Introduction
A Search for Nonsteroidal Anti-Inflammatory Compounds: Introduction

In search of new, effective and safe drugs for the treatment of the immunological system, the progress of research has been so remarkable and significant, that there now lays before mankind a wealth of new starting points and opportunities still to be unexplored and discover. But there remains a considerable gap in the range of drugs available to treat the diseases of the immunological system.

Inflammation\(^1\) can be defined as a normal, essential, protective response to any noxious stimulus that may threaten the host and may vary from a localized reaction to a complex response involving the whole organisms. In other words, it is a host defensive but exaggerates local tissue mechanism in response to various infections, injury or destruction of tissues or any metabolic stimulus. It is a complex phenomenon comprising biochemical as well as immunological factors. The manifestation of acute inflammation is recognized by the symptoms such as redness, swelling and pain. The inflammatory response begins with a release of inflammatory chemicals into the extra cellular fluid, the most important sources of these inflammatory mediators are histamine, prostaglandins and cytokines are products of injured tissue cells, lymphocytes, mast cells and blood proteins. The presence of these chemicals promotes further reactions to inflammation which are redness, heat, swelling, and pain.

Pain is not only associated with physical suffering or hurting but has an emotional or mental component hence its definition by the international association for the studies of pain\(^2\) as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage so, the emotional as well as the physical aspects needs to be considered during treatment". One classification of pain is to consider it either acute or chronic. Since it is now recognized that the etiologies, functions, diagnoses and therefore means of treatment for these two types of pain differ. Hence it is useful to view them on this basis.

Acute pain is as set of unpleasant and emotional experience often culminating in behavioral response. Acute pain is invariably produced by
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disease, injury, noxious chemicals, or some physical stimulation (e.g. heat). Much of our knowledge about acute pain has been acquired from studies of experimentally induced pain in laboratory animals or even human volunteers.

Chronic pain, by its persistent and pathological form, appears to have no biological function. It imposes physical, emotional, and social stresses of severe magnitude. The patient's response to chronic pain is very different than to acute pain.

The currently accepted pathogenesis of these disorders can be summarised as an unknown antigen gains access to the patients' tissues and combines with an antibody in the joint activating the complement sequence. An antigen complement-antibody immune complex then precipitates in the synovial and joint fluid, generating the release of chemical mediators, which subsequently cause the immigration of numerous polymorph nuclear leucocytes. Lysosomal membrane becomes unstable and discharge hydrolytic enzymes (proteases, collagenase etc.) from the leucocytes and synovial cells. Tissue damage ensues with continuing inflammation, tissue destruction, collagen depolymerisation and loss of physical properties of connective tissue and joints. Anti-inflammatory agents may thus act by interfering with any one of several metabolism including immunologic mechanisms such as antibody production or antigen-antibody complexation, activation of complement cellular activities such as phagocytosis interference with the formation and release of chemical mediators of inflammation, or stabilization of lysosomal membrane. Thus anti-inflammatory drugs block or suppress the inflammatory response, preventing or reducing the appearance of adverse reactions to the irritant.

Hence, pain either acute or chronic is the most pervasive, frightening and important symptom of injury and much of the diseases. Since pain is both psychological and physical phenomenon, the search for anti-arthritis therapy to relieve the swelling, redness, pain and fever associated with inflamed joints and to restore impaired physical functions, dates back to antiquity. Non-steroidal anti-inflammatory drugs (NSAIDs) have acquired much higher position among the

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most widely used remedies for the treatment of pain and inflammation. Salicylic acid and it's derivatives like sodium salicylate and aspirin are used as analgesic, antipyretic and anti-inflammatory since more than a century.

In the latter part of the 20th century several other non-steroidal anti-inflammatory drugs (NSAIDs) were discovered including antipyrine, phenacetin, phenylbutazone and more recently the fenamates, indomethacin, naproxen, ibuprofen, diclofenac, ketoprofen, nimesulid, meloxicam and many more. They also share but not equally number of side effects including damage to the gastric mucosa.

**Classification of NSAIDs**

The various anti-inflammatory agents can be classified as

I. Salicylic acid derivatives

\[ \text{Salicylic acid} \]
\[ \text{Aspirin} \]

\[ \text{Salicyloyl salicylic acid} \]
\[ \text{Salicylamide} \]
II. Anthranilic acid (Mefenates)

Mefenamic acid

III. Aryl acetic acid

Ibuprofen

Fenoprofen

Ketoprofen

Flubiprofen

Naproxen

Diclofenac
IV. Indole acetic acids

- Indomethacin
- Tenidap

- Etodolac
- Tolmetin

- Ketorolac
- Metiazinic acid

V. Pyrazolidine Derivatives

- Phenylbutazone
- Kebuzone
VI. Sulfonamide (cyclic)

Piroxicam

Meloxicam

VII. Others

Sulindac

Caprofen

Benorylate

Parecoxib sodium

Rofecoxib

Celecoxib
Classification of present NSAIDs show that a large number of aryl/heteroaryl alkanoic acid and related classes of compounds are the most studied and has been reported for their anti-inflammatory activity. The potentiality of NSAIDs and the drawbacks associated with the present NSAIDs make the 21st century chemists to continue investigations in regard to the development of potent anti-inflammatory drugs to minimize side effect(s).

It is an established fact that the pharmacological activity of a compound depends upon three factors. The first and perhaps the most important is the heterocyclic moiety present in the particular compound. The second factor is the nature of the substituents and the third is the position of the substituents in the compound. These traditional structure activity relationship investigations are useful tool in the search for new biologically active compounds.

Organic compounds which share same feature of structure or functionality often exhibit similar biological effects. However they usually exhibit differences in potency and unwanted side effects and in some cases different activities. Drugs are classified in different ways depending on where and how the drugs are being used. The method of interest to organic chemist is chemical structure and pharmacological action. Keeping these factors in view, it was thought worth while to synthesise a series of new aryl alkanoic acids having different
heterocyclic moieties with a variety of substituents in different position and evaluate their anti-inflammatory activity.

Although an ideal Nonsteroidal anti-inflammatory drug (NSAIDs) has not been yet developed, efforts have been made continuously since the introduction of aspirin in 1899. Literature survey reveals that many workers reported the synthesis and anti-inflammatory activity of different heterocyclic nuclei.

Dunwell D. W. et al.\textsuperscript{6,7} reported the synthesis and anti-inflammatory activity of some 2-aryl-6-benzoxazoleacetic acid and 2-substituted alpha-methyl-5-benzimidazoleacetic acid derivatives.

In 1975 Abignente E. et al.\textsuperscript{8} reported some new heteroaryl acetic acids with anti-inflammatory action while Nelson P. H. et al.\textsuperscript{9} reported the synthesis and anti-inflammatory activity of some 1,6-methano[10] annulene acetic acids.

Ueno K. et al.\textsuperscript{10} in 1976 synthesised 6,11-dihydro-11-oxodibenzo [b,e] oxepin acetic acids and studied its anti-inflammatory activity. Hirose N. et al.\textsuperscript{11} reported the anti-inflammatory activity of some 2,3-dihydrobenzofuran-5-acetic acids. Abignente E. et al.\textsuperscript{12} synthesised Imidazo/2,1-b/thiazole-6-acetic acids and imidazo/2,1-b/benzothiazole-2-acetic acids from 2-aminothiazoles and 2-aminobenzothiazoles by reaction with ethyl 4-bromoacetoacetate and have been tested for their anti-inflammatory activity.

Dibenz[b,e]oxepinalkanoic acids as nonsteroidal anti-inflammatory agents have been reported by Aultz D. E. et al.\textsuperscript{13-15}. Kaltenbronn J. S.\textsuperscript{16} studied the anti-inflammatory activity of isomeric phenyl naphthalene acetic acids. Evans D. et al.\textsuperscript{17} and Dunwell D. W. et al.\textsuperscript{18} reported the synthesis and anti-inflammatory activity of benzoxazoleacetic acid derivatives.

Jakobiec T. et al.\textsuperscript{19} synthesised some derivatives of 2-amino-4-p-chlorophenylthiazole-5-acetic acid and reported their anti-inflammatory activities. Ackrell J. et al.\textsuperscript{20} synthesised 6,11-dihydro-11-oxodibenzo [b,e]thiepinalkanoic acids and studied their anti-inflammatory activity. Yoshioka Y. et al.\textsuperscript{21} prepared the dibenz[b,e]oxepin-3-acetic acid and found that it exhibits
anti-inflammatory activity. Raman K. et al. observed that substituted oxothiazolyl acetic acids act as anti-inflammatory agents.

Derivatives of thiazole-5-acetic acid and their anti-inflammatory activity have been studied by Jakobiec T. et al., Raffa L. et al. and Andrisano et al. published a article on heteroarylalkanoic acids with potential anti-inflammatory activity. Similarly Nash D. P. in 1980 had published a comparison of the new nonsteroidal anti-inflammatory agents.

Tamura Y. et al. studied the 4',5-disubstituted 3-biphenylacetic acids and their derivatives for their anti-inflammatory and analgesic activities. Similarly Guarnieri et al. observed the Chiral 4-biphenylacetic acid homologs as non-steroidal anti-inflammatory agents. Biere et al. synthesised pyrazole acetic acids from enamines and evaluate their anti-inflammatory activity. Atkinson D. C. et al. prepared the substituted (2-phenoxyphenyl) acetic acids and reported its anti-inflammatory activity.

In 1985 Nagatomi H. and Ando K. studied the anti-inflammatory activity and ulcerogenic adverse effect of thiazole derivatives, especially 2-amino-thiazole acetic acid derivatives. Faber et al. reported the synthesis and anti-inflammatory activity of 4-hydroxy-1-methyl-2-oxodihydroquinolin-3-yl acetic acid and related tetrazolyl derivatives.

Guarnieri A. et al. studied the anti-inflammatory activity of stereomeric 3-aryl-biphenyl hydroxy propionic acids. Bonina F. et al. tested the anti-inflammatory, analgesic and antipyretic activities of 2-arylethenylthiazol-4-acetic and 4-carboxylic acids.

Humber L. G. A. et al. reported the Etodolac, (1,8-diethyl-1,3,4,9-tetrahydropyran-3,4-b]indole-1-acetic acid) as a potent anti-inflammatory drug. Synthesis, anti-inflammatory and analgesic activity of 5-aryl-6-(methylthio)-1,2- dihydro -3H- pyrrolo [1,2-a] pyrrole -1- carboxylic acids and 1-methyl-4-(methylthio)-5-arylpyrrole-2-acetic acids were reported by Muchowski J. M. et al.
Corelli et al.\textsuperscript{38} in 1990 reported the synthesis of 10-oxo-5H-pyrrolo[1,2-b]isoquinoline-3-acetic acid which is conformationally restricted analog of Tolmetin. Pandeya S. N. et al.\textsuperscript{39} synthesised the 2,4-di-n-butyl-3,5-diarylimino-1,2,4-thiadiazolidines from butyl isothiocyanate and tested their anti-inflammatory and analgesic activities. Bordi F. et al.\textsuperscript{40} had prepared the 4-(1,2-Benzisothiazol-3-yl)alkanoic and phenyl alkanoic acids and tested it for anti-inflammatory, analgesic and antipyretic activities. Lagorce J. F. et al.\textsuperscript{41} studied the synthesis and anti-inflammatory activity of 2-pyridyl-2-thiobenzothiazole derivatives.

Synthesis and anti-inflammatory activity of some indazole derivatives are reported by Wrzeciono U. et al.\textsuperscript{42}. Menozzi G. et al.\textsuperscript{43} had prepared the 1-Aryl-1H-pyrazole-5-acetic acids and reported its anti-inflammatory and analgesic activities. Previtera T.\textsuperscript{44} synthesised and studied SARs and anti-inflammatory activity of some chiral 3,3'-Bi-[1,3-thiazolidine-4-one]. Savini L.\textsuperscript{45} prepared 1-[quinolyl(4)]-1,2,3-triazoles by reacting 4-azidoquinolines with ethyl p-nitrobenzoylacetic acid and evaluated their anti-inflammatory and analgesic properties.

In 1994 among the various NSAIDs, Winiwarter S. and Roth H. J.\textsuperscript{46} studied the molecular modeling study of top ten NSAIDs. The synthesis, anti-inflammatory and analgesic activity of imidazo [1,2-b]pyridazine-2-acetic acid derivatives were checked by Luraschi E. et al.\textsuperscript{47}. Passarotti C. M. et al.\textsuperscript{48} synthesised thiazole (3,2-a)pyrimidine derivatives by reacting 2-amino-4-alkylthiomethylthiazole with ethyl 4-chloro-3-oxobutanoate and evaluated their anti-inflammatory activity.

Palagiano F. et al.\textsuperscript{49} reported the synthesis and SAR studies of imidazo[2,1-b]benzothiazole acids and some related compounds with anti-inflammatory and analgesic activities. el-Bendary E. R. et al.\textsuperscript{50} synthesised some new quinazolines and quinoxalines compound with potential anti-inflammatory activity.

Dimitra H. L.\textsuperscript{51} studied a quantitative structure activity studies on a new class of highly potent anti-inflammatory agents. 2-Mercaptobenzoxazole
derivatives were synthesised and tested for analgesic and anti-inflammatory effects by Safak C. et al. Lazer E. S. et al. studied the effect of structural modification of enol-carboxamide-type nonsteroidal anti-inflammatory drugs on COX-2/COX-1 selectivity. Synthesis and anti-inflammatory activity of novel pyrimidine derivatives were studied by al-Ashmawy M. I. et al.

Mpango G. B. and Metwally M. A. prepared 2-Pyrazolin-5-ones structurally related to certain analgesics and antipyretic drugs and studied their anti-inflammatory activity. Romeo G. et al. carried the synthesis of new thieno [2,3-d]pyrimidine-2,4(1H,3H)-diones and studied their analgesic and anti-inflammatory activities. Pau A. et al. synthesised some of 1-methyl-4-(N-aryl)-piperidinamides with anti-inflammatory and analgesic activities. Lesyk R. et al. reported new thiazolidones-4 with pyrazolone as the potential NSAIDs.


Tozkoparan B. et al. synthesised 6-Benzylidenethiazolo [3,2-b]-1,2,4-triazole-5(6H)-ones and evaluated its anti-inflammatory activity. Khanna I. K. et al. synthesised 1,2-diarylimidazoles as potent, orally active anti-inflammatory agents. Synthesis, anti-inflammatory and analgesic activities of pyridyloxy- and phenoxy alkanoic acid derivatives has been studied by Shi K. H. et al.

In 2000, Palomba M. et al. synthesised some substituted N-cyclo alkyl benzamides, cinnamamides, and indole-3-carboxamides and evaluated it for their analgesic, anti-inflammatory activities. Baraka M. M. studied analgesic and anti-inflammatory activities of novel 2,4 (1H, 3H)-quinazolinedione derivatives.
Vigorita M. G. et al. synthesized and evaluated anti-inflammatory and analgesic activity of 3,3′-(1,2-ethanediyl)-bis[2-aryl-4-thiazolidinone]. Ozturk G. et al. synthesized 4(1H)-pyridinone derivatives and investigated their analgesic and anti-inflammatory activities.

Fahmy H. H. et al. carried out the synthesis of new salicylamide derivatives with evaluation of their anti-inflammatory, analgesic and antipyretic activities. The anti-inflammatory planar chiral [2,2]-paracyclophaneacetic acid enantiomers are reported by Imming P. et al. Habeeb A. G. et al. reported design and synthesis of 4,5-diphenyl-4-isoxazolines along with their analgesic and anti-inflammatory activities.

From the above literature survey it is observed that aryl alkanoic acids have major contribution to NSAIDs. It is also observed that a little attention is given on synthesis and evaluation of activity of heterocyclic alkanoic acids. In view of these findings it was proposed to synthesise heterocyclic alkanoic acids containing pyrimidine, pyridine, thiazole, thiazolidinone moieties with the hope to obtain new compounds with enhanced anti-inflammatory activity.

Therefore, the present work entitled "A Search for Nonsteroidal Anti-inflammatory Compounds" is described in four parts,

Part I covers the synthesis of [4-(substituted aryl)-2-oxo-6-substituted phenyl-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid in section A, [4-(substituted aryl)-6-(4-substituted phenyl)-2-thioxo-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid in section B and [2-Amino-4-(4-substituted aryl)-6-(4-substituted phenyl)-1,6-dihydro pyrimidin-5-yl]-acetic acid in section C.

Part II describes the synthesis of [4-(3,5-dicarboxylic-2,6-dimethyl-4-substituted aryl-4H-pyridin-1-yl)-phenyl]-acetic acid in section A, [4-[1,7-di substituted -4-(4-substituted aryl)-3,5-dimethyl-4,7-dihydro-1H-dipyrazolo[3,4-b]-4(3H)-pyridin-8-yl]-phenyl]-acetic acid B and [4-[1,7-Bis-(4-substituted phenyl)-8-(substituted aryl) -2,6-dimino -1,2,6,7-tetrahydro-8H -3,5-dithia -1,4,7-triaza-s-indacen-4-yl]-phenyl]-acetic acid in section C.
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Part III deals with the synthesis of [3-(substituted phenyl)-2-(6-substituted benzothiazol-2-ylimino)-4-oxo-thiazolidin-5-yl]-acetic acid in section A, [2-[4-(4-substituted benzylidene)-5-oxo-2-phenyl-4,5-dihydro-imidazol-1-yl]-4-oxo-4,5-dihydro thiazol-5-yl]-acetic acid and [2-[6-(4-substituted phenyl)-1-(4-substituted phenyl)-8-phenyl-2-thioxo-1,2,5,6-tetrahydro purin-9-yl]-4-oxo-4,5-dihydro thiazol-5-yl]-acetic acid in section B and [2-(6-substituted benzothiazol-2-yl amino)-4-substituted phenyl-thiazol-5-yl]-acetic acid in section C.

The structures of the new compounds were established on the basis of elemental and spectral analysis. Some of the newly synthesized compounds mentioned in part I, II and III have been screened for their anti-inflammatory activities and the results and speculations of the activities are discussed in part IV.
References


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Part I

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Pyrimidine derivatives have gained unique importance in the field of medicinal chemistry. Pyrimidine also known as m-diazine is the parent substance of a large group of heterocyclic compounds. Compounds belonging to this group were known as breakdown products of uric acid from very early date in the history of organic chemistry. Pinner\textsuperscript{1} studied the ring system systematically and used the name pyrimidine for the parent nucleus.

Pyrimidines can be referred as a cyclic amidine and the chemical behavior of these derivatives is dominated by this fact. In terms of the reactivity positions 2,4 and 6 are similar whereas position 5 stands somewhat different being more aromatic in character.

Pyrimidine forms an integral part of a large number of therapeutically important compounds like thiamine, riboflavin, purinbases, sulfadiazine etc. The role of pyrimidine derivatives in biochemical process is now known with reasonable accuracy and the researchers in this field are regularly adding to our knowledge, the chemistry and biochemistry of pyrimidine derivatives. Quite a good number of pyrimidine derivatives have been found to have physiological activities like anti-hepatitis B virus\textsuperscript{2-5}, anticonvulsant\textsuperscript{6,7}, anti-Rubella\textsuperscript{8,9}, antimicrobial\textsuperscript{10-16}, antiinflammatory\textsuperscript{17-28}, antitumor\textsuperscript{29-36}, antibacterial\textsuperscript{37,38}, antiviral\textsuperscript{39-48}, calcium channel modulators\textsuperscript{49}, anti-HIV-1\textsuperscript{50-51}, anti-herpesvirus\textsuperscript{52,53}, antimitotic\textsuperscript{54}, antineoplastic\textsuperscript{55}, antifungal\textsuperscript{56}, antifolate\textsuperscript{57}, leishmanicides\textsuperscript{58}, serotonin and dopamine receptors\textsuperscript{59}, aromatase inhibitors\textsuperscript{60}, glycinamide ribonucleotide transformylase with potent cell growth inhibition\textsuperscript{61} and selective pneumocystis carinii dihydrofolate reductase inhibitors\textsuperscript{62} etc.

Methods of preparation

A number of methods have been reported in literature for the synthesis of pyrimidine derivatives. They can be mainly classified into three types according to fundamental nature of the fragments which combine together to form pyrimidine nucleus. The three basic types of synthesis can be schematically represented as follows (Fig. I).
Type-I, this is common type adopted for synthesizing pyrimidine derivatives. In this the cyclization is usually involves a double condensation with the elimination of water, alcohol or hydrogen halide between amino and carbonyl, carboxylic acid, carboxylic ester and chloride or enol ether groups or condensation by addition of amino to cyano groups or to polarized double bonds without an elimination reaction.

Type II, in this the aminomethylene compound is formed as an intermediate by the action of ethoxymethylene compound with ammonia or iminoether, amide or amidine with reactive methylene compound. This amino methylene compound then undergoes cyclization with the reagents like imino ether, amide, amidines, etc. producing pyrimidine derivatives.

Type III, this type of pyrimidine synthesis involves the insertion of a single carbon atom between the nitrogens of 1,3-diamine to produce hydrogenated pyrimidine.

Grimaux\textsuperscript{63} condensed urea with malonic acid in the presence of phosphoryl chloride and obtained barbituric acid (Fig. II).

Later, this method was modified by Michael\textsuperscript{64} by condensing malonic ester with urea using sodium alkoxide as a catalyst. This process finds application in the preparation of barbiturate drugs\textsuperscript{65}.
Behrend originally showed that β-keto esters or their enol ethers are suitable reagents for condensation with urea in the preparation of 4-methyl uracil.

Mitchell have shown that the synthesis of orotic acid (uracil-4-carboxylic acid) form urea and oxal acetic ester involves an hydantoin intermediate which rearranges to the pyrimidine derivative on treatment with alkali (Fig. III).

![Fig. III](image)

β-Diketones also undergo condensation with urea under similar experimental conditions as those used in β-keto esters to give pyridines.

In 1900 Traube found that the alkali-catalysed addition of an amino group to a cyano group is convenient process for pyrimidine synthesis. Rupe et al. have synthesized 4-amino-2,6-dihydroxy pyrimidine from cyano-acetyl urea (Fig. IV).

![Fig. IV](image)

Dihydropyrimidines were synthesised by Fischer et al. by the addition of the amino group to a polarized double bond. These dihydropyrimidines may be further dehydrogenated by oxidizing agents like bromine water as shown in (Fig. V).

![Fig. V](image)
Biginelli\textsuperscript{74} synthesized dihydropyrimidines by the condensation of urea, β-Keto ester and aldehyde. Karn Folkers et al.\textsuperscript{75} have synthesized various 2-keto-6-methyl-5-carbethoxy-4-substituted phenyl-1,2,3,4-tetrahydropyrimidines by applying Biginelli reaction. The reaction sequence as shown in (Fig. VI).

\[
\text{H}_2\text{N} \quad \text{NH}_2 \quad + \quad \text{R} \quad \text{H} \quad + \quad \text{Me} \quad \text{COOEt} \quad \rightarrow \quad \text{O} \quad \text{N} \quad \text{NH} \quad \text{COOEt} \\
\text{Me} \\
\text{Fig. VI}
\]

Folkers\textsuperscript{76} have synthesised 2-keto-4-benzyl-5-phenyl-1,2,3,4 tetrahydropyrimidine with 65% yield by condensing phenyl acetaldehyde and acetophenones with urea in absolute ethyl alcohol containing conc. hydrochloric acid.

Condensation of benzoyl acetone, an aldehyde and urea\textsuperscript{77} accelerated by hydrochloric acid, proceeded smoothly by Biginelli reaction affording 2-oxo-1,2,3,4-tetrahydropyrimidines having 5-acetyl or 5-benzoyl groups as shown in (Fig. VII).

\[
\text{H}_2\text{N} \quad \text{NH}_2 \quad + \quad \text{R} \quad \text{H} \quad + \quad \text{R'} \quad \text{H} \quad \text{Me} \quad \rightarrow \quad \text{R} \quad \text{R'} \quad \text{R'} \quad \text{R'} \\
\text{O} \quad \text{N} \quad \text{NH} \quad \text{COOEt} \quad \text{Me} \\
\text{Fig. VII}
\]

A number of 4-substituted 5-acetyl-2-oxo-6-methyl-1,2,3,4-tetrahydro pyrimidines\textsuperscript{78} were prepared by acid catalysed condensation of urea with acetyl acetone and various aldehyde.

Whitehead\textsuperscript{79} described a new and quite general synthesis applicable to a wide variety of pyrimidines. Ethyl orthoformate reacts with urea or thiourea which on heating gives N,N'-dicarbamyl formamidine. Reaction of N,N'-dicarbamyl formamidines with active methylene compounds in boiling ethylene dichloride gives ureido ethylenes. The ureido ethylene undergo ready cyclization.

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with diethyl malonate in the presence of a basic catalyst to give corresponding pyrimidines. The reaction sequence may be depicted as under (Fig. VIII).

![Chemical reaction diagram showing the synthesis of pyrimidines]

Fig. VIII

Thiourea undergoes all the cyclization reactions of urea but with considerably greater ease, since 2-thiol group may be readily converted into other substituents like -H, -OH and -SR etc. S-alkyl thioureas are more reactive & condenses readily with β-Keto ester^{80} and their enol ethers^{81} yielding 2-alkylthiopyrimidines (Fig. IX).

![Chemical reaction diagram showing the synthesis of S-alkylthiopyrimidines]

Fig. IX

Similarly, thiourea also reacts with malonic esters^{82}, β-keto esters^{83} or their enol ethers^{84}, cyanoacetic esters^{85}, malononitrile^{86} and α-β-unsaturated carbonyl compounds^{87}.

When S-benzyl or S-methylthiourea is condensed with ethyl-γ-bromoacetoacetate, the product is a pyrimidine rather than a imidazole (Fig. X) which would produce by condensation of the thiourea with the α-bromoketone. This indicates the ease with which the pyrimidine ring is formed in these reactions^{88}.

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McCasland et al.⁹⁹ have synthesised various 1,4-dihydro-2-pyrimidine thiols from chalcones and ammonium thiocyanate under reflux (Fig. XI).

It is also reported that various 2-thio-4-hydroxy tetra hydro primidines⁹⁰ are prepared by refluxing α-β-unsaturated ketones with thiourea using sodium and methanol (Fig. XII).

Zimmerman et al.⁹¹ condensed various β-hydroxy and α-β-unsaturated ketones with thiourea in the presence of alkoxide and obtained the corresponding 4,6-disubstituted 2-thiono-4-hydroxy hexahydropyrimidines.

From the above reactions, it is clear that all these cyclization involve the nucleophilic attack of nitrogen atom on the electrophilic center of a carbonyl group. Therefore, basicity of nitrogen is an important factor in determining the pace of reaction. Thus thiourea is more reactive than urea and their O- and S-alkylated tautomers are still more reactive.

Guanidine, the strong base finds very convenient application in the synthesis of pyrimidine derivatives. Condensation with guanidine is generally
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carried out in alcoholic media in presence of alkali. Strong acid has also been used as a catalyst in some reactions. Synthesis of pyrimidines from guanidine and β-ketoester, β-diketones, enol ethers, cyanoacetic esters, α-β-unsaturated carbonyl compounds have been reported in literature. Reaction of guanidine with β-ketoester to give pyrimidine is written as follows (Fig. XIII).

Fig. XIII

Substituted guanidines eg. alkyl and aryl guanidines, dicyandiamide, arylsulfonyl guanidines and arylbiguanidines are reported to react with β-ketoester, β-diketones, enol ethers, cyanoacetic esters, α-β-unsaturated carbonyl compounds etc. to yield 2-substituted amino pyrimidine derivatives (Fig. XIV).

Fig. XIV

Pinner found that amidines condenses with acetoacetic ester, yielding 2-substituted-6-hydroxy-4-methyl pyrimidines. Similarly, amidines undergoes condensation reaction with β-keto ester, malonic esters and β-diketones.

4-amino-5-cyano-2-methyl pyrimidines are prepared by condensation of acetamidine with ethoxymethylene malonitrile and ethoxymethylene malonic ester respectively.

Todd and Burge studied in detail the reaction of acetamidine with ethoxy methylene cyano acetic ester. Ethyl-α-cyano-β-acetamidinoacrylate, formed as an intermediate during this reaction, can undergo cyclization into possible ways. A detailed examination of the reaction mechanism revealed that the condensation of an amidine of a carboxylic ester should strongly catalysed by

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alkali, and that with a cyano group should be favored by an acid. The reaction sequence may be depicted as under (Fig. XV).

\[
\begin{align*}
\text{Me} - \text{NH} & \quad + \quad \text{EtO} - \text{C} - \text{C} & \quad \xrightarrow{\text{Alkali}} \quad \text{Me} - \text{NH} - \text{C} & \quad \xrightarrow{\text{Neutral or Acid}} \quad \text{OH} - \text{C} \\
\text{Me} & \quad \text{CN} & \quad \text{Me} & \quad \text{CN} \\
\text{EtO} - \text{C} & \quad \text{COOEt} & \quad \text{Me} & \quad \text{CN} \\
\text{Me} & \quad \text{NH}_2 & \quad \text{EtO} - \text{C} & \quad \text{COOEt}
\end{align*}
\]

Fig. XV

Milcent\textsuperscript{107} had described the synthesis of alkyl 2-amino-4,6-diaryl-1,4-dihydropyrimidine-5-carboxylates from alkyl 3-aryl-2-benzoylpropenoates and guanidine in presence of an inorganic base (Fig. XVI).

\[
\begin{align*}
\text{EtO}_2\text{C} & \quad \text{Ph} & \quad \xrightarrow{\text{Ar}} \quad \text{NH} & \quad \xrightarrow{\text{Ar}} \quad \text{NH}_2 \\
\text{EtO}_2\text{C} & \quad \text{Ph} & \quad \text{NH} & \quad \text{NH}_2
\end{align*}
\]

Fig. XVI

Dodson and Seyler\textsuperscript{108} have reported the reaction of benzamidine with α-β-unsaturated carbonyl compound in alcoholic potassium hydroxide. It has been found that the dihydropyrimidine formed first undergoes dehydrogenation by unreacted unsaturated ketone to give 2,4,6-trisubstituted pyrimidines (Fig. XVII).

\[
\begin{align*}
\text{NH} & \quad + \quad \xrightarrow{\text{R'}} \quad \xrightarrow{\text{R''}} \quad \text{R'} & \quad \xrightarrow{\text{R''}} \quad \text{R'} \quad \text{Ph} \\
\text{NH} & \quad + \quad \text{R'} & \quad \xrightarrow{\text{R''}} \quad \text{R'} & \quad \text{Ph}
\end{align*}
\]

Fig. XVII

\textit{Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University}  
Ph.D. Thesis
Selection of Method

Impressed by the concerted endeavors that have been made by a large number of workers to synthesise various pyrimidine derivatives of physiological and pharmacological importance, it was thought worth while to synthesise some new pyrimidine derivatives having acetic acid moiety at fifth position. With this moderate objective in mind, a number of pyrimidine derivatives have been synthesized by adopting the Biginelli’s method.

The selection of this method was made on the basis of following facts:

1. Starting materials are easily available.
2. Yields are quantitative.
3. Simple experimental techniques are required.

Various 2-oxo, thioxo, and amino pyrimidines, which were synthesized for the first time and are discussed in section-A, section-B and section-C of this part.
Section-A

[4-(Substituted aryl)-2-oxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid

In recent years there has been increasing interest in the design of 1,4-dihydropyrimidine (1,4-DHPMs) and related Biginelli-like compounds which are presented as valuable medicinal properties e.g. anti-hepatitis B, anticonvulsant, antimicrobial, antitumor, antibacterial, antiviral, calcium channel modulators, anti-HIV-1 and antifungal. Oxo pyrimidines having its unique importance as it present in RNA and DNA [2,4-dioxo pyrimidine (Uracil), 2,4-dioxo-5-methyl pyrimidine (Thymine), 2-oxo-4-amino pyrimidine (Cytosine)]. The purpose of the present work is to extend the scope of oxo pyrimidine derivatives and especially to evaluate their anti-inflammatory activity.

Present work

In this section we have reported the synthesis of [4-(substituted aryl)-2-oxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid which were prepared by the condensation of β-aroyl propanoic acid, urea and the appropriate aldehyde in presence of acid catalyst with good yield (40-50%) for plane and p-substituted halogen analog derivatives. But it is found to have poor synthetic value for the preparation of p-alkyl and hetero analog. Therefore, we have carried the base catalysed condensation of the β-aroyl propanoic acid and urea with the appropriate aldehyde. This method found to be of wide applicability as a number of variously substituted pyrimidine derivatives could be prepared in good yield.

General procedure

To synthesise the title compounds following starting materials have been used.

1. β-aroyl propanoic acid
   a. β-benzoyl propanoic acid
   b. β-(4-chlorobenzoyl) propanoic acid
   c. β-(4-methylbenzoyl) propanoic acid

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2. Aldehyde
   a. Benzaldehyde
   b. 4-Chlorobenzaldehyde
   c. 4-Methoxybenzaldehyde
   d. Thiophene-2-carboxylic aldehyde
   e. Furfuraldehyde
   f. Nicotinaldehyde

3. Urea

[4-(Substituted aryl)-2-oxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid (IA1-18):

A reaction mixture of β-aryloyl propanoic acid (0.06 m), urea (0.06 m), aldehyde (0.06 m) and anhydrous K₂CO₃ (0.06 m) in ethanol was refluxed on oil bath. The reaction mixture was cooled and the solid obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The product thus obtained was recrystallised from suitable solvent. Purity of the compounds was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

Where
R = H, Cl, Me.
R_1 = Aryl

Scheme IA
Discussion of IR

IR spectra of some of the representative compounds of this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1680-1725 cm\(^{-1}\) due to >C=O stretching, 1600-1675 cm\(^{-1}\) due to C=C stretching in aromatic nucleus and 1200-1350 cm\(^{-1}\) due to C-N stretching. It is observed that absorption band in the region 3300-3400 cm\(^{-1}\) are due to -NH- stretching and broad absorption band in 2600-3300 cm\(^{-1}\) region are attributed to acidic -OH.

The spectrum No.1 represents the IR spectrum of (2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydro pyrimidin-5-yl)-acetic acid (IA\(_1\)).

Discussion of PMR

\(^1\)HNMR spectra in CDCl\(_3\) on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Chemical shifts in \(\delta\) (ppm) scale. The spectrum No.2 represents the PMR spectrum of (2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydro-pyrimidin-5-yl)-acetic acid as it displayed following PMR signal 3.1 (s, 2H, -CH\(_2\)-COOH), 5.0 (s, 1H,-CH-), 6.8-7.5 (m, 10H, Ar-H), 8.5 (s, 2H, -NH br), 10.5 (s, 1H,-OH br).

Experimental Protocol

(2-Oxo-4,6-diphenyl-1,2,3,4-tetrahydro pyrimidin-5-yl)-acetic acid (IA\(_1\)):

A reaction mixture of \(\beta\)-benzoyl propanoic acid (0.06 m), urea (0.06 m), benzaldehyde (0.06 m) and anhydrous K\(_2\)CO\(_3\) (0.06 m) in 100 ml ethanol was refluxed on oil bath for 7hr. The reaction was monitored by TLC. After completion of reaction the reaction, mixture was cooled, filtered and the solid thus obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The product thus obtained was recrystallised from ethyl acetate to get IA\(_1\). M.P.-270\(^\circ\)C, Yield- 40%.

All other compounds of this series were synthesised by following above procedure. Physical data of these compounds have been recorded in Table IA.
## Table IA: Characterization data of [4-(Substituted aryl)-2-oxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl] acetic acid (IA1-18)

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*Elemental analysis values are provided for carbon (C), hydrogen (H), nitrogen (N), and sulfur (S) on a calculated (Calc.) and found (Found) basis.

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* Recrystallised from ethyl acetate  # Recrystallised from acetone

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University
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Section-B

[4-(Substituted aryl)-2-thioxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid

The pharmacological action of drug depends upon structure, conformation, configuration, substitutens and their position etc. The need for newer drugs with high activity than existing coupled with the development of thioxopyrimidines.

Thioxopyrimidine forms an integral part of a large number of therapeutically important thiopurines, 6-thioguanine and 6-mercaptopurine, are antileukemic agents that are incorporated into DNA following retrieval by the purine salvage pathway. They also show many important medicinal applications such as anti human immunodeficiency virus (HIV), antibacterial, antiviral, antitumor, antimicrobial.

Present work

In previous section attempt was made to synthesis of [4-(substituted aryl)-2-oxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid. Similar attempt was made to synthesise [4-(substituted aryl)-2-thioxo-6-(substituted phenyl)-1,2,3,4-tetrahydro pyrimidin-5-yl]-acetic acid by the condensation of β-aryl propanoic acid, thiourea, and the appropriate aldehyde in the presence of ethanol and base.

General procedure

To synthesise the title compounds following starting materials have been used.

1. β-aryl propanoic acid
   a. β-benzoyl propanoic acid
   b. β-(4-chlorobenzoyl) propanoic acid
   c. β-(4-methylbenzoyl) propanoic acid
2. Aldehyde
   a. Benzaldehyde
b. 4-Chlorobenzaldehyde

c. 4-Methoxybenzaldehyde

d. Thiophene-2-carboxylic aldehyde

e. Furfuraldehyde

f. Nicotinaldehyde

3. Thiourea

[4- (Substituted aryl ) -2-thioxo -6-( substituted phenyl ) -1,2,3,4- tetrahydro pyrimidin-5-yl]-acetic acid (IB118):

A reaction mixture of β-arylo propanoic acid (0.06 m), thiourea (0.06 m), benzaldehyde (0.06 m) and anhydrous K₂CO₃ (0.06 m) in ethanol was refluxed on oil bath. The reaction mixture was cooled and the solid obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The product thus obtained was recrystallised from suitable solvent. Purity of the compounds was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

\[ \text{Present Work} \]

Where

- \( R = H, \text{Cl, Me.} \)
- \( R_1 = \text{Aryl} \)

Scheme IB

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University

Ph.D. Thesis
Discussion of IR

IR spectra of some of the representative compounds of this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1680-1740 cm\(^{-1}\) due to >C=O stretching, 1450-1600 cm\(^{-1}\) due to C=C in aromatic nucleus, 1180-1350 cm\(^{-1}\) due to C-N stretching and 1600-1650 cm\(^{-1}\) due to C=S stretching. It is also observed that absorption band in the region 3250-3400 cm\(^{-1}\) are due to –NH-stretching and the broad absorption band in 2600-3300 cm\(^{-1}\) region are attributed to acidic –OH. The spectrum No.3 represents the IR spectrum of (4-Phenyl-2-thioxo-6-p-tolyl-1,2,3,4-tetrahydro pyrimidin-5-yl)-acetic acid (IB\(_{13}\)).

Discussion of PMR

\(^1\)HNMR spectra in CDCl\(_3\) on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Chemical shifts in \(\delta\) (ppm) scale. The spectrum No.4 represents the PMR spectrum of (4-Phenyl-2-thioxo-6-p-tolyl-1,2,3,4-tetrahydro pyrimidin-5-yl)-acetic acid (IB\(_{13}\)) as it displayed following PMR signal 2.6 (s, 3H, -CH\(_3\)), 3.4 (s, 2H, -CH\(_2\)-COOH), 4.9 (s, 1H, -CH=), 7.0-7.7 (m,10H, Ar-H), 8.5 (s, 2H, -NH br), 10.5 (s,1H, -OH br).

Experimental Protocol

(4-Phenyl-2-thioxo-6-p-tolyl-1,2,3,4-tetrahydro pyrimidin5-yl)-acetic acid(IB\(_{13}\)):

A reaction mixture of \(\beta\)-(4-methylbenzoyl)propanoic acid (0.06 m), thiourea (0.06 m), benzaldehyde (0.06 m) and anhydrous K\(_2\)CO\(_3\) (0.06 m) in 100 ml ethanol was refluxed on oil bath for 11hr. The reaction was monitored by TLC. After completion of reaction, reaction mixture was cooled, filtered and the solid thus obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The solid product thus obtained was recrystallised from acetone to get IB\(_{13}\). M.P.=229\(^\circ\)C, Yield- 64%.

All other compounds of this series were synthesised by following above procedure. Physical data of these compounds have been recorded in Table IB.
Table IB: Characterization data of \([4\text{-}(\text{substituted-aryl})\text{-}2\text{-}\text{thioxo-6\text{-}(substituted-phenyl})\text{-}1\text{,}2\text{,}3\text{,}4\text{-}\text{tetrahydro pyrimidin-5-yl}]\)
-acetic acid (IB$_1$-IB$_8$)

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\[\text{Department of Chemical Technology, Dr.Babasaheb Ambedkar Marathwada University}\]

\[\text{Ph.D. Thesis}\]

41
### Table: A Search for Nonsteroidal Anti-Inflammatory Compounds: Pyrimidine

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* Recrystallised from acetone  # Recrystallised from ethanol  + Recrystallised from ethyl acetate

---

Department of Chemical Technology, Dr. Babasaheb Ambedkar Marathwada University

Ph.D. Thesis
Section-C

[2-Amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydro pyrimidin-5-yl]-acetic acid

The diverse pharmacological activities and therapeutic importance of pyrimidine derivatives have been widely recognized. Literature survey reveals that 2-amino pyrimidine is one of the moieties having important medicinal use as anticonvulsant, antitumor, antibacterial, antifolate, antimicrobial and antiviral.

A recent work of Milcent describes the synthesis of alkyl 2-amino-4,6-diaryl-1,4-dihydropyrimidine-5-carboxylates from alkyl 3-aryl-2-benzoyl propenoates and guanidine in DMF and in the presence of an inorganic base. The procedure affords the desired heterocycles within reaction times ranging from 8 to 48 hours but reported yields (not optimized) do not exceed 40%.

Present work

In continuation of efforts to incorporate pyrimidine moiety in pharmacologically active heterocycles, in this section we have reported the synthesis of [2-Amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydro pyrimidin-5-yl]-acetic acid. It is prepared by the condensation of β-arylo propanoic acid, guanidine and the appropriate aldehyde in presence of base. The pyrimidine derivatives could be prepared in good yield.

General procedure

To synthesise the title compounds following starting materials have been used.

1. β-arylo propanoic acid
   a. β-benzoylo propanoic acid
   b. β-(4-chlorobenzoylo) propanoic acid
   c. β-(4-methylbenzoylo) propanoic acid

2. Aldehyde
   a. Benzaldehyde
   b. 4-Chlorobenzaldehyde
c. 4-Methoxybenzaldehyde  
d. Thiophene-2-carboxylic aldehyde  
e. Furfuraldehyde  
f. Nicotinaldehyde  

3. Guanidine

[2-Amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidin-5-yl]acetic acid (IC\textsubscript{1/2}):

A reaction mixture of β-aryloyl propanoic acid (0.06 m), guanidine (0.06 m), benzaldehyde (0.06 m) and anhydrous K\textsubscript{2}CO\textsubscript{3} (0.06 m) in ethanol was refluxed on oil bath. The reaction mixture was cooled and the solid obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The product thus obtained was recrystalised from suitable solvent. Purity of the compound was checked by TLC. Structure of the newly synthesised compounds was established by the spectral analysis.
Present Work

\[
\text{Phenylacetic acid} + \text{Urea} + \text{Formaldehyde} \rightarrow \text{Pyrimidine derivative}
\]

Where

R = H, Cl, Me.
\( R_1 \) = Aryl

Scheme IC
Discussion of IR

IR spectra of some of the representative compounds of this series have been scanned on JASCO spectrophotometer using KBr pellets.

All the compounds showed absorption bands in the region 1690-1750 cm\(^{-1}\) due to >C=O stretching, 1400-1600 cm\(^{-1}\) due to C=C in aromatic nucleus, 1030-1200 cm\(^{-1}\) due to N-H stretching, 1600-1650 cm\(^{-1}\) due to C=N stretching and broad absorption band in 2600-3300 cm\(^{-1}\) region are due to acidic -OH.

The spectrum No.5 represents the IR spectrum of (2-Amino-4-phenyl-6-p-tolyl-1,4-dihydro pyrimidin-5-yl)-acetic acid (IC\(_{13}\)).

Discussion of PMR

\(^1\)HNMR spectra in CDCl\(_3\) on a sophisticated multinuclear FT-NMR spectrophotometer model Ac-300 F (Bruker) 300 MHz using TMS as an internal standard. Chemical shifts in \(\delta\) (ppm) scale. The spectrum No-6 represents the PMR spectrum of (2-Amino-4-phenyl-6-p-tolyl-1,4-dihydro pyrimidin-5-yl)-acetic acid (IC\(_{13}\)) as it displayed following PMR signal 2.2 (s, 3H, -CH\(_3\)), 2.8 (s, 2H, -CH\(_2\)-COOH), 4.4 (s, 1H, -CH-), 7.0–7.8 (m, 9H, Ar-H), 8.7 (s, 3H, -NH br), 10.8 (s, 1H, -OH br).

Experimental Protocol

(2-Amino-4-phenyl-6-p-tolyl-1,4-dihydro pyrimidin-5-yl)-acetic acid (IC\(_{13}\)) :

A reaction mixture of \(\beta\)-(4-methylbenzoyl)propanoic acid (0.06 m), guanidine (0.06 m), benzaldehyde (0.06 m) and anhydrous K\(_2\)CO\(_3\) (0.06 m) in 100 ml ethanol was refluxed on oil bath for 9hr. The reaction was monitored by TLC. After completion of reaction, reaction mixture was cooled, filtered and the solid thus obtained was dissolved in hot water and filtered. The filtrate was neutralised with acetic acid. The solid product thus obtained was recrystallised from acetone to get IC\(_{13}\). M.P.-179\(^\circ\)C, Yield- 60%.

All other compounds of this series were synthesised by following above procedure. Physical data of these compounds have been recorded in Table IC.
A Search for Nonsteroidal Anti-Inflammatory Compounds: Pyrimidine

Table IC: Characterisation data of [2-Amino-6-(4-substituted aryl)-4-(1-substituted phenyl)-1,6-dihydro pyrimidin-5-yl]-acetic acid (IC<sub>1-8</sub>)

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A Search for Nonsteroidal Anti-Inflammatory Compounds: Pyrimidine

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* Recrystallised from acetone  # Recrystallised from ethanol  + Recrystallised from ethyl acetate

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A Search for Nonsteroidal Anti-Inflammatory Compounds: References

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