location of the halogens, not their quantity, is the determining factor of inhibitory action (Ashraf et al., 2019).

Even though ibuprofen was not evaluated in this study, previous research has shown that it provides limited inhibitory effect against MCF-7 (Pedro-Hernández et al., 2017). Several amide derivatives of ibuprofen have shown enhanced antiproliferative effects when compared to the parent drug (Abourehab et al., 2021). This supports that dexibuprofen-amide derivatives are more effective in inhibiting MCF-7 than the parent drug, ibuprofen (He et al., 2021).

Anti-Inflammatory Activity of Ibuprofen Conjugated with Silicon

In 2017, novel silicon-containing amides derived from ibuprofen were successfully synthesised and investigated for their anti-inflammatory efficacy against nuclear transcription factor kB

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

(NF-kB). There were four potential derivative compounds of silicon-containing amide derivatives that offered better activities for inhibiting NF-kB when compared to ibuprofen as the parent drug. The presence of better biological activity coordinated with the increase in the derivative compound's lipophilicity supports its ability to pass through the cell membrane, making it easier to reach cytosol as the target area of NF-kB activation. From these results, it appeared that the conversion of ibuprofen to the form of amides can affect their anti-inflammatory activity (Pérez et al., 2017).

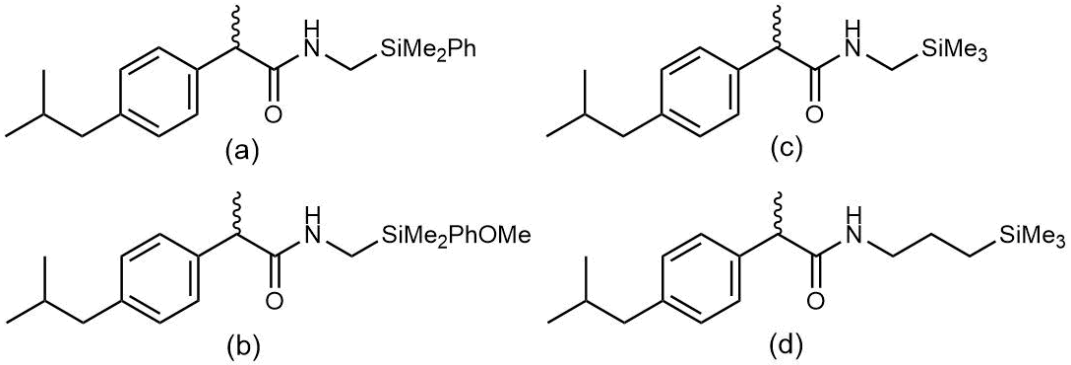
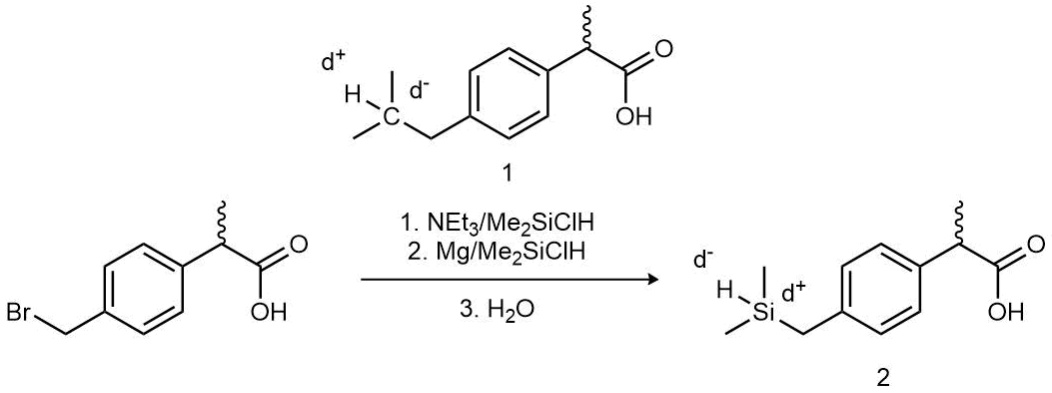


Figure 16. Chemical structure of silicon-containing amide derivatives of ibuprofen

Other studies conducted a modification at the alkyl side chain of ibuprofen by substituting silicon. The synthesis of silicon ibuprofen conjugate, which was later named sila-ibuprofen, was done by reacting 2-[(4-bromo-methyl) phenyl] propionic acid and dimethylchlorosilane (Me_2SiClH) in a one-pot reaction (Scheme 7) (Kleemiss et al., 2020).



Scheme 7. Synthesis of silicon ibuprofen conjugate

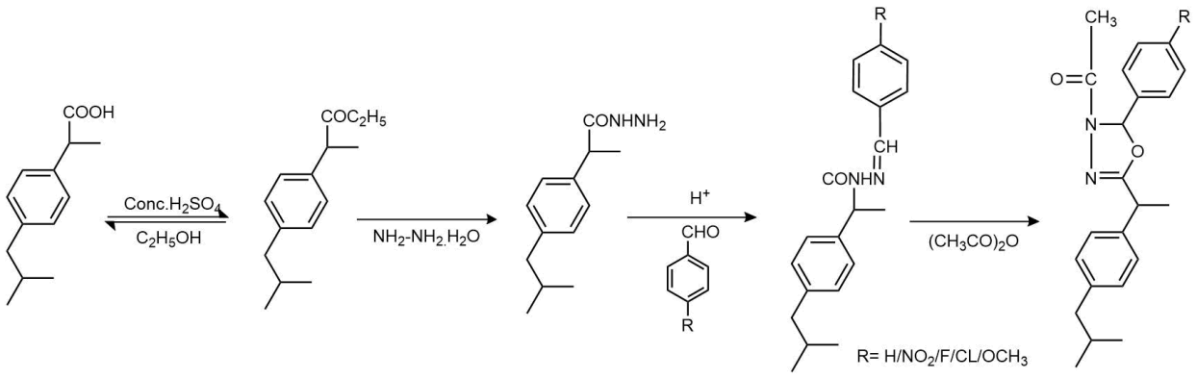
Although there was no significant enhancement in its anti-inflammatory activity as a COX inhibitor, the substitution of silicon onto ibuprofen's structure showed the improvement of physical properties, especially in its solubility. Sila-ibuprofen has four times higher solubility in physiological media than ibuprofen and this property can be useful for further development (Kleemiss et al., 2020).

Anticancer Activity of Ibuprofen with N-Acyl-1,3,4-Oxadiazole Derivatives

Researchers in the field of medical and pharmaceutical chemistry are interested in heterocyclic compounds with nitrogen atoms. Examples of these types of molecules include oxadiazole moieties. Due to its versatility in terms of its effects on living things, the 1,3,4-oxadiazole heterocyclic ring is regarded as one of the most important heterocyclic moieties (Ahsan, 2018; Siwach & Verma, 2020). 1,3,4-oxadiazole derivatives have been reported to exhibit therapeutic activities, such as antibacterial (Glomb & Świątek, 2021), anti-inflammatory (Chawla et al., 2018), antioxidant (Mihailović et al., 2017), and antitumor (Nayak et al., 2021). The compounds have different mechanisms of action that are significant in perceiving the resistance of tumours to standard drug treatment (Glomb et al., 2018).

It was discovered that ibuprofen that is associated with 1,3,4-oxadiazole derivatives with halogen, methoxy, and nitro-substituents exhibited promising results in anticancer studies (Alderawy et al., 2020). The synthesis of the compounds can be summarised as below (Scheme 8).

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)



Scheme 8. Synthesis of ibuprofen-N-acyl-1,3,4-oxadiazole

Compounds (a)–(d) (Figure 17) were studied against MCF-7, and it was found that most of the compounds gave high percentage inhibition (Table 11) (Alderawy et al., 2020).

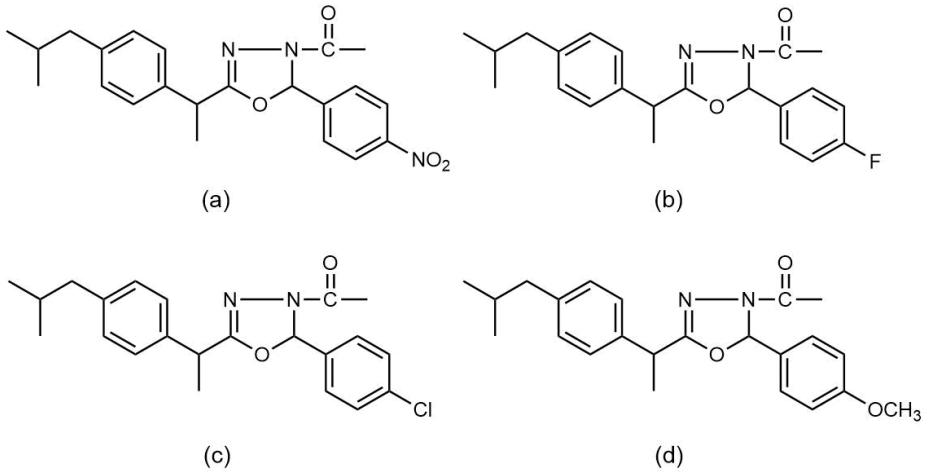


Figure 17. Structure of ibuprofen-N-acyl-1,3,4-oxadiazole with (a) 4-NO_2, (b) 4-Fl, (c) 4-Cl, and (d) 4-OCH_3

Table 11. Percentage Inhibition of MCF-7 by Ibuprofen-N-acyl-1,3,4-Oxadiazole Derivatives

Compound	% Inhibition of MCF-7
(a)	84.9
(b)	85.1
(c)	74.7
(d)	83.8
Control	0

Among all the tested compounds, compound (b) containing 4-fluoro gave the highest inhibition against MCF-7 cell line (85.1%) (Alderawy et al., 2020). The presence of 4-fluoro on 1,3,4-oxadiazole derivatives exhibited great focal adhesion kinase (FAK), which is a common intracellular kinase that regulates signalling pathways related with cellular migration, proliferation, and survival, making it a significant aim in developing anticancer drugs (Liew et al., 2020).

As presumed, NO_2 and 1,3,4-oxadiazole gave one of the highest inhibitions among derivatives, up to 84.9%. These moiety and substitute are quite common in compound derivatives to study the anticancer and antiproliferation activities and were found to be successful in several studies, especially against MCF-7 cell line (Alghamdi & Nazreen, 2020; Hassanzadeh et al., 2020; Khanam et al., 2017; Yadav et al., 2020). It has been demonstrated that derivatives containing aromatic rings and nitro groups exhibit significant cytotoxicity, especially when used against MCF-7 cancer cells.

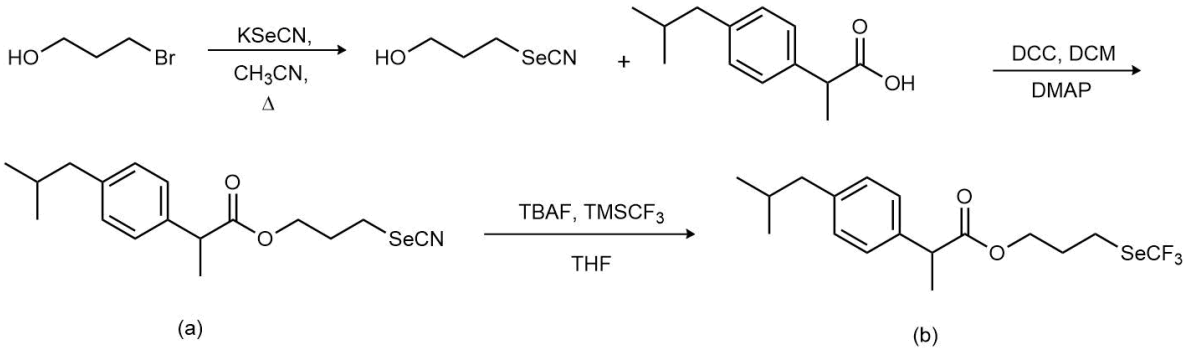
As 4-methoxy is introduced as a substitute, there was a slight decrease in antitumor activity to 83.8% (Alderawy et al., 2020). Studies found that the methoxy group can contribute to positive results in anticancer activity (Bonakdar et al., 2017; El-Sayed et al., 2017). The number and positioning of the methoxy substituent are also crucial in cytotoxicity (Novilla et al., 2019).

Previous research demonstrated that ibuprofen has limited effectiveness (<20%) against MCF-7 (Pedro-Hernández et al., 2017), but this was not evaluated in the current study. However, the result indicates that the presence of N-acyl-1,3,4-oxadiazole contributes to the anticancer effect against breast cancer cells.

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Anticancer Activity of Organoselenides-Ibuprofen Derivatives

Compounds containing organoselenium are becoming more significant in the fields of enzymology, medicine, and bio-organic chemistry (Mugesh et al., 2001). Organoselenium-based molecular probes allow accurate detection of physiologically relevant analytes, such as ROS. Production of ROS is linked to Alzheimer, Parkinson, and cancer, where excess production is a key cause (Kumawat et al., 2021; Madibone et al., 2020). The organoselenides-ibuprofen derivatives are synthesised according to Scheme 9.



Scheme 9. Synthesis of organoselenides-ibuprofen derivatives. Compound (a) cyano substituted and compound (b) trifluoromethyl substituted

The capability of organoselenides-ibuprofen derivatives to suppress the development of human tumour cell lines, such as $CaCO_2$ (human epithelial colorectal adenocarcinoma cell line), BGC-823 (human gastric cancer cell line), MCF-7, and PC-3 (human prostate cancer cell line) was examined, and the results are presented in Table 12. MTT assay was used to evaluate anticancer activities in vitro while the positive control used was 5-fluorouracil as it is often used in cancer treatment, both adjuvant and palliative.

Table 7. Cytotoxic Activity against $CaCO_2$, BGC-823, MCF-7, and PC-3 by Organoselenides-Ibuprofen Derivatives, Ibuprofen, and 5-Fluorouracil

Compounds	IC_{50} (μM)			
	$CaCO_2$	BGC-823	MCF-7	PC-3
(a)	14.5 ± 1.8	17.3 ± 2.3	8.9 ± 0.8	11.2 ± 2.3
(b)	11.3 ± 1.5	8.2 ± 0.7	7.7 ± 0.6	10.4 ± 0.9
Ibuprofen	>50	>50	>50	>50
5-Fluorouracil	7.8 ± 3.1	15.4 ± 1.8	12.3 ± 2.2	9.5 ± 1.1

Although compound (a) was effective in inhibiting $CaCO_2$, BGC-823, and PC-3 cancer cells, it could not surpass the performance of 5-fluorouracil. However, it was still superior to standard ibuprofen.

Compound (b) was discovered to have higher inhibitory efficacy against $CaCO_2$, BGC-823, MCF-7, and PC-3 cells when the derivatives were compared to ibuprofen. The drug showed lower IC_{50} values against BGC-823 and MCF-7 cells in comparison to the standard anticancer drug, 5-fluorouacil. Compound (b) contains trifluoromethyl ($-CF_3$), which is known to have anticancer effects. It is possible that this factor contributed to the suppression of cancer cells (Lanquist et al., 2021; Olszewska et al., 2020; Scattolin et al., 2020; Wang et al., 2019). Fluorine-containing groups, notably perfluorinated fragments, can drastically modify pharmacological characteristics (Scattolin et al., 2020).

Anticancer Activity of Ibuprofen-Organotin Complexes

Figure 18 illustrates an example of an organotin compound, which is defined as bearing at least one covalent connection between a carbon (C) atom and a tin (Sn) atom. They are usually denoted by the formula $RaSnX_{4-a}$ (a = 1–3, R = aryl or alkyl, X = halogen ion or carboxylate, etc.) (Ghani & Yousif, 2021).

Figure 18. Chemical structure of organotin

Organotin compounds have two stable states, which are (II) and (IV) (Ghani & Yousif, 2021). Since the past few years, organic tin(IV) complexes have been used in the field of cancer treatment and have proven their effectiveness to treat lung cancer (A-549), cervical cancer (HeLa), and breast adenocarcinoma (MDA-MB-231) (Hazra et al., 2016). Lately, the cytotoxicity effect of organotin(IV) has been reported to have great complex synergy with NSAIDs (Antonenko et al., 2022). Complexes of ibuprofen with triorganotin(IV), IBF-dimethyltin(IV), and IBF-dibutyltin(IV) were successfully synthesised by Kumari et al. in 2020. In the same year, Farooqi et al. (2020) also reported on the synthesis of triphenyltin(IV) ibuprofen. The synthesis was done through a single-step reaction by reacting the mixture of triphenyltin

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

hydroxide and ibuprofen in dry ethanol under 7 h reflux. The yield of the product was favourable and it was characterised spectroscopically (Farooqi et al., 2020).

The synthesised compounds (Figure 19) were tested against human cancer cell lines viz. prostate cancer (DU145), colon adenocarcinoma (HCT-15), colorectal cancer ($CaCO_2$), breast cancer (MCF-7), androgen-sensitive prostate adenocarcinoma (LNCaP), and HeLa (Kumari et al., 2020).

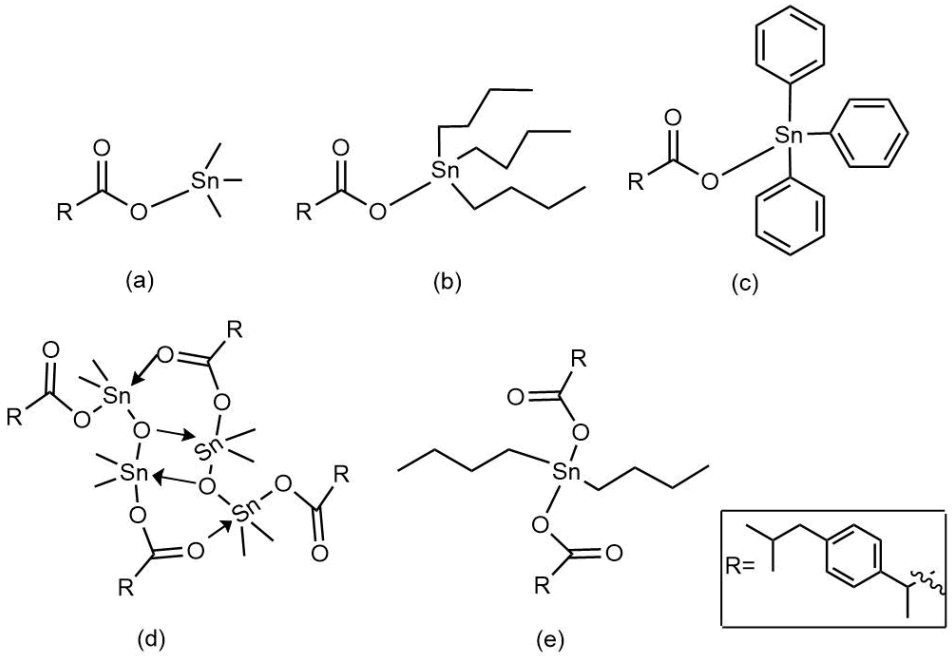


Figure 19. Chemical structure of organotin(IV) complexes with ibuprofen

According to the results (Table 13), the complexes exhibited several activities against various cell lines. Except for compound (a) [$Me_3Sn(IBF)$], all the compounds (b, c, d, and e) induced the cytotoxicity in the researched cancer cell lines. Compound (c) [$Ph_3Sn(IBF)$] exhibited the greatest cytotoxicity against colorectal cancer ($CaCO_2$), with an IC_{50} value of 1.21 µM, which was superior compared to cisplatin, followed by compound (b) [$Bu_3Sn(IBF)$] (IC_{50} = 2.48 µM) and compound (d) [$[Me_2Sn(IBF)]_2O_2$] (IC_{50} = 13.38 µM). Furthermore, IBF demonstrated potent cytotoxicity only against prostate cancer cells (DU145) (IC_{50} = 1.65 µM) while being non-cytotoxic (IC_{50} 100 µM) against HCT-15 and $CaCO_2$ cell lines. In terms of IC_{50} value against DU145, compound (d) and (e) [$Bu_2Sn(IBF)_2$] demonstrated approximately 2.6–4.0 times higher activity than 5-fluorouracil. Compound (c) was moderately cytotoxic to DU145. Compound (d) (IC_{50} = 2.188 µM) also demonstrated the greatest cytotoxicity against colon cancer cells (HCT-15), which was approximately 6 and 2 times greater than 5-fluorouracil and cisplatin, respectively. As a result, compound (d) was highly cytotoxic, with the greatest cytotoxicity against prostate and colon cancer cell lines among compound (a)–(e), whereas compound (c) was very cytotoxic to colorectal cancer cell lines (Kumari et al., 2020).

Table 8. Cytotoxicity of Synthesised Compounds against Tested Cancer Cell Lines

Compounds	IC_{50} (µM)		
	DU145	HCT-15	$CaCO_2$
(a)	100	100	100
(b)	100	100	2.48 ± 0.1
(c)	19.22 ± 0.8	100	1.21 ± 0.84
(d)	3.97 ± 0.81	2.188 ± 0.67	13.38 ± 1.5
(e)	5.92 ± 1.54	32.32 ± 2.1	100
Ibuprofen	1.65 ± 0.2	100	100
5-Fluorouracil	15.4 ± 0.8	12.2 ± 0.5	-
Cisplatin	-	5.04 ± 1.4	96.38 ± 32.03

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

4. Conclusions

The modification of drugs to find other or better biological activities that can benefit humankind has become increasingly common. This review article offers a comprehensive synthesis and analysis of common drugs, including their modifications and effects on potential biological activities. The introduction of metal complexes (Cu, Co, Mg, etc.) in over-the-counter drug modification, especially acetaminophen and ibuprofen, enhanced the effectiveness of ligands to inhibit bacterial growth. The antimicrobial activities of M-piperaquine-acetaminophen, M-prednisolone-acetaminophen, Mg(II)acetaminophen, and M-acetaminophen-ascorbic acid against Gram-positive and Gram-negative bacteria are higher compared to standard acetaminophen. The metal complex of ibuprofen-thiourea is a great urease inhibitor compared to ibuprofen, especially at meta-position with chloro-substituent. Chlorine is more electronegative and has smaller atoms, which may affect the urease inhibitory activity. The removal of carboxylic acid in ibuprofen (affect gastrointestinal) is replaced by ammonium moieties, which are slightly better than ibuprofen in terms of anti-inflammatory activity. Ibuprofen-amide derivatives also showed positive anti-inflammatory results compared to standard celecoxib, and the presence of halogen (Br) affected cell permeability, thus increasing the potency of FAAH/substrate-selective COX inhibitors. Ibuprofen silicon conjugate has high antioxidant activity. Ibuprofen with 1,3,4-oxadiazole gives promising results in the anticancer activity of breast cancer cells, especially in halogen-, methoxy-, and nitro-substituted compounds. Furthermore, ibuprofen with organotin complexes has better anticancer activity compared to the parent drug. According to the findings of this review article, the majority of the derivatives or metal complexes of acetaminophen and ibuprofen exhibited promising biological activities, although further research is necessary to fully exploit the potential of these compounds in developing novel therapeutics. This includes studying their safety, pharmacokinetics, and pharmacodynamics, as well as optimising novel modifications or metal complexes of current acetaminophen and ibuprofen to improve their therapeutic applications.

5. Acknowledgement

The authors wish to express their gratitude to the Malaysia Ministry of Higher Education (MOHE) for the support through Fundamental Research Grant Scheme (FRGS/1/2020/STG04/UNISZA/03/1).

6. References

Abd El-Halim, H. F., Mohamed, G. G., & Anwar, M. N. (2018). Antimicrobial and anticancer activities of Schiff base ligand and its transition metal mixed ligand complexes with heterocyclic base. Applied Organometallic Chemistry, 32(1), e3899. https://doi.org/10.1002/aoc.3899

Abourehab, M. A. S., Alqahtani, A. M., Almalki, F. A., Zaher, D. M., Abdalla, A. N., Gouda, A. M., & Beshr, E. A. M. (2021). Pyrrolizine/Indolizine-NSAID Hybrids: Design, Synthesis, Biological Evaluation, and Molecular Docking Studies. Molecules, 26(21), 6582. https://doi.org/10.3390/molecules26216582

Ahmadi, A., Khalili, M., Olama, Z., Karami, S., & Nahri-Niknafs, B. (2017). Synthesis and Study of Analgesic and Anti-inflammatory Activities of Amide Derivatives of Ibuprofen. Mini-Reviews in Medicinal Chemistry, 17(9), 799–804. https://doi.org/10.2174/1389557516666161226155951

Ahmed, E. F., El-baky, R. M. A., Ahmed, A. B. F., Gameel, N., Aziz, N. A., Fadl, G., & Gad, M. (2016). Evaluation of antibacterial activity of some non- steroidal anti-inflammatory drugs against Escherichia coli causing urinary tract infection. African Journal of Microbiology Research, 10(34), 1408–1416. https://doi.org/10.5897/AJMR2016.8179

Ahn, K., Johnson, D. S., & Cravatt, B. F. (2009). Fatty acid amide hydrolase as a potential therapeutic target for the treatment of pain and CNS disorders. Expert Opinion on Drug Discovery, 4(7), 763–784. https://doi.org/10.1517/17460440903018857

Ahsan, M. J. (2018). Synthesis and cytotoxicity evaluation of [(2,4-dichlorophenoxy)methyl]-5-aryl-1,3,4-oxadiazole/4H-1,2,4-triazole analogues. Turkish Journal of Chemistry, 42(5), 1334–1343. https://doi.org/10.3906/kim-1803-25

Akhondzadeh, S. (2016). The importance of clinical trials in drug development. Avicenna Journal of Medical Biotechnology, 8(4), 2016.

Al-Amiery, A. A., Kadhum, A. A. H., & Mohamad, A. B. (2012). Antifungal and antioxidant activities of pyrrolidone thiosemicarbazone complexes. Bioinorganic Chemistry and Applications, 2012(L). https://doi.org/10.1155/2012/795812

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Alderawy, M. Q. A., Raheem Alrubaie, L. A., & Sheri, F. H. (2020). Synthesis, characterization of ibuprofen n-acyl-1,3,4 oxadiazole derivatives and anticancer activity against MCF-7 cell line. Systematic Reviews in Pharmacy, 11(4), 681–689. https://doi.org/10.31838/srp.2020.4.100

Alghamdi, A., & Nazreen, S. (2020). Synthesis, characterization and cytotoxic study of 2-hydroxy benzothiazole incorporated 1,3,4-oxadiazole derivatives. Egyptian Journal of Chemistry, 63(2), 471–482. https://doi.org/10.21608/ejchem.2019.17265.2059

Alkabodi, I., Almekhlafi, S., & Ibrahim, D. A. (2016). Synthesis and anti-inflammatory activity of novel aspirin and ibuprofen amide derivatives. Chemical and Pharmaceutical Research, 8(May 2019), 307–313.

AlKhalil, M., Al-Hiari, Y., Kasabri, V., Arabiyat, S., Al-Zweiri, M., Mamdooh, N., & Telfah, A. (2020). Selected pharmacotherapy agents as antiproliferative and anti-inflammatory compounds. Drug Development Research, 81(4), 470–490. https://doi.org/10.1002/ddr.21640

Amin, R. R., Abo-elkassem, M., & Anwar, A. (2017). Synthesis , Characterization , and Spectroscopic Studies for New Cu (II), Co (II), Zn (II), Fe (III) And Zr (II) Complexes of Oxytetracycline Antibiotic , In vitro Antimicrobial Assessment Studies. Research and Reviews : Journal of Pharmacy and Pharmaceutical Sciences, 6(1), 38–48.

Amir, M., Akhter, M. W., & Alam, O. (2016). Synthesis, characterization, and biological evaluation of furoxan coupled ibuprofen derivatives as anti-inflammatory agents. Monatshefte Fur Chemie, 147(3), 493–508. https://doi.org/10.1007/s00706-015-1557-x

Annerberg, A., Lwin, K. M., Lindegardh, N., Khrutsawadchai, S., Ashley, E., Day, N. P. J. J., Singhasivanon, P., Tarning, J., White, N. J., & Nosten, F. (2011). A Small Amount of Fat Does Not Affect Piperaquine Exposure in Patients with Malaria □ †. 55(9), 3971–3976. https://doi.org/10.1128/AAC.00279-11

Ansari, A., Ali, A., Asif, M., & Shamsuzzaman. (2017). Review: biologically active pyrazole derivatives. New Journal of Chemistry, 41(1), 16–41. https://doi.org/10.1039/C6NJ03181A

Antonenko, T. A., Gracheva, Y. A., Shpakovsky, D. B., Vorobyev, M. A., Tafeenko, V. A., Mazur, D. M., & Milaeva, E. R. (2022). Cytotoxic activity of organotin compounds containing non-steroidal anti-inflammatory drugs. Journal of Organometallic Chemistry, 960, 122191. https://doi.org/10.1016/j.jorganchem.2021.122191

Ashraf, Z., Mahmood, T., Hassan, M., Afzal, S., Rafique, H., Afzal, K., & Latip, J. (2019). Dexibuprofen amide derivatives as potential anticancer agents: Synthesis, in silico docking, bioevaluation, and molecular dynamic simulation. Drug Design, Development and Therapy, 13, 1643–1657. https://doi.org/10.2147/DDDT.S178595

Assefa, D. G., Zeleke, E. D., Bekele, D., Tesfahunei, H. A., Getachew, E., Joseph, M., & Manyazewal, T. (2021). Efficacy and safety of dihydroartemisinin – piperaquine versus artemether – lumefantrine for treatment of uncomplicated Plasmodium falciparum malaria in Ugandan children : a systematic review and meta - analysis of randomized control trials. Malaria Journal, 1–25. https://doi.org/10.1186/s12936-021-03711-4

Attia, M., Essa, E. A., Zaki, R. M., & Elkordy, A. A. (2020). An overview of the Antioxidant Effects of Ascorbic Acid and Alpha Lipoic Acid (In Liposomal Forms) as Adjuvant in Cancer Treatment. Antioxidants, 9(5), 1–15. https://doi.org/10.3390/antiox9050359

Ayipo, Y. O., Obaleye, J. A., & Badeggi, U. M. (2016). Novel metal complexes of mixed piperaquine-acetaminophen and piperaquine-acetylsalicylic acid: Synthesis, characterization and antimicrobial activities. Journal of the Turkish Chemical Society, Section A: Chemistry, 4(1), 313–313. https://doi.org/10.18596/jotcsa.287331

Ayipo, Y., Osunniran, W., Badeggi, U., Saheed, I., Jimoh, A., & Babamale, H. (2021). Synthesis, characterization and antibacterial study of Co(II) and Cu(II) complexes of mixed ligands of piperaquine and diclofenac. Journal of the Turkish Chemical Society Section A: Chemistry, 8(2), 633–650. https://doi.org/10.18596/jotcsa.898523

Babamale, H., Lawal, A., Rajee, O., & Oloyede, E. (2016). Synthesis , Characterization and Biological Activity Studies of Mixed Paracetamol- Ascorbic Acid Metal Complexes . Applied Science Environment, 20(4), 1157–1161. https://doi.org/http://dx.doi.org/10.4314/jasem.v20i4.32

Badea, G. I., & Radu, G. L. (2018). Introductory Chapter: Carboxylic Acids - Key Role in Life Sciences. In Carboxylic Acid - Key Role in Life Sciences (pp. 1–6). InTech. https://doi.org/10.5772/intechopen.77021

Bamigboye, M. O., Ejidike, I. P., & Ahmed, R. N. (2019). Antibacterial activities of Some Mixed Isoniazid-Ibuprofen Metal Complexes : Chelation and Characterization. Natural & Applied Science Journal, 2(2). https://doi.org/10.38061/idunas.631229

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Barba, F. J., Esteve, M. J., & Frígola, A. (2014). Chapter 11 - Bioactive Components from Leaf Vegetable Products. In B. T.-S. in N. P. C. Atta-ur-Rahman (Ed.), Studies in Natural Products Chemistry (Vol. 41, pp. 321–346). Elsevier. https://doi.org/https://doi.org/10.1016/B978-0-444-63294-4.00011-5

Bateman, D. N., Carroll, R., Pettie, J., Yamamoto, T., Elamin, M. E. M. O., Peart, L., Dow, M., Coyle, J., Cranfield, K. R., Hook, C., Sandilands, E. A., Veiraiah, A., Webb, D., Gray, A., Dargan, P. I., Wood, D. M., Thomas, S. H. L., Dear, J. W., & Eddleston, M. (2014). Effect of the UK's revised paracetamol poisoning management guidelines on admissions, adverse reactions and costs of treatment. British Journal of Clinical Pharmacology, 78(3), 610–618. https://doi.org/10.1111/bcp.12362

Bhandari, S. V., Bothara, K. G., Raut, M. K., Patil, A. A., Sarkate, A. P., & Mokale, V. J. (2008). Design, Synthesis and Evaluation of Antiinflammatory, Analgesic and Ulcerogenicity studies of Novel S-Substituted phenacyl-1,3,4-oxadiazole-2-thiol and Schiff bases of Diclofenac acid as Nonulcerogenic Derivatives. Bioorganic and Medicinal Chemistry, 16(4), 1822–1831. https://doi.org/10.1016/j.bmc.2007.11.014

Biancatelli, R. M. L. C., Berrill, M., & Marik, P. E. (2020). The antiviral properties of vitamin C. Expert Review of Anti-Infective Therapy, 18(2), 99–101. https://doi.org/10.1080/14787210.2020.1706483

Bonakdar, A. P. S., Vafaei, F., Farokhpour, M., Esfahani, M. H. N., & Massah, A. R. (2017). Synthesis and anticancer activity assay of novel chalcone-sulfonamide derivatives. Iranian Journal of Pharmaceutical Research, 16(2), 565–568.

Caparrotta, T. M., Antoine, D. J., & Dear, J. W. (2018). Are some people at increased risk of paracetamol-induced liver injury? A critical review of the literature. European Journal of Clinical Pharmacology, 74(2), 147–160. https://doi.org/10.1007/s00228-017-2356-6

Chawla, G., Naaz, B., & Siddiqui, A. A. (2018). Exploring 1,3,4-Oxadiazole Scaffold for Anti-inflammatory and Analgesic Activities: A Review of Literature From 2005-2016. Mini-Reviews in Medicinal Chemistry, 18(3), 216–233. https://doi.org/10.2174/1389557517666170127121215

Chudobova, D., Dostalova, S., Ruttkay-Nedecky, B., Guran, R., Rodrigo, M. A. M., Tmejova, K., Krizkova, S., Zitka, O., Adam, V., & Kizek, R. (2015). The effect of metal ions on Staphylococcus aureus revealed by biochemical and mass spectrometric analyses. Microbiological Research, 170(June 2014), 147–156. https://doi.org/10.1016/j.micres.2014.08.003

Collignon, P. C., Conly, J. M., Andremont, A., McEwen, S. A., & Aidara-Kane, A. (2016). World Health Organization Ranking of Antimicrobials According to Their Importance in Human Medicine: A Critical Step for Developing Risk Management Strategies to Control Antimicrobial Resistance From Food Animal Production. Clinical Infectious Diseases, 63(8), 1087–1093. https://doi.org/10.1093/cid/ciw475

Cong, W., Sun, Y., Sun, Y. F., Yan, W. Bin, Zhang, Y. L., Gao, Z. F., Wang, C. H., Hou, G. G., & Zhang, J. J. (2021). Trifluoromethyl-substituted 3,5-bis(arylidene)-4-piperidones as potential anti-hepatoma and anti-inflammation agents by inhibiting NF-κB activation. Journal of Enzyme Inhibition and Medicinal Chemistry, 36(1), 1622–1631. https://doi.org/10.1080/14756366.2021.1953996

Corey, D. R. (2007). Chemical modification: The key to clinical application of RNA interference? Journal of Clinical Investigation, 117(12), 3615–3622. https://doi.org/10.1172/JCI33483

Dainese, E., Oddi, S., Simonetti, M., Sabatucci, A., Angelucci, C. B., Ballone, A., Dufrusine, B., Fezza, F., De Fabritiis, G., & Maccarrone, M. (2020). The endocannabinoid hydrolase FAAH is an allosteric enzyme. Scientific Reports, 10(1), 2292. https://doi.org/10.1038/s41598-020-59120-1

Damilola, A., Olagboye, S. A., & Akinwunmi, O. . (2019). Antimicrobial Activities of Novel Synthesized Cu(II) and Co(II) Mixed Ligand Complexes of Prednisolone and Paracetamol. International Journal of Scientific & Engineering Researc, 10(September). https://www.researchgate.net/publication/344429477_ANTIMICROBIAL_ACTIVITIES_OF_NOVEL_SYNTHESIZED_Cu_II_and_Co_II_MIXED_LIGAND_COMPLEXES_OF_PREDNISOLONE_AND_PARACETAMOL?channel=doi&linkId=5f746650299bf1b53e004bc5&showFulltext=true

Deplano, A., Cipriano, M., Moraca, F., Novellino, E., Catalanotti, B., Fowler, C. J., & Onnis, V. (2019). Benzylamides and piperazinoarylamides of ibuprofen as fatty acid amide hydrolase inhibitors. Journal of Enzyme Inhibition and Medicinal Chemistry, 34(1), 562–576. https://doi.org/10.1080/14756366.2018.1532418

Deplano, A., Karlsson, J., Svensson, M., Moraca, F., Catalanotti, B., Fowler, C. J., & Onnis, V. (2020). Exploring the fatty acid amide hydrolase and cyclooxygenase inhibitory properties of novel amide derivatives of ibuprofen. Journal of Enzyme Inhibition and Medicinal Chemistry, 35(1), 815–823. https://doi.org/10.1080/14756366.2020.1743283

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Dinarello, C. A. (2010). Anti-inflammatory Agents: Present and Future. Cell, 140(6), 935–950. https://doi.org/10.1016/j.cell.2010.02.043

El-Sayed, S., Metwally, K., El-Shanawani, A. A., Abdel-Aziz, L. M., Pratsinis, H., & Kletsas, D. (2017). Synthesis and anticancer activity of novel quinazolinone-based rhodanines. Chemistry Central Journal, 11(1), 1–10. https://doi.org/10.1186/s13065-017-0333-x

Ennis, Z. N., Dideriksen, D., Vægter, H. B., Handberg, G., & Pottegård, A. (2016). Acetaminophen for Chronic Pain: A Systematic Review on Efficacy. Basic and Clinical Pharmacology and Toxicology, 118(3), 184–189. https://doi.org/10.1111/bcpt.12527

Fang, W. Y., Ravindar, L., Rakesh, K. P., Manukumar, H. M., Shantharam, C. S., Alharbi, N. S., & Qin, H. L. (2019). Synthetic approaches and pharmaceutical applications of chloro-containing molecules for drug discovery: A critical review. European Journal of Medicinal Chemistry, 173, 117–153. https://doi.org/10.1016/j.ejmech.2019.03.063

Fejzagić, A. V., Gebauer, J., Huwa, N., & Classen, T. (2019). Halogenating enzymes for active agent synthesis: First steps are done and many have to follow. Molecules, 24(21). https://doi.org/10.3390/molecules24214008

Garza-Cervantes, J. A., Chávez-Reyes, A., Castillo, E. C., García-Rivas, G., Ortega-Rivera, O. A., Salinas, E., Ortiz-Martínez, M., Gómez-Flores, S. L., Peña-Martínez, J. A., Pepi-Molina, A., Treviño-González, M. T., Zarate, X., Cantú-Cárdenas, M. E., Escarcega-Gonzalez, C. E., & Morones-Ramírez, J. R. (2017). Synergistic antimicrobial effects of silver/transition-metal combinatorial treatments. Scientific Reports, 7(1), 1–16. https://doi.org/10.1038/s41598-017-01017-7

Gerriets, V., Anderson, J., & Nappe, T. M. (2023). Acetaminophen. In StatPearls. http://www.ncbi.nlm.nih.gov/pubmed/24099020

Ghani, H., & Yousif, E. (2021). Chemistry of Some Organotin Compounds. Al-Nahrain Journal of Science, 24(3), 9–15. https://doi.org/10.22401/ANJS.24.3.02

Glomb, T., & Świątek, P. (2021). Antimicrobial Activity of 1,3,4-Oxadiazole Derivatives. International Journal of Molecular Sciences, 22(13), 6979. https://doi.org/10.3390/ijms22136979

Glomb, T., Szymankiewicz, K., & Świątek, P. (2018). Anti-Cancer Activity of Derivatives of 1,3,4-Oxadiazole. Molecules, 23(12), 3361. https://doi.org/10.3390/molecules23123361

Golonka, I., Oleksy, M., Junka, A., Matera-witkiewicz, A., Bartoszewicz, M., & Musiał, W. (2017). Selected Physicochemical and Biological Properties of Ethyl Ascorbic Acid Compared to Ascorbic Acid. Biol. Pharm. Bull., 40(8), 1199–1206. https://doi.org/10.1248/bpb.b16-00967

Gomaa, S. (2018). Adverse effects induced by diclofenac , ibuprofen , and paracetamol toxicity on immunological and biochemical parameters in Swiss albino mice. Basic and Applied Zoology, 79(5), 1–9. https://doi.org/10.1186/s41936-018-0025-7

Goodman, M. C., Xu, S., Rouzer, C. A., Banerjee, S., Ghebreselasie, K., Migliore, M., Piomelli, D., & Marnett, L. J. (2018). Dual cyclooxygenase–fatty acid amide hydrolase inhibitor exploits novel binding interactions in the cyclooxygenase active site. Journal of Biological Chemistry, 293(9), 3028–3038. https://doi.org/10.1074/jbc.M117.802058

Guo, Z.-R. (2012). [Modification of natural products for drug discovery]. Yao xue xue bao = Acta pharmaceutica Sinica, 47(2), 144–157. http://www.ncbi.nlm.nih.gov/pubmed/22512023

Haider, S., Alam, M. S., Hamid, H., Umar, S., Kumar, D., & Nazreen, S. (2018). Synthesis of novel amide containing Schiffs bases of 5-(4-chloro-phenyl)-furan-2-carboxaldehyde: Their in vivo anti-inflammatory, antioxidant and antinociceptive activities with ulcerogenic risk evaluation. Journal of Reports in Pharmaceutical Sciences, 7(1), 44–63.

Hassanzadeh, F., Jafari, E., Zarabi, M., Khodarahmi, G., & Vaseghi, G. (2020). Synthesis, cytotoxic evaluation, and molecular docking studies of some new 1, 3, 4-oxadiazole-based compounds. Research in Pharmaceutical Sciences, 15(5), 454. https://doi.org/10.4103/1735-5362.297848

Hazra, S., Paul, A., Sharma, G., Koch, B., da Silva, M. F. C. G., & Pombeiro, A. J. L. (2016). Sulfonated Schiff base Sn(IV) complexes as potential anticancer agents. Journal of Inorganic Biochemistry, 162, 83–95. https://doi.org/10.1016/j.jinorgbio.2016.06.008

He, X., Nie, Y., Zhong, M., Li, S., Li, X., Guo, Y., Liu, Z., Gao, Y., Ding, F., Wen, D., & Zhang, Y. (2021). New organoselenides (NSAIDs-Se derivatives) as potential anticancer agents: Synthesis, biological evaluation and in silico calculations. European Journal of Medicinal Chemistry, 218, 113384. https://doi.org/10.1016/j.ejmech.2021.113384

Hegde, P., Boshoff, H. I. M., Rusman, Y., Aragaw, W. W., Salomon, C. E., Dick, T., & Aldrich, C. C. (2021). Reinvestigation of the structure-activity relationships of isoniazid. Tuberculosis, 129, 102100. https://doi.org/10.1016/j.tube.2021.102100

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Hernandez-Patlan, D., B.Solis-Cruz, Mendez-Albores, A., Latorre, Hernandez-Velasco, J. D., X., R., L.-A., & Tellez, G. (2017). Comparison of PrestoBlue â and plating method to evaluate antimicrobial activity of ascorbic acid , boric acid and curcumin in an in vitro gastrointestinal model. Applied Microbiology, 124(2), 423–430. https://doi.org/10.1111/jam.13659

Hill, R. G., & Rang, H. P. (2013). Drug Discovery & Development - Technology in Transition (R. G. Hill & H. P. Rang (eds.); 2nd ed.). Churchill Livingstone, ELSEVIER.

Hu, Y., Zhang, S., Zhao, F., Gao, C., Feng, L., Lv, Z., Xu, Z., & Wu, X. (2017). SC. European Journal of Medicinal Chemistry. https://doi.org/10.1016/j.ejmech.2017.04.002

Hughes, J. P., Rees, S., Kalindjian, S. B., Philpott, K. L., Philpott, K., & Building, H. (2011). Principles of early drug discovery Correspondence. https://doi.org/10.1111/j.1476-5381.2010.01127.x

Iqbal Farooqi, S., Arshad, N., Perveen, F., Ali Channar, P., Saeed, A., Javed, A., Hökelek, T., & Flörke, U. (2020). Structure and surface analysis of ibuprofen-organotin conjugate: Potential anti-cancer drug candidacy of the compound is proven by in-vitro DNA binding and cytotoxicity studies. Polyhedron, 192, 114845. https://doi.org/10.1016/j.poly.2020.114845

Iseh, A., Adegbola, A., & Adeagbo, B. (2017). Pharmacokinetic Characterization of Piperaquine in Nigerian Healthy Volunteers after Co-administration with a Commercial Brand of Moringa Tea. British Journal of Pharmaceutical Research, 15(4), 1–10. https://doi.org/10.9734/BJPR/2017/32723

Kafarski, P., & Talma, M. (2018). Recent advances in design of new urease inhibitors: A review. Journal of Advanced Research, 13, 101–112. https://doi.org/10.1016/j.jare.2018.01.007

Khanam, R., Ahmad, K., Hejazi, I. I., Siddique, I. A., Kumar, V., Bhat, A. R., Azam, A., & Athar, F. (2017). Inhibitory growth evaluation and apoptosis induction in MCF-7 cancer cells by new 5-aryl-2-butylthio-1,3,4-oxadiazole derivatives. Cancer Chemotherapy and Pharmacology, 80(5), 1027–1042. https://doi.org/10.1007/s00280-017-3414-6

Khosroshahi, A. M., Aflaki, F., Saemiyan, N., Abdollahpour, A., & Asgharian, R. (2016). Simultaneous determination of paracetamol, 4-Aminophenol, 4-Chloroacetanilid, Benzyl alcohol, Benzaldehyde and EDTA by HPLC method in paracetamol injection ampoule. Journal of Pharmaceutical and Health Sciences, 4(1), 61–69.

Kilburg, M., & Tyler, R. (2017). Ibuprofen Synthesis – Writing Anthology. https://central.edu/writing-anthology/2019/04/11/ibuprofen-synthesis/

Kingsley Ogemdi, I. (2019). A Review on the Properties and Uses of Paracetamol. International Journal of Pharmacy and Chemistry, 5(3), 31. https://doi.org/10.11648/j.ijpc.20190503.12

Kiriiri, G. K., Njogu, P. M., & Mwangi, A. N. (2020). Exploring different approaches to improve the success of drug discovery and development projects: a review. Future Journal of Pharmaceutical Sciences, 6(1). https://doi.org/10.1186/s43094-020-00047-9

Kleemiss, F., Justies, A., Duvinage, D., Watermann, P., Ehrke, E., Sugimoto, K., Fugel, M., Malaspina, L. A., Dittmer, A., Kleemiss, T., Puylaert, P., King, N. R., Staubitz, A., Tzschentke, T. M., Dringen, R., Grabowsky, S., & Beckmann, J. (2020). Sila-Ibuprofen. Journal of Medicinal Chemistry, 63(21), 12614–12622. https://doi.org/10.1021/acs.jmedchem.0c00813

Kowalska-Krochmal, B., & Dudek-Wicher, R. (2021). The Minimum Inhibitory Concentration of Antibiotics: Methods, Interpretation, Clinical Relevance. Pathogens, 10(2), 165. https://doi.org/10.3390/pathogens10020165

Kumari, R., Banerjee, S., Roy, P., & Nath, M. (2020). Organotin(IV) complexes of NSAID, ibuprofen, X-ray structure of Ph3Sn(IBF), binding and cleavage interaction with DNA and in vitro cytotoxic studies of several organotin complexes of drugs. Applied Organometallic Chemistry, 34(1), 1–24. https://doi.org/10.1002/aoc.5283

Kumawat, A., Raheem, S., Ali, F., Dar, T. A., Chakrabarty, S., & Rizvi, M. A. (2021). Organoselenium compounds as acetylcholinesterase inhibitors: Evidence and mechanism of mixed inhibition. Journal of Physical Chemistry B, 125(6), 1531–1541. https://doi.org/10.1021/acs.jpcb.0c08111

Kumria, R., Nair, A. B., Goomber, G., & Gupta, S. (2016). Buccal films of prednisolone with enhanced bioavailability. Drug Delivery, 23(2), 471–478. https://doi.org/10.3109/10717544.2014.920058

Lanquist, A. P., Gupta, S., Al-Afyouni, K. F., Al-Afyouni, M., Kodanko, J. J., & Turro, C. (2021). Trifluoromethyl substitution enhances photoinduced activity against breast cancer cells but reduces ligand exchange in Ru(II) complex †. https://doi.org/10.1039/d1sc03213e

Liew, S. K., Malagobadan, S., Arshad, N. M., & Nagoor, N. H. (2020). A review of the structure—activity relationship of natural and synthetic antimetastatic compounds. Biomolecules, 10(1), 1–28. https://doi.org/10.3390/biom10010138

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Lobo, S. (2020). Is there enough focus on lipophilicity in drug discovery? Expert Opinion on Drug Discovery, 15(3), 261–263. https://doi.org/10.1080/17460441.2020.1691995

Ma, R., Guo, D.-X., Li, H.-F., Liu, H.-X., Zhang, Y.-R., Ji, J.-B., Xing, J., & Wang, S.-Q. (2019). Spectroscopic methodologies and molecular docking studies on the interaction of antimalarial drug piperaquine and its metabolites with human serum albumin. Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy, 222, 117158. https://doi.org/https://doi.org/10.1016/j.saa.2019.117158

Maddila, S., Gorle, S., Sampath, C., & Lavanya, P. (2016). Synthesis and anti-inflammatory activity of some new 1,3,4-thiadiazoles containing pyrazole and pyrrole nucleus. Journal of Saudi Chemical Society, 20, S306–S312. https://doi.org/10.1016/j.jscs.2012.11.007

Madibone, K. S., Deshmukh, P. P., Navalkar, A., Maji, S. K., Badani, P. M., & Manjare, S. T. (2020). Cyclic Organoselenide BODIPY-Based Probe: Targeting Superoxide in MCF-7 Cancer Cells. ACS Omega, 5(23), 14186–14193. https://doi.org/10.1021/acsomega.0c02074

Malik, M. A., Dar, O. A., Gull, P., Wani, M. Y., & Hashmi, A. A. (2018). Heterocyclic Schiff base transition metal complexes in antimicrobial and anticancer chemotherapy. MedChemComm, 9(3), 409–436. https://doi.org/10.1039/c7md00526a

Marrs, W., & Stella, N. (2009). Measuring Endocannabinoid Hydrolysis: Refining our Tools and Understanding. AAPS, 11(No.2). https://doi.org/10.1208/s12248-009-9109-0

Martínez, M., Carranza, M. P., Massaguer, A., Santos, L., Organero, J. A., Aliende, C., De Llorens, R., Ng-Choi, I., Feliu, L., Planas, M., Rodríguez, A. M., Manzano, B. R., Espino, G., & Jalón, F. A. (2017). Synthesis and Biological Evaluation of Ru(II) and Pt(II) Complexes Bearing Carboxyl Groups as Potential Anticancer Targeted Drugs. Inorganic Chemistry, 56(22), 13679–13696. https://doi.org/10.1021/acs.inorgchem.7b01178

Mata, A. M. O. F. da, Carvalho, R. M. de, Alencar, M. V. O. B. de, Cavalcante, Melo, A. A. de C., & Silva, B. B. da. (2016). Ascorbic Acid in the Prevention and Treatment of Cancer. 62(7), 680–686. https://doi.org/10.1590/1806-9282.62.07.680

Mehta, N., Aggarwal, S., Thareja, S., Malla, P., Misra, M., Bhardwaj, T. R., & Kumar, M. (2010). Synthesis, pharmacological and toxicological evaluation of amide derivatives of ibuprofen. International Journal of ChemTech Research, 2(1), 233–238.

Mian, P., van den Anker, J. N., van Calsteren, K., Annaert, P., Tibboel, D., Pfister, M., Allegaert, K., & Dallmann, A. (2020). Physiologically Based Pharmacokinetic Modeling to Characterize Acetaminophen Pharmacokinetics and N-Acetyl-p-Benzoquinone Imine (NAPQI) Formation in Non-Pregnant and Pregnant Women. Clinical Pharmacokinetics, 59(1), 97–110. https://doi.org/10.1007/s40262-019-00799-5

Mihailović, N., Marković, V., Matić, I. Z., Stanisavljević, N. S., Jovanović, Ž. S., Trifunović, S., & Joksović, L. (2017). Synthesis and antioxidant activity of 1,3,4-oxadiazoles and their diacylhydrazine precursors derived from phenolic acids. RSC Advances, 7(14), 8550–8560. https://doi.org/10.1039/C6RA28787E

Mittapally, S., Taranum, R., & Parveen, S. (2018). Metal ions as antibacterial agents. Journal of Drug Delivery and Therapeutics, 8, 411–419. https://doi.org/9http://dx.doi.org/10.22270/jddt.v8i6-s.2063

Motwani, M. P., Bennett, F., Norris, P. C., Maini, A. A., George, M. J., Newson, J., Henderson, A., Hobbs, A. J., Tepper, M., White, B., Serhan, C. N., Macallister, R., & Gilroy, D. W. (2018). Potent Anti-Inflammatory and Pro-Resolving Effects of Anabasum in a Human Model of Self-Resolving Acute Inflammation. 104(4), 675–686. https://doi.org/10.1002/cpt.980

Mugesh, G., du Mont, W.-W., & Sies, H. (2001). Chemistry of Biologically Important Synthetic Organoselenium Compounds. Chemical Reviews, 101(7), 2125–2180. https://doi.org/10.1021/cr000426w

Mumtaz, A., Arshad, J., Saeed, A., Nawaz, M. A. H., & Iqbal, J. (2018). Synthesis, Characterization and Urease Inhibition Studies of Transition Metal Complexes of Thioureas Bearing Ibuprofen Moiety. Journal of the Chilean Chemical Society, 63(2), 3934–3940. https://doi.org/10.4067/s0717-97072018000203934

Murahari, M., Mahajan, V., Neeladri, S., Kumar, M. S., & Mayur, Y. C. (2019). Ligand based design and synthesis of pyrazole based derivatives as selective COX-2 inhibitors. Bioorganic Chemistry, 86, 583–597. https://doi.org/https://doi.org/10.1016/j.bioorg.2019.02.031

Nandanwar, S. K., & Kim, H. J. (2019). Anticancer and Antibacterial Activity of Transition Metal Complexes. ChemistrySelect, 4(5), 1706–1721. https://doi.org/https://doi.org/10.1002/slct.201803073

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Narsinghani, T., & Sharma, R. (2017). Synthesis, anti-inflammatory activities and docking studies of amide derivatives of meclofenamic acid. Chemical Papers, 71(4), 857–868. https://doi.org/10.1007/s11696-016-0102-7

Nayak, S., Gaonkar, S. L., Musad, E. A., & Dawsar, A. M. AL. (2021). 1,3,4-Oxadiazole-containing hybrids as potential anticancer agents: Recent developments, mechanism of action and structure-activity relationships. Journal of Saudi Chemical Society, 25(8), 101284. https://doi.org/10.1016/j.jscs.2021.101284

Njus, D., Kelley, P. M., Tu, Y.-J., & Schlegel, H. B. (2020). Ascorbic Acid: The Chemistry Underlying Its Antioxidant Properties. Free Radical Biology and Medicine, 159, 37–43. https://doi.org/https://doi.org/10.1016/j.freeradbiomed.2020.07.013

Novilla, A., Mustofa, M., Astuti, I., Jumina, J., & Suwito, H. (2019). Cytotoxic Activity of Methoxy-4'amino Chalcone Derivatives Against Leukemia Cell Lines. Molecular and Cellular Biomedical Sciences, 3(1), 34. https://doi.org/10.21705/mcbs.v3i1.44

Ohashi, N., & Kohno, T. (2020). Analgesic Effect of Acetaminophen: A Review of Known and Novel Mechanisms of Action. Frontiers in Pharmacology, Frontiers Media S.A. https://doi.org/10.3389/fphar.2020.580289

Olszewska, P., Cal, D., Zagórski, P., & Mikiciuk-Olasik, E. (2020). A novel trifluoromethyl 2-phosphonopyrrole analogue inhibits human cancer cell migration and growth by cell cycle arrest at G1 phase and apoptosis. European Journal of Pharmacology, 871. https://doi.org/10.1016/j.ejphar.2020.172943

Osowole, A. A., Agbaje, O. B. A., & Ojo, B. O. (2014). Synthesis , characterization and antibacterial properties of some heteroleptic metal (II) complexes of paracetamol and vanillin. Asian Journal of Pharmaceutical and Clinical Research, 7(3).

Ouellette, R. J., & Rawn, J. D. (2018). 24 - Amines and Amides (R. J. Ouellette & J. D. B. T.-O. C. (Second E. Rawn (eds.); pp. 763–800). Academic Press. https://doi.org/https://doi.org/10.1016/B978-0-12-812838-1.50024-4

Ozawa, M., Kubo, T., Lee, S. H., & Oe, T. (2019). LC-MS analyses of N-acetyl-p-benzoquinone imine-adducts of glutathione, cysteine, N-acetylcysteine, and albumin in a plasma sample: A case study from a patient with a rare acetaminophen-induced acute swelling rash. The Journal of Toxicological Sciences, 44(8), 559–563. https://doi.org/10.2131/jts.44.559

Paul, E. D., Dallatu, Y. A., & Akwu, F. J. (2018). Antimicrobial, Acute Toxicity and Anti-inflammatory Investigations of Mg(II) Complex of Acetaminophen. 3(2), 959–963.

Pedro-Hernández, L., Martínez-Klimova, E., Cortez-Maya, S., Mendoza-Cardozo, S., Ramírez-Ápan, T., & Martínez-García, M. (2017). Synthesis, Characterization, and Nanomedical Applications of Conjugates between Resorcinarene-Dendrimers and Ibuprofen. Nanomaterials, 7(7), 163. https://doi.org/10.3390/nano7070163

Pérez, D. J., Díaz-Reval, M. I., Obledo-Benicio, F., Zakai, U. I., Gómez-Sandoval, Z., Razo-Hernández, R. S., West, R., Sumaya-Martínez, M. T., Pineda-Urbina, K., & Ramos-Organillo, Á. (2017). Silicon containing ibuprofen derivatives with antioxidant and anti-inflammatory activities: An in vivo and in silico study. European Journal of Pharmacology, 814, 18–27. https://doi.org/10.1016/j.ejphar.2017.07.046

Permala, J., Tarning, J., Nosten, F., & White, N. J. (2017). Prediction of Improved Antimalarial Chemoprevention with Weekly Dosing. Antimicrobial Agents and Chemotherapy, 61(5), e02491-16.

Ragab, F. A., Heiba, H. I., El-Gazzar, M. G., Abou-Seri, S. M., El-Sabbagh, W. A., & El-Hazek, R. M. (2017). Anti-inflammatory, analgesic and COX-2 inhibitory activity of novel thiadiazoles in irradiated rats. Journal of Photochemistry and Photobiology B: Biology, 166, 285–300. https://doi.org/10.1016/j.jphotobiol.2016.12.007

Ramachandran, A., & Jaeschke, H. (2019). Acetaminophen Hepatotoxicity. Semin Liver Dis, 39, 221–234. https://doi.org/10.1055/s-0039-1679919

Rashid, M., Rafique, H., Roshan, S., Shamas, S., Iqbal, Z., Ashraf, Z., Abbas, Q., Hassan, M., Ur, Z., Qureshi, R., Hassham, M., Asad, H. Bin, & Com, M. (2020). Enzyme Inhibitory Kinetics and Molecular Docking Studies ofHalo-Substituted Mixed Ester/Amide-Based Derivatives as JackBean Urease Inhibitors. https://doi.org/10.1155/2020/8867407

Rasmussen, S. A., Ceja, F. G., Conrad, M. D., Tumwebaze, P. K., Byaruhanga, O., Katairo, T., Nsobya, S. L., Rosenthal, P. J., & Cooper, R. A. (2017). Changing Antimalarial Drug Sensitivities in Uganda. Antimicrobial Agents and Chemotherapy, 61(12). https://doi.org/10.1128/AAC.01516-17

Reygaert, W. (2018). An overview of the antimicrobial resistance mechanisms of bacteria. AIMS Microbiology, 4(3), 482–501. https://doi.org/10.3934/microbiol.2018.3.482

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Rizvi, F., Khan, M., Jabeen, A., Siddiqui, H., & Choudhary, M. I. (2019). Studies on Isoniazid Derivatives through a Medicinal Chemistry Approach for the Identification of New Inhibitors of Urease and Inflammatory Markers. Scientific Reports, 9(1), 1–14. https://doi.org/10.1038/s41598-019-43082-0

Rizzotto, M. (2012). Metal Complexes as Antimicrobial Agents. In A Search for Antibacterial Agents (pp. 74–89). InTech. https://doi.org/10.5772/45651

Roberts, E., Nunes, V. D., Buckner, S., Latchem, S., Constanti, M., Miller, P., Doherty, M., Zhang, W., Birrell, F., Porcheret, M., Dziedzic, K., Bernstein, I., Wise, E., & Conaghan, P. G. (2016). Paracetamol: Not as safe as we thought? A systematic literature review of observational studies. Annals of the Rheumatic Diseases, 75(3), 552–559. https://doi.org/10.1136/annrheumdis-2014-206914

Sangcharoen, N., Klaypradit, W., & Wilaipun, P. (2017). Antimicrobial activity optimization of nisin, ascorbic acid and ethylenediamine tetraacetic acid disodium salt (EDTA) against Salmonella Enteritidis ATCC 13076 using response surface methodology. Agriculture and Natural Resources, 51(5), 355–364. https://doi.org/https://doi.org/10.1016/j.anres.2017.12.005

Santis, M. De, & Saad, F. (2016). Corticosteroids in the Treatment of Metastatic Castration-resistant Prostate Cancer. Urology, 96, 156–164. https://doi.org/10.1016/j.urology.2016.02.010

Sasso, O., Migliore, M., Habrant, D., Armirotti, A., Albani, C., Summa, M., Moreno-sanz, G., Scarpelli, R., & Piomelli, D. (2015). Multitarget fatty acid amide hydrolase / cyclooxygenase blockade suppresses intestinal in fl ammation and protects against nonsteroidal anti-in fl ammatory drug-dependent gastrointestinal damage. FASEB, 29(6), 2616–2627. https://doi.org/https://doi.org/10.1096/fj.15-270637

Scarpelli, R., Sasso, O., & Piomelli, D. (2016). A Double Whammy : Targeting Both Fatty Acid Amide Hydrolase (FAAH) and Cyclooxygenase (COX) To Treat Pain and Inflammation. ChemMedChem, 11(12), 1242–1251. https://doi.org/10.1002/cmdc.201500395

Scattolin, T., Bortolamiol, E., Visentin, F., Palazzolo, S., Caligiuri, I., Perin, T., Canzonieri, V., Demitri, N., Rizzolio, F., & Togni, A. (2020). Palladium(II)-η 3 -Allyl Complexes Bearing N -Trifluoromethyl N -Heterocyclic Carbenes: A New Generation of Anticancer Agents that Restrain the Growth of High-Grade Serous Ovarian Cancer Tumoroids. Chemistry – A European Journal, 26(51), 11868–11876. https://doi.org/10.1002/chem.202002199

Seraj, F., Kanwal, Khan, K. M., Khan, A., Ali, M., Khalil, R., Ul-Haq, Z., Hameed, S., Taha, M., Salar, U., & Perveen, S. (2021). Biology-oriented drug synthesis (BIODS), in vitro urease inhibitory activity, and in silico studies on ibuprofen derivatives. Molecular Diversity, 25(1), 143–157. https://doi.org/10.1007/s11030-019-10032-x

Shakeel, A. (2016). Thiourea Derivatives in Drug Design and Medicinal Chemistry: A Short Review. Journal of Drug Design and Medicinal Chemistry, 2(1), 10. https://doi.org/10.11648/j.jddmc.20160201.12

Shenoy, N., Creagan, E., Witzig, T., & Levine, M. (2018). Ascorbic Acid in Cancer Treatment: Let the Phoenix Fly. Cancer Cell, 34(5), 700–706. https://doi.org/10.1016/j.ccell.2018.07.014

Shetty, A., & Dick, T. (2018). Mycobacterial Cell Wall Synthesis Inhibitors Cause Lethal ATP Burst. 9(August), 1–9. https://doi.org/10.3389/fmicb.2018.01898

Shoaib, M., Hussain, H., Shah, S. W. A., Umar, M. N., & Ullah, A. (2017). Synthesis, acute toxicity, analgesic activity & cytotoxicity of Some bisthiourea derivatives. Pakistan Journal of Pharmaceutical Sciences, 30(4), 1351–1356.

Singh, B. R., Yadav, A., & Ravichandran, K. (2021). Comparative Antimicrobial Activity of Aspirin, Paracetamol, Flunixin Meglumine, Tolfenamic Acid, Diclofenac Sodium and Pheniramine Maleate. Acta Scientific Veterinary Science, 3(September), 30–42.

Siwach, A., & Verma, P. K. (2020). Therapeutic potential of oxadiazole or furadiazole containing compounds. BMC Chemistry, 14(1), 1–40. https://doi.org/10.1186/s13065-020-00721-2

Stratan, E., Ţurcan, N., Crudu, V., Romancenco, E., Cotelea, T., Niţulescu, G. M., Chiriţă, C., & Moruşciag, L. (2018). Biological evaluation of new 2-phenethylbenzoyl thiourea derivatives as antituberculosis agents. Farmacia, 66(1), 97–106.

Straub, R. H., & Cutolo, M. (2016). Glucocorticoids and chronic inflammation. 6–14. https://doi.org/10.1093/rheumatology/kew348

Syahri, J., Yuanita, E., Nurohmah, B. A., Armunanto, R., & Purwono, B. (2017). Chalcone analogue as potent anti-malarial compounds againstPlasmodiumfalciparum: Synthesis, biological evaluation, and docking simulation study. Asian Pacific Journal of Tropical Biomedicine, 7(8), 675–679. https://doi.org/10.1016/j.apjtb.2017.07.004

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)

Torfs, E., Piller, T., Cos, P., & Cappoen, D. (2019). Opportunities for Overcoming Mycobacterium tuberculosis Drug Resistance : Emerging Mycobacterial Targets and Host-Directed Therapy.

Turner, R. J. (2017). Metal-based antimicrobial strategies. Microbial Biotechnology, 10(5), 1062–1065. https://doi.org/10.1111/1751-7915.12785

Ullah, N., Huang, Z., Sanaee, F., Rodriguez-Dimitrescu, A., Aldawsari, F., Jamali, F., Bhardwaj, A., Islam, N. U., & Velázquez-Martínez, C. A. (2016). NSAIDs do not require the presence of a carboxylic acid to exert their anti-inflammatory effect – why do we keep using it? Journal of Enzyme Inhibition and Medicinal Chemistry, 31(6), 1018–1028. https://doi.org/10.3109/14756366.2015.1088840

Vedavathi, P., Sudhamani, H., & Raju, C. N. (2017). Synthesis and antimicrobial activity of new urea and thiourea derivatives of (2'-(1H-tetrazol-5-yl)biphenyl-4-yl)methanamine. Research on Chemical Intermediates, 43(5), 3251–3263. https://doi.org/10.1007/s11164-016-2823-1

Verghese, R. J., Mathew, S. K., & David, A. (2018). Antimicrobial activity of Vitamin C demonstrated on uropathogenic Escherichia coli and Klebsiella pneumoniae. Current Research in Scientific Medicine, 3(2), 88–93. https://doi.org/10.4103/jcrsm.jcrsm

Verma, A. K., Mittal, D., Goel, A., Shadija, L., & Singh, N. (2020). To Assess the Antimicrobial Action of Paracetamol. Acta Scientific Microbiology, 3(8), 65–71.

Wang, H., Zhai, Z.-W., Shi, Y.-X., Tan, C.-X., Weng, J.-Q., Han, L., Li, B.-J., & Liu, X.-H. (2019). Novel Trifluoromethylpyrazole Acyl Thiourea Derivatives: Synthesis, Antifungal Activity and Docking Study. Letters in Drug Design & Discovery, 16(7), 785–791. https://doi.org/10.2174/1570180815666180704103047

Yadav, A., Mohite, S., & Magdum, C. (2020). Synthesis, Characterization and Biological Evaluation of Some Novel 1,3,4-Oxadiazole Derivatives as Potential Anticancer Agents. International Journal of Scientific Research in Science and Technology, 275–282. https://doi.org/10.32628/IJSRST207234

Zhang, J., Tan, Y., Li, G., Chen, L., Nie, M., Wang, Z., & Ji, H. (2021). Coumarin Sulfonamides and Amides Derivatives: Design, Synthesis, and Antitumor Activity In Vitro. Molecules, 26(4), 786. https://doi.org/10.3390/molecules26040786

Zuegg, J., Solutions, S., Frei, S. A., Blaskovich, M. A. T., Willans, C. E., Wilson, J. J., & Cooper, A. (2020). Metal complexes as a promising source for new antibiotics. Chemical Science, 11, 2627–2639. https://doi.org/10.1039/c9sc06460e

DOI:https//doi.org/10.22452/mjs.vol43no1.8
Malaysian Journal of Science 43(1): 86-112 (March 2024)