Ministry of Higher Education and Scientific Research

University of Babylon

College of Pharmacy

Synthesis & Anti-inflammatory Evaluation of New small molecules as NSAIDs

BSc graduation project

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Content:

Abstract

this study, new derivatives of ortho hydroxy benzaldehyde were synthesized by electrophilic substitutions and cyclization reactions, in a satisfactory yield. The reaction of ortho hydroxy benzaldehyde derivatives with ethyl bromoacetate in absolute ethanol afforded the ester derivative (1) then further heated under reflux with addition of potasium carbonate to cyclization of (1) to afforded benzofuran derivatives . All the synthesized compounds were screened for their in vivo in animal, some of these compound's give moderate anti-inflammatory activity.

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) are the most frequently prescribed medicines for analgesia in primary care. Since the isolation of salicyclate from willow bark in around 1830s, followed by the discovery of aspirin (acetyl salicyclate) by Felix Hoff man of Bayer industry, Germany, in 1897. Nonsteroidal anti-inflammatory drugs (NSAIDs) are a drug class FDA-approved for use as antipyretic, anti-inflammatory, and analgesic agents. These effects make NSAIDs useful for treating muscle pain, dysmenorrhea, arthritic conditions, pyrexia, gout, migraines, and used as opioid-sparing agents in certain acute trauma cases. However:

- NSAIDs can cause serious side effects, some of which may be life-threatening.
- NSAIDs may interact with other medicines and cause unwanted effects.
- NSAIDs should always be used cautiously, for the shortest time possible and at the lowest effective dose.

Mechanism of action:

The main mechanism of action of NSAIDs is the inhibition of the enzyme cyclooxygenase (COX).Cyclooxygenase is required to convert arachidonic acid into thromboxanes, prostaglandins, and prostacyclins. The therapeutic effects of NSAIDs are attributed to the lack of these eicosanoids. Specifically, thromboxanes play a role in platelet adhesion, prostaglandins cause vasodilation, increase the temperature set-point in the hypothalamus, and play a role in anti-nociception.

There are two cyclooxygenase isoenzymes, COX-1 and COX-2. COX-1 gets constitutively expressed in the body, and it plays a role in maintaining gastrointestinal mucosa lining, kidney function, and platelet aggregation. COX-2 is not constitutively expressed in the body; and instead, it inducibly expresses during an inflammatory response. Most of the NSAIDs are nonselective and inhibit both COX-1 and COX-2. However, COX-2 selective NSAIDs (ex. celecoxib) only target COX-2 and therefore have a different side effect profile. Importantly, because COX-1 is the prime mediator for ensuring gastric mucosal integrity and COX-2 is mainly involved in inflammation, COX-2 selective NSAIDs should provide anti-inflammatory relief without compromising the gastric mucosa.

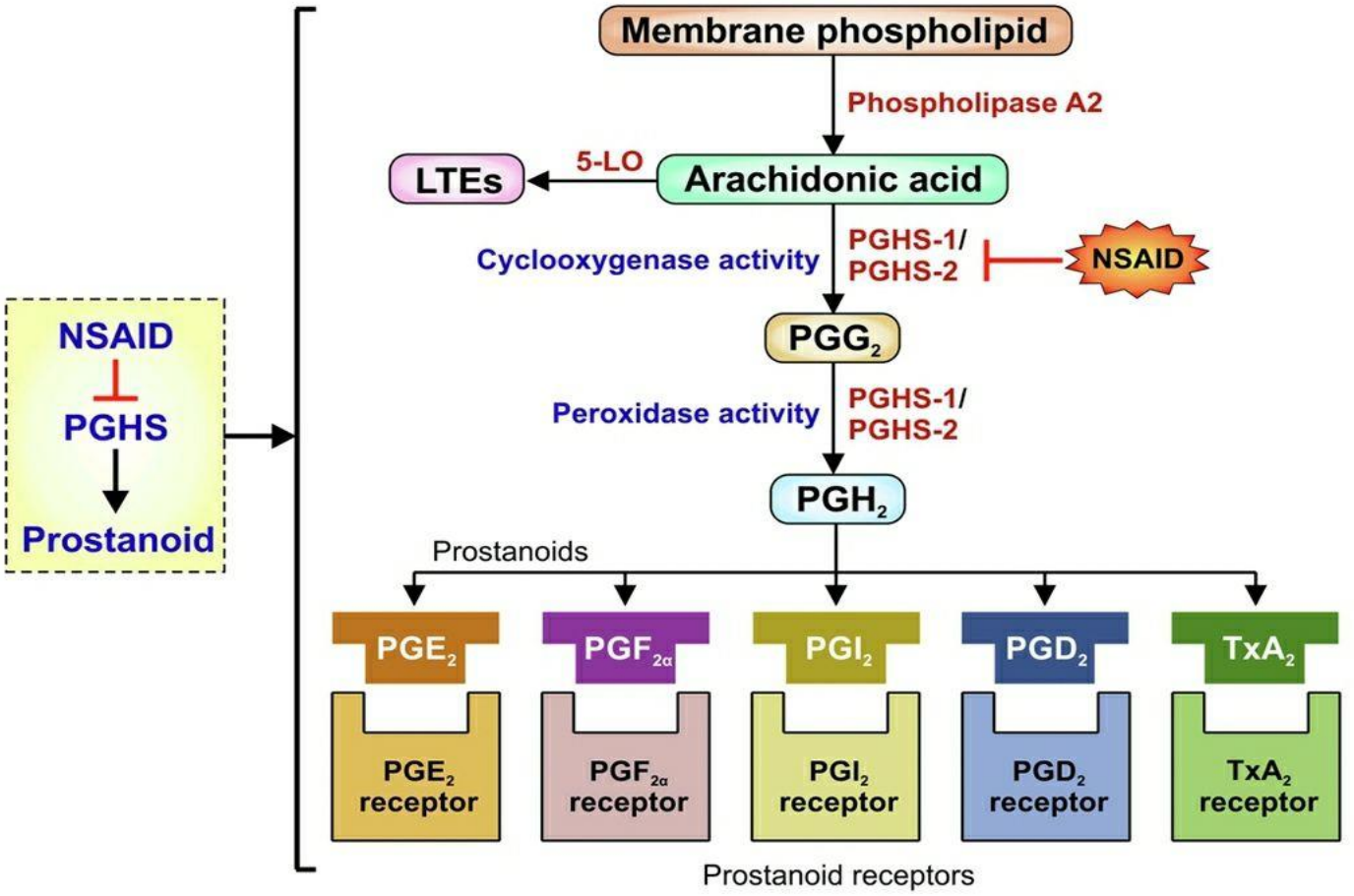


Table 1 – Nonsteroidal anti-inflammatory drugs according to their cyclooxygenase selectiveness

Nonsteroidal anti-inflammatory drugs Classification	
Non-selective (COX-1 and 2) (traditional, conventional)	**Selectives (COX-2) COXIBs**
Aspirin	Rofecoxib
Acetaminophen	Valdecoxib
Indomethacin (Indocin)	Parecoxib
Ibuprofen (Advil, Motrin)	Celecoxib
Naproxen (Aleve, Naprosyn)	Etoricoxib
Sulindac (Clinoril)	Lumiracoxib
Diclofenac (Voltaren, Cataflam)	
Piroxicam (Feldene)	
β- Piroxicam (Cycladol)	
Meloxicam (Movatec)	
Ketoprofen (Profenid)	

Adverse effect:

Gastric adverse effects: are likely due to the inhibition of COX-1, preventing the creation of prostaglandins that protect the gastric mucosa. The damage is more likely in a patient that has a prior history of peptic ulcers. Since it is COX-1 specific, the use of COX-2 selective NSAIDs is a lower-risk alternative.

Renal adverse effects: are because COX-1 and COX-2 facilitate the production of prostaglandins that play a role in renal hemodynamics. In a patient with normal renal function, inhibition of prostaglandin synthesis does not pose a large problem; however, in a patient with renal dysfunction, these prostaglandins play a greater role and can be the source of problems when reduced via NSAIDs. Complications that can occur include acute renal dysfunction, fluid and electrolyte disorders, renal papillary necrosis, and nephrotic syndrome/ interstitial nephritis.

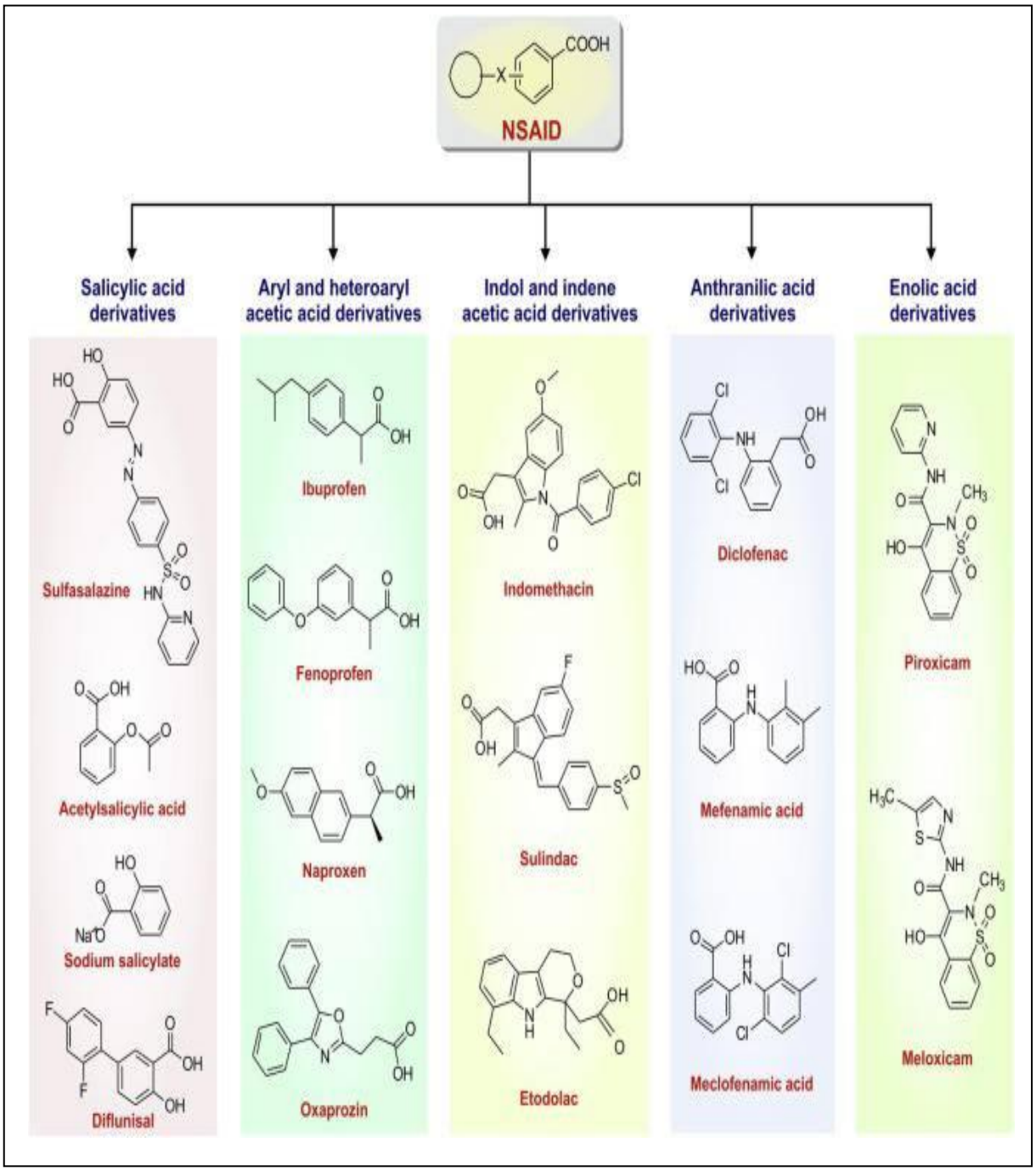
Cardiovascular adverse effects: can also be increased with NSAID use; these include MI, thromboembolic events, and atrial fibrillation. Diclofenac seems to be the NSAID with the highest reported increase in adverse cardiovascular events.

Hepatic adverse effects: are less common NSAID-associated risk of hepatotoxicity (raised aminotransferase levels) is not very common, and liver-related hospitalization is very rare. Among the various NSAIDs, Diclofenac has a higher rate of hepatotoxic effects.

Hematologic adverse effects: are possible, particularly with nonselective NSAIDs due to their antiplatelet activity. This antiplatelet effect typically only poses a problem if the patient has a history of GI ulcers, diseases that impair platelet activity (hemophilia, thrombocytopenia, von Willebrand, etc.), and in some perioperative cases.

Other minor adverse effects: include anaphylactoid reactions that involve the skin and pulmonary systems, like urticaria and aspirin-exacerbated respiratory disease.

NSAIDs are typically divided into groups based on their chemical structure and selectivity: acetylated salicylates (aspirin), non-acetylated salicylates (diflunisal, salsalate), propionic acids (naproxen, ibuprofen, acetic acids (diclofenac, indomethacin), enolic acids (meloxicam, piroxicam) anthranilic acids (meclofenamate, mefenamic acid), naphthylalanine (nabumetone), and selective COX-2 inhibitors (celecoxib, etoricoxib).



Experimental work:

Materials

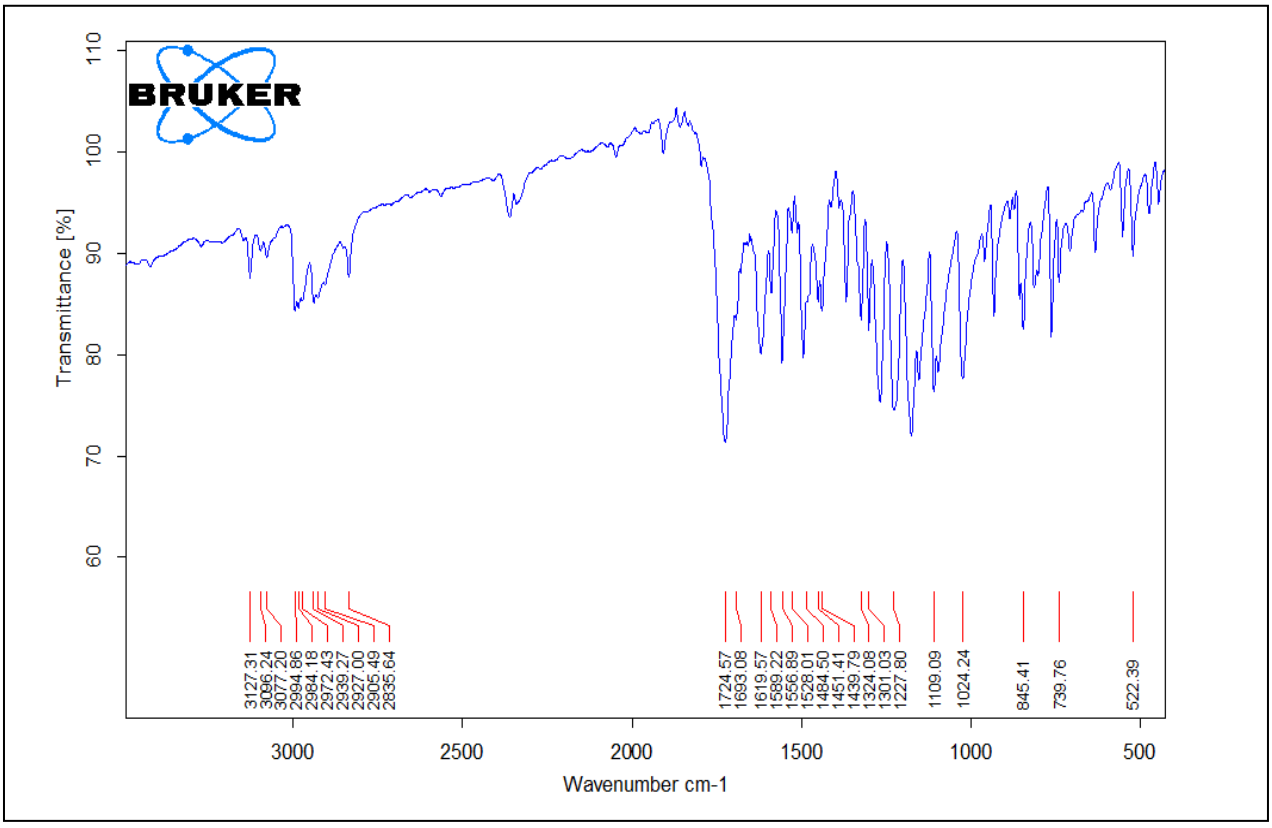
2-hydroxy-4methoxybenzaldehyde (C8H8O3), 2-hydroxy-3-methoxybenzaldehyde (C8H8O3), dimethyllformamid (DMF),1-bromoethyl acetate (C4H7BrO2), Potassium carbonate (K2Co3) all chemicals were purchased from commercial sources and used as received without further purification.

General method for synthesis of ethyl-7-methoxybenzofuran-2-carboxylate and ethyl-6-methoxybenzofuran-2-carboxylate:

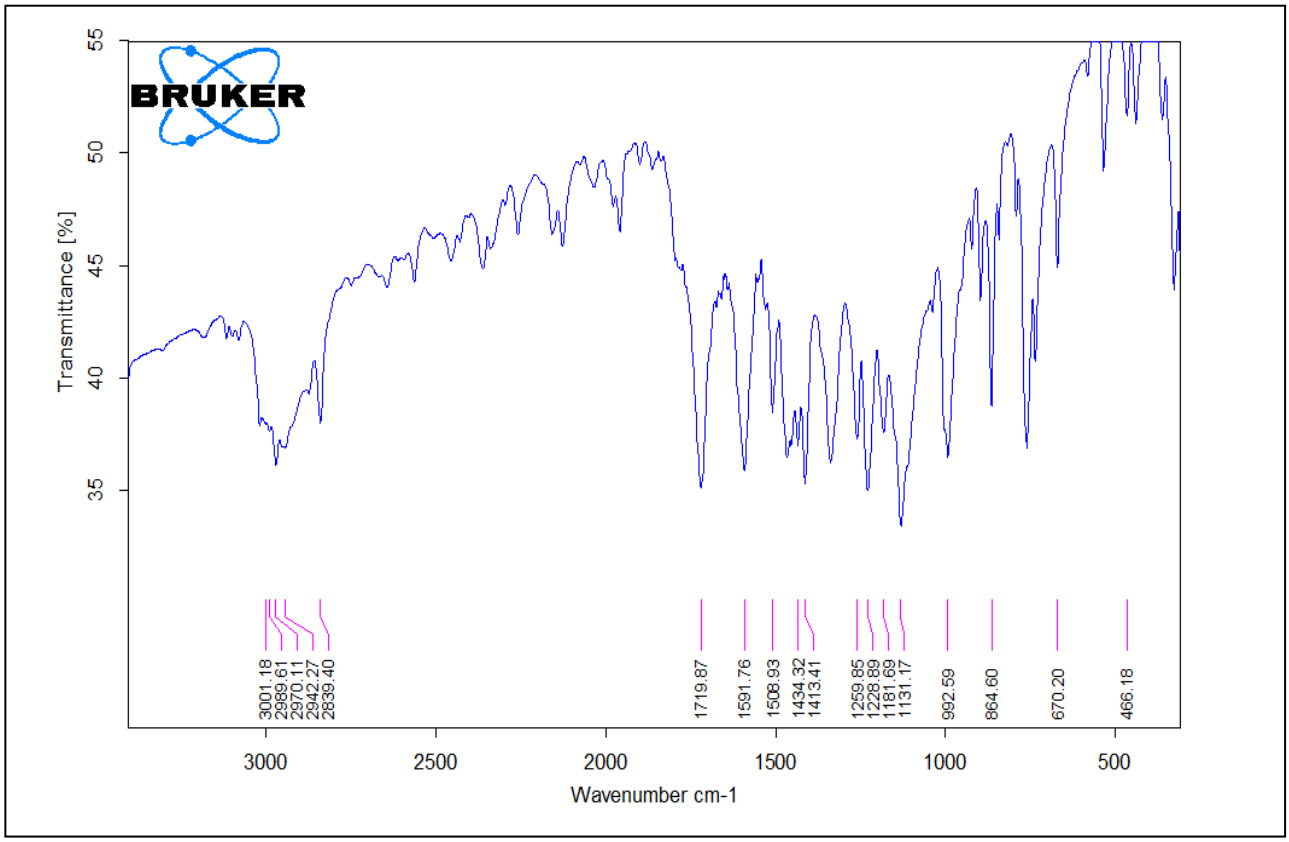
We use (0.5g) from (2-hydroxy-3-methoxybenzaldehyde)in the first reaction and (0.5) from (2-hydroxy-4-methoxybenzaldehyde) in the second reaction both dissolved by DMF followed by the addition Of (0.356ml) 1-bromoethyl acetate and (0.57g) Of Potassium carbonate then refluxed under heat for 4hr after that the second addition Of Potassium carbonate (0.441g) was add and refluxed under heat for another 6hr after the reaction is over excess of D.W was added and cooled by air cooler. We used the solvent extraction method in both reactions by using ethyl acetate as solvent followed by removal the ethyl acetate by drying and the two products compound was obtained.

IR result:

Ethyl-6-methoxybenzofuran-2-carboxylate



Ethyl-7-methoxybenzofuran-2-carboxylate



Biological screening and anti inflammatory activity test:

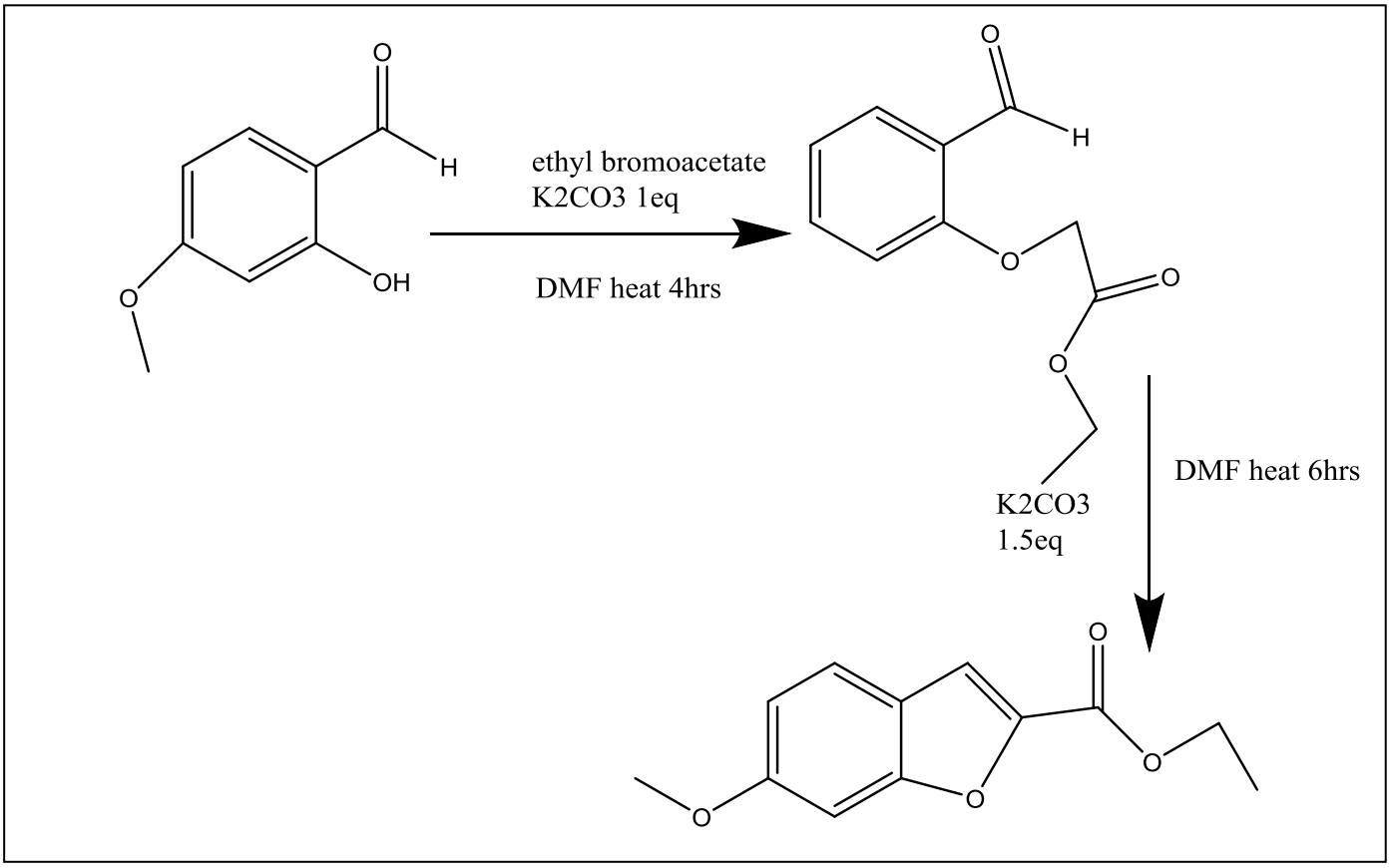
The anti inflammatory activity of the synthesized compounds was performed in vitro, by using groups of rats, the rats was injected with (0.8 ml) solution of the products after it dissolved in dimethyl sulfoxide (DMSO) intraperitoneal. One group was treated as control and the other groups were pretreated with the test products and the result was as below:

	30 min	Healthy foot	60 min	120 min	180 min
control	5	3	8.0	7.5	5.5
naproxen	6.7	3	6.3	6	5
	6.3	3	6.0	5.2	4.8
products	4.7	3.9	5.5	5.0	4.5
	5	3.4	6.0	6.0	5.2

Results and discussion:

Chemistry:

Ethyl-6-methoxybenzofuran-2-carboxylate was synthesized from (2-hydroxy-3-methoxybenzaldehyde) and dissolved by DMF treated with1-bromoethyl acetate to remove the (OH) group from it by electrophilic substitution .Potassium carbonate was used for ionization the (OH) group then refluxed under heat for 4hr the intermediated compound was formed after that the second addition Of Potassium carbonate was add and refluxed under heat for another 6hr the cycle was closed and the yield compound was formed . After the reaction is over excess of D.W was added and cooled by air cooler. We used the solvent extraction method in both reactions by using ethyl acetate as solvent followed by removal the ethyl acetate by drying and the products compound was obtained .The same reaction steps repeated by using (2-hydroxy-4-methoxybenzaldehyde) to synthesized ethyl-7-methoxybenzofuran-2-carboxylate as shown in the below scheme.



As we see the result of the biological activity, the new compound has more anti inflammatory activity than the control treatment.

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