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A Greener Route for Synthesis of three Aza Heterocycles and their Computational Screening by Molecular docking.

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Abstract

The present work was aimed at finding out green protocol for synthesis of selected three aza heterocyclic compounds viz. 1, 4-dihydro-2, 3-quinoxalinedione; 2,3-diphenyl quinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester. Heterocyclic compounds have gained importance in recent years because of their immense biological and pharmacological potency. Heterocyclic compounds due to their synthetic versatility and effective biological activities such as antimicrobial, antiviral, anti-inflammatory, antidepressant, antitubercular, antiamoebic, analgesic activities have numerous applications. The selected compounds were synthesized using 3 different methods and the most efficient-greener method was evaluated. The spectral analysis of compounds was done by Infra Red Spectroscopy, Nuclear Magnetic Resonance Spectroscopy and Mass Spectra. On finding out the best green synthetic protocol; computational modeling studies were performed using MVD (Molegro Virtual Docker) 2013.6.0. software to predict the biological activity of these therapeutic compounds. Our study concluded that the best method for efficient synthesis of **1,4-dihydro-2,3-quinoxalinedione** was by mechano-chemistry under solvent free condition by employing simple mortar pestel leading to a yield of 96% at a reaction time of 15 minutes, while that for the synthesis of **4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester** was under the presence of microwave irradiation (yield 96%, reaction time of 3 minutes). Whereas, in case of **2,3 diphenyl quinoxaline** all the three methods i.e., application of sonicator and solvents like ethanol, water gave almost comparable yields (97, 95 and 94 % respectively), the reaction time was also competent viz., 8, 10 and 20 minutes. The docking analysis demonstrated that **1,4-dihyroxyquinoxaline-2,3-dione exhibits anti inflammatory activity** whereas **2,3-diphenylquinoxaline was found to exhibit anti-microbial activity** with the help of molecular docking process on selected protein. The minimum binding energy indicated that the target protein was successfully docked with 1,4-dihyroxyquinoxaline-2,3-dione structure. Drug discovery being a complex, expensive and arduous process; *in-silico* drug discovery employing computational modeling reduces the time, efforts and cost significantly.

Keywords

Green chemistry, Aza heterocycles, *In-silico* analysis, Computational modeling, Molegro Virtual Docker

Introduction

Green chemistry and its twelve principles are a familiar term in present era. It is a philosophical approach that contributes to sustainable development via application and extension of the principles of green chemistry. This approach is also known as "Environmentally benign" chemistry, "Clean chemistry" and "Benign-by-design chemistry". The term "Green chemistry" has been defined in numerous ways. P.T Anastas referred to this term for the first time in a special US Environmental Protection Agency (USEPA) program in 1991. The program was regarding implementation of sustainable development in chemistry and chemical technology by industries, academics and government. The objective of green or sustainable chemistry is enhancing the availability of useful compounds to human race at the same time preventing the harmful effects of the processes to the environment. This approach has become obligatory in present day's chemistry [1].

The industrial production involves numerous chemical reactions that exploit enormous quantities and wide varieties of molecules, reagents, solvents, acidic substances, alkaline

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reagents etc. The side effect of these chemical processes is the generation of large quantities of undesired and harmful substances along with the generation of required products. The undesired substances may be in the form of solid, liquid or gas and pose the greatest challenge that chemistry has to deal with. So, it has become imperative for the chemists involved in synthesis to reduce chemical pollution. There has been significant enhancement of work in this direction in the last few decades. The intention is modification in chemical processes that will impact less on environment and human health. By inventing new chemical processes that prevent pollution green chemistry safeguards the environment. According to the principles of green chemistry, a threat can be eliminated in a simpler way, by applying safe raw materials for production process[2].

Ionic liquids have extensively been used in recent years as alternative solvents in organic synthesis. No special apparatus and methodologies are required to carry out reactions in ionic liquids, along with the ability of them being recyclable[3]. These liquids are considered as good solvents for future improvements that can give "green" credentials to their use and applications[4]. In recent years, organic reactions in aqueous media have received considerable attention. The fact is that water is the inexpensive, most abundant, non-toxic, and environmentally friendly solvent. It exhibits unique reactivity and selectivity, which is different from those in conventional organic solvents[5]. Hence, water is proved to be an excellent solvent for many synthetic methods. One approach to making chemical synthesis greener is to use existing chemical synthesis processes but make the process itself safer and less polluting while also making the reagents required for it by greener processes. An example of the former might be to substitute a less volatile, less toxic solvent as are action medium for a chemical synthesis reaction. In some cases, a reagent may be made more safely by using biological processes for its preparation in place of chemical processes. A second general approach to making chemical preparations greener is to use different reagents for the synthesis that are safer and less likely to pollute[6]. The pharmaceutical industries are in need of new innovative alternate synthetic routes for synthesizing therapeutic and pharmacologically important compounds[7]. The development of economic and environmentally responsible methodologies for their inter-conversion remains a challenge, since conventional processes often lead to significant amounts of wastes and/or are performed under strong reaction conditions[8]. Facing with the ever-growing concern for environmental issues, methods with traditional organic synthesis has been greatly challenged. Thus, it places higher expectations on the future work for all the organic chemists[9].

Heterocyclic compounds are acquiring more importance in recent years because of their immense biological and pharmacological potency. Various biologically active synthetic compounds have five membered nitrogen containing heterocyclic rings in their structures. Many compounds bearing pyrazoles and their reduced forms pyrazolines constitute an interesting class of heterocycles due to their synthetic versatility and effective biological activities such as antimicrobial, antiviral, anti-inflammatory, antidepressant, antitubercular, antiamoebic, analgesic activities. The presence of this core in any molecule has the ability to enhance its activity which has been verified by literature survey studies on synthetic protocols[10].

Pyrimidine and its derivatives have been recognized as important heterocyclic compounds due to their variety of chemical and biological significance to medicinal chemistry. It is well known that the condensation of amino heterocycles and pyrimidine gives rise to the formation of bicyclic heterocycles known as triazolopyrimidines. The 1,2,4-triazolopyrimidines have attracted growing interest due to their important pharmaceutical

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properties , and they appear in a variety of synthetic pharmacophores which possess anti-parasitic, antimicrobial, anticancer and antibiotic activities**.**

A pertinent category of nitrogen containing benzo heterocyclic compounds containing a ring complex made up of a benzene ring and a pyrazine ring are Quinoxaline derivatives [11] **.**These compounds have immense therapeutic values and potential activities; having ability to act as antimicrobial agents[12,13], cytotoxic agents, anti-tubercular, anxiolytic, anti-HIV, antioxidant[13], anti-inflammatory[14,15], antimalarial, anticancer, antidepressant[12], antibacterial, antifungal[14]. They are recognized to inhibit growth of gram positive bacteria and are active against various transplantable tumors thus used in antibiotics[15,16]**,** as well as cancer, diabetes, diabetic retinopathy, rheumatoidarthritis, hemangioma and Kaposi's sarcoma [17,18]. Because of their diverse pharmacological and biological properties, they have emerged as privileged structures in combinatorial drug discovery libraries[19].

Most of the reported methods of traditional synthesis have the flaw of usage of expensive reagents/additives, metal catalysts, inflammable organic solvents or harsh reaction conditions, as well as the difficult experimental/work-up procedures. Hence, it is highly preferable to develop mild eco-friendly one-pot synthetic protocol for these highly significant classes of compounds. The goal of computational docking is to find the 3D configuration of the complex that minimizes the energy. *In-silico* molecular docking has been widely used to determine the binding mode (pose) of a small molecule to a binding site. Computational and bioinformatics tools have become very important resources to identify the potential targets for various ligands in present scenario[20].

In view of above present work was aimed at finding out green protocol for synthesis of selected aza heterocyclic compounds viz. 1, 4-dihydro-2, 3-quinoxalinedione; 2,3-diphenyl quinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester. After selecting the best green synthetic protocol; computational modeling studies will be performed using MVD (Molegro Virtual Docker) 2013.6.0. software to predict the biological activity of these therapeutic compounds.

Materials and Methods

All the glass wares used in the present study were of Borosil make. Prior to use, the glass wares were soaked in the chromic acid solution for 24 hours. The glass wares were then washed with tap water, further rinsed with the distilled water and completely dried in the oven (at 110°C). Following chemicals were used in this study, the compounds, their molecular formulae, structural formulae, relative molecular mass are given in **Table 1**. All the Chemicals and reagents used for the study were of analytical grade. O-phenylenediamine, Benzil, 4-Hydroxybenzaldehyde, Diethyl oxalate and Urea (extra pure) were procured from Lobachem, Mumbai. p-TSA was procured from Rankem. Ethanol, Diethyl acetoacetate (procured from MERCK, Germany), Acetic Acid Glacial (procured from SDFCL, Mumbai) and Water (extra pure double distilled) were used as solvents. **Table 2** states the analytical instrumental details used in the study for synthesis and spectral analysis.

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Table 1. Properties of Chemicals used in synthesis

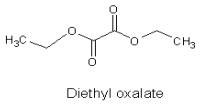
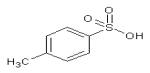
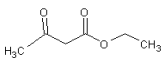
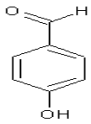
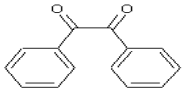
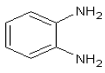
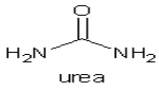
Compound Name	Molecular formula	Molecular weight (gms)	Structure
Diethyl oxalate	$C_6H_{10}O_4$	146.14	 Diethyl oxalate
p-TSA (monohydrate)	$C_7H_8O_3S.H_2O$ $C_7H_8O_3S$	190.22 172	 p-Toluene sulphonic acid
Ethyl acetoacetate	$C_6H_{10}O_3$	130.14 (g/mol)	 Ethyl acetoacetate
4-Hydroxy benzaldehyde	$C_7H_6O_2$	122.12	 4-hydroxybenzaldehyde
Benzil	$C_{14}H_{10}O_2$	210.23	 1,2-diphenylethane-1,2-dione
Ethanol	C_2H_5OH	46.07 (g/mol)	$H_3C—CH_2OH$ ethanol
O-phenylenediamine	$C_6H_4(NH_2)_2$	108.14	 o-phenylenediamine
Urea	CH_4N_2O	60.05	 urea
Acetic Acid Glacial	CH_3COOH	60.05	 Acetic acid glacial

Table 2. Analytical Techniques and Instruments Used

Analytical Techniques or Instruments	Model/Make/Maufacturer	Features
Weighing balance	Shimadzu Japan	Fully Automatic Self-Calibration, One Touch Calibration and Display Data Memory Function, Automatic Adjustable Environment Setting.
Microwave	Magic cook (Model no. 20S, Mech) Manufacturer: Whirlpool	600W, 50 Hz frequency, 230 Volt AC with timer.
Sonicator	Company: Rivotek	Ultrasonic probe sonicator with accessories, In-put Power 230 V, 50 Hz, AC. Ultrasonic power 250 W. Horn diameter 10mm and

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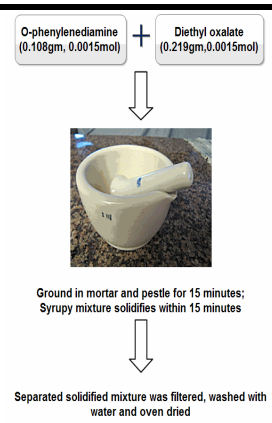
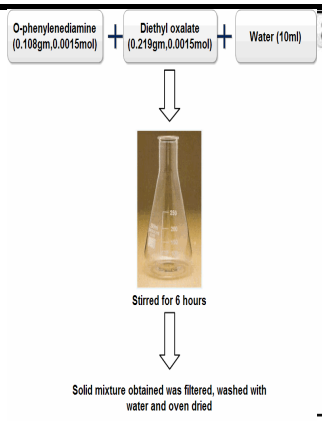
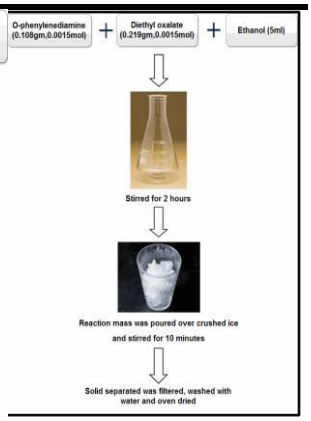
		20mm with timer.
Orbital Shaker	Scientech (INSTAMES IN-1011)	Orbital incubator shaker
Gallenkamp's Melting point apparatus	Model No. IC0949	Melting points of the synthesized aza-heterocycles were determined on Gallenkamp's apparatus, and were uncorrected.
Nuclear Magnetic Resonance spectrometer	BrukerPvt. Ltd. Switzerland, Bruker-Tensor 27	NMR spectrometer used for the analysis was Bruker-Avance-III, 400MHz
Fourier Transform-Infra Red spectrometer	Bruker Pvt. Ltd. Germany	
High Resolution Mass spectrometer	Bruker Pvt. Ltd. Germany	Bruker-MicrOTOFQ-II

The spectral analysis of the synthesized aza-heterocycles was performed in ambient conditions at IIT, Indore

All the three selected compounds viz. **1,4-dihydro-2,3-quinoxalinedione**; **2,3-diphenyl quinoxaline** and **4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester** were synthesized by 3 different methods detailed in **Table 3**. Scheme 1-3 states the general reaction of the synthesis of compounds respectively. After synthesis the compounds were confirmed by finding out melting point by Gallenkamp's Melting point apparatus. The spectral analysis of the synthesized aza-heterocycles was performed at IIT, Indore by FT-IR, NMR and Mass Spectroscopy. The yields of synthesized compounds were also calculated.

Table 3. Various experimental routes for synthesis of selected compounds

Compound	Method 1	Method 2	Method 3
1, 4-dihydro-2, 3-quinoxalinedione			

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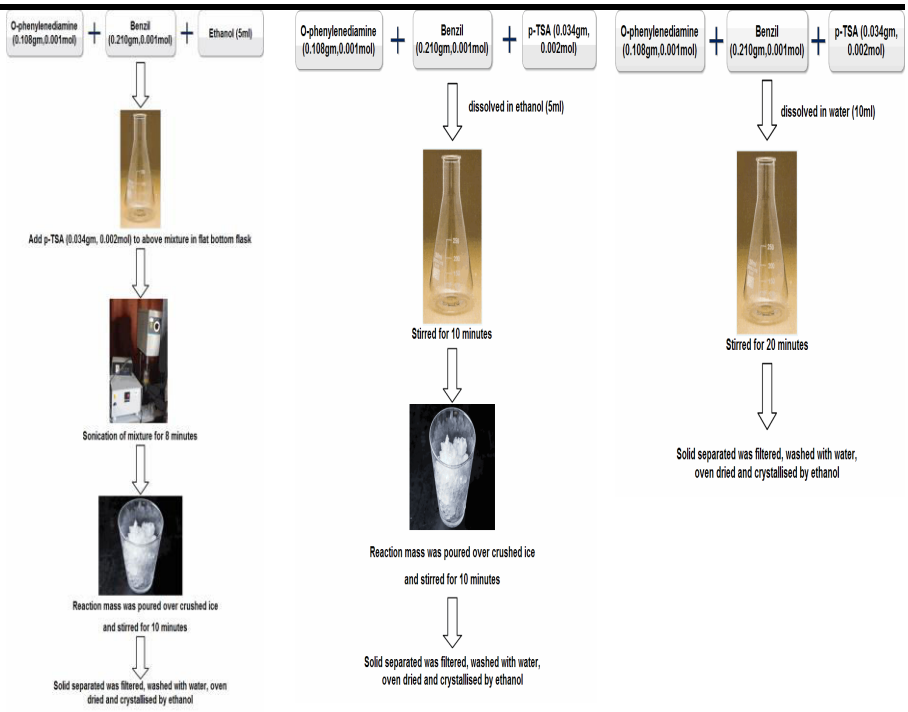
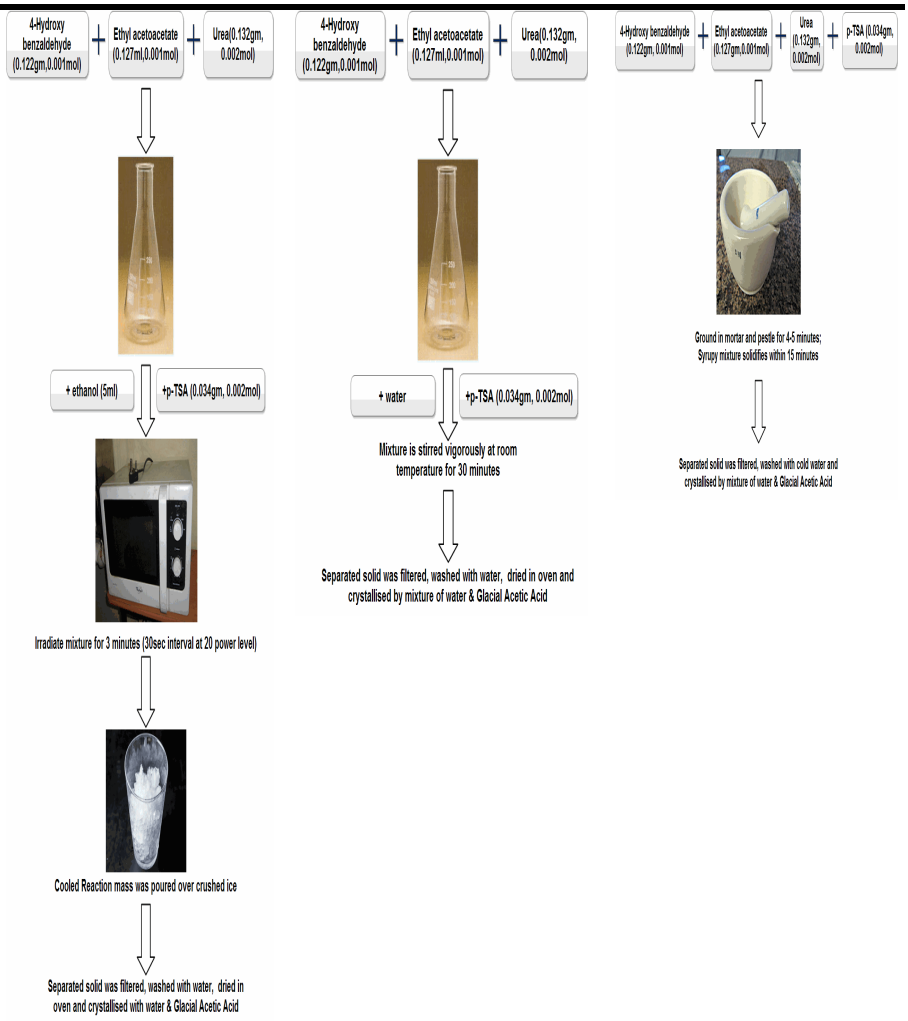
2, 3-diphenylquinoxaline [21]



4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester [22]



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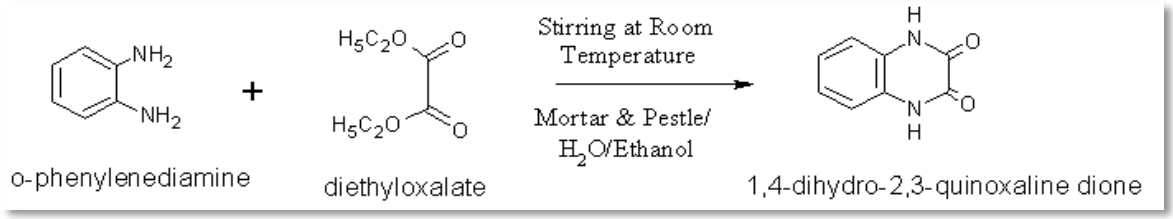
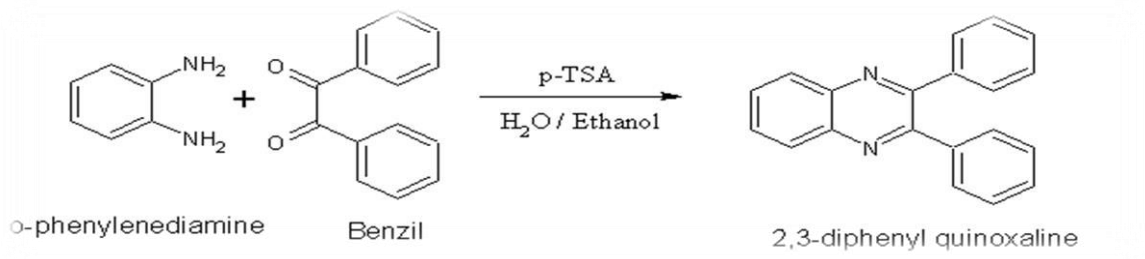
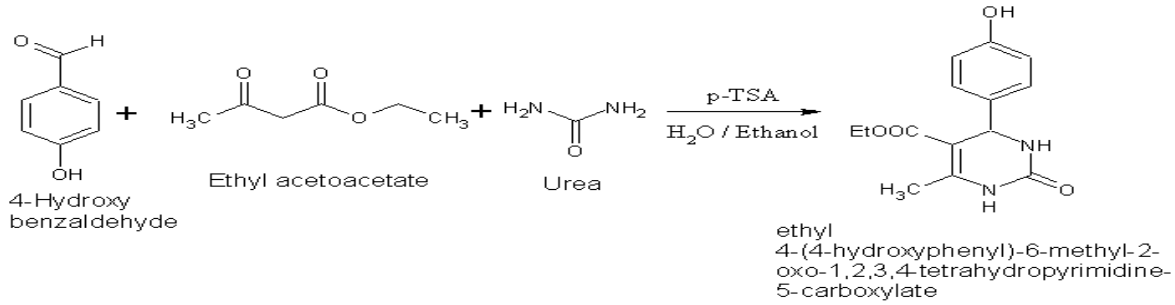
Synthesis Reaction Schemes of 1,4-dihydro-2,3-quinoxalinedione; 2,3-diphenyl quinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester



Scheme-1. Synthesis of 1, 4-dihydro-2, 3-quinoxalinedione



Scheme-2. Synthesis of 2, 3-diphenylquinoxaline



Scheme-3. Synthesis of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1, 2, 3, 4-tetrahydropyrimidine-5-carboxylic acid ethyl ester

Molecular Docking Studies

The three dimension structure of receptor (PDB ID 3HSW) was downloaded from RCSB Protein data bank (Available from: http://www.rcsb.org/pdb/home/home.do). For docking analysis PDB coordinates of the target protein and 1,4-dihydroxy quinoxaline 2,3 dione molecule were optimize by MVD (Molegro Virtual Docker) 2013.6.0. In our study molecular docking was performed on receptor (PDB ID 3HSW) for above mentioned Quinoxaline derivatives, molecular dynamics stimulation provide information about docking pose stability. Another derivative of quinoxaline which used in our study is 2,3 diphenyl quinoxaline ,docking was performed on receptor (PDB ID 3ZV6).

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RESULTS

Table 4. Percentage yield, reaction time and melting point of the synthesized aza-heterocycles

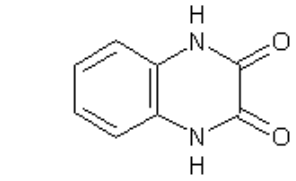
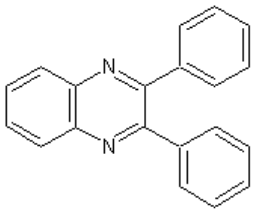
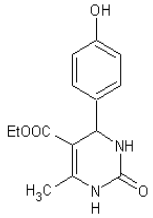
Sr. No.	Compound	Molecular wt. (gms)	Formula	Methods	Time	Yield (%)	Melting point (°C)
1	 1,4-dihydroquinoxaline-2,3-dione	162	$C_8H_6N_2O_2$	**1**	15 minutes reaction	96	298
				2	6 hrs reaction	88	298
				3	2hr reaction	79	296
2	 2,3-diphenylquinoxaline	282	$C_{20}H_{14}N_2$	**1**	8 minutes reaction	97	126
				2	10 minutes reaction	95	125
				3	20 minutes reaction	94	127
3	 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetra hydropyrimidine-5-carboxylic acid ethyl ester	276	$C_{14}H_{16}N_2O_4$	**1**	3 minutes reaction	96	236
				2	30 minutes reaction	80	238
				3	4-5 minutes reaction	90	236

Table 5. Energy and RMSD values obtained during docking analysis of 1,4-dihyroxyquinoxaline-2,3-dione as a ligand molecule

Docking Pose	PDB code	Moldock score	RMSD
1	3HSW _ligand	19.2112	11.1316
2	3HSW _ligand	19.2112	9.8562
3	3HSW _ligand	19.2112	8.8888
4	3HSW _ligand	19.2112	12.0354
5	3HSW _ligand	19.2112	9.4533

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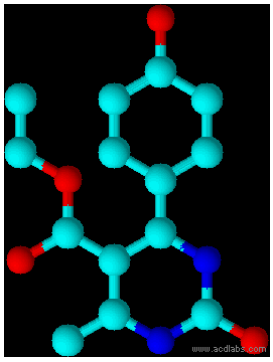
Table 6. Energy and RMSD values obtained during docking analysis of 2,3-diphenylquinoxaline as a ligand molecule

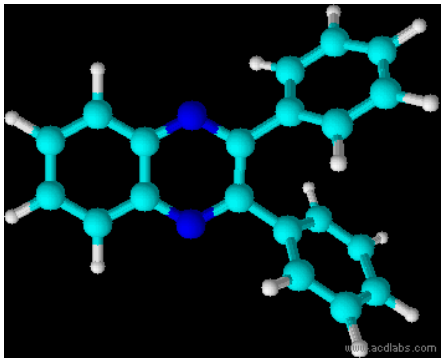
Docking Pose	PDB code	Moldock score	RMSD
1	3ZV6 _ligand	30.0426	5.4313
2	3ZV6 _ligand	30.0427	6.1986
3	3ZV6 _ligand	30.0427	3.6356
4	3ZV6 _ligand	30.0427	5.3784
5	3ZV6 _ligand	30.0427	6.2503

Table 7. Energy and RMSD values obtained during docking analysis of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester as a ligand molecule

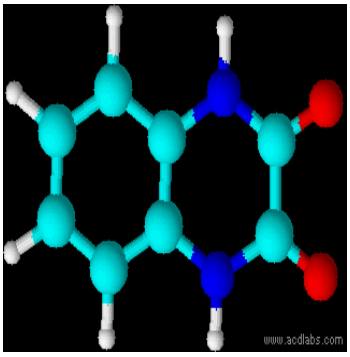
Docking Pose	PDB code	Moldock score	RMSD
1	3ZV6_ligand	-0.8593	5.6602
2	3ZV6_ligand	-0.8593	8.3054
3	3ZV6_ligand	-0.8592	3.4673
4	3ZV6_ligand	-0.8592	5.4109
5	3ZV6_ligand	-0.8592	3.7634



4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester



2,3-diphenylquinoxaline



1,4-dihyroxyquinoxaline-2,3-dione

Figure 1. 3D structures of synthesized Quinoxaline derivatives

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Discussion

The selected compounds were synthesized by Methods 1, 2 and 3 as stated in the Methodology of previous section. With **Method 1**; 96% yield of 1,4-dihyroxyquinoxaline-2,3-dione was obtained by grounding reactants in mortar and pestle for 15 minutes. The melting point of the compound was observed to be 298°C **(Table 4).** In **Method 2**; there was 88% yield of the compound and melting point of 298°C was observed. **Method 3**; yielded 79% of the compound with melting point of 296°C.

On spectral analysis with FT-IR, NMR and Mass spectrometer the following peaks were observed: **IR (cm^{-1}):** 3372.94, 1631.13, 1590.07, 1498.21, 1458.78, 1267.91, 927.97, 809.52, 748.24 The absorption band at 1590 cm^{-1} is due to C--- C stretching of aromatic ring system, at 3372.94 cm^{-1} is due to -NH group, while that at 1631.13 cm^{-1} is due to –C=O group. **1H-NMR (400MHz, $CDCl_3$),** δ ppm 7.76, 7.75, 7.65, 7.64, 5.63, 5.50, 5.48; the peaks in the region δ 7.6-7.7 are due to 4 aromatic protons. **MS (m/z)** 162.14 (calc.), 163 (exp.)

Similarly 2,3-diphenyl quinoxaline was synthesized by Methods 1, 2 and 3 [21] **. Method 1**; gave 97% yield of compound and melting point 126°C was observed. **Method 2**; gave 95% yield and melting point of compound was observed to be 125°C. **Method 3**; gave 94% yield and melting point of 127°C was observed **(Table 4**).

On spectral analysis with FT-IR, NMR and Mass spectrometer the following peaks were observed. **IR (cm^{-1}):** 1665.51, 1585.40, 1446.19, 1317.39, 1210.31, 1167.94, 1069.76, 995.32, 873.21, 786.54, 716.79, 639.85. The absorption bands at 1665 cm^{-1} and 1585.40 cm^{-1} are due to C-C stretching of aromatic ring (phenyl nucleus), at 1210.31 cm^{-1} due to plain bending of C-H in aromatic phenyl ring, weak absorption band at 3061 cm^{-1} due to aromatic C--H stretching, strong absorption band at 716.79 cm^{-1} and 786.54 cm^{-1} indicate mono substituted benzene ring. The weak absorption band at 1446 cm^{-1} is due to –C=N stretching. **1H-NMR (400MHz, $CDCl_3$),** δ ppm 8.01, 7.99, 7.69, 7.67, 7.65, 7.54, 7.53, 7.51. **MS (m/z)** 282.33 (calc.), 283.13 (exp.) [21]

4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester was synthesized by Methods 1, 2 and 3 [22]. By applying **Method 1**; 96% of compound was yielded in reaction time of 3 minutes which had a melting point of 236°C. **Method 2**; gave 80% yield and melting point of 238° C was observed. **Method 3**; gave 90% yield of compound and melting point of 236°C was observed **(Table 4)**.

On spectral analysis with FT-IR, NMR and Mass spectrometer the following peaks were observed **IR (cm^{-1}):** 3510.63, 3150.20, 1674.20, 1596.10, 1452.33, 831.42, 776.55, 707.62, 646.66.The characterstics broad band in the region 3150.20 cm^{-1} is due to hydroxyl group (-OH).The absorption band at 3510 cm^{-1} is due to –NH group. The absorption band at 1596.10 cm^{-1} is due to C-C stretching. The absorption band at 831.42 cm^{-1} is due to paradisubstituted benzene. **1H-NMR (400MHz, $CDCl_3$)**, δ ppm 10.59, 9.78, 9.56, 9.32, 9.11, 7.64, 7.74, 7.62, 7.05, 7.03, 6.94, 6.92, 6.70, 6.69, 5.51, 5.06, 3.97, 3.95, 3.47, 2.50, 2.24, 2.07, 1.90, 1.10, 1.08. Anal. calculated for $C_{14}H_{16}N_2O_4$, MS (m/z) 276 (calc.), 277 (exp.) [22].

Chemistry plays a significant role in bridging between physics, material sciences and life sciences. Our society has become dependent on chemical products in order to maintain our current standard of living and to improve quality of life. The last century has been highly productive in this aspect as it emerges in development in water treatment, pharmaceutical

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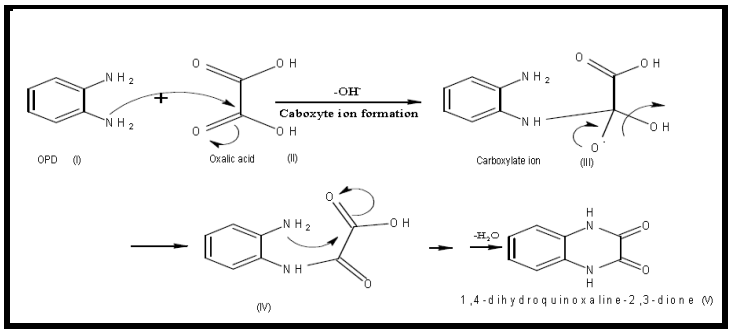
development, material science, polymers, agriculture pesticides and fungicides, detergents, petroleum additives and so forth. According to Anastas, the goal of green chemistry is not just clean-up, it is about redesigning chemical processes from the ground up. It is about making industrial chemistry safer, cleaner and more energy efficient throughout the product's life cycle, from synthesis to clean up to disposal.

Quinoxaline-2,3-diones are mainly prepared by condensation of *o*-phenylenediamines with various ketoacid derivatives[23,24]. The last and crucial step is the ring closure of an *o*-phenylenediamine with oxalate derivatives forming a *para*diazine ring of quinoxaline-2,3-dione. Normally, this step is carried out using the method of Phillips[25] under the catalysis of strong acid[26,27,28]. Frequently a solvent is also employed. It is desirable to perform the ring closure in the synthesis of quinoxaline-2,3-dione under mild reaction conditions in order to avoid any side reactions. The general Phillips reaction carried out under harsh conditions, as commented by Piguet et al[29] requires modification for various reasons.

As far as possible, catalysts and solvents should be avoided, as these substances are potential impurities in the final product. In our modified procedure, green solvents and no catalysts have been employed. The reaction temperature is low, *i.e*. room temperature. Excess diethyl oxalate, a reactant, serves as a mild solvent and can be easily removed from the solid product by simply washing with ether. **Table 4** depicts the results.

Organic synthesis in aqueous media is rapidly gaining popularity because of the fact that the use of many toxic and volatile organic solvents, particularly chlorinated hydrocarbons, contribute to the pollution. Furthermore, using water as a solvent offers many advantages, such as simple operation and high efficiency in many organic reactions that involve water soluble substrates, reagents such as carbohydrates. Jaberi and Amiri[30] synthesized 2-substituted benzimidazoles by one pot reaction of o-phenylenediamine with aldehydes in presence of boric acid in water at room temperature in good yields.

Ratnadeep Ghadage and Pramodkumar[11] synthesised 1,4-dihydro-2,3-quinoxalinedione using oxalic acid dihydrate, conc. HCl and o-phenylenediamine. On stirring the mixture at 100 °C for 20 min, 77% of the compound was synthesized. They observed melting point of the compound at 300°C. While the melting point of our compound was (296-298°C) **(Table 4)**, which was in conformity to that observed by Ghadage et al.,[11]. They found spectra of the synthesized compound as; IR (cm^{-1}): 3404, 3176, 3113, 1682, 1618, 1522, 1499, 1426, 1383, 755, 744; 1H-NMR ($CDCl_3$), δ ppm 8.003 (s,2H, NH), 6.978 (t, 2H, CH), 6.715 (d, 2H,CH). They have proposed a condensation reaction mechanism (Scheme 4) for the synthesis of 1,4-dihydro-2,3-quinoxalinedione under the same conditions[11].



Scheme-4: Mechanism for synthesis of 1,4-dihydroquinoxaline-2,3-dione from oxalic acid and o-phenylene diamine [11]

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Thakuria and Gopal Das[31] performed efficient synthesis of the potential pharmacophore 1,4-dihydro-quinoxaline-2,3-dione in a one-pot reaction at room temperature from substituted o-phenylene diamine and oxalic acid under solvent-free conditions by a simple grinding method with unsurpassed atom economy. They found the mass spectra of compound MS (m/z): 162.0 (M+), whereas we observed it at 163. The time required by Thakuria et al.,[31] was 0.5 hrs with 98 % yield, while we found the yield under solvent free conditions to be 96% at a reaction time of 15 minutes.

Grinding technique has been very successful in fulfilling the principles of green chemistry. Using this technique the reactions are carried out under solvent free conditions with maximum yield and minimum cost. Grinding of reactants can be carried out manually using a pestle and mortar or by using a high speed vibrating mill[32,33]. According to conventional approach, the collisions between reactants are necessary to carry out the reaction. Here also grinding let the molecules of the reactants to undergo forced collisions and thus leads to the formation of products. As compared to conventional methods, the time required for completion of reaction using grinding is much shorter and this can be attributed to the large number of collisions at faster rate between the reacting molecules during the grinding process. In addition to this, the amount of heat produced because of friction during grinding process also helps in the completion of reaction. The general usefulness of solvent free conditions in chemical reaction has been well described by Toda[34] and Tanaka[35]in a review which covers a number of synthetically useful reactions.

Green chemistry is established as national responsibility in present time. It is highly amenable to have a convenient and rapid synthetic procedure that is energy efficient. Such a procedure should be suitable for large-scale operation also having a practically applicable orientation. Grindstone Chemistry is useful for desktop synthesis as well as kilogram scale operation.

The pioneering work of Toda et al[34] has shown that many exothermic reactions can be accomplished in high yield by just grinding solids together using mortar and pestle, a technique known as 'Grindstone Chemistry' which is one of the 'Green Chemistry Techniques'. The energy generated through friction initiates the reactions. Grindstone Chemistry leads to reduction in wastes generation along with being highly reactive and energy efficient. It is simple to tackle such reactions, they reduce pollution, are more economical and ecologically favorable. Solid-state reactions are efficient and selective as compared to reactions in solution[36]. This method is superior to conventional method; as it is eco-friendly, the yield is high, does not require any special apparatus, it's non-hazardous, operationally simple and convenient. A hand held electric food mixer with stainless steel rotor is a simple and inexpensive option for conducting Grindstone Chemistry on a large scale.

Conventional Method of synthesis of 2,3-Diphenyl quinoxaline: 1.26 gm of benzil was dissolved in 8 ml of warm rectified spirit and transferred into 100 ml round bottomed flask containing 1.08 gm of O-Phenylene diamine dissolved in 8 ml of rectified spirit. Refluxing was done for 1 hour on a boiling water bath. Then, water was added until slight cloudiness persists. The crude product was filtered and recrystallized from rectified spirit (75% yield, 1-1.5hrs)[37,38]. Significant yield improvement at a shorter reaction time was observed when we synthesized the same compound with the help of ultrasound (97%, 8 minutes).

Joshi et al.[39], synthesized 2,3-Diphenyl quinoxaline by microwave irradiation of benzil (0.01M), o-phenylene diamine (0.01M) and ethanol (16ml) which gave 60% yield in a

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reaction time of 55 seconds, while we achieved 97% yield after 8 minutes of sonication. The yield of our compound was found to be significantly higher than the conventional method of synthesis which led to 51% yield at a reaction time of 0.5 hrs[304]. Although the reaction time by Joshi et al.[39] was less, the yield could be increased by modifying the technique and slightly varying the reaction time.

Jyotidas and Sarkar[40] synthesised quinoxalines in aqueous medium in the presence of tetraethylammonium bromate. They found spectral data of 2,3-Diphenylquinoxaline ^{1}H NMR: (300MHz, CDCl3) ∂ 8.193(t, 2H, J1=2.7 Hz, J2=3.6 Hz, ArH),7.77-7.803(m, 2H, ArH), 7.519-7.544(m, 4H, ArH), 7.344-7.365(m, 6H, ArH).13C NMR: (75MHz, CDCl3) ∂ 153.43, 141.17, 138.99, 129.95, 129.79,129.15, 128.78, 128.25.IR (cm^{-1}): 3057.17, 3028.24, 1548.84. The yield was found to be as high as 92% [41] ; they synthesized 2,3 diphenyl quinoxaline applying efficient practical techniques like- sonication (sonochemistry sythesis), UV radiations and simple mechanochemistry using mortal-pastel method. They monitored the progress of reaction by TLC and performed characterization by IR and NMR. Compared with traditional methods, these methods are more convenient and reactions lead to higher yield (95.8-98.3%), shorter reaction time (10, 15, 17 minutes) and milder conditions, without generation of pollution and safer to analyst. The melting point of the compound observed by Bendale et al., [41] was in the range 122-124°C, whereas we observed the melting point to be between 125-127°C. The spectroscopic studies revealed λmax: 292 nm IR: Characteristic IR (KBr) bands found at: 3065, 1441, 1395, 768, (νmax/cm-1). Our observation of MS was (m/z): 283.13. As observed by Bendale et al.,[41] we also found that in comparison with traditional methods our methods are more convenient and reactions can be carried out in higher yield (94-97%), shorter reaction time (8-20 minutes) and milder conditions (sonication and stirring at room temperature), without generation of pollution and safer to analyst.

To investigate the role of ultrasonic irradiation in our method, the reactions were carried out in the presence of p-TSA, dissolving O-phenylene diamine and benzil in EtOH; sonicating the above mixture at room temperature. From the results that are summarized in **Table 4**, it is clear that, under the same reaction conditions, reactions under ultrasonic irradiation led to relatively higher yields and shorter reaction times. It is presumed that the efficiency using ultrasound irradiation is due to the cavitation phenomena. An ultrasonic wave breaks intermolecular forces due to its pressure wave with alternate compressions and rarefactions. The chemical and physical effects of ultrasound derive primarily from acoustic cavitation which includes formation, growth and collapse of the cavity [42,43.] Bubble collapse in liquids results in an enormous concentration of energy from the conversion of kinetic energy of liquid motion into heating of the contents of the bubble. The high local temperatures and pressures produced by cavitation lead to a diverse set of applications of ultrasound such as accelerating the rate of the reaction, changing the reaction pathway, enhancing chemical reactivity and important uses in synthetic organic compounds[44.]

The two main sources of ultrasound in organic synthesis are ultrasonic cleaning baths and ultrasonic immersion probes, which typically operate at frequencies of 40 and 20 kHz, respectively[45]. The former are more commonly employed in organic synthesis simply because they are less expensive and hence more widely available to chemists, even though the amount of energy transferred to the reaction medium is lower than that of ultrasonic probe systems, which deposit the acoustic energy directly into the reaction medium.

Compared with traditional method, our method is more convenient and reactions can be carried out in higher yield, shorter reaction time and milder conditions, without generation of

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pollution and safer to analyst. This approach has several advantages, such as excellent yield, short reaction time, low cost, simple experimental as well as isolation procedures, and finally, it is in agreement with the green chemistry protocols.

Some organic reactions using water as the medium suffer from a serious disadvantage, the non-homogeneity of the reaction mixture because most of the organic chemicals are almost insoluble in water and this results in decrease in reaction rates many folds or sometimes reaction does not happen at all. This problem can be overcome by providing the activation energy to the reaction by using microwave irradiation. The microwave dielectric heating effect uses the ability of some liquids and solids to transform electromagnetic energy into heat and thereby drive chemical reactions. This in situ mode of energy conversion has many attractions for chemists, because its magnitude depends on the properties of the molecules. This allows some control of the material's properties and may lead to reaction selectivity. There are a variety of methods for carrying out microwave-assisted organic reactions using domestic or commercial ovens; this is basically known as microwave-induced organic reaction enhancement (MORE) chemistry. Most of the published chemistry has been performed using domestic microwave ovens. The key reasons for using a device intended for heating food items to perform synthesis are that they are readily available and inexpensive[46].

Anil Kumar Jogula et al.,[47] used Cyanuric chloride as a new catalyst for the one-pot Biginelli reaction coupling of β-ketoester, aldehydes and urea to afford the corresponding tetrahydropyrimidinones. The reaction time required was 12 hrs, with 80% yield and the melting point to be within 198-200°C. When we synthesized the same compound viz. 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester under the presence of p-TSA using 4-hydroxybezaldehye, ethyacetoacetate, ethanol and urea applying microwave irradiation, we observed a yield of 96% within 3 minutes reaction time and melting point was 236-238°C [22]. Yadav et al. [48], performed microwave assisted synthesis of tetrahydropyrimidinones in presence of TTSA. They irradiated equimolar mixture (2 mmol each) of aldehyde, β-keto ester and urea or thio-urea in acetonitrile, with catalytic amount of TTSA (3 mol%) and the contents were irradiated to microwave (450 wt) at the interval of 10 sec. They found the yield of 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester to be 95% and melting point 201°C Yadav M.V. [48], Nayak et al.[49], synthesized Ethyl 4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate monohydrate with a mixture of ethylacetoacetate (0.1 mol), para hydroxy substituted benzaldehyde (0.1 mol) and urea was refluxed in 50.0mL of ethanol for 2.0 hrs in presence of concentrated hydrochloric acid as catalyst. The quenching of reaction mixture was done in ice cold water. The precipitate obtained was filtered, dried and crystallized from methanol to obtain the title compound[49].

Heating under reflux for several hours is logical for endothermic reactions. For exothermic reactions, however, such energy input would be superfluous. The convenience and the time saving that results from the use of Grindstone Chemistry—for small scale as well as large scale reactions—is illustrated here in our work by describing the successful application of this technique to the multicomponent Biginelli reaction. We employed p-toluene sulfonic acid (p-TSA), an inexpensive and common organic chemical, which was an efficient catalyst for this reaction.

Bose et al.[50], synthesized tetrahydropyrimidinone using grindstone technique and found the yield to be 95%, with melting point 236–238°C. While Sun et al. [51] also reported the melting point of the compound to lie between 236–238°C. Ushati Das et al.,[52] also synthesized Ethyl

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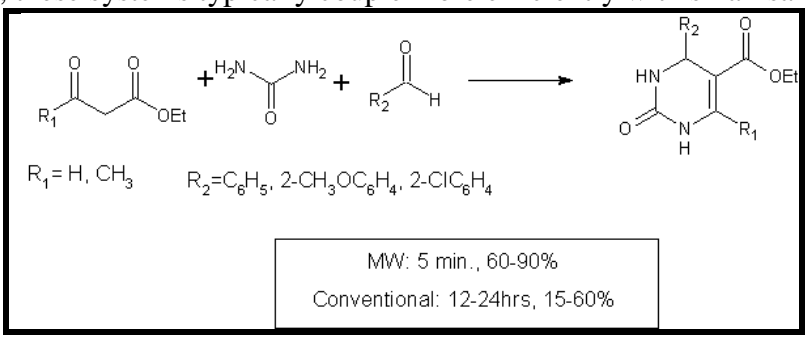
4-(4-hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylate monohydrate using 4-Hydroxybenzaldehyde, ethyl acetoacetate, urea and p-TSA in mortar and pestel (yield 95%, m.p. 509–511 K). The observations by Ushati et al. [52], and Bose et al.[50], were almost similar to those noted by us under solvent free conditions of grindstone technique in terms of yield (our yield 90%, m.p. 236°C) and at a reaction time of 4-5 minutes.

Mohideen et al.[53], synthesized Ethyl 6-methyl-2-oxo-4-phenyl-1,2,3,4-tetrahydropyrimidine-5-carboxylate by grounding a mixture of benzaldehyde (0.106 g, 1 mmol), ethyl acetoacetate (0.130 g, 1 mmol) and urea (0.070 g, 1.17 mmol) with four drops of *ortho* phosphoric acid for about 30 minutes. The reaction mixture was cooled for 15 minutes and poured into a beaker containing 50 ml of cold water. The precipitate obtained was filtered, washed with water and ethanol to get white solid (0.26 g, 92% yield; mp 203–204). Physiologically active tetrapyrimidinones were successfully prepared by Biginelli reaction by grinding aryl aldehydes, ethylacetoacetate and urea/ thiourea in presence of p-toluenesulphonic acid at room temperature[54] Several mechanisms have been proposed for the synthesis along with that given by Folkers and Johnson Folkers K. [55] A proposal was given by Kappe in 1997 (Kappe, C.O.[56]).

The Biginelli reaction is important for the preparation of dihydropyrimidine derivatives and excellent results are found for reactions carried out with microwave enhancement as observed by Hayes[57]. He found that single-mode cavities offer more consistent and predictable energy distribution. Single-mode instruments produce one homogeneous, intense pocket of energy that is highly reproducible. Due to their uniform energy distribution and higher power density, these systems typically couple more efficiently with small samples[57].



Scheme 5 Biginelli reaction

The original Biginelli reaction was carried out by refluxing a mixture of the three components such as ethyl acetoacetate, benzaldehyde and urea in presence of ethanol catalyzed by small amount of HCl[58] which often resulted in poor to variable yields of desired products (20-70%)[59].

Multi-component being more efficient and economical have attracted the attention of organic chemists. Further, these reactions can be carried out without isolation of the intermediates (One pot and one step synthesis) and avoid the protection deprotection strategies in the synthesis as well as time consuming purification processes. Hugel, H.M.[60] and Shete et al [61], aimed to check the efficiency of various metal phosphates(NaH_2PO_4, KH_2PO_4 and K_2HPO_4) as promoter in the multicomponent dihydropyrimidine synthesis. They synthesized 5- acetyl / ethoxycarbonyl, 4-aryl / substituted aryl, 6-methyl, 3, 4- dihydropyrimidine-2-one / thione using a mixture of urea / thiourea, appropriate aldehyde, acetyl acetone / ethyl acetoacetate and metal phosphate in 20 mL of glacial acetic acid solvent which was heated at 45 -50° C under magnetic stirring for 20-40 min. They found Glacial acetic acid to perform well as a

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solvent as compared to that when employing ethanol as a solvent. With glacial acetic acid all products were obtained in satisfactory yields (moderate to excellent). Further, all metal phosphates they used were cheap and nontoxic. With NaH_2PO_4 the yield of 5-ethoxycarbonyl, 6-methyl, 4-phenyl, 3, 4-dihydropyrimidine-2(1H)-one was 66% and melting point was found to be between 192-195°C, with KH_2PO_4 yield was 89% and melting point between 204-206°C, while with K_2HPO_4 yield was 50% and melting point between 200-202°C. The melting point reported was 202-203°C [62]. The lower meting points of these products (than the reported) indicated low purity of the compounds. It can be seen that, catalyzing the reaction by KH_2PO_4 gave superior results over the other two metal phosphates both in terms of yields and purity.

It is well known that Biginelli reaction is an acid catalyzed versatile one pot multi-component reaction for the synthesis of 3, 4-dihydropyrimidin-2(1*H*)-one / thione derivatives. The reaction occurs via formation of metal-enolate ion pairs and metal-*N*-acylimine intermediates which govern the overall progress of Biginelli reaction. The stabilization of *N*-acylium intermediate by the cation of the catalyst is the exact mechanism involved in this reaction[63].

Computational modeling in drug discovery utilizes *in-silico* tools towards drug design or for identifying 'lead' compounds from existing databases that exhibit potential of inhibitory effects. For docking analysis PDB coordinates of the target protein and synthesized molecules were optimize by MVD Software as described in methodology section. **Table 5,6 and 7** states the results of docking analysis of 1,4-dihyroxyquinoxaline-2,3-dione; 2,3-diphenylquinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester respectively. The 3D structures of selected compounds were optimized by ACD Lab softwere i.e. given in **Figure 1**. These coordinates were found to have minimum energy and stable conformation. The 1,4-dihyroxyquinoxaline-2,3-dione shows anti inflammatory activity with the help of molecular docking process. This can be used as lead compound for development novel anti-inflammatory drugs. In our study molecular docking was performed on receptor (PDB ID 3HSW) for above mentioned quinoxaline derivatives, molecular dynamics stimulation provided information about docking pose stability. Another derivative of quinoxaline which used in our study is 2,3-diphenylquinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester; docking was performed on receptor (PDB ID 3ZV6). 2,3-diphenylquinoxaline was found to exhibit anti-microbial activity. The minimum binding energy indicated that the target protein was successfully docked with 1,4-dihyroxyquinoxaline-2,3-dione structure. The top five poses given in **Tables 5, 6 and 7**.

Conclusion

Our study summarizes that we have developed efficient method for the synthesis of **1,4-dihydro-2,3-quinoxalinedione; 2 ,3 diphenyl quinoxaline and 4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester**. The reaction of O-phenylene diamine and Benzil in ethanol and p-TSA by using sonicator, has several advantages, such as excellent yield, short reaction time, low cost, simple experimental as well as isolation procedures, and finally, it is in agreement with the green chemistry protocols. We have found that p-toluenesulfonic acid (p-TSA), an inexpensive and common organic chemical, is an efficient catalyst for this reaction. The catalyst used in an inexpensive chemical that is commonly found in most of organic laboratories.

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The synthesis of **1,4-dihydro-2,3-quinoxalinedione** by the reaction of O-phenylene diamine and Diethyloxalate by Grindstone technique is a simplified and rapid synthetic procedure. This procedure is much simpler and faster. The methodology does not require the use of any organic solvent, catalyst and additional oxidant, thus eminently meeting green chemistry objectives. Another useful aspect is that this procedure is energy efficient. This reaction can be easily adapted for use as an interesting experiment in an organic chemistry teaching laboratory.

Microwave technique is beneficial over conventional methods due to shorter reaction times, dry media (thus avoiding the use of harmful solvents), cleaner reactions, easy work up, and minimization of thermal decomposition products for synthesis of **4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester. The** microwave assisted method is an efficient (increasing yield), rapid, simple, feasible and eco-friendly method for the synthesis of a large number of organic heterocyclic molecules. However, there is still a lot of scope to gain evolving knowledge about these fascinating and useful reactions.

Hence our study concludes that the best method for efficient synthesis of **1,4-dihydro-2,3-quinoxalinedione** was by mechano-chemistry under solvent free condition by employing simple mortar pestel leading to a yield of 96% at a reaction time of 15 minutes, while that for the synthesis of **4-(4-Hydroxyphenyl)-6-methyl-2-oxo-1,2,3,4-tetrahydropyrimidine-5-carboxylic acid ethyl ester** was under the presence of microwave irradiation (yield 96%, reaction time of 3 minutes). Whereas, in case of **2,3 diphenyl quinoxaline** all the three methods i.e., application of sonicator and solvents like ethanol, water gave almost comparable yields (97, 95 and 94 % respectively), the reaction time was also competent viz., 8, 10 and 20 minutes.

Drug discovery is a complex, expensive and arduous process and *in-silico* drug discovery employing computational modeling reduces the time, efforts and cost significantly. The docking analysis demonstrates that **1,4-dihyroxyquinoxaline-2,3-dione shows anti inflammatory activity** whereas **2,3-diphenylquinoxaline was found to exhibit anti-microbial activity** with the help of molecular docking process on selected protein. The minimum binding energy indicated that the target protein was successfully docked with 1,4-dihyroxyquinoxaline-2,3-dione structure.

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