WWW.IJRPR.COM

International Journal of Research Publication and Reviews

Journal homepage: www.ijrpr.com ISSN 2582-7421

Review on Synthesis and Characterization of Mutual Prodrug of Naproxen

[1]Mr. Prathamesh Manjaba Dhulgude, [2]Mr. Ravikumar Ravsaheb Patil

[1]Student, L.N.B.C. Institute of Pharmacy, Satara
[2]Asst. Prof., L.N.B.C. Institute of Pharmacy, Satara

ABSTRACT:

Non-steroidal anti-inflammatory drugs (NSAIDs) such as naproxen have been conjugated with naturally occurring and synthetic phenolic antioxidants with the objective of obtaining NSAIDs antioxidant prodrugs as gastrosparing NSAIDs with improving therapeutic efficacy by masking of carboxylic group chemically. Promoieties like vanillin was selected with the aim of getting synergistic effect and antioxidant property. Synthesized naproxen derivative characterized by MP, TLC and IR spectroscopy.

Objective:

- Synthesis of mutual prodrug of naproxen.
- Characterization of mutual prodrug.

Introduction:

Non-steroidal anti-inflammatory drugs (NSAIDs) are among the most widely used medications in the world, owing to their analgesic, anti-inflammatory and antipyretic properties. However, the use of "traditional" NSAIDS results in serious upper gastrointestinal (GI) adverse events e.g. indomethacin and ibuprofen. The pharmacological activity of NSAIDs is related to their ability to inhibit the activity of the enzyme cyclooxygenases (COXS) involved in the biosynthesis of prostaglandin. It is now well known that COX exists in two isoforms, namely COX-I and COX- II, which are regulated differently. COX-I is constitutively expressed in stomach to provide cytoprotection in the GIT. COX-II is inducible and plays a major role in prostaglandin biosynthesis in inflammatory cells. Since most of the NSAIDS used clinically inhibit both isoforms, there is enough evidence that inhibition of COX-I rather than that of COX-II underlies gastric ulcer formation. However, long term uses of these agents have shown some potential limitation, including ulcer exacerbation in high-risk patients, delayed GI ulcer healing, kidney toxicity and cardiovascular side effects. Hence safety of these agents is questionable on their long-term use and some of these agents have been withdrawn from the market. Thus, need of safer NSAID still remains.[13]

Prodrug design is a choice of approach in solving many of the stability, solubility, permeability and targeting problems that has the ability to keep promising new drug candidates alive through development and improving the safety and efficacy of existing drug products. It is effective for drugs suffering from undesirable side effects. A mutual prodrug normally comprises of two biologically active agents coupled together so that each act as a pro-moiety for the other agent.The carrier may have synergistic effect or it may have some additional pharmacological properties lacking in the parent drug.

Esters are the most common prodrugs used, and it is estimated that approximately 49% of all marketed prodrugs are activated by enzymatic hydrolysis. Ester prodrugs are most often used to enhance the lipophilicity, and thus the passive membrane permeability, of water-soluble drugs by masking charged groups such as carboxylic acids and phosphates. The synthesis of an ester prodrug is often straightforward. Once in the body, the ester bond is readily hydrolysed by ubiquitous enzyme esterases found in the blood, liver and other organs and tissues, including carboxyl esterases, acetylcholinesterases, butyrylcholinesterases, paraoxonases and arylesterases.

Indomethacin was conjugated with PEG or TEG by an ester or amide linkage. Mefenamic acid was conjugated with B-cyclodextrin via ester bond. After oral administration, cyclodextrins are not hydrolysed during their transit time through the stomach, but its hydrolysis occurs only in colon by colonic micro flora. Hence, this approach can be used for colon targeting and to avoid the exposure of free drug to the stomach.

Literature reveals that many efforts have been made to synthesize prodrugs of ketoprofen, aceclofenac, diclofenac, flurbiprofen, naproxen, ibuprofen, etc., via masking the carboxylic acid group by forming ester and amide prodrugs using various amino acids, dextran and sulpha drug. Glucosamine hydrochloride, an amino sugar, is being used as anti-arthritic agents, was used to mask COOH group of flurbiprofen. It has been well known that reactive

oxygen species (ROS) plays a significant role in the formation of gastric ulceration associated with NSAID therapy. Co- administration of antioxidants with NSAIDS in formulated dosage forms have shown decrease the risk of NSAIDS induced GI toxicity and ulcerogenic side effects. These observations indicate that antioxidants may be used to prevent NSAIDS induced gastric ulcers.

During the past few decades, a large number of naturally occurring compounds have been identified as antioxidants and anti-inflammatory such as vanillin, and chalcone (phenyl styryl ketone) and which are viewed as promising therapeutic agents for treating free radical mediated diseases including NSAID induced peptic ulcers. Based on these observations, it has been suggested that co-administration of antioxidants and NSAID's in formulated dosage form may possibly decrease the risk of NSAIDS induced gastrointestinal side effects.

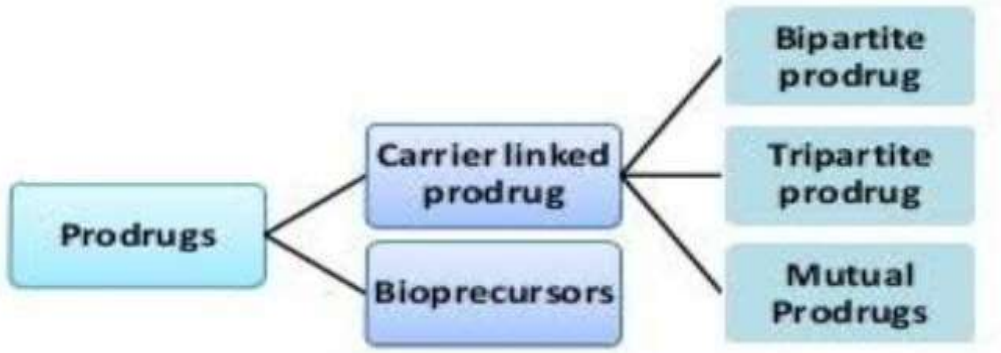
Thus, introduction of mutual prodrugs in human therapy had been successful in overcoming the undesirable properties like poor absorption, poor bioavailability, non-specificity and GIT toxicity. In the view of this background, the present study was conducted to design, synthesis, and preliminary kinetics study of mutual prodrugs of NSAIDs with different antioxidants to get NSAIDS with lesser ulcerogenic side effects while retaining the anti-inflammatory and analgesic activity.[14]

PRO DRUG

The concept of "prodrug" was first introduced by Adrian Albert in 1958 to describe compounds that undergo biotransformation prior to eliciting their pharmacological effect. A prodrug is defined as a biologically inactive derivative of a parent drug molecule that usually requires a chemical or enzymatic transformation within the body to release the active drug, and possess improved delivery properties over the parent molecule. The development of prodrugs is now well established as a strategy to improve the physicochemical, biopharmaceutical or pharmacokinetic properties of pharmacologically potent compounds, and thereby increase usefulness of a potential drug.[1]

CLASSIFICATION:

1. **Double prodrug:** pro- prodrugs or arcade-initiated prodrug
2. **Macromolecular prodrug :** macromolecular like polysaccharide, dextron, cyclodextrins, proteins ,peptides & polymers are used carrier
3. **Site specific prodrug:** a carrier act as transporter of the active drug to a specific targeted site.
4. **Mutual prodrug:** carrier used is another biological active drug instead of some inert molecule.



OBJECTIVE:

- **Pharmaceutical Objectives:**

1. To improve solubility, chemical stability, and organoleptic properties.
2. To decrease irritation and/or pain after local administration,
3. To reduce problems related with the pharmaceutical technology of the active agent.

- **Pharmacokinetic Objectives**:

1. To improve absorption (oral and by non-oral routes).
2. To decrease presystemic metabolism to improve time profile. *To increase organ/ tissue- selective delivery of the active agent.

APPLICATION OF PRO DRUG:

1. Improved physicochemical properties (e.g., better solubility in the intended formulation).
2. Enhanced delivery characteristics and/or therapeutic value of the drug.
3. To improve drug penetration through biological membranes.
4. To increase site specificity of the drug.
5. To improve the drug's stability and solubility.
6. To increase duration of pharmacological activity.
7. To decrease the drug's toxicity and adverse effects.[2]

ADVANTAGES:

- Help in reduction of side effect of parent drugs.
- Produces synergistic effect
- Give additional biological actions as that of parent drug.
- Reduction in dose due to synergistic effect.

LIMITATIONS:

- Problems at the pharmacological level
- Problems at the toxicological level.
- Problem at the pharmacokinetics studies.
- Problem at the clinical stage[3]

MUTUAL PRODRUG

Mutual prodrug, where the carrier used is another biologically active drug instead of some inert molecule. A mutual prodrug consists of two pharmacologically active agents coupled together so that each act as a promoiety for the other agent and vice versa. The carrier selected may have the same biological action as that of the parent drug and thus might give synergistic action, or the carrier may have some additional biological action that is lacking in the parent drug, thus ensuring some additional benefit. The carrier may also be a drug that might help to target the parent drug to a specific site or organ or cells or may improve site specificity of a drug. The carrier drug may be used to overcome some side effects of the parent drugs as well.

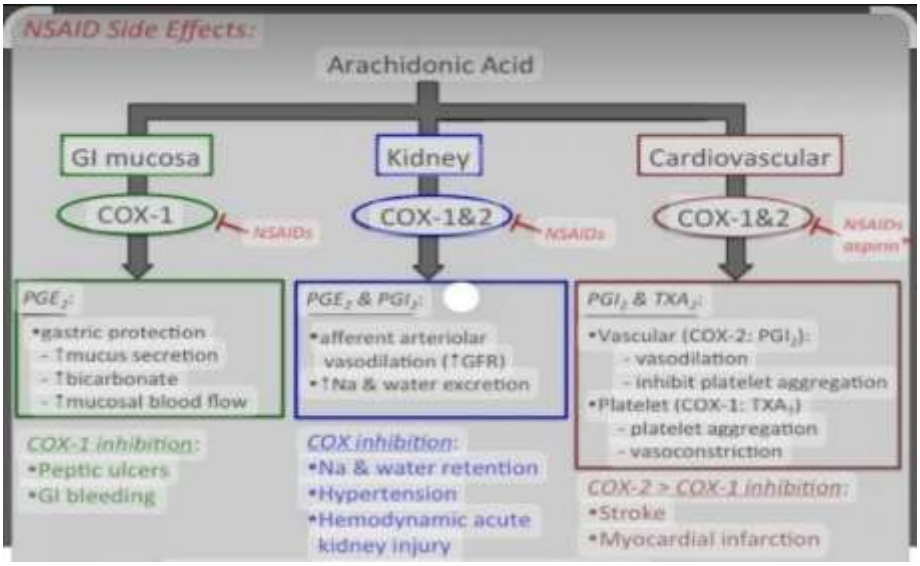
OBJECTIVE:

- To bring both active drugs to their respective active sites.
- To provide the desired pharmacological effects while minimizing adverse metabolic and/or toxicological.
- To improve the clinical and therapeutic effectiveness of those drugs which suffer from some undesirable properties that otherwise hinder their clinical usefulness.[3]

NSAID

Non-steroidal anti-inflammatory drugs (NSAIDs) are medicines that are widely used to relieve pain, reduce inflammation, and bring down a high temperature. They're often used to relieve symptoms of headaches, painful periods, sprains and strains, colds and flu, arthritis, and other causes of long-term pain.

SIDE EFFECT OF NSAID:

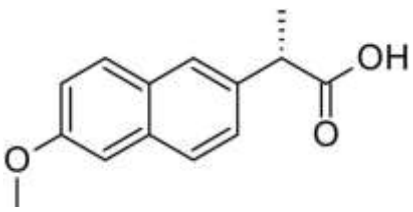


- Indigestion – including stomach aches, feeling sick and diarrhoea.
- stomach ulcers – these can cause internal bleeding and anaemia; extra medicine to protect your stomach may be prescribed to help reduce this risk.
- headaches.
- drowsiness.
- dizziness.
- allergic reactions.[4]

HOW TO WORK NSAID

NSAIDs block the production of substances in the body called "prostaglandins." Thosechemicals play a role in pain, inflammation, fever, and muscle cramps and aches. At low doses. NSAIDs work mainly as pain relievers. At higher doses, they may also reduce the bodies. Inflammatory response to tissue damage as well as relieve pain However, the clinical importance of any anti-inflammatory effects is uncertain, and for osteoarthritis, inflammation is usually not a major issue more specifically, NSAIDs block two different enzymes, called COX-1 and COX-2, which the body uses to make prostaglandins. The gastrointestinal bleeding problems can be traced specifically to the blocking of COX-1. Prostaglandins produced by the COX-1 enzyme help protect the lining of the stomach from acid, so blocking this enzyme increases the risk of stomach bleeding and ulcers. Some people have an especially high risk of this problem, but it's difficult to tell in advance who they are NSAIDs differ in how much they block the COX-1 enzyme relative to the COX-2 enzyme, NSAIDs that block both enzymes are referred to as "nonselective" NSAIDs and those that mainly block the COX-2 enzyme are called "elective" NSAIDs. One selective NSAID, Vinxxx, was withdrawn from the market in 2004 because it was linked to an increased risk of heart attacks and strokes. Another selective NSAID, Bextra, was withdrawn in 2005 because it was associated with an increased risk of serious cardiovascular problems in people who had undergone coronary artery bypass graft surgery as well as higher risk of life-threatening skin reactions than other NSAIDs. The only selective NSAID currently available in the US is Celebrex (celecoxib).[9]

EXPERIMENTAL WORK



Chemical name: 2-(6-methoxy naphthalene 2-yl propionic acid)

Synonym: axer BonyNaxem:Naxyn:Xenar;cg3117:Naixan Napren: Naprux:Prexan

Molecular Formula: CHO Molecular weight: 230.26 gm

Melting point: 152-154 ^{0} C

Naproxen is a non-steroidal anti-inflammatory drug it is a PG synthase inhibitor, which can inhibit prostaglandin syntheses, it has significant analgesic and antipyretic effects, oral absorption is rapid and complete, 2 to 4 hours after a dose plasma concentration reaches the peak, in the blood, more than 99% is bound to plasma proteins, 11/2 is 13 to 14 hours, about 95% is discharged from the urine with the prototype and metabolites it is clinically used For the treatment of rheumatic and rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, gout, arthritis, tenosynovitis.it can also be used to alleviate pain caused by musculoskeletal sprains, contusions, damages and dysmenorrhea. But it should be noted that like other non-steroidal anti-inflammatory drugs, the same serious gastrointestinal adverse reactions could occur at any time while taking naproxen during treatment, so the active gastro duodenal ulcer patients are hanged, other gastrointestinal tract disease patients should take this drug under close medical supervision.

Chemical property:

White crystal or crystalline powder. Melting point 155.3 °C. Soluble in acetone, soluble in methanol, ethanol, acetic acid, insoluble in benzene, practically insoluble in water. In case of light, it is colour-graded, odourless, and tasteless. White to light yellow crystal powder

Uses:

It is a non-steroidal anti-inflammatory drug for the relief of fever and inflammation and associated with arthritis or other symptoms, it has anti-inflammatory, antipyretic and analgesic effects. Naproxen plays a role by inhibiting the cyclooxygenase. which generates prostaglandin and is one kind of enzymes related to inflammatory mediators. It is recommended to take the drug during meals to reduce stomach irritation.An anti-inflammatory, analgesic, antipyretic. A non-steroidal anti-inflammatory

Naproxen side effect:

- Indigestion, heartburn, stomach pain, nausea.
- Diarrhea, constipation.
- Headache, dizziness, drowsiness.
- Swelling in your hands or feet .
- Bruising, itching mash, sweating; or ringing in your ears.[6]

IDENTIFICATION AND CHARACTERIZATION OF SYNTHESIZED PRODUCTS

The synthesized compounds were scaled for yield and purified by recrystallization with suitable solvent system: The purified compounds were assigned for physical constant determination and further subjected for spectral analysis like thin layer chromatography, Infrared spectroscopy. Nuclear magnetic resonance spectroscopy.

Melting Point Determination:

The melting points of the synthesized compounds were determined by using the Thiel tube apparatus.

Thin layer chromatography:

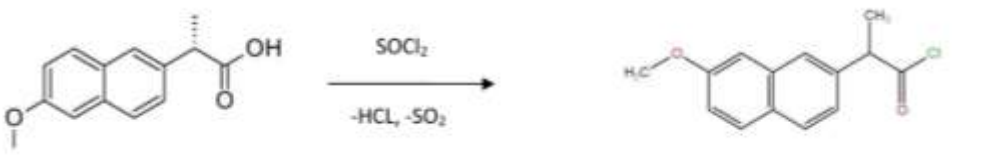
Thin layer chromatography was performed on silica gel plates with suitable solvent system. The RFvalue were recorded accordingly.

Infrared spectroscopy:

The infrared spectra for the synthesized compounds were recorded.

Procedure for synthesis of Acid chloride of Naproxen:[12]

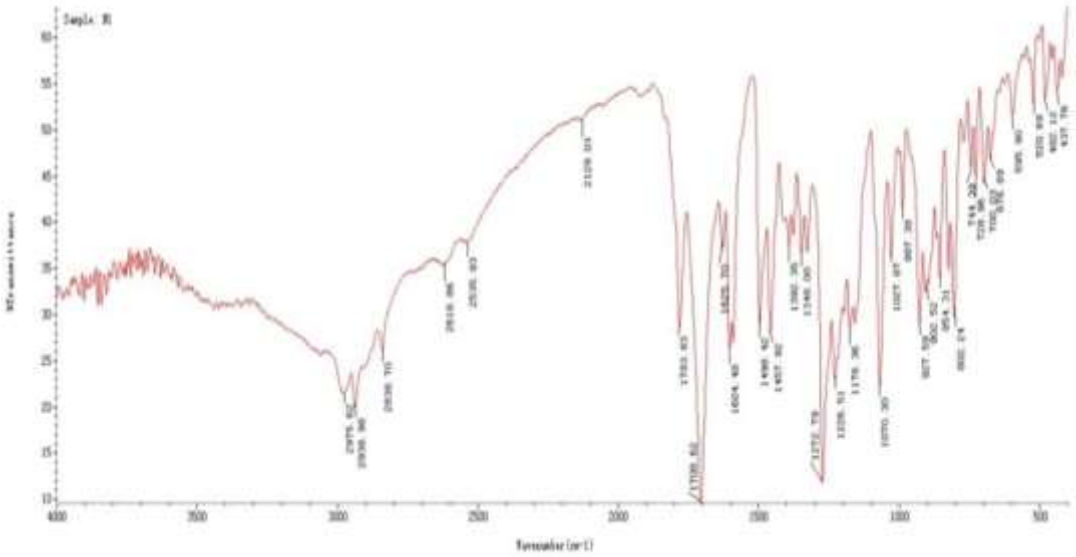
0.05 mol of Naproxen (1) was taken in a beaker and 10 mL of thionyl chloride was added. This mixture was heated on a water bath with continuous stirring until evolution of sulphur dioxide and hydrochloric acid was completed. The resultant acid chloride was cooled and the excess of thionyl chloride was removed under reduced pressure.



Naproxen 2-(7-methoxynaphthalen-2-yl) propanoyl chloride

Characterization by MP and TLC and Practical yield:

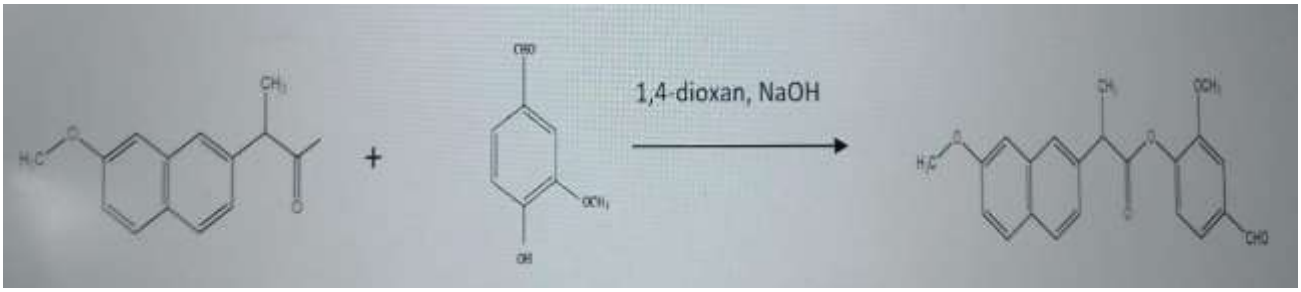
Derivative	Mobile Phase	Molecular weight	RF value	Melting point	%Practical yield
Naproxen Chloride	Hexane: Ethyl Acetate	248.703	0.5123	153-163^{0}c	72.72%



Sr. No.	Functional Group	Observation Value
1	Cl	802.24
2	C-O-C	1272.79
3	C=O	1783.83
4	C=C	1457.92
5	C-C	1070.30

Synthesis of Mutual Prodrug of Vanillin and Naproxen

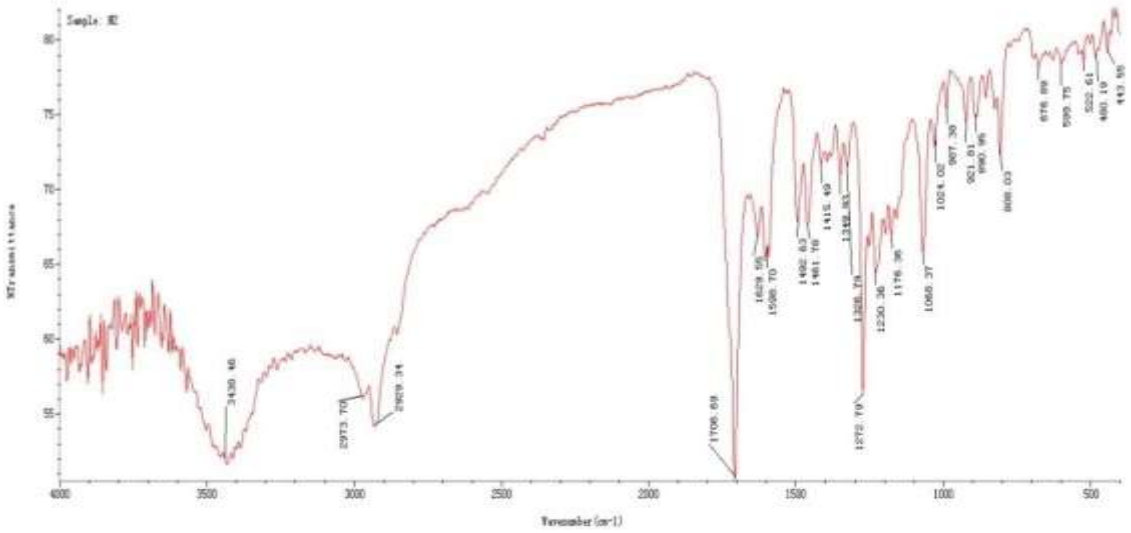
Equimolar quantities of Naproxen acid chloride and paracetamol was dissolved in 1, 4-dioxan and 10% sodium hydroxide solution respectively. The solution of acid chloride was added dropwise to the solution of paracetamol with continuous stirring for 1 h. The reaction mixture was stirred continuously for another 1 h and then 50% hydrochloric acid was added dropwise with continuous stirring so that the prodrug precipitates in the form of hydrochloride salt.[12]



2-(7-methoxynaphthalen-2-yl) Vanillin 4-formyl-2-methylphenyl propanoyl chloride 2-(7-methoxynaphthalen-2-yl) propanoate

Characterization by MP and TLC and Practical yield:

Derivative	Mobile Phase	Molecular weight	RF value	Melting point	%Practical yield
4-formyl-2- methylphenyl 2-(7- methoxynaphthalen- 2-yl) propanoate	Hexane: Ethyl Acetate	348.4	0.515	168 ^{0}C	77.14%



Sr. No.	Functional Group	Observation Value
1	CHO	2929.34
2	C-O-C	1272.79
3	C=O	1706.69
4	C-C	1068.89
5	C=C	1492.63

Result:

Mutual prodrug was synthesized by proposed rout of reaction. Naproxen NSIADs was used. Reaction was monitored by thin layer chromatography (TLC) and used to assess the purity of intermediates and the final compound, by using different solvent system. The physicochemical properties of anticipated compounds showed desirable solubility and acceptable melting point range. The structural elucidation of the synthesized compounds was carried out with the help of IR spectroscopy. The IR spectrum of synthesized derivatives exhibits various bands that at frequencies values are

Sr. No.	Functional Group	Observation Value
1	CHO	1706.89
2	C-O	1272.89
3	C=O	1706.89
4	C-C	1068.89
5	C=C	2929.34

Conclusion:

The mutual prodrug of Naproxen with vanillin was successfully synthesized and characterized by spectral (IR. NMR) data. Hence vanillin could be used as promoities for Naproxen. Mutual prodrug approach therefore gives an opportunity in medicinal chemistry to improve the clinical and therapeutic effectiveness of a drug that is suffering from some undesirable properties hindering its clinical usefulness.

Expected Outcomes: After completion of project work student will able

- To gain knowledge on synthesis of Mutual Prodrug.
- To develop practical skills.

Mapping with POs:

Program Outcomes:

PO 1:Pharmacy Knowledge PO 2: Planning Abilities

PO 3: Problem Analysis PO 4: Modern tool usage

PO 5: Leadership skills PO 6: Professional identity

PO7: Pharmacist ethics PO 8: Communication

PO 9: Pharmacist & society PO 10: Environment & sustainability PO 11: Lifelong learning

Example