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Green Chemistry Approaches Towards Synthesis of Various Non – Steroidal Anti- Inflammatory Drugs (Nsaids) Particularly Derivatives of Propanoic Acid, Ethanoic Acid and Fenamic Acid (A Review Article)

G.M.Nazeruddin[1*],Sanakauser R. Shaikh[2], Vasi Ahmed E. Shaikh[3]

[1]Department of Chemistry and Post Graduate Research Centre, Abeda Inamdar Senior College, Pune, Maharashtra, India

[2]Department of Chemistry (P.G. & Research Centre), Poona College of Arts, Science & Commerce, Pune, Maharashtra, India

[3]Department of Polymer Engineering, Maharashtra Institute of Technology (MIT), Kothrud, Pune, Maharashtra, India

ABSTRACT

Green chemistry approaches are the synthetic procedures which have to follow the principles of green chemistry i.e. in case of NSAIDs new leads, particularly novel derivatives of Propanoic acid, Ethanoic Acid and Fenamic Acid will be selected on the basis of virtual screening based on computer aided drug designing and development, followed by their synthesis which should maintain atom economy preferably through multicomponent reaction free from hazardous solvent, should consume less energy i.e. supported by grinding technique, micro-wave or ultrasound irradiation with excellent yield of the product. In short a procedure should be environmentally benign. We wish to present here with a brief review of such procedures for selection of good leads and synthesis of various derivatives of Propanoic acid, Ethanoic Acid and fenamic Acid as (NSAIDs).

Keywords: Green Chemistry, NSAIDs, CADDD, Multi component Reaction.

I. INTRODUCTION

Anti-inflammatory drugs[1] are used to alleviate pain[2] caused by inflammation. It inhibits or blocks the effect of (COX) enzymes. (COX) enzymes called as cyclo-oxygenase. COX enzymes are responsible for making the chemicals called prostaglandins. Some prostaglandins are involved in the production of pain and inflammation at sites of injury or damage. So the blocking of prostaglandin production either eliminates or reduces pain. There are two types of COX enzymes - COX-1 and COX-2. It is the COX-2 enzyme that is mainly involved in production of prostaglandins that are involved with pain and inflammation. The following NSAIDs block the action of COX-1 and COX-2 enzyme.

Propanoic Aacid derivatives: Ibuprofen, Naproxen, Fenoprofen, Ketoprofen, Dexketoprofen, Flurbiprofen, Oxaprozin, Loxoprofen, **Ethanoic acid derivatives:** Indomethacin, Sulindac, Etodolac, Ketorolac, Diclofenac, Nabumetone, **Fenamic acid derivatives**: Mefenamic acid, Meclofenamic acid, Flufenamic acid, Tolfenamic acid. Discovery of new NSAIDs with improved action and less side effect has attracted attention of medicinal/organic chemists over the years. All over the world there is a severe problem of environmental pollution. Therefore medicinal /organic chemists also develop synthetic protocols, which follow principles of green chemistry i.e. new leads of NSAIDs particularly derivatives of Propanoic acid, Ethanoic Acid and Fenamic Acid will be selected

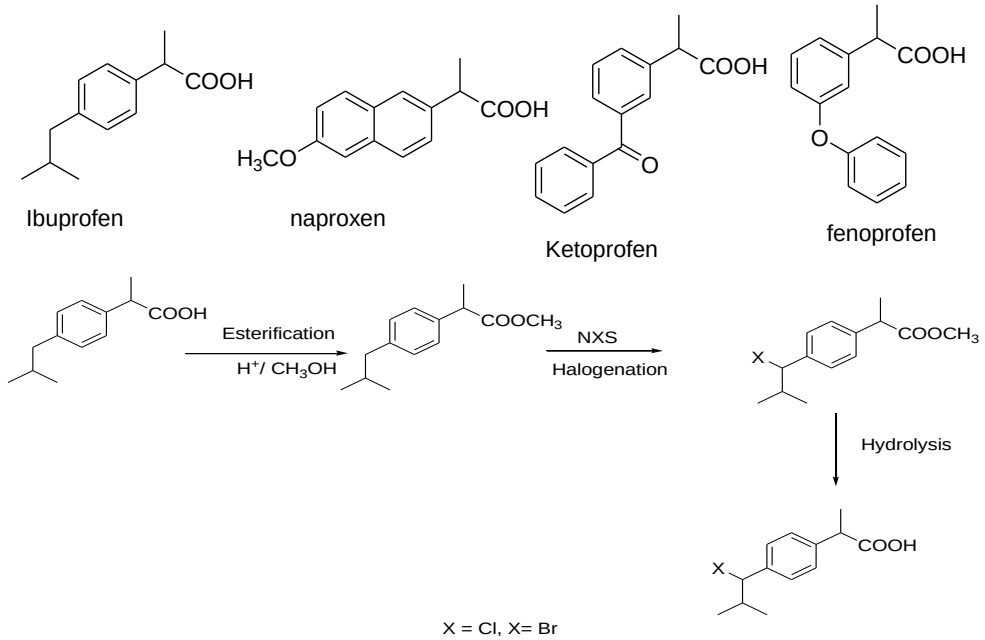
on the basis of virtual screening based on computer aided drug designing, development and discovery (CADDD)[3] followed by their synthetic procedure which should maintain atom economy preferably through multi component reaction[4] free from hazardous solvent, should consume less energy i.e. supported by grinding technique, micro-wave or ultrasound irradiation with excellent yield of the product. In short a procedure should be environmentally benign. We wish to present here with a brief review of such procedures for selection of good leads and synthesis of various derivatives of Propanoic acid, Ethanoic Acid and Fenamic Acid as (NSAIDs).

II. STRUCTURE BASED VIRTUAL SCREENING BY COMPUTER

In silico-chemico-biological approach computer plays very important role in discovery of new drug, not only it can save money but also time [5]. It is nothing but virtual screening and indirectly a green chemistry approach. Both computational and experimental techniques have important roles in drug discovery and development and represent complementary approaches. Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases. Following commonly used computational approaches will be discussed.

I. The quantitative structure-activity/property relationships (QSAR/QSPR) [6]
II. Ligand-based design (pharmacophore) - pharmacophore models are frequently used methods in the ligand-based drug design process [7].
III. Structure (target)-based design (docking)[8]

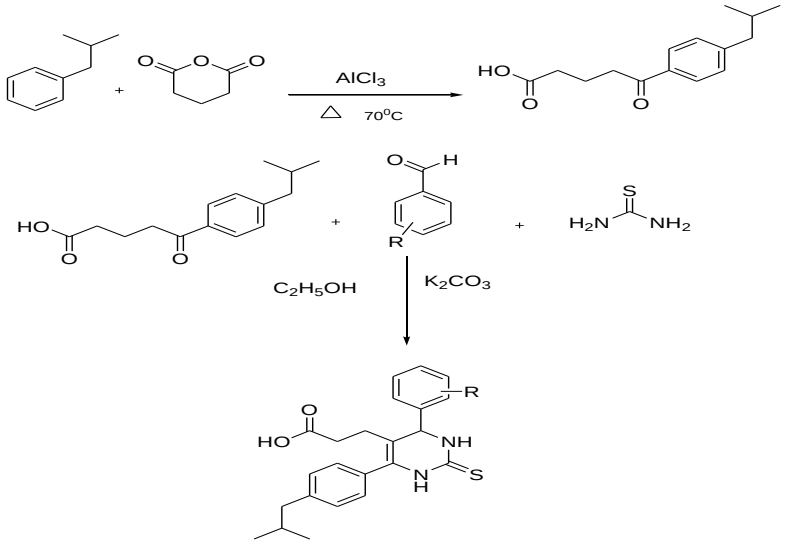
Nazeruddin et.al.[9] designed various Propanoic acid derivatives and calculated various physical properties and molecular descriptors like log P, pka by using different software such as Vega zz, Mopac, and Chem Draw etc. and they are compared with the lead compound Ibuprofen. And amongst them five new α-aryl propanoic acid derivatives were selected on the basis of similar physical properties and synthesized as depicted in Scheme I .



Scheme-I

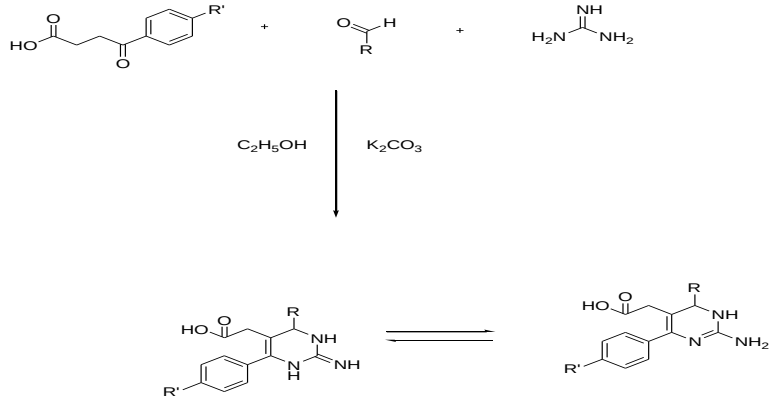
In this way five novels anti-inflammatory drug are selected by virtual screening and they are synthesized. Further, these novel NSAIDs are evaluated and found to have comparable anti inflammatory activity.

Osman et.al.[10] reported designing of series of derivatives of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid derivatives and different physicochemical properties were calculated such as logP, Hydrogen Donor, Hydrogen-Acceptor, Molecular weight and pka etc by using different software and these properties are compared with Ibuprofen. Out of them ten compounds having similar physicochemical properties were selected for the synthesis. They were synthesized by condensation of thiourea, 5-(4-isobutylphenyl)-5-oxopentanoic acid and substituted aldehyde. The synthesized compounds were obtained in good yield, and after biological evaluation were found to have potential anti-inflammatory activity. The reaction is depicted in the following scheme-II



Scheme II, Synthesis of 3-(4,6-disubtituted-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl) propanoic acid

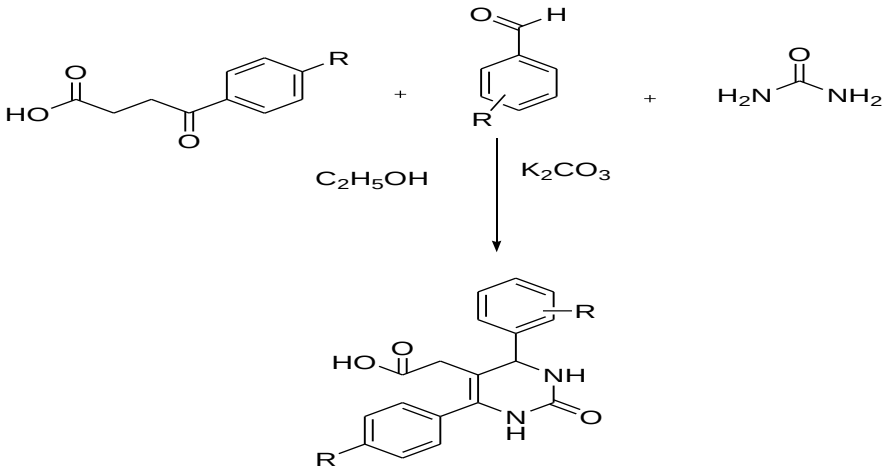
Bahekar et .al. [11] has discovered a synthesis of series of 2-amino-6-(4-substituted aryl)-4-(4-substituted phenyl)-1,6-dihydropyrimidine-5-yl-acetic acid derivatives by condensation reaction of aryl propanoic acid, guanidine nitrate and aromatic aldehydes in presence of K_2CO_3 as a catalyst (Scheme-III)



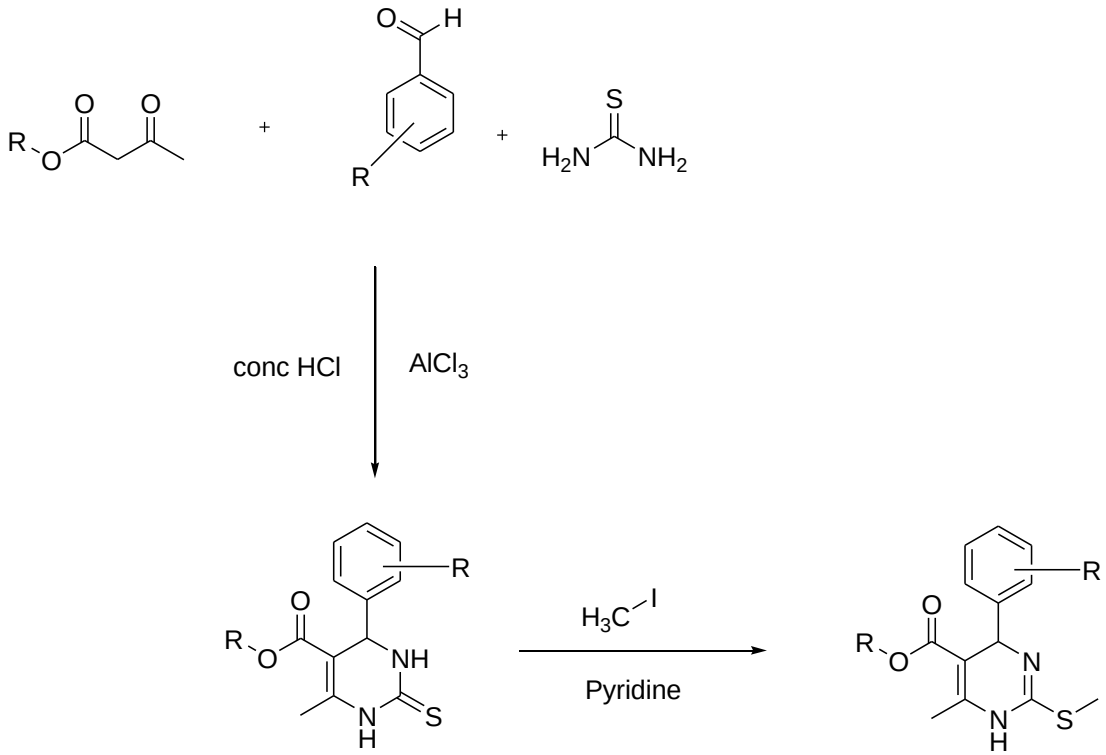
Scheme-III: Synthesis of 2-amino-6-(4-substituted aryl)-4-(4-substitutedphenyl)-1,6-dihydropyrimidine-5-yl-acetic acid derivatives

Mokale et. al. [12] has investigated synthesis of a series of [4,6-(substituted aryl)-2-oxo-1,2,3,4-tetrahydro-pyrimidin-5-yl]-acetic acid has been synthesized by the base catalyzed condensation of 4-(4-

substitutedphenyl)oxobutanoic acid, urea with aldehyde in ethanol. The synthesized compounds were evaluated for anti-inflammatory activity (Scheme-IV).



Scheme-IV: Synthesis of [4, 6-(4 substituted aryl)-2-oxo-1,2,3,4-tetrahedropyrimidin-5-yl]-acetic acid derivatives Sawant et. al [13] has investigated synthesis of a series of methylthio-1,4-dihydropyrimidine derivatives were synthesized in good yields by alkylation of 1,2,3,4-tetrahydropyrimidines with methyl iodide in the presence of pyridine (Scheme-V). The synthesized compounds were tested for analgesic activity.

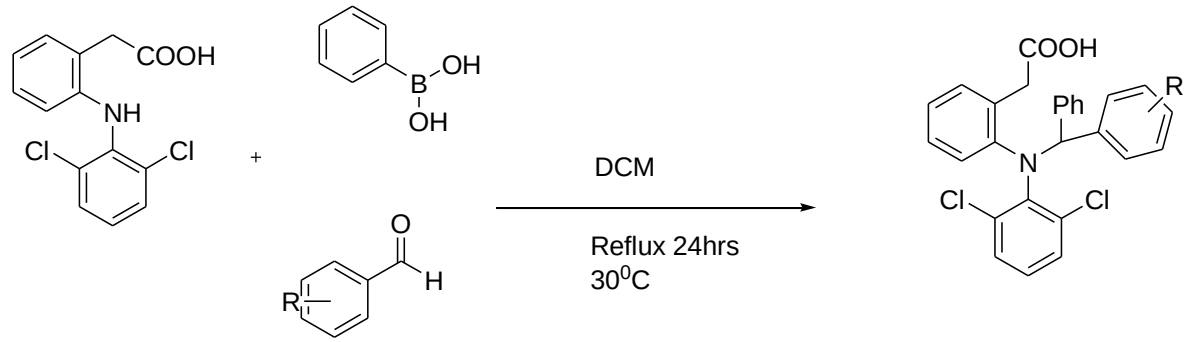


R= CH_3

Scheme-V: Synthesis of 2-methylthio-1,4-dihydropyrimidines

Various new analogues of diclofenac were designed by Osman[14] et. al. and their physiochemical properties such as log P, HOMO, LUMO and pKa etc. were calculated and out of them five compounds were selected for

synthesis and Petasis reaction was exploited, which is multicomponent reaction. The reaction is depicted in following Scheme -VI



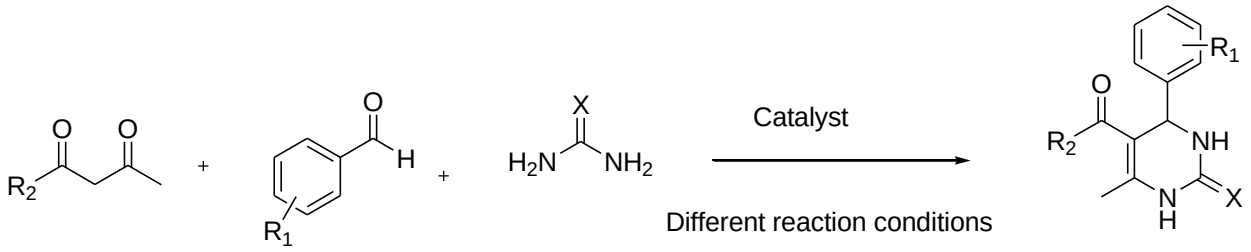
R = H, -OH, -OMe, -Cl, -NO_2

Scheme-VI

III. MULTICOMPONENT REACTIONS

It is observed that synthesis of various derivatives of Propanoic acid, Ethanoic Acid and fenamic Acid as (NSAIDs) were accomplished by exploiting various multicomponent reactions such as Biginelli reaction[15], Petasis reaction [16]. Multicomponent reactions (MCRs) are chemical reactions in which three or more compounds react to form a single product. The reaction gives highly selective products that retains majority of atoms present in starting material. MCRs provide great possibility for getting molecular diversity and complexity in few steps within less time. In short they follow the principles of green chemistry.

The Biginelli reaction is a multiple-component chemical reaction that produces 3,4-dihydropyrimidin-2(1H)-ones from ethyl acetoacetate, aldehyde, urea. This reaction is named by Italian chemist Pietro Biginelli in 1891. Thus the development of facile and environmental friendly first synthetic method for the preparation of dihydropyrimidine-2(1H)ones (DHPMs) was recorded, that involves the one pot three component condensation of aldehyde, 1,3-dicarbonyl compounds and urea or thiourea in ethanol under strongly acidic conditions producing DHPMs, albeit in low yields. In the view of the pharmaceuticals importance of these compounds many improved catalytic methods have been developed. [17-21] The reaction is shown in scheme-VII.

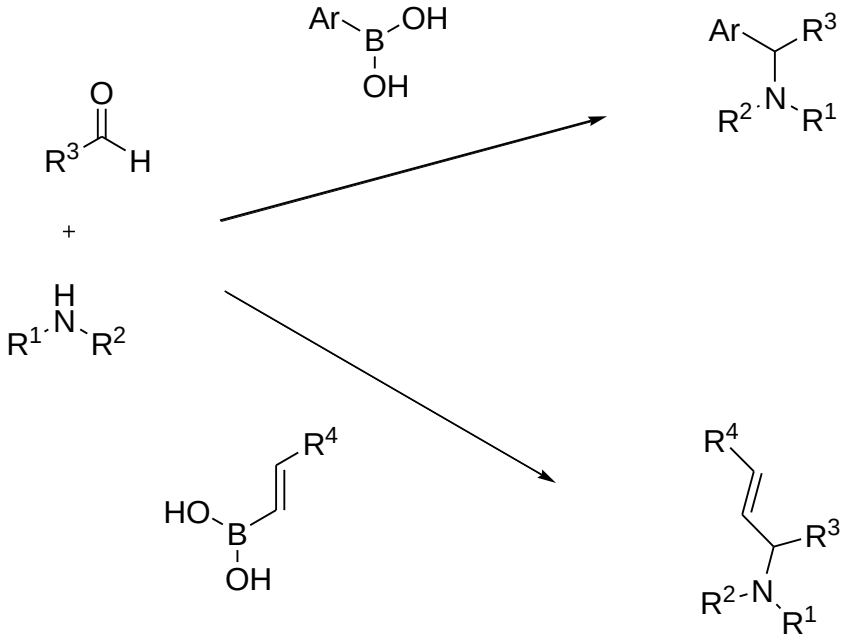


R_1 = Different substituents, R_2 = OEt, OMe ; X = O / S

Scheme-VII: The synthesis of Dihydropyrimidine-2(1h) derivatives

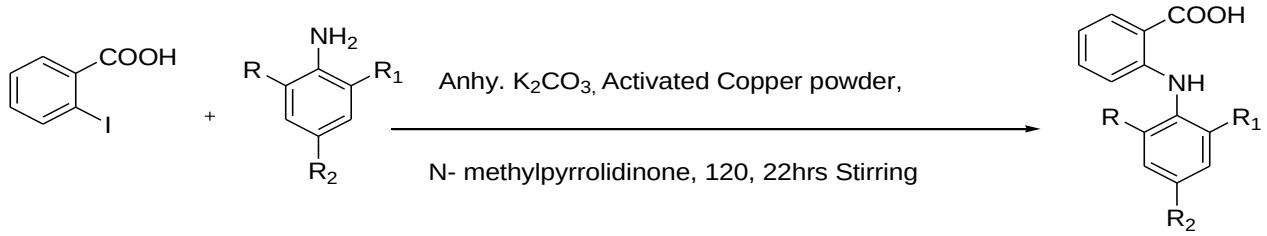
Petasis reaction is the chemical reaction of an amine, aldehyde, and vinyl- or aryl-boronic acid to form substituted amines. In the Petasis reaction, the vinyl group of the organoboronic acid serves as the nucleophile.

In comparison to other methods of generating allyl amines, the Petasis reaction allows multifunctional scaffold, with a variety of amines and organo boronic acids as potential starting materials. The reaction does not require anhydrous or inert conditions. As a mild, selective synthesis, the Petasis reaction is useful in generating α-amino acids, and is useful in combinatorial chemistry and discovery. The reaction is depicted in scheme VIII



Scheme- VIII: Petasis Reaction

Docking studies were performed using (Auto Dock 4.2.) 2006.02 (CCG Inc.)20 and runs on a cluster of 12 Pentium IV processors, the results were in accordance with the biological evaluation. Similarly Suryawanshi et.al.[22] designed various derivatives of fenamic acid and calculated different physicochemical properties and compared with fenamic acid. All the new non-steroidal anti-inflammatory drugs (NSAID) selected for designing, have to follow Lipinski's Rule of Five [23]. Out of them five compounds having similar physicochemical properties were selected for the synthesis as depicted in Scheme-IX. They were found to have potential anti-inflammatory activity.



1. R = H, R_1 = H, R_2 = Br
2. R = Br, R_1 = Br, R_2 = Cl
3. R = Cl, R_1 = Cl, R_2 = Br
4. R = Br, R_1 = Br, R_2 = CH_3
5. R = Br, R_1 = Br, R_2 = Br

Scheme-IX

IV. CONCLUSION

Virtual screening is used to discover new drug candidates from different chemical scaffolds by searching commercial, public, or private 3-dimensional chemical structure databases. Multicomponent reaction (MCR) is a green approach towards the synthesis of various heterocyclic

compounds and for a researcher there is lot of scope to change the reaction condition, to change the catalyst or to modify the catalyst or even to develop various novel multicomponent reactions. Apart from all these a polyfunctionalized heterocyclic product obtained from a multicomponent reaction can be tailored to novel pharmacophore as per the need.

V. ACKNOWLEDGEMENT

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