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A BRIEF REVIEW ON RECENT ADVANCEMENTS AND BIOLOGICAL ACTIVITIES OF ARYL PROPIONIC ACID DERIVATIVES

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Keywords:

Ulcerogenic activity, Antinociceptive activity, Anti-cancer activity, Anti-convulsant activity, Aryl propionic acid, Anti-inflammatory activity

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ABSTRACT: Arylpropionic acid derivatives are an important class of NSAIDs. Ibuprofen, 2- (4-isobutylphenyl) propionic acid, is known as NSAIDs. Arylpropionic acid derivatives have a broad biological activity, including antibacterial, anticonvulsant and anticancer activity, analgesic, and anti-inflammatory. In addition to the most powerful ingredients used in analgesic and antipyretic fields, such as ibuprofen, Oxaprozin, Ketoprofen, and Phenoprofen, aryl propionic acid derivatives play an important role in treating other symptoms. The possible improvements in the activity can be further achieved by slight modifications in the substituent on the basic aryl propionic acid. According to Grigoryan *et al.*, 2019 studies reveal that the replacement of the carboxyl group by tetrazole ring, hydroxamate, ester, alcohol, and amide groups forms compound showing lower activity (anti-inflammatory, anti-nociceptive, ulcerogenic activity). The presence of a carboxyl group in the parent molecule of aryl propionic acid is important for broad-spectrum pharmacological activity. This review focused on recent advances and recent research on aryl propionic acid derivatives compared to medicinal chemistry.

INTRODUCTION: Medical chemistry is an area that determines the effect of chemical composition on biological activity. Medical chemistry has been expanded with the help of experimental methods for predicting the composition of new compounds that rely heavily on structural changes and the determination of biological properties.

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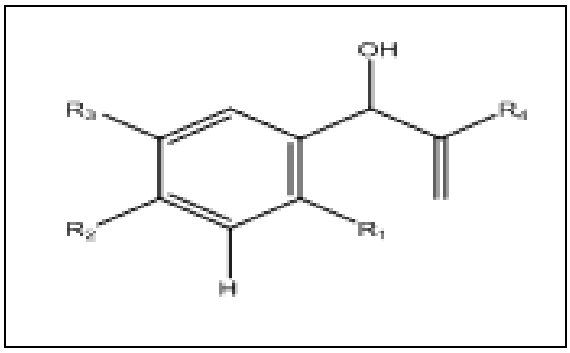
Medical chemistry also provides for the detection, development, explanation, and validation of the mechanism of action of biologically active molecules at the molecular level [1, 2]. Arylpropionic acid derivatives are a large and important family of non-steroidal anti-inflammatory drugs (NSAIDs) [2, 5]. NSAIDs are often used to treat various arthritis and musculoskeletal disorders [6-9].

The biological response of NSAIDs is the result of inhibition of prostaglandin biosynthesis (PG), where cyclooxygenase enzyme (COX) plays a key role in prostaglandin biosynthesis derived from arachidonic acid [10, 14]. In the early 1990s, COX was found to have two forms, namely the COX-1

component, which provides gastrointestinal cyto-protection (GI) and the other inducible COX-2, which mediates inflammation [15, 16]. One of the NSAIDs *viz.* Ibuprofen, a chemical called propionic acid 2- (4-isobutylphenyl), is a popular pain relief [14, 15]. This is known for its use in the relief of arthritis pain. Long-term use of NSAIDs leads results in gastrointestinal ulceration, bleeding and nephrotoxicity [18, 20]. The gastrointestinal damage is generally associated with two factors which include local irritation by carboxylic acid moiety, which is common in most NSAIDs (topical effect) and decreased the production of tissue prostaglandin (PGs), which minimizes the physiological role of cytoprotective prostaglandins in maintaining GI health and homeostasis [21].



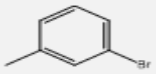
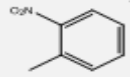
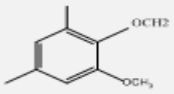
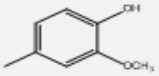
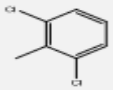
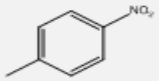
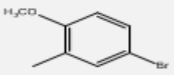
BAYLIS-HILLMAN ADDUCT

TABLE 1: 3-HYDROXY-2-METHYLENE-3PHENYL-PROPIONIC ACID DERIVATIVES

Compounds	R_1	R_2	R_3	R_4
1	H	NO_2	H	COOMe
2	H	NO_2	H	CN
3	NO_2	H	H	COOMe
4	NO_2	H	H	CN
5	H	CI	H	COOEt
6	H	CI	H	CN
7	H	F	H	CN
8	H	F	H	COOEt
9	CI	H	H	CN
10	CI	H	H	COOEt
11	CI	CI	H	COOEt
12	CI	CI	H	CN
13	H	H	NO_2	COOEt
14	H	H	NO_2	CN
15	H	NO_2	H	COOEt

Studies showed that forming the derivative of the carboxylate function of representative NSAIDs resulted in an enhanced anti-inflammatory activity with reduced ulcerogenic effect. Moreover, certain compounds bearing 1, 3, 4-oxadiazole/thiadiazole and 1, 2, 4-triazole nucleus have been reported to bear significant anti-inflammatory activity [19, 20]. In the last two decades, there has been a considerable amount of work in the role of reactive oxygen species in inflammation. Inflammation is one of the manifestations of oxidative stress and the pathways that generate the mediators of inflammation, such as adhesion molecules and interleukins [21].

TABLE 2: DERIVATIVES OF 3- (4, 5-DIPHENYL-1, 3-OXAZOLE-2-YL) PROPIONIC ACID

S. no.	R
1	
2	
3	
4	
5	
6	
7	

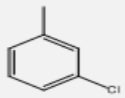
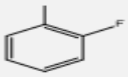
2. Pharmacological Activities:

2.1 Anti-Bacterial Activity: Singh S. A. and Bhat S. V. synthesized twenty Baylis-Hillman adducts (3-hydroxy-2methylene-3-phenyl propionic acid derivatives) from different aromatic aldehydes and activated vinyl derivatives. These were screened for their antimicrobial activity *in-vitro* by serial dilution method. The synthesized compounds (1-15) showed potent antibacterial activity **Table 3** [22-25].

TABLE 3: β, β -DIPHENYL PROPIONIC ACID AMIDES

S. no.	R
1	H
2	C_6H_4
3	C_6H_4
4	p.$(CH_3O)C_6H_4$
5	2-C_5H_4N
6	2$COOCH_3$ C_6H_4
7	SO_2NH_2 C_6H_4
8	-NH-CH_2-COOH

TABLE 4: 2-[5, 6-DIPHENYL-3(2H) PYRIDAZINONE-2-YL] ACETIC ACID DERIVATIVES

S. no.	R
1	
2	
3	
4	

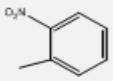
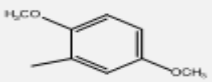
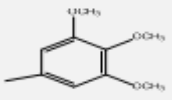
2.2 Anti-Cancer Activity: Rayam P. *et al.,* synthesized a series of acyl hydrazones derivatives of 3-(4, 5-diphenyl-1, 3-oxazole-2-yl) propionic acid. The intermediate N- acyl hydrazine was prepared from NSAID oxaprozin, was coupled with a variety of aromatic aldehydes under conventional as well as microwave irradiation conditions.

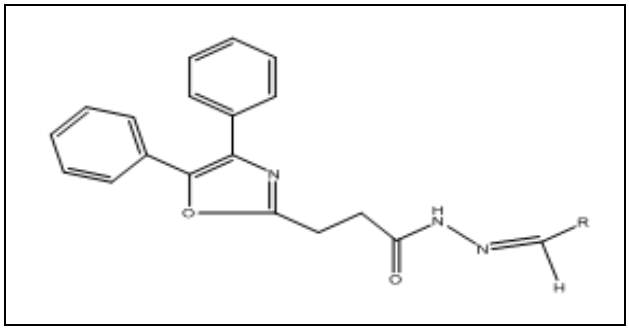
The synthesized compounds in **Table 2** were further screened for *in-vitro* anticancer activity. Compounds (1-7) showed potent anticancer activity when the comparison was made with Cisplatin [26-30].

2.3 Anti-convulsant Activity: Semwal A. synthesized a series of b, b- diphenyl propionic acid amides, which were evaluated for anti-convulsant activity using Maximal electroshock seizures (MES) method.

The compounds (1-8) showed mild to moderate anticonvulsant activity ranging from 0.0% to 50% in **Table 3**. Indomethacin was taken as standard drug [31-33].

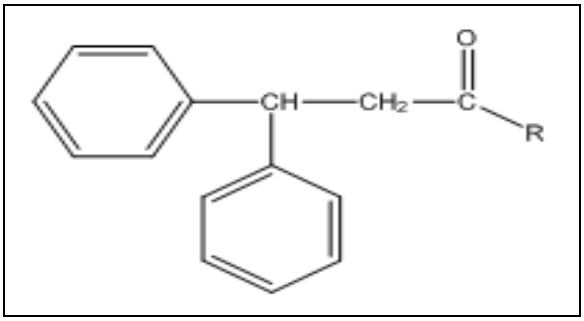
TABLE 5: ACYL HYDRAZONE DERIVATIVES OF 3-(4, 5-DIPHENYL-1, 3-OXAZOLE-2-YL) PROPIONIC ACID

S. no.	R
1	
2	
3	



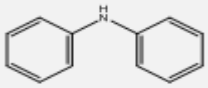
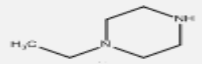
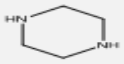
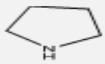
2.4 Analgesic Activity: Puneet K. *et al.*, synthesized five new β, β-diphenyl propionic acid derivatives. β, β-diphenyl propionyl chloride (Intermediate compound) was prepared by the reaction of β,β-diphenyl propionic acid, and thionyl chloride. β, β-diphenylpropanoyl chloride was reacting to several aromatic amines in the presence of potassium carbonate in acetone. The synthesized compound is characterized by physical properties, IR, 1HNMR, Mass spectral data.

Synthesis derivatives are examined to find out an analgesic activity (the method of working hot plates and tails Flik method) and anti-inflammatory activity (a method induced by Carrageenan induced edema) with Diclofenac and Indomethacin as standard drug. AK-1(diphenylamine derivative) and AK-3 (Morpholine derivative) and are potent analgesics and anti-inflammatory compounds. The derivatives of Arylpropionic acid have pain relief and a great space for further development as a similar and anti-inflammatory agent [30, 34, 35].



Dogruer D. S. *et al.*, synthesized sixteen new amide derivatives by treatment of 2-[5, 6-diphenyl-3(2H)-pyridazinone-2-yl] acetic acid or 3-[5, 6-diphenyl-3(2H)-pyridazinone-2-yl] propionic acid with appropriate amine derivatives in the presence of triethylamine and ethyl chloroformate in dichloro-methane at room temperature **Table 4**. Out of which, Compounds (1-4) showed higher analgesic activity. Aspirin was taken as standard drug [36-37].

TABLE 6: β, β -DIPHENYL PROPIONIC ACID DERIVATIVES

S. no.	Name	R
1	Diphenylamine	
2	Ethyl Piperazine	
3	Morpholine	
4	Piperazine	
5	Pyrrolidine	

Rayam P. *et al.*, synthesized a series of acyl hydrazone derivatives of 3-(4, 5-diphenyl-1, 3-oxazole-2-yl) propionic acid. The key intermediate N- acyl hydrazine was prepared in good yield from NSAID oxaprozin, was coupled with a variety of aromatic aldehydes under conventional as well as microwave irradiation conditions. The compounds were screened for *in-vivo* analgesic activity and compounds (1-3) exhibited significant *in-vivo* analgesic activity **Table 5**. Oxaprozin was taken as reference drug [38, 39, 40].

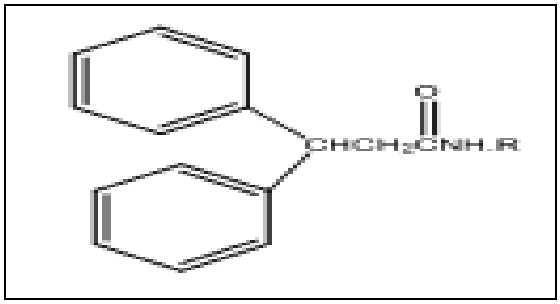


TABLE 7: β, β-DIPHENYL PROPIONIC ACID AMIDES

S. no.	R
1	H
2	C_6H_4
3	C_6H_4
4	p.(CH_3O) C_6H_4
5	2-C_5H_4N
6	2$COOCH_3$ C_6H_4
7	SO_2NH_2 C_6H_4
8	-NH-CH_2-COOH

2.5 Anti-inflammatory Activity: Semwal A. synthesized a series of β, β - diphenyl propionic acid amides. The synthesized compounds were evaluated for its anti-inflammatory activity by Carrageenan induced paw edema method.

The compounds (1-8) showed mild to moderate anti-inflammatory activity ranging from 36.13% to 90% after 3 h whereas the standard drug Indo-methacin showed 81.25% inhibition **Table 7** [40-42]. Dogruer D. S. *et al.*, synthesized sixteen new amide derivatives **Table 7** by treatment of 2-[5,6diphenyl-3(2H)-pyridazinone-2-yl] acetic acid or 3-[5, 6-diphenyl-3 (2H)-pyridazinone- 2-yl] propionic acid with appropriate amine derivatives in the presence of triethylamine and ethyl chloro-formate in dichloromethane at room temperature. Out of which, compounds (1-3) showed potent anti-inflammatory activity [43, 44].

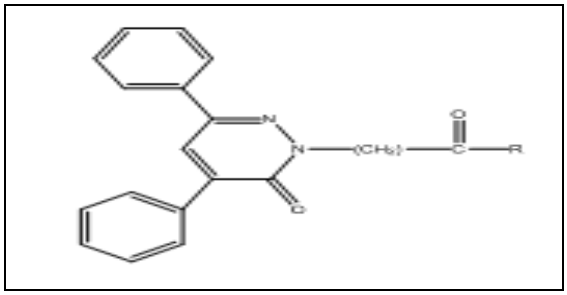
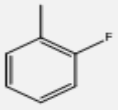


TABLE 8: 2-[5, 6-DIPHENYL-3(2H) PYRIDAZINONE-2-YL] ACETIC ACID DERIVATIVES

S. no.	R
1	
2	
3	

Rayam P. *et al.*, synthesized a series of acyl hydrazone derivatives of 3-(4, 5-diphenyl-1, 3-oxazole-2-yl) propionic acid. The key intermediate N- acyl hydrazine was prepared in good yield from NSAID oxaprozin, was coupled with a variety of aromatic aldehydes under conventional as well as microwave irradiation conditions.

The synthesized compounds in **Table 9** were screened for *in-vivo* anti-inflammatory activity, and compounds (1-3) exhibited significant *in-vivo* anti-inflammatory activity. Oxaprozin was taken as reference compound [45, 46]. Dilber S. P. *et al.*, synthesized b-hydroxy-aryl propanoic acids by a two-step process. The first step involves the synthesis of diastereomeric 3-hydroxy-2-methyl-3-

(4-biphenylyl) butanoic acids whereas the second step was a modified Reformatsky reaction in presence of Zn in tetra-hydrofuran (THF) at -5 to 10 ºC between the synthesized compound of the first step and 4-acetyl phenyl. The synthesized compounds were screened for anti-inflammatory activity, and only two compounds (1, 2) showed the strongest anti-inflammatory activity [47, 48].

Puneet K. *et al.,* synthesized five new β, β-diphenyl propionic acid derivatives. β, β-diphenyl propionyl chloride (Intermediate compound) was prepared by the reaction of β, β-diphenyl propionic acid, and thionyl chloride. β, β-diphenylpropanoyl chloride was reacting to several aromatic amines in the presence of potassium carbonate in acetone. The synthesized compound is characterized by physical properties, IR, 1HNMR, Mass spectral data. Synthesis derivatives are examined to find out the anti-inflammatory activity (a method induced by Carrageenan induced edema) with Diclofenac and Indomethacin as standard drug.

AK-1(diphenylamine derivative) and AK-3 (Morpholine derivative) and are potent analgesics and anti-inflammatory compounds. The derivatives of Arylpropionic acid have pain relief and a great space for further development as a similar and anti-inflammatory agent [49].

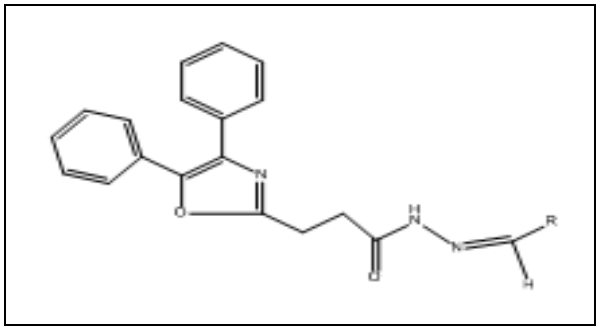
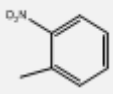
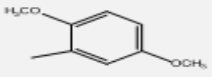
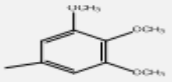


TABLE 9: ACYL HYDRAZONE DERIVATIVES OF 3-(4, 5-DIPHENYL-1, 3-OXAZOL-2-YL) PROPIONIC ACID

S. no.	R
1	
2	
3	

Gupta R. *et al.*, synthesized 2-(4-secbutyl-phenyl)-propionic acid-pyrrolidin-2-ylcarbamoyl methyl esters by refluxing ibuprofen with 2-aminopyridine in chloroacetyl chloride in presence of glacial acetic acid. The synthesized compounds were evaluated for anti-inflammatory activity. Compounds (1-6) showed potent anti-inflammatory activity **Table 10** [50, 51].

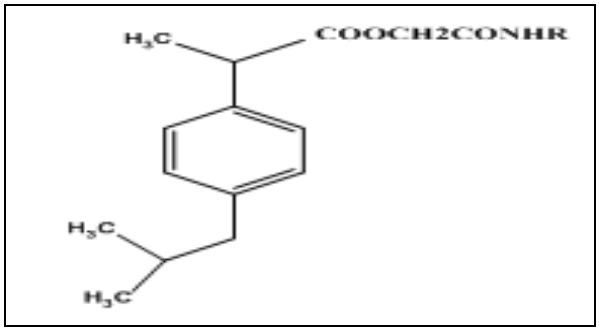
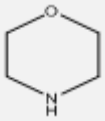
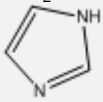


TABLE 10: 2-(4-SEC-BUTYL-PHENYL) PROPIONIC ACID-PYRROLIDIN -2-YLCARBAMOYL METHYL ESTERS

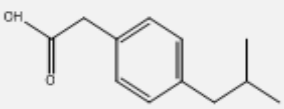
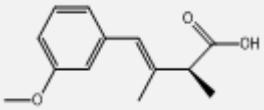
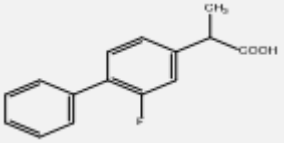
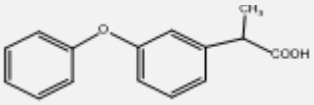
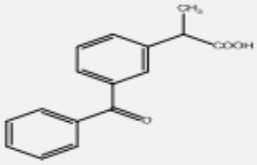
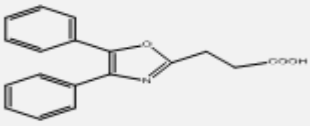
S. no.	R
1	
2	
3	NH_2NH2
4	
5	$NH(CH_3)_2$
6	$NH(C_2H_5)_2$

2.6 Anti-nociceptive Activity and Ulcerogenic Activity: Grigoryan *et al.,* 2019 synthesized a new method of a non-protein amino acid (NPAA) which showed that this compound injected in a dose of 10 mg/kg (i.p.) inhibited xylene-induced ear edema by about 31.1%, which proved its anti-inflammatory properties. The anti-nociceptive activity of NPAA-36 was assessed in the tail-flick test by the ability to increase the tail cut-off latency by 36.78% within 60 min after injection at the same dose.

Investigation of the ulcerogenic properties of NPAA-36 demonstrated that it exhibited lower gastrointestinal toxicity than a well-known aryl propionic acid derivative NSAID. Results of *in-vitro* experiments showed the Anti-platelet activity registered not in all (only in 41.2%) cases, which

might imply lower bleeding. The obtained data indicate that the new NPAA derivative can be a potential basis for the development of new anti-inflammatory drugs with weak side effects [52].

TABLE 11: POTENT COMPOUNDS AND THEIR PHARMACOLOGICAL SIGNIFICANCE

Drug name	Structure	Pharmacological activity
Ibuprofen		It is used in the treatment of chronic particular rheumatism, pain, fever and inflammation. It is also used in treating primary dysmenorrhea[55-57].
Naproxen		It is frequently used in the treatment of arthritis, acute gouty inflammation and primary dysmennorhea[58].
Flurbiprofen		(R)-flurbiprofen is clinically used in the treatment of pain and Alzheimer's disease[60].
Fenoprofen		It is preferred in the treatment of pain associated with osteoarthritis, rheumatoid arthritis and ankylosingspondilytis[64].
Ketoprofen		It is a potent NSAID used for the treatment of rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, acute and chronic musculoskeletal disorders and mild to moderate pain[66-68].
Oxaprozin		It is indicated for the management of the pain of osteoarthritis and rheumatoid arthritis[70].

Studies on the structure-activity relationship (SAR) were conducted on 3-aryl propionic acids as selective agonists by introducing substituents to the chain of propionic acid the adjacent phenyl ring with pyridine chain was replaced to develop a series of containing modified 3-aryl propionic acids with an enhanced half-life in rat [30, 64, 65]. The important members of this class, ibuprofen, naproxen, and Ketoprofen are now available as OTC medicines.

However, the indiscriminate use of these drugs without a physician's prescription has resulted in an increased incidence of acute and chronic renal failure in adolescents [70, 57]. All compounds belonging to aryl and heteroaryl propionic acids (except Oxaprozin) possess a chiral carbon in the á-position of the acetic acid side chain. Although most of the compounds are marketed as racemates, only the (S)-enantiomer was found to have any inhibitory activity against the COX isoenzymes [72]. Therefore, only (S)-enantiomer is believed to be responsible for the observed therapeutic action as well as the drug-induced GI side effects and nephrotoxicity [68, 67].

The details of some potent compounds and their pharmacological activities associated are presented in **Table 11**.

CONCLUSION: Based on various literature surveys, aryl propionic acid derivatives show broad-spectrum various activities such as anti-bacterial, anti-cancer, anti-Convulsant, analgesic, and anti-inflammatory, antinociceptive activity and ulcerogenic activity. The possible improvements in the activity can be further achieved by slight modifications in the substituent on the basic aryl propionic acid.

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