"ONE POT SYNTHESIS OF N-(2-NITROPHENYL) ACETAMIDE"

UG-PROJECT 2019-2020

"One POT synthesis of N-(2-nitrophenyl) acetamide"

Submitted in partial fulfillment of the requirements for the degree of
Bachelor of Pharmacy

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This is to certify that the project entitled **One POT synthesis of N-(2-hydroxyphenyl) acetamide** is a bonafide work of **Sumaiya Banu Rehmansha (Roll No.:16PH56), Khan Shifa Mohsin (Roll No: 15PH24), Shaikh Taqdees (Roll No: 16PH57), Shaikh Md Umar Imran (Roll No: 16PH51)** submitted for the appreciation of the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry.

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Approval for Bachelor of Pharmacy

This project One-Pot Synthesis of N-(2-hydroxyphenyl) acetamide By N-Acetylation using Mg-Acetate as Catalyst by Sumaiya Banu Rehmansha, Khan Shifa Mohsin, Shaikh Taqdees, Shaikh Md Umar Imran is approved for the degree of Bachelor of Pharmacy in Department of Pharmaceutical Chemistry.

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Declaration

I declare that this written submission represents my ideas in my own words and where others ideas or words have been included; I have adequately cited and referenced the original sources. I also declare that I have adhered to all principles of academic honesty and integrity and have not misrepresented or fabricated or falsified any idea/data/fact/source in my submission. I understand that any violation of the above will be cause for disciplinary action by the Institute and can also evoke penal action from the sources which have thus not been properly cited or from whom proper permission has not been taken when needed.

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V Keywords and Glossary

1	TM	Target Molecule
2	P1	Precorsore-1
3	P2	Precorsore-2
4	XRD	X-Ray diffraction scanning
5	FT-IR	Fourier-transform infrared spectroscopy
6	C13 NMR	Carbon 13 nuclear magnetic resonance
7	ESI-MS	Electrospray ionization Mass spectroscopy

VI ABSTRACT

The project was merely focusing on to carry out the disconnection approach, with existing Tylenol (acetaminophen) to develop the sustainable protocol, on one-pot synthesis. The extensive literature survey projected the background data of work done on Tylenol and its derivatives, by adopting different chemical methods, our study prime focused on to design the sustainable protocol by applying the one-pot methodology, with N-Acetylation using Mg-acetate which was the first time approach. It is also observed that the use of a catalytic amount of Mg-acetate in acetic acid is sufficient enough for smooth running of N-acetylation reactions. The procedure was chemo-selective with respect to phenols, acids and alcohols. Herein we reported a simple, efficient, cost-effective and environmentally benign alternative method for N-acetylation of amines using catalytic amount of Magnesium acetate in I mole of acetic acid under rotation on magnetic stirrer for 1hr at 250rpm. The reaction procedure requires no other solvent and it was a rapid process with good to excellent yields. The synthesized molecular structure was confirmed by FT-IR, NMR, and Mass spectral data during XRD-analytical diffraction scan, which suggested the complete agreement on key functionality identification structure of the molecule using powdered diffractometer preliminary analysis, the data scanned and calculated accurately with 2θ coverage the detection of good reflections was noted and hence we prove, on the basis of spectra the stereochemistry of functionality was different from existing Tylenol the toxicity study and biological screening are under process in our laboratory. This project would be the novel method in the future for development of antipyretic antiviral molecules if it gave positive results for the activity.

Keywords: Magnetic rotation, amines, acetic acid, Magnesium acetate, N-acetylation, chemo-selectivity, Toxicity, biological screening

INTRODUCTION

Efficiency and environmental sustainability are central issues in contemporary organic chemistry. Both need to be addressed carefully when making a valuable target molecule over several distinct steps. When feasible, an effective approach is to synthesize the target in a single reaction vessel. This approach is often termed 'one-pot', and can apply to a multi-step reaction, method, or synthesis. It is effective because several synthetic transformations and bond-forming steps can be carried out in a single pot, while circumventing several purification procedures at the same time.

One-pot synthesis is much desired by chemists because avoiding a lengthy separation process and purification of the intermediate chemical compounds can save time and resources while increasing chemical yield. An example of a one-pot synthesis is the total synthesis of tropinone or the Gasman indole synthesis. Sequential one-pot synthesis can be used to generate even complex targets with multiple stereo centers, such as oseltamivir, [1] which may significantly shorten the number of steps required overall and has important commercial implications. A sequential one-pot synthesis with reagents added to a reactor one at a time and without work up is also called a **telescoping synthesis**.

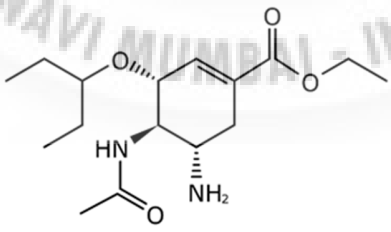


Fig-1: Oseltamivir (brand name Tamiflu) antiviral drug

For instance, Robinson's one-pot synthesis of tropinone is a landmark achievement in organic chemistry, which was reported nearly 100 years ago (eqn (1)). [2]

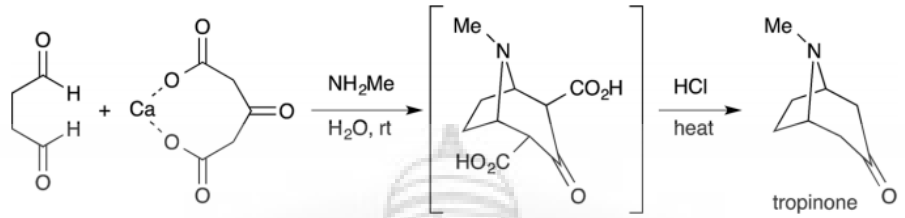


Fig-2 synthesis of tropinone

Among many other classic examples involving single-pot procedures, one-pot reactions have been elegantly utilized in the biomimetic syntheses of progesterone by Johnson, [3] Endiandric acid by Nikolaou, [4] and proto-daphniphylline by Heathcock.[5] In the growing field of organocatalysis, [6] organocatalysts are particularly effective reagents in achieving a one-pot, multi-step synthesis. This is evidenced by a dramatic increase of impressive syntheses over the past decade. [7] For example, Enders reported a breakthrough one-pot synthesis of a chiral cyclohexenecarbaldehyde with excellent enantioselectivity using a diphenylprolinol silyl ether-mediated [8, 9] Michael reaction as a key step (eqn (2)). [10]

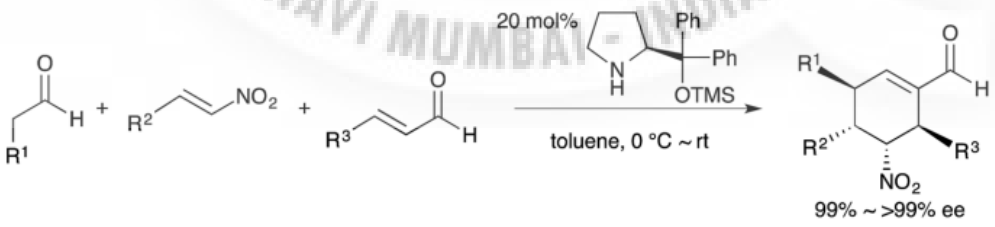


Fig-3 percentage yield of the tropinone

This catalyst was independently developed by our group [8] and the group of Jorgensen [9]. Herein, we review the characteristics of one-pot synthesis employing prolinol-based organo catalysts as developed in our laboratories. By detailing the criteria for a successful multi-step synthesis, the insights and concepts presented are intended to be transferable to other organic reaction methods, synthetic strategies, and the field of targeted synthesis in general.

The vast majority of drugs and medicines available are small organic molecules. A chemist designing new drugs will synthesize new molecules then send them off for biological testing; the structure of the molecule will continue to be modified until a compound with the optimum properties has been obtained. A chemist, therefore, needs to be able to prepare molecules and analyze them to ensure the correct compound has been made before sending them for testing.

In this investigation, the synthesis of acetaminophen was attempted using a one-step experiment. Acetaminophen is a well-known drug that is used to relieve headaches, fever, body aches and pains in joints muscles. It is also a main ingredient in many cold and flu medications and prescriptions. It is considered a safe and effective drug when used in the recommended dosages. The acetaminophen compound counteracts the enzyme cyclooxygenase which synthesizes prostaglandins. Prostaglandins serve many different protective functions within the human body, such as producing pain and raising body temperature. By hindering this synthesis of prostaglandins, the body's response to elevating temperature and increasing pain can then be reduced. Acetaminophen is different from other pain controlling drugs, such as aspirin or ibuprofen, because it has no anti-inflammatory properties. It is unlike other non-steroidal anti-inflammatory drugs (NSAIDS) because it seldom irritates the lining of the stomach, and does not affect blood clotting, or the kidneys

Literature survey

The background of the entitled work was based on the following step to set the target

1. Description of One-pot/domino/cascade/tandem reaction
2. Description of Pot economy/atom economy/step economy/redox economy
3. Description of Telescope reaction/one-pot reaction

1. Description of One-pot/domino/cascade/tandem reaction

There are several terminologies to describe multi-step reactions that take place in one pot. These include: “domino reaction”, “cascade reaction”, and “tandem reaction”. Nikolaou pointed out that these descriptions are comparatively interchangeable in his 2006 review titled “Cascade Reactions in Total Synthesis”.[11] Tietze suggested the usage of “domino reaction” rather than “cascade reaction” or “tandem reaction”, and defined a domino reaction as a process involving two or more bond-forming transformations (usually C–C bonds) that take place under the same reaction conditions without adding additional reagents and catalysts, and in which subsequent reactions result as a consequence of the functionality formed in the previous step.[12] Denmark proposed to keep the all-encompassing definition of “tandem reactions” as reactions that occur one after the other, and to use the modifiers cascade (or domino), consecutive, and sequential to specify how the two (or more) reactions follow.[13] Fogg classified one-pot processes as one-pot reaction, domino catalysis, or tandem catalysis, the latter of which being further subdivided into orthogonal catalysis, auto-tandem catalysis, and assisted-tandem catalysis.[14] In spite of all these terminologies, a one-pot synthesis is defined as a strategy to improve the efficiency of a chemical reaction, whereby a reactant is subjected to successive chemical reactions in just one reactor.[15] As long as a particular sequence of reactions is carried out in the same reactor, it is considered to be “one-pot” in this review. Thus, a one-pot synthesis has a much wider meaning than a cascade,

domino or tandem reaction, and the concept of a one-pot synthesis encompasses all such reaction types as well as the multi-step strategies that are adopted in a single vessel or reactor.

2. Description of Pot economy/atom economy/step economy/redox economy

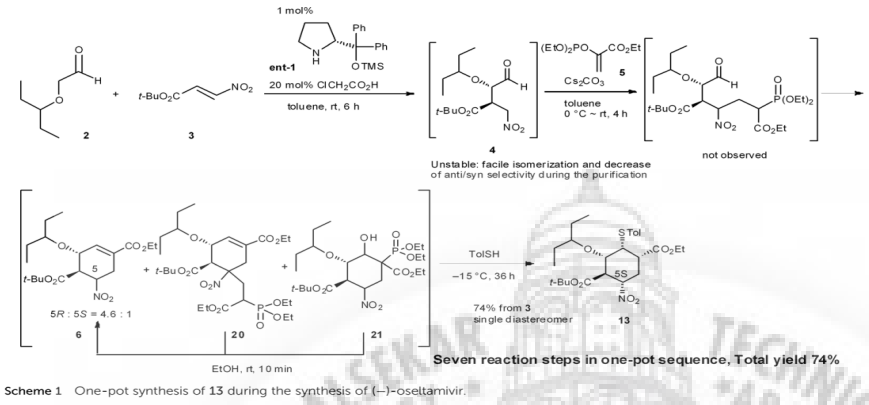
'Green'[16] and 'efficiency' are two principal issues in science and industry. These issues can be characterized in terms of atom economy, step economy, and redox economy.[17] Atom economy was proposed by Trost, who stated that synthetic methods should be designed to maximize the incorporation of all materials used in the process into the final product (ACS Green Chemistry Principle #2).[18] Reactions with no byproducts[19] are thus desirable and it is necessary to employ "clean" and reliable reactions when planning the synthesis of a target molecule. Step economy was proposed by Wender and is another fundamental economy to consider in order to minimize the number of reaction steps to a target molecule; this thereby reduces the length, cost, development time, execution time, effort, separation methods, and environmental impact of a synthesis.[20] Step economy is clearly influenced by selecting the right reaction method and sequence to allow for an optimal increase in target-relevant complexity. Redox economy was recently proposed by Baran and Hoffmann and relates to minimizing unnecessary changes in the oxidation states of isolatable intermediates, and thereby relates to reducing the number of steps in a given synthetic sequence.[21] the concepts of redox and step economy are thus important in the synthetic design and strategic implementation of reaction methods to a target molecule. An additional economy to consider is in the number of pots required for each reaction method. In other words, the workup and isolation of intermediates is not always necessary. Indeed, chemists have omitted workup procedures and carried out several reactions in the same reactor for a long time. When several reactions are conducted in a single reactor, without isolating or purifying the intermediates, we can reduce the amounts of solvent, waste, time, labor and cost. Thus, "pot-economy"[22] is also important in

synthesizing a target molecule in terms of 'greenness' and practicability. Thus, in realizing a multistep synthesis, chemist's first retro-synthesize the target molecule, in which they choose a synthetic strategy and reaction sequence according to the principles of step and redox economy. Next, appropriate reagents and reaction conditions are selected according to the atom economy. Today, during these design and development stages, chemists are now adopting the principles of pot economy. Such aspects are discussed next.

3. Description of Telescope reaction/one-pot reaction

Process chemists often carry out several reactions in a single reactor without the need to isolate intermediates. This multistep approach is termed as a "telescoped reaction". According to Dr. J. Dunetz at Gilead Sciences, [23] a telescoped reaction is defined as follows: while there is no formal definition, in general terms, telescoping are the execution of multiple transformations (including quenches and other workup operations) without the direct isolation of intermediates. Telescoped solutions of intermediates can be extracted, filtered (as long as the product remains in the filtrate), and solvent exchanged, but the intermediate is ultimately held in solution and carried forward to the subsequent transformation. These workup operations add to the expense of a process, and the best telescoped processes will minimize solvent exchange, etc. As long as a reaction sequence is conducted in the same reactor, this approach is a one-pot reaction. However, telescoped reactions and one-pot reactions are not always the same. For instance, the (-)-oseltamivir synthesis given in Fig-2 (Scheme 1 and 2),[24] is regarded as a one-pot reaction but this synthesis is not telescoped due to the need to concentrate reactor contents to dryness in order to replace solvents. Such work-up steps are regarded as an isolation of the crude intermediates or product material. The one-pot synthesis of (-)-oseltamivir given in Fig 3 (Scheme 3),[25] however,

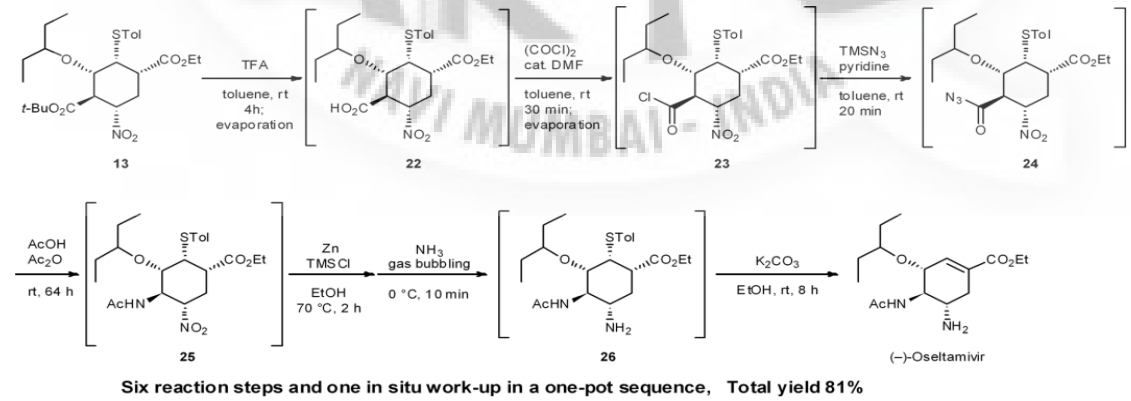
is regarded as both one-pot and telescoped, because all reagents are added successively to one reactor without the need to evaporate or replace solvents



Scheme 1 One-pot synthesis of 13 during the synthesis of (–)-oseltamivir.

Fig-4 (-)-Oseltamivir synthesis[26]

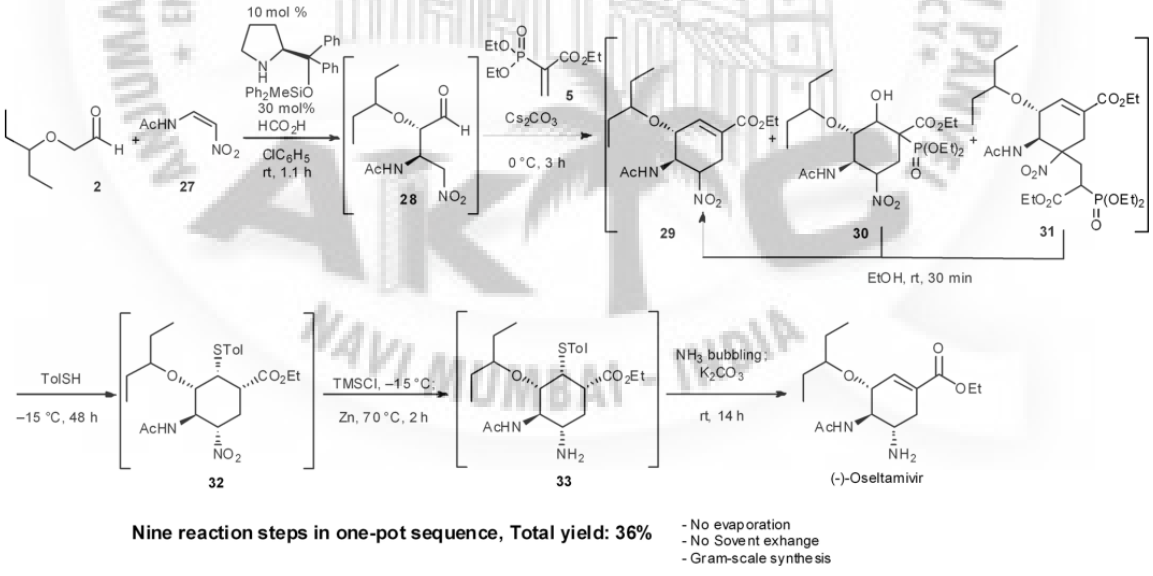
Fig explains a highly functionalized chiral cyclohexane framework with the correct relative and absolute configuration was synthesized over seven reaction steps: (1) a diphenylprolinol silyl ether-mediated, asymmetric Michael reaction (2 and 3 / 4), (2) a domino Michael reaction and (3) Horner–Wadsworth–Emmons reaction (4 / 6) combined with (4) a retro-aldol/(3) Horner Wadsworth–Emmons elimination (21 / 6), (5) a retro-Michael reaction (20 / 6), (6) a base-catalyzed isomerization, and (7) a thiol-Michael reaction (6 / 13).



Scheme 2 One-pot synthesis of (–)-oseltamivir from 13.

Fig-5 (-)-Oseltamivir synthesis

During our second generation synthesis of (-)-oseltamivir, six reaction steps were conducted in a second, one-pot reaction sequence from 13 (Scheme 2). These include: (1) deprotection of a tert-butyl ester (13 / 22) and (2) its conversion to the acid chloride 23, then (3) transformation to the acid azide 24, (4) the domino Curtius rearrangement/amide formation of 25, (5) the nitro reduction of 25 to the amine 26, and (6) the retro-Michael reaction of the thiol group. In this case, several evaporation procedures were employed to change solvents and remove volatile components from the reaction mixture. After the reduction of the nitro moiety with Zn, NH3 bubbling is necessary to cleave zinc chelates in situ. This is comparable to a "stop and-go" synthesis, whereby the Zn chelates are cleaved by acid treatment during aqueous workup. In the one-pot sequence, this kind of "in situ work-up" modification is necessary to carry out sequential one-pot reactions successfully.



Scheme 3 One-pot targeted synthesis of (–)-oseltamivir.

Fig-6 (-)-Oseltamivir synthesis

Michael reaction (2 and 27 / 28), (2) a domino Michael reaction/(3) Horner–Wadsworth–Emmons reaction (28 / 29), combined with (4) a retro-aldol/(3) Horner– Wadsworth–Emmons elimination (30 / 29), (5) a retro-Michael reaction (31 / 29), (6) a base-catalyzed isomerization, (7) a thiol-Michael reaction (29 / 32), (8) reduction of the nitro group to an amine (32 / 33), and finally (9) a retro-Michael reaction of the thiol.

A noteworthy synthetic advantage in the above one-pot synthesis does not involve any evaporation processes or solvent swapping. Also, the work done on synthesis is the first example of a stereo chemically complex drug being synthesized in a single reactor, in significant yield, without the need to evaporate or swap solvents. This achievement shows the power of a carefully developed one-pot reaction sequence [29]. By referring to the above mentioned literature based reports we focused to carry out the project by adopting one pot synthetic strategy.

The literature survey also revealed that there is no work has been done on one-pot synthesis of analgesic from Tylenol till date hence the effort was made to carry out the process by referencing the article Brahmacharya Get all, they elaborated the green synthesis of N-acetylation of amine using catalytic amount of zinc acetate and acetic acid. The novelty of the project was N-acetylation using One-pot synthetic approach by replacing the catalyst and modification of reaction condition, to improve the product yield and to optimize the reaction condition

Aim

The present study was undertaken to carry out one-pot synthesis of N-(2-nitrophenyl) acetamide from Tylenol by N-acetylation using Mg-Acetate as catalyst

Plan of work.

- Tylenol is the brand name of acetaminophen which is an analgesic and anti-inflammatory drug.
- Enormous work has been done on this well-known drug, but there was no reference data available on one-pot synthesis from Tylenol (acetaminophen).
- Hence effort was made to proceed with the methodology to increase the yield and reduce the reaction time with following objectives

Objectives

1. Elegant utilization of one pot synthesis on magnetic-stirrer.
2. Synthesis of N-acetylated amines by using catalytic amount of magnesium acetate $Mg(CH_3COO)_2$
3. Characterization and chromatographic evaluation of synthesized molecule

MATERIALS AND METHODS

The experimental work is divided into three parts-

1. Description of selected molecule
2. Disconnection approach
3. Synthetic design

Description of selected molecule

- Brand Name: Tylenol
- Generic name: Acetaminophen or Paracetamol
- Structure: N-(4-hydroxyphenyl)acetamide

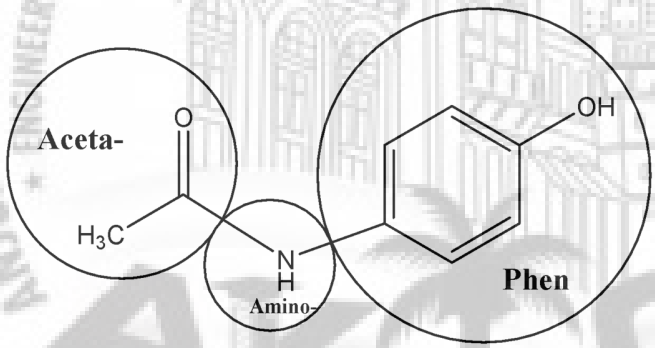


Fig:-7 Acetaminophen functional linkage of the structure to apply Disconnection

Uses.

It is used as effective antipyretic and analgesic activity, the drug follows dual mechanism Primarily it act on hypothalamic heat regulating center to reduce the body temperature secondary it also act on **COX-2 inhibitors directly targeting to cyclooxygenase-2** enzyme responsible for inflammation and pain.

Reagents and solvents

All the chemicals used for experimental work were of laboratory grade and commercially procured from different chemical vendors E. Merck (Darmstadt, Germany), CDH and S.D. Fine Chemicals (Mumbai, India). The solvent and reagents were purified before use. Progress of the reactions was monitored by thin layer chromatography using TLC plates (silica gel G) as stationary phase and TEF (toluene: ethyl acetate: formic acid; 5:4:1, v/v/v) and chloroform: methanol (9:1, v/v) as solvent systems. The spots were located by exposure to iodine vapors or under UV-light. PNP (Para nitro phenol), MAH (magnesium acetate Hydroxide), and GAA (Glacial acetic acid) were obtained from Sigma Aldrich.

Instrument and Equipment

Melting points were determined by the open tube capillary method and were uncorrected. Purity of the compounds and the progress of the reactions was monitored by thin-layer chromatography (TLC) plates (silica gel G), which were visualized by exposing to iodine vapours and UV (ultra violet) light. IR spectra were recorded on a Shimadzu Infra-Red Spectrometer (FTIR-8400S) using KBr pellets. 1H NMR was recorded in DMSO-$\partial 6$ or CDCl3 on Bruker 300/400 MHz instruments using tetramethylsilane (TMS) as internal standard. Chemical shifts (δ) are expressed in ppm relative to TMS and coupling constants (J values) are expressed in Hz. Mass spectra were recorded on LC-MS/MS (Perkin-Elmer and LABINDIA, Applied Bio system) model no. API 3000, presented as m/z. Elemental analyses performed on a Perkin-Elmer 240 analyzer and found in the range of ± 0.4% for each element analyzed (C, H and N). Bio-Rad Titer plate reader and Bio-Rad Universal Hood II Gel Doc System were used for MTT and Topoisomerase inhibition assays respectively.

DISCONNECTION APPROACH

Scheme-I

Disconnection on the Target Molecule distributes the structure into two precursors, which are termed as synthons, this fragments helps to design the synthetic paten, orientation and reactivity during scheme designing of synthesis

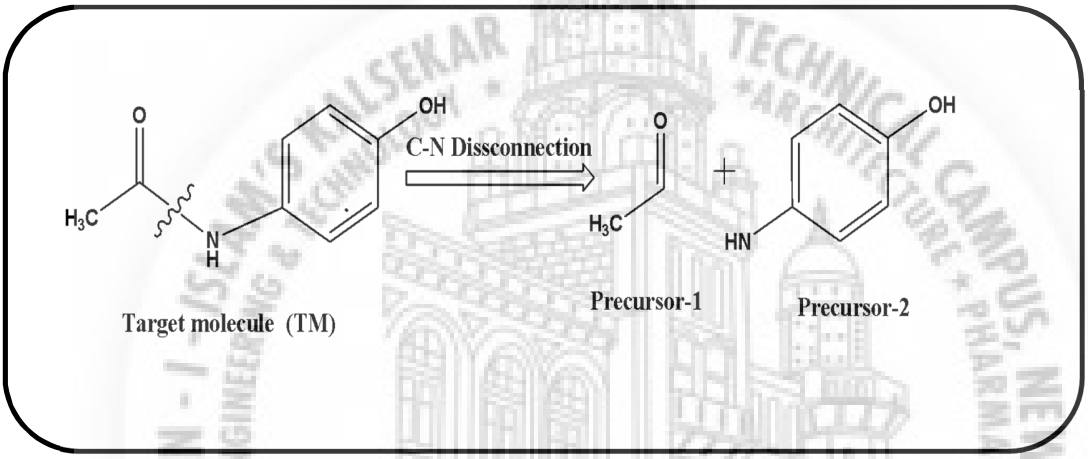


Fig:-8 Schematic depiction of retrosynthetic analysis: Imaginary breakdown of Target Molecule**, lead to formation of two precursors, which help Transfer synthons into active starting material**

Scheme-II (Analysis)

Following the above analysis, the functional replacement and inversion has been carried on precursor-2; by replacing –OH to get –NO2 is the first step in the designing to get Target Molecule.

Novelty in the designing of product is, instead of –OH, introducing -NO2 to increase the nucleophilic properties on the target receptor,

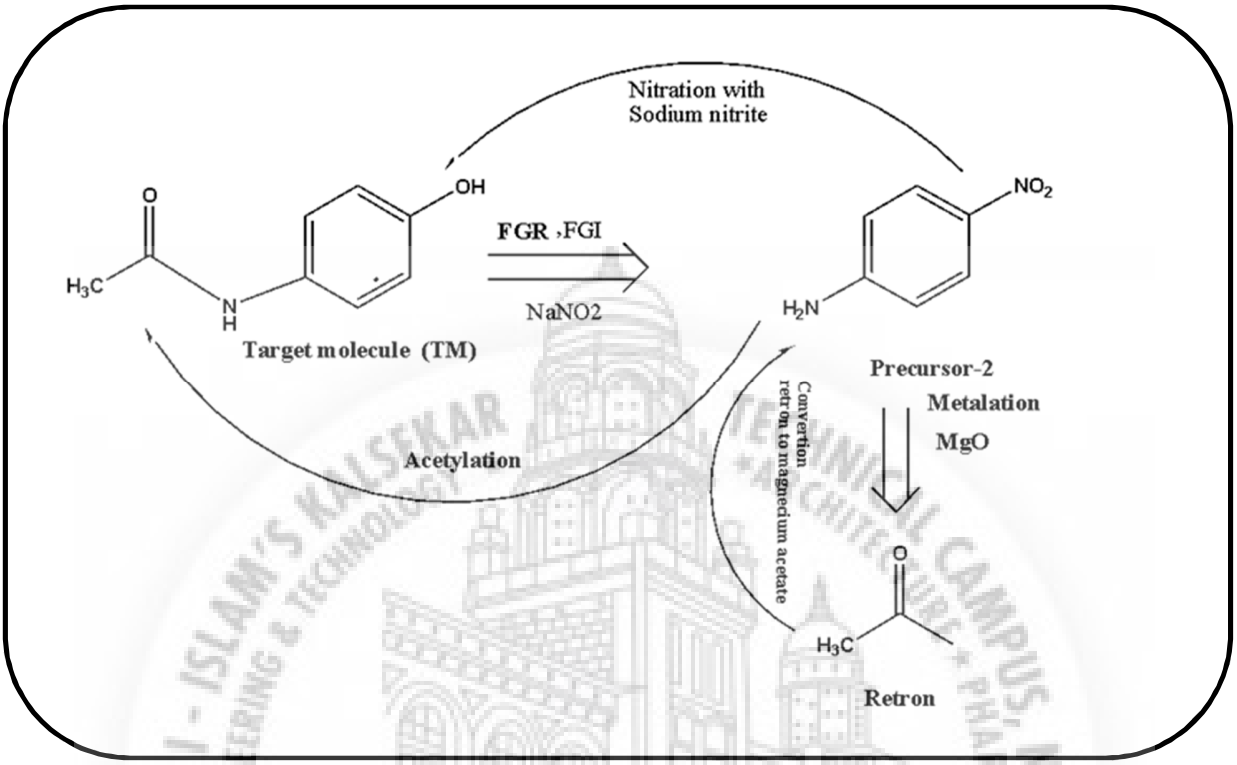


Fig:-9 application of disconnection on selected molecule to arrange the reaction condition

Scheme-III: - (One pot synthesis by N-acetylation of amine in Tylenol)

The synthetic designed based on the retrosynthetic analysis is acetylation with magnesium acetate used as acetylating agent; followings are the general steps to design a protocol in One-Pot by utilizing point in a single step

- ✓ Application of Diazotization & heating with (1. NaNO2 + HCl and 2. Sn/HCl) FGR
- ✓ Application of reaction condition based on Retro-Analysis N-Acetylation
- ✓ An Efficient One pot-synthetic strategy to obtained the target by using magnetic stirrer
- ✓ RB-Flask as reactor

General synthetic strategy

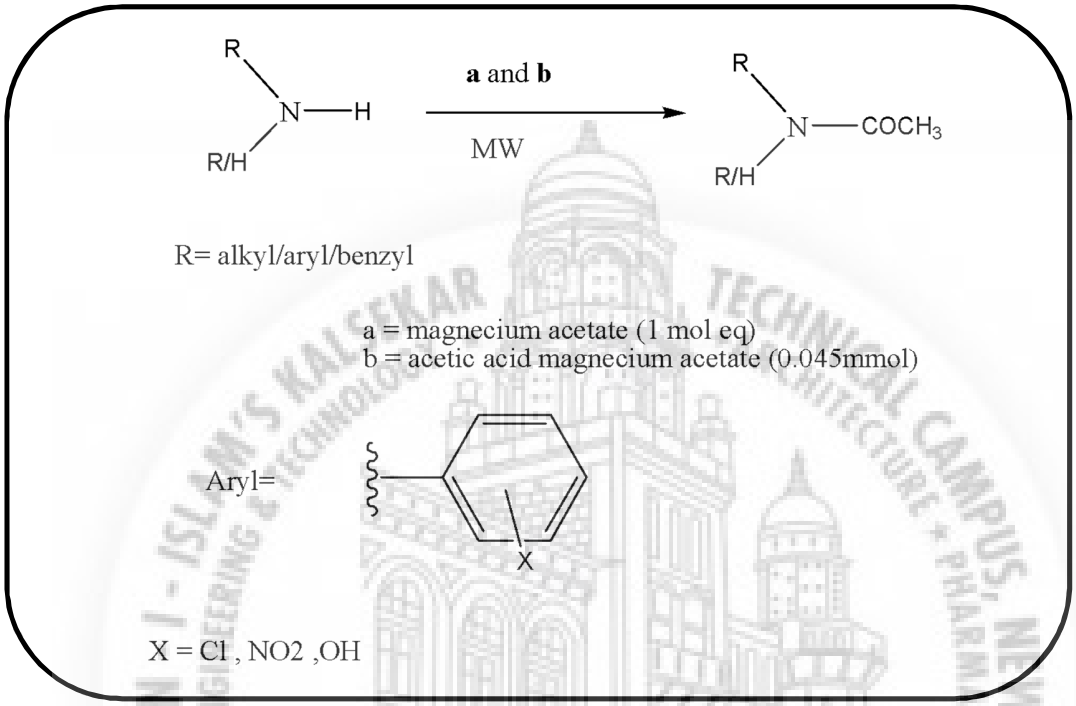


Fig:-10 general scheme to carry out the reaction protocol to get the Target molecule

Principle

The reaction process based on the principle of acetylation, Mg $(CH_3COO)_2$ is used as catalyst, for N-acetylation to form C-N bound to get the Target Molecule.

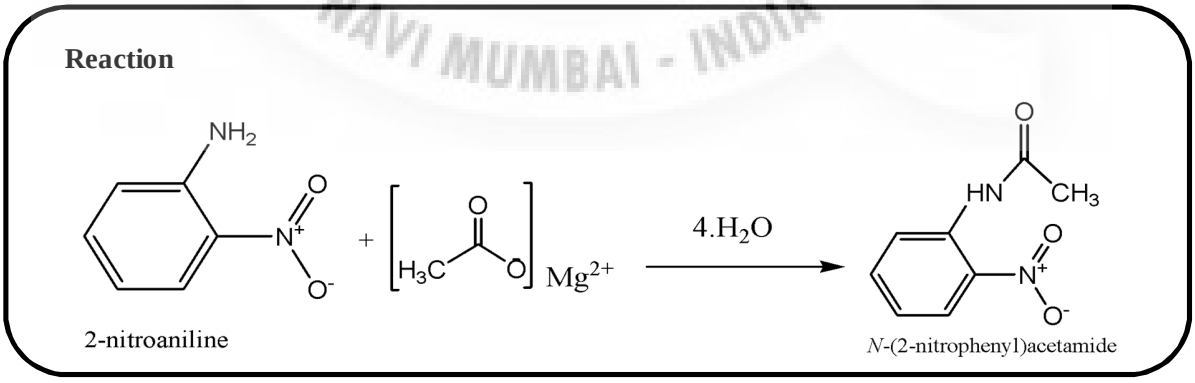


Fig:11 – Synthesis of N-(2-nitrophenyl) acetamide

Procedure

To a solution of 2-nitroaniline (1.1gm) in water (5ml), containing magnesium acetate (1gm), and stir the content on magnetic stirrer at 240 rpm for 30minuts, during rotation after 20 minutes added glacial acetic acid to the content drop wise to maintain the Ph of the reaction process

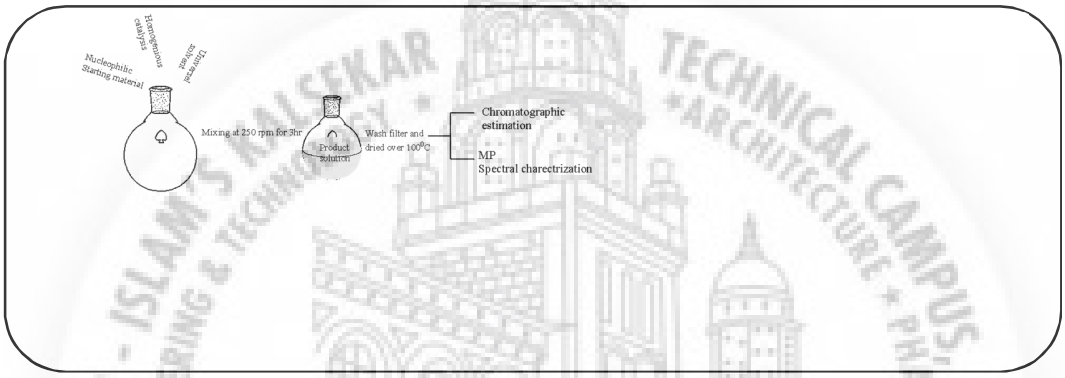


Fig:- 12 Graphical representation of procedure

I Experimental

Fig-13:- FT-IR spectroscopy of N-(2-nitrophenyl) acetamide

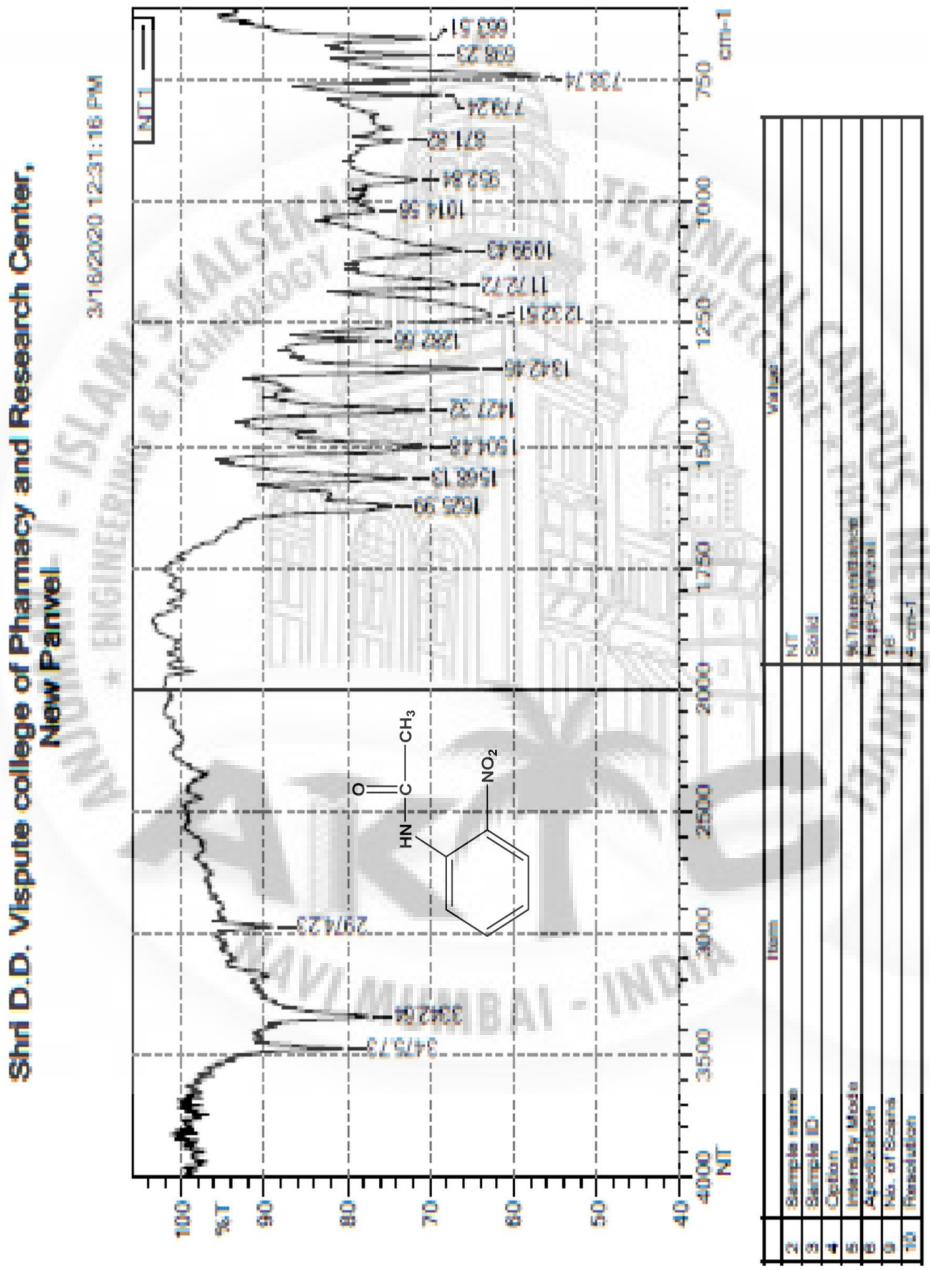


Fig-14:-C13 NMR Spectroscopy of Nitro-Tylenol

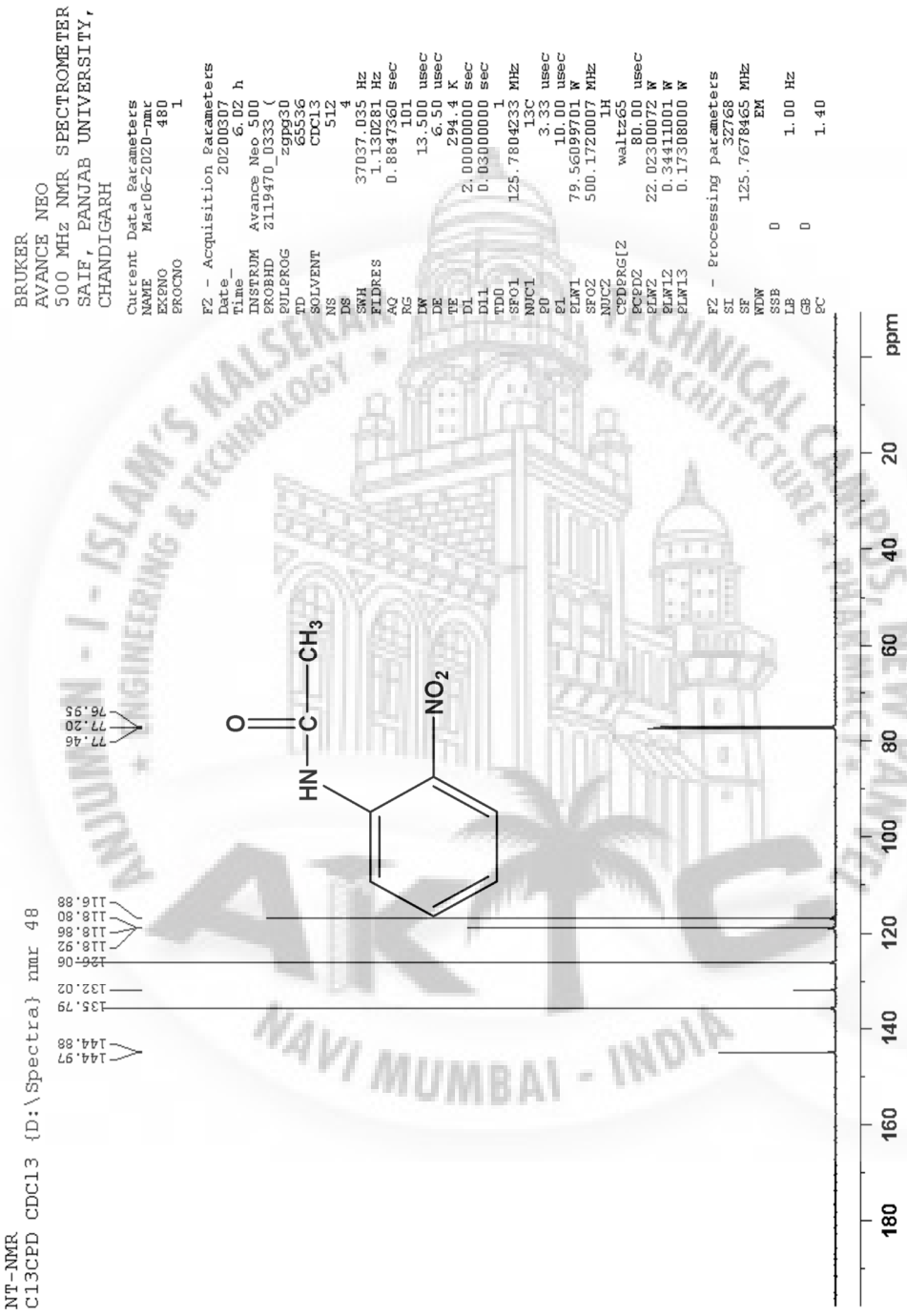


Fig-15:- XRD crystallography of N-(2-nitrophenyl) acetamide

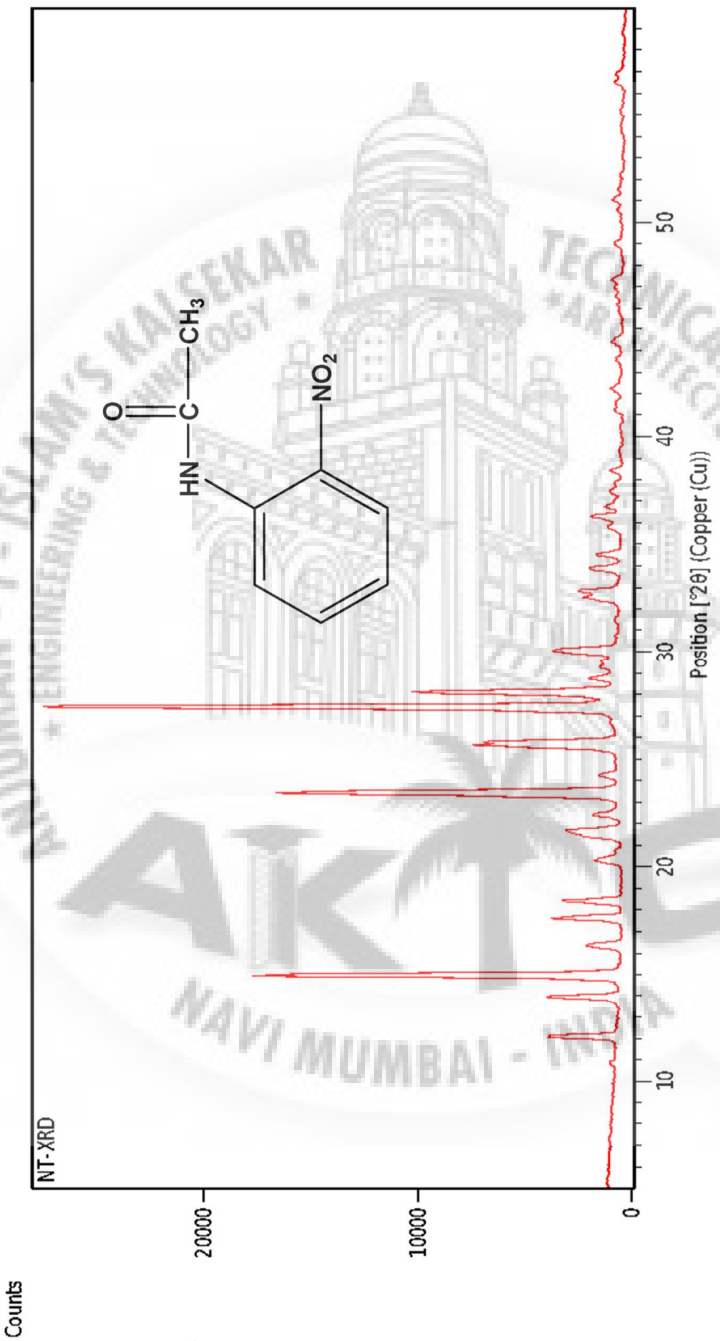


Table-1 Measurement Conditions: *(Bookmark 1)*

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Sample Identification	NT-XRD
Comment	Configuration=Reflection Spinner Stage, Owner=User-1, Creation date=20-09-2016 16:48:22

Goniometer=PW3050/60 (Theta/Theta); Minimum step size 2Theta:0.001; Minimum step size Omega:0.001

Sample stage=Spinner PW3064

Diffractometer system=XPERT-PRO

Measurement program=C:\PANalytical\Data Collector\Programs\SAIF 5°-60°.xrdmp, Identifier={D10E5B4D-3F2F-4F90-8E6D-1DA7E4BA540D}

Batch program=C:\PANalytical\Data Collector\Programs\SAIF(10°-90°).xrdmp, Identifier={8D087DEC-93E6-43E9-87AB-079A7AF3E004}

PHD Lower Level = 6.52 (keV), PHD Upper Level = 12.80 (keV)

Measurement Start Date/Time	13-03-2020 11:16:06
Operator	User
Raw Data Origin	XRD measurement (*.XRDML)
Scan Axis	Gonio
Start Position [°2θ]	5.0167
End Position [°2θ]	59.9947
Step Size [°2θ]	0.0330
Scan Step Time [s]	59.6900
Scan Type	Continuous
PSD Mode	Scanning
PSD Length [°2θ]	2.12
Offset [°2θ]	0.0000
Divergence Slit Type	Fixed
Divergence Slit Size [°]	0.4354
Specimen Length [mm]	10.00
Measurement Temperature [°C]	25.00
Anode Material	Cu

K-Alpha1 [Å]	1.54060
K-Alpha2 [Å]	1.54443
K-Beta [Å]	1.39225
K-A2 / K-A1 Ratio	0.50000
Generator Settings	40 mA, 45 kV
Diffractometer Type	0000000011023505
Diffractometer Number	0
Goniometer Radius [mm]	240.00
Dist. Focus-Diverge. Slit [mm]	100.00
Incident Beam Monochromator	No
Spinning	Yes

Main Graphics, Analyze View: ***(Bookmark 2)***

Table-2 Peak List: ***(Bookmark 3)***

Pos. [°2θ]	FWHM Total [°2θ]	d-spacing [Å]	Rel. Int. [%]	Area [cts*°2θ]
10.8163	1.1649	8.17293	0.61	285.01
12.0761	0.2155	7.32299	11.61	501.16
13.9414	0.2148	6.34711	11.63	529.36
14.9463	0.2163	5.92256	62.15	2829.08
16.3622	0.2552	5.41312	5.05	258.21
17.6229	0.2276	5.02862	10.38	473.33
18.4231	0.2271	4.81195	8.82	401.07
20.2987	0.2852	4.37136	3.91	223.27
20.7221	0.3496	4.28300	0.81	56.44
21.4388	0.2968	4.14142	6.36	378.38
21.7019	0.2346	4.09179	7.71	362.46
22.4093	0.2410	3.96419	4.91	332.98
23.4191	0.2659	3.79549	56.91	3291.63

24.2325	0.2432	3.66990	3.55	255.99
25.6169	0.2529	3.47463	24.13	1621.53
25.8048	0.1409	3.44976	14.87	477.97
27.3903	0.2089	3.25356	100.00	5098.06
28.0775	0.2602	3.17547	32.26	1682.29
28.7573	0.2623	3.10193	4.94	429.98
29.2968	0.2763	3.04603	2.74	240.88
29.5635	0.2319	3.01915	2.37	168.12
30.0558	0.3054	2.97081	11.29	779.75
31.3185	1.7424	2.85385	0.68	402.46
32.5325	0.3298	2.75007	5.82	466.49
32.8390	0.1591	2.72510	7.30	304.04
33.8666	0.2571	2.64473	5.51	344.85
34.5179	0.2170	2.59630	4.44	233.10
35.8210	0.4211	2.50478	2.25	213.88
36.2611	0.2018	2.47539	5.03	203.62
36.7362	0.2749	2.44446	3.05	285.02
37.4556	0.3398	2.39914	1.84	186.47
37.8345	0.1654	2.37598	1.22	52.22
38.3866	0.2167	2.34307	2.04	90.35
39.2738	0.3466	2.29216	0.62	50.40
40.4387	0.1706	2.22878	0.54	25.46
41.3563	0.4885	2.18142	1.32	129.34
42.2054	0.3321	2.13948	2.03	197.68
42.6886	0.1871	2.11637	0.45	16.90

43.5518	0.1805	2.07640	1.50	108.54
44.4025	0.3782	2.03858	1.73	143.63
45.9211	0.5319	1.97463	0.58	64.84
46.5819	0.3426	1.94815	1.51	207.22
47.2507	0.4284	1.92212	1.46	125.13
48.9788	0.2422	1.85827	1.75	127.89
50.5708	0.4309	1.80344	0.99	170.80
51.0222	0.1923	1.78854	1.91	76.79
51.5250	0.2437	1.77226	0.99	97.07
52.1692	0.2407	1.75188	0.39	19.01
53.0011	0.0751	1.72633	0.29	8.73
54.4966	0.2665	1.68244	0.68	72.17
55.1773	0.2607	1.66328	0.57	37.19
56.4917	0.2118	1.62766	1.86	102.75
56.8914	0.2500	1.61717	1.51	126.42
58.8189	0.2413	1.56869	0.41	20.05

3D structures of XRD-Phase recognition of the molecule

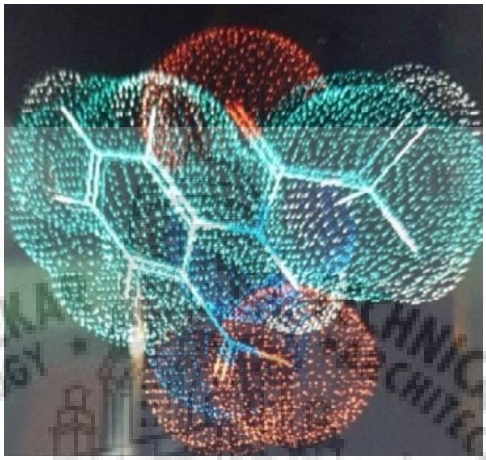


Fig-16:- Cloudy rotation

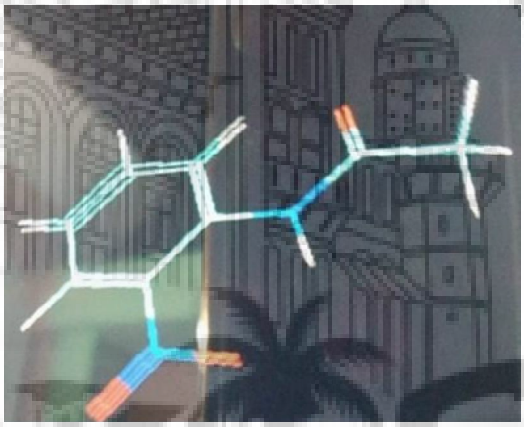


Fig-17 Bound spacing

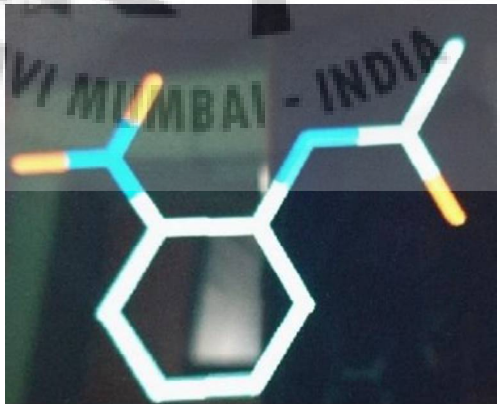
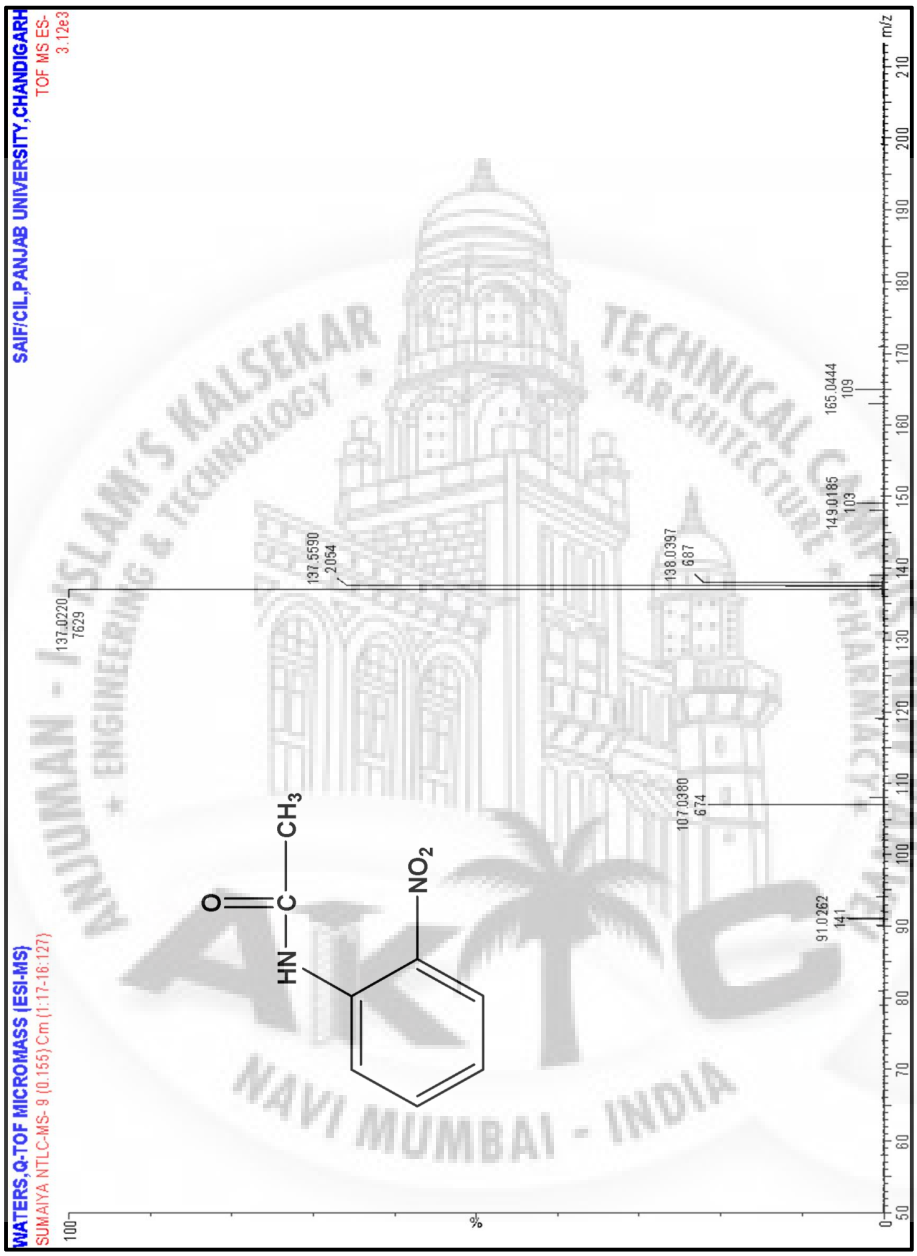


Fig:-18 Structure of molecule

Fig-19:- Mass spectroscopy of Nitro-Tylenol



II. ANALYTICAL

Yield 72%, m.p. 212-214 °C, IR (KBr; cm-1): 3475 (N-H str.), 3117 (Ar.C-H str.), 1625 (C=O str.), 1427 (NO2 str); 1H NMR (400 MHz, DMSO-d6, δ ppm): 2.46 (3H, s, CH3), 6.92-6.96 (2H, t, Ar.H), 7.097.12 (2H, m, Ar.H), 7.22-7.26 (3H, m, Ar.H), 7.45-7.50 (2H, t, Ar.H), 7.96-7.98 (2H, d, Ar.H), 8.29-8.39 (1H, q, Ar,H), 8.57-8.59 (1H, d, Ar,H), 10.71 (1H, s, NH); 13C NMR (100 MHz, DMSO-d6, δ ppm): 76.46, 77.20,76.95 (NHCOCH$_3$), (C-NO2) 144.99, 110.92, 110.96, 119.90, 116.99, ; LC-MS (m/z): 312 [M+H]; Elem. Anal. Calc. for $C_8H_8N_2O_3$: C, 81.00; H, 5.50; N, 13.49. Found: C, 81.03; H, 5.48; N, 13.47.

XRD Analysis. The synthesized nitro acetaminophen were Centrifuged at 10,000 rpm for 15 minutes and the pellets were re-dispersed in sterile double distilled and centrifuged at10,000 rpm for 10 minutes. The purified pellets were dried at 50 °C in an oven and analyzed by X-ray Diffraction Unit (XRD) (Pan Analytical, X-pert pro, and SAIF 5 °-60 ° .xrdp).

The X-ray diffraction (XRD) measurement of Nitro-acetaminophen synthesized by Total synthetic and Cu-Kα radiation source in scattering range $m(2\theta)$ of 20– 80 on the instrument operating at a voltage of 45kV and a current of 40mA. The presence, crystalline nature, phase variety, and grain size of synthesized molecules were determined by X-ray diffraction spectroscopy. The particle size of the prepared sample was determined by using Scherer's Equation as follows:

$$D = \frac{K\lambda}{\beta 1/2 \cos\theta},$$

Where the average crystallite size and β is line broadening in radians (full width at half maximum of the peak in radians). λ is the wavelength of X-ray and θ is Bragg's angle. K is constant (geometric factor = 0.94).

Pharmacological study:

Future work ……

DISCUSSION

To prepare an organic compound (target, TG), we need a readily obtainable starting materials and reagents. This process usually begins with the design of a synthetic plan (Strategy). Retrosynthetic analysis is a problem solving procedure for transforming the (TG) gradually to simpler structures (Synthon), through a pathway known as retro synthesis tree, which finally leads to commercially available starting materials for a chemical synthesis [38], as given in Fig-1. How to design a retro synthesis tree first, deal with point of disconnect [39], as given in Fig-2. Second; for heterocyclic aromatic ring, we have to deal with saturated system, all unsaturated bonds must resolve. Third, synthetically equivalent synthons are to be given in its simplest way, synthetic equivalents in case of heteroaromatic rings mainly consisting of active methylene and carbonyl compounds [40]. Pyridine as 6-membered heteroaromatic ring is one of most important bioactive compounds, naturally and synthetically occurred [41]. For Pyridine synthesis; main pathway is Hantzsch pyridine synthesis, where (α, β-unsaturated compound is added to active methylene as ethyl acetoacetate (EAA) [42], also Knorr synthesis is available, by adding 1,5-dicarbonyl to heteroatom to give pyridine [43]. Michael addition is also one of possible pathway [44]. Retro synthesis tree of pyridine are discussed aside with its synthetically available pathways of Pyrimidine, is considered as most important ring as main components of DNA and privilege structure for dozens of bioactive drugs [45]. Using same steps as pyridine retro synthesis pathways can also be designed. One of the most applicable pathways is reaction between urea derivatives as (thiourea, guanidines) with 1,3-dicarbonyl compounds [46].

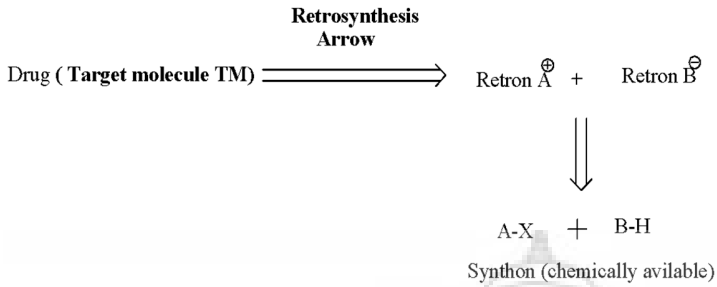


Fig 20-General rules of disconnection

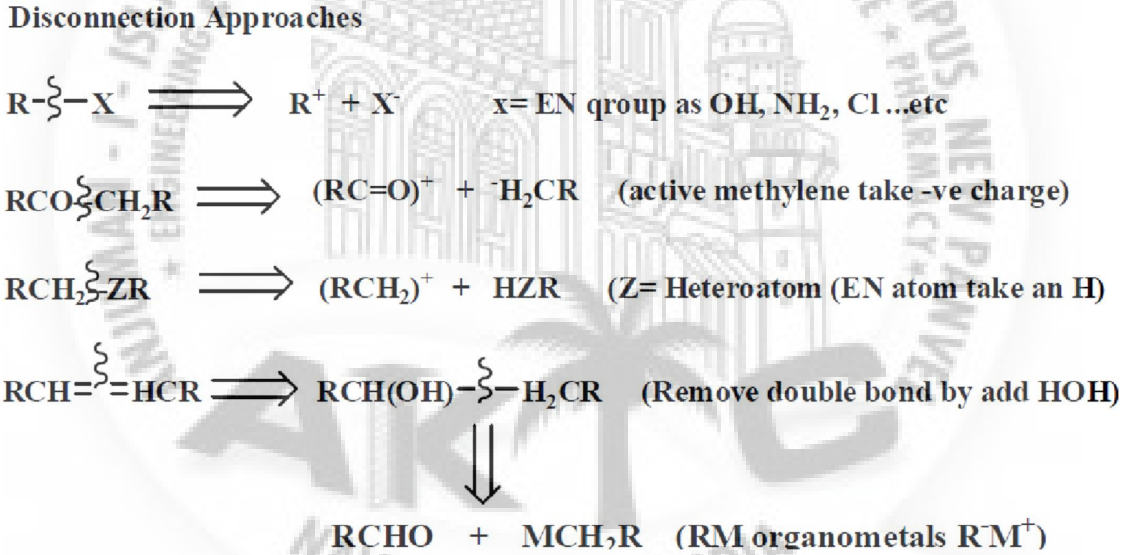


Fig 21- Step by step general strategic approach to disconnection

The conducted study based on the above mentioned general scheme, the Target Molecule was N-(4-nitrophenyl) acetamide as mentioned the chemical properties in fig-7, the general theoretical disconnection leads to formation of two precursors (Retrones), the functional group replacement and interchange described in fig-8 and 9 was theoretical workout to build synthetic scheme, the reaction designed with the lab available chemical, instead of **4-aminophenol** we used **2-**

nitrophenol as starting material by application of FGI –OH replaced with -NO2, the stereochemistry of entire Target Molecule was changed. The extensive literature survey revealed that the No2 molecule act as paramagnetic effect which increase the aromaticity of phenol and we can carry out the N-acetylation on NH2 without using any protection group. Based on this theoretical workout we selected One-Pot synthetic approach on scheme-III which was successfully accomplished with 99% of yield. Hence we proved that one-pot synthetic approach was the novel methodology we applied to synthesize the Target Molecule, it was reported on the basis of chromatographic, Spectroscopic spectrophotometric and XRD analysis. The work was in progress in our laboratory for its pharmacological properties on antiviral and antipyretic activity.

Conclusion

Paracetamol inhibits PG synthesis in intact cells when the rate of synthesis is low and the peroxide tone is also low. The pathway involving COX-2 is predominant when the concentration of arachidonic acid is low, and it follows that paracetamol is selective for this pathway. Functionally, paracetamol is acting as a selective COX-2 inhibitor. Paracetamol may have its most potent effects on the central nervous system because peroxide (Fig-) tone and arachidonic acid levels are likely to be lower than at peripheral sites of substantial inflammation, as in rheumatoid arthritis..

It should be emphasized that the molecular mechanism by which paracetamol inhibits the synthesis of PGs and related compounds is not known, although inhibition of COX-3 appears to be unlikely. The effect of paracetamol on PG synthesis appears similar to other phenols. Thus, several other phenols have biphasic effects on PG synthesis in broken cell systems yet are potent inhibitors of PG synthesis by intact cells [30, 31, 32, and 33]. The key to the similarity is possibly that many phenols are, like paracetamol, oxidizable. In the present work, we designed the total synthesis on **N-(2-nitrophenyl) acetamide**, which is the brand name of acetaminophen, we successfully done with selected strategy by increasing the potency with modifying the synthetic methodology.

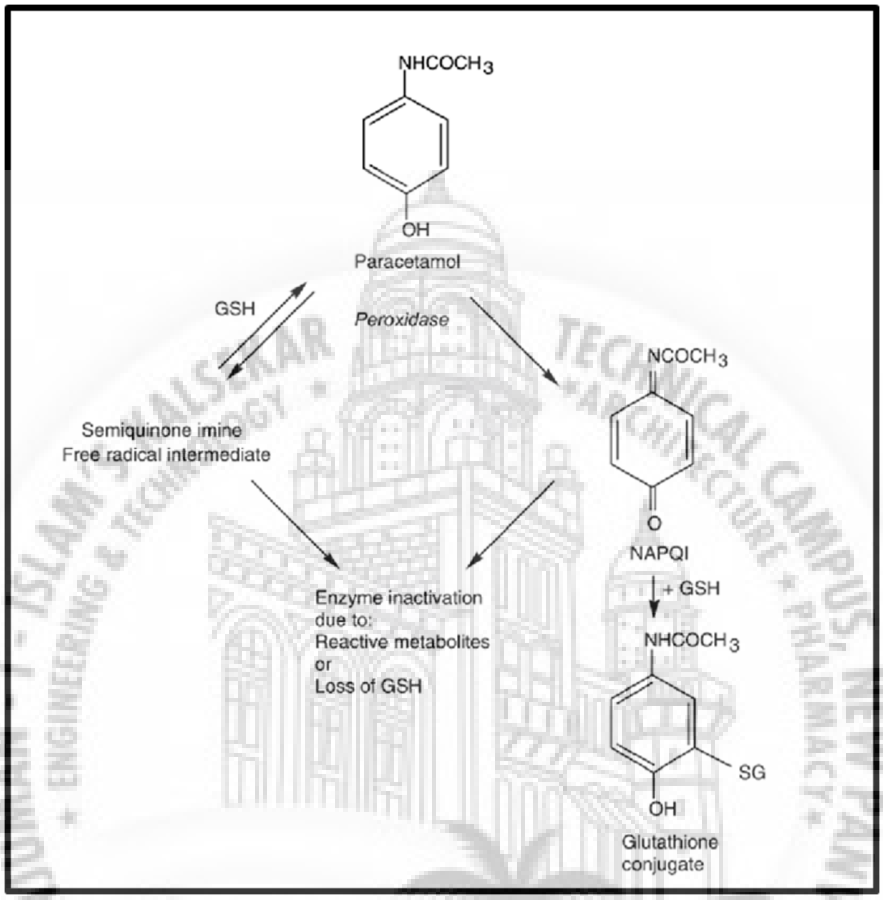


Fig:22 - Metabolism of paracetamol by the peroxidase function of COX-1. It is anticipated that similar metabolism occurs with COX-2. Either the utilization of reduced glutathione (GSH) may inhibit enzymes, such as PGE synthase, for which GSH is a cofactor or the reactive metabolites of paracetamol may inactivate enzymes involved with PG synthesis

The application of one-pot synthesis, under an impetus to determine that this process of modification was most efficient strategy to synthesize a molecule, one-pot approaches have been widely used [34, 35], in our first approach the single-step of organic synthesis, which carry-out by using same reaction condition in one reactor will be the unique style, which is the first time in the history of synthesis of antipyretic drug.

The target molecule is merely a linear combination of optimization of reaction and logical changes in the reaction conditions to moderate reactivity by minimize the by-products, circumvent or reverse side reactions, were blocked by adopting tactical selection of reagents (Magnesium acetate as acetylating agent) that can play multiple roles in reactions downstream in the synthesis.

Which minimize the time effort and steps in the reaction, (Fig-s) Scheme-I proved the stable disconnection of molecule which leads to formation of a retrons (precursor-I and II) , the scheme was built by replace the FG (functional) –OH to -NO2 because it makes the benzene molecule stable by pulling its electrons and thus -NH2 group in aniline easily interact with acetyl group in Mg ($CH_3CO_2)_2$ gives N-Acetylated reaction condition in sustainable environment , further study on the molecule is carrying in the laboratory to find out the Insilco in-vitro study to assess the target receptor by molecular docking study, we successfully completed our primary study of synthesis, further study is in progress in college laboratory.

Hence we conclude that a one-pot synthesis is thus, not only a useful methodology to adopt for the production of organic molecules, but also a promising green approach to contemporary synthesis.

FUTURE WORK

The present work was focused particularly to synthesize the Target Molecule by applying the disconnection approach, which was successfully carried in the laboratory. Henceforth the pharmacological screening of the molecule was going to be done with in-vitro and in-vivo antipyretic ant anti-viral activity.

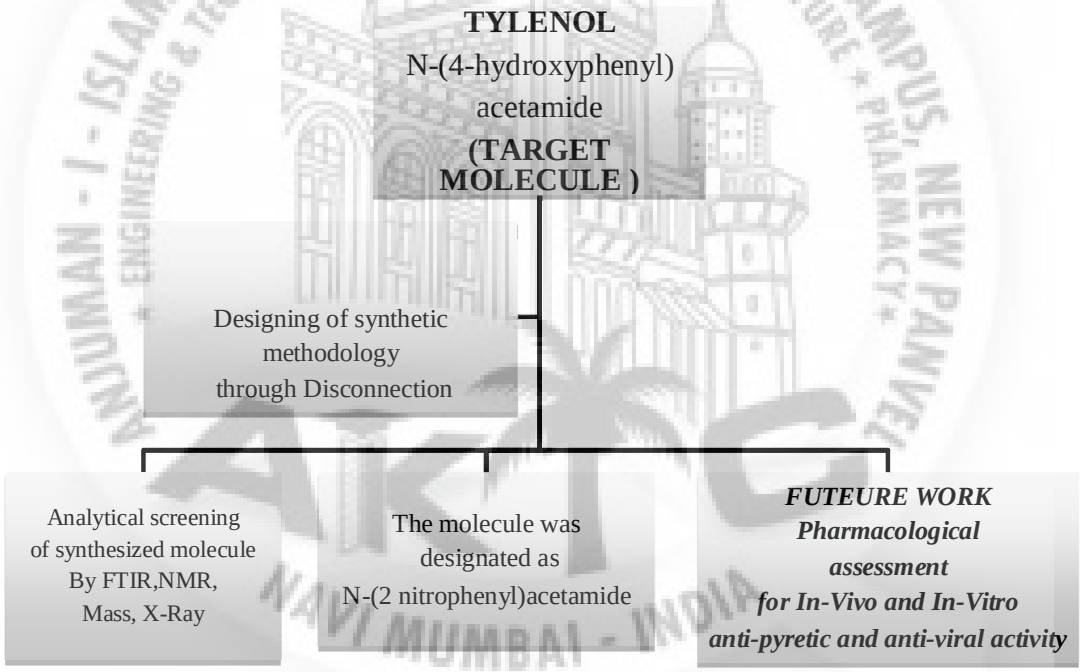


Fig:- 20 Future report

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ANNEXURE

Publications

1. Paper was accepted in Dubai conviction 2020 (got postponed due to Lockdown entitled as

   AN EFFICIENT ONE-POT SYNTHESIS OF N-(2-nitrophenyl) acetamide

2. Paper has been communicated entitled as

   AN EFFICIENT ONE-POT SYNTHESIS OF N-(2-nitrophenyl) acetamide