PART-I Introduction to Glycerol.

5.1.1 INTRODUCTION:

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“It is better to prevent waste than to treat or clean up waste after it is formed”
5.1.1 INTRODUCTION TO GLYCEROL:

Most of the organic reactions occur in a liquid phase. The solvent not only allows a better contact between reactants, stabilizes or destabilizes intermediates and/or transition states but also determines the choice of work up procedures and recycling or disposal strategies. Taking into account the impact of chemical processes on the environment, the search for innovative concepts for the substitution of volatile organic solvents has become a tremendous challenge in academia and industry. According to the twelve principles of green chemistry (Table 1), a green solvent should meet numerous criteria such as low toxicity, non-flammability, non-mutagenicity, non-volatility and widespread availability among others. Moreover these green solvents have to be cheap and easy to handle and recycle.

In the past decade, water, ionic liquids, polyethylene glycol, supercritical fluids (particularly supercritical carbon dioxide (scCO2)) and perfluorinated solvents appeared as the most promising approaches for current solvent innovation. Although fascinating results have been reported, use of these solvents is still subject to strict limitations such as high cost equipment for scCO2, or high prices and lack of data about the toxicity and bio-compatibility for ionic liquids, or product separation for aqueous-based processes. In other words, a universal green solvent doesn’t exist and for this reason, the scientific community is continuously searching for new sustainable media in order to widen their use in catalytic and organic processes.

Nowadays, most solvents are prepared from fossil oil reserves. With the predicted disappearance of oils, interest in utilization of biomass-derived solvents has grown. So far, many naturally available products, such as soy methyl ester, lactate ester, D-limonene and polyhydroxyalkanoates among others have been proposed as safer solvents for catalysis, organic reactions or separations. Many others have also been used as precursors for the synthesis of potentially safer green solvents, for example, bio-based ionic liquids. As compared to the traditional petrochemical-derived solvents, these biomass-based solvents exhibit many advantages such as biodegradability, low vapor pressure and high boiling point which perfectly fit with the different international legislations pushing forward the reduction of volatile...
organic compounds (VOCs) in the atmosphere. If these biomass-derived solvents are attractive from the viewpoint of green chemistry, it is also noteworthy that their broad utilization in industry requires them to be cost profitable which represents a prerequisite for their viable utilization.

In this context, the possible use of glycerol as a solvent for catalysis or organic chemistry has become of particular interest. This topic is mainly boosted by the rapid emergence of biodiesel on the market. Indeed, glycerol is the main co-product of the vegetable oil industry and new applications are now strongly researched for this natural polyol.\(^\text{18}\) Most efforts in this area focus on conversions of glycerol to higher value-added chemicals and some comprehensive reviews have already summarized this work.\(^\text{19}\) Although promising works have been reported, other methods that are capable of economically utilizing glycerol waste have also to be considered. In particular, the utilization of glycerol as a solvent or as a precursor for the synthesis of biomass-based solvents has recently emerged in the literature as a feasible and promising approach. Even if this topic does not aim to consume glycerol as a reactant, it is noteworthy that the direct use of glycerol as a solvent offers an indisputable economically and environmentally viable application for this natural polyol.

In this perspective, we develop a method for the synthesis of N-heterocycle, using glycerol as solvent in a catalyst free condition.

Water is the first solvent of choice regarding the aforementioned considerations, yet the negligible solubility of many organic and organo-metallic compounds in water limits its applications. Using organic, petroleum-based, solvents that allow dissolving a large variety of solid, liquids, and gases is usually accompanied with air, water, and land contamination. Fluorous phases\(^\text{20}\) and ionic liquids\(^\text{21}\) have been reported as recyclable environmentally benign reaction media. However, not only that ionic liquids and perfluorinated solvents are non-biodegradable and toxic, their production is also associated with use of high amounts of hazardous and volatile organic solvents. Supercritical fluids and especially supercritical CO\(_2\) have also been reported as green solvents, but their high critical properties still limits their practical use.\(^\text{22}\)
Glycerol is usually produced as a byproduct of the trans etherification of a triglyceride in the production of natural fatty acid derivatives. These derivatives are utilized in many areas from pharmaceuticals and food industry to alternative fuels, e.g., biodiesel, and thus as the production of glycerol raises its price decreases. In addition, glycerol has also promising physical and chemical properties. It has a very high boiling point and negligible vapor pressure; it is compatible with most organic and inorganic compounds, and does not require special handling or storage. Glycerol, as other polar organic solvents such as DMSO and DMF, allows the dissolution of inorganic salts, acids, and bases, as well as enzymes and transition metal complexes (TMCs), but it also dissolves organic compounds that are poorly miscible in water and is non-hazardous. Different hydrophobic solvents such as ethers and hydrocarbons which are immiscible in glycerol allow removing the products by simple extraction. Distillation of products is also feasible due to the high boiling point of glycerol.

5.1.2 OBJECTIVE OF WORK:

The purpose of this study is to explore the scope and limitations of glycerol as alternative green reaction medium. Glycerol, which is a non-toxic, biodegradable, and recyclable liquid manufactured from renewable sources, shows similar properties as an ionic liquid and has a high potential to serve as green solvent for organic syntheses. This has led us to study its possible use as such in a variety of ways. Several non-catalytic and catalytic reactions using homogeneous and heterogeneous chemo- and bio-catalysts have been thus studied in glycerol. The unique physico-chemical nature of glycerol enables easy separation of the product by extraction or distillation together with catalyst recycling. These properties can also be translated into other processes which require non-aqueous polar solvents such as non-aqueous emulsions, as well as applications in microwave promoted synthesis.
5.1.3 DESIGN AND DEVELOPMENT:
Solvents are used daily in numerous industrial processes as reaction medium, in separation procedures, and as diluters. As reaction medium, solvent are employed to bring reactants and/or catalysts together and to deliver heat and momentum. In addition, the solvent may also affect activity and selectivity. The choice of the right solvent; i.e., its chemical, physical, and biological nature, also plays a key role from environmental, economic, safety, handling, and products isolation point of views. Considering properties of glycerol as a green solvent we choose it for the synthesis of nitrogen heterocycles. The points are discussed.

5.1.3.1 SOLVENT PROPERTIES OF GLYCEROL:
In its pure form, glycerol is a sweet-tasting, clear, colorless, odorless and viscous liquid. Because it is a trihydric alcohol, glycerol is a polar protic solvent with a dielectric constant of 42.5 (at 25°C) which is intermediate between that of water (78.5) and an ionic liquid such as 1-buyl-3-methylimidazolium hexafluorophosphate ([BMIIm]PF6,11.4). Glycerol is completely soluble in water and short chain alcohols, sparingly soluble in many common organic solvents (ethyl acetate, dichloromethane, diethyl ether, etc…), and is insoluble in hydrocarbons. At low temperatures (<17.8, glycerol forms crystals. Its specific density is 1.26 and its molecular weight is 92.09. Prior to using glycerol as a potentially safer solvent, some specific points have to be taken into consideration in order to maximize as much as possible its solvent properties:

(1) Solubility:
Like polar solvents such as water, DMSO and DMF, glycerol is able to facilitate dissolution of inorganic salts, acids, bases, enzymes and many transition metal complexes. Furthermore, it also dissolves organic compounds that are poorly miscible in water. Many hydrophobic solvents, such as ethers and hydrocarbons, are immiscible in glycerol. This enables the reaction products to be removed by simple liquid–liquid phase extraction.
(2) **Volutility and boiling point:**
As mentioned above, glycerol is nonvolatile under normal atmospheric pressure and has a high boiling point (290°C), thus making distillation of the reaction products a feasible separation technique. Moreover, taking advantage of its high boiling point, reactions in glycerol can be carried out at high temperatures, thus allowing acceleration of the reaction, or making possible reactions that do not proceed in low boiling point solvents.

(3) **Safety:**
Data about the toxicity and environmental compatibility have to be collected before utilization of a green solvent on a large scale. In this context, glycerol has a clear advantage compared with most organic solvents. Indeed, glycerol is a nontoxic (LD50 (oral rat)=12600 mg/Kg), biodegradable and nonflammable solvent for which no special handling precautions or storage is required. In particular, the low toxicity of glycerol also allows its use as a solvent in the synthesis of pharmaceutically active ingredients, in which the toxicity and residue of solvents have to be carefully controlled.

(4) **Availability:**
To be viable, a green solvent has to be cheap and available on a large scale. Glycerol meets these criteria since it is available on a large scale from the vegetable oil industry. For instance, the production of glycerol reached 1.5 Mt in 2009. Glycerol is also very cheap (0.50 €/Kg for pharmaceutical grade (99.9%) and 0.15€/Kg for the technical grade (80%)) and, sometimes, even cheaper than water.
5.1.3.2 LIMITATIONS:

Despite these clear advantages, the possible use of glycerol as a solvent also requires chemists to overcome a few obstacles such as:

(1) The high viscosity of glycerol that can induce important mass transfer problems. Fortunately, at temperatures higher than 60°C, glycerol is much less viscous. Therefore, reactions involving glycerol as solvent have to proceed at temperatures higher than 60°C. Otherwise, a fluidifying co-solvent has to be used.

(2) The chemical reactivity of hydroxyl groups which can lead to the formation of side products. In particular, the three hydroxyl groups of glycerol are reactive in extremely acidic or basic conditions. Therefore, glycerol has to be used as a solvent in a chemically inert environment for the hydroxyl groups to remain intact.

(3) The coordinating properties of glycerol which may induce some problems when transition metal complex catalysts are used in this solvent. In particular, deactivation of organometallic complexes might occur in glycerol.

Taking into account these advantages and disadvantages, research dealing with the possible use of glycerol as a solvent is no longer a simple transfer of a known method from a conventional solvent system to glycerol. Therefore, innovative solutions have to be thought of in order to maximize the advantages of glycerol. Although it seems very difficult, after a few years of exploration, researchers involved in this field have developed some successful examples that not only have demonstrated the feasibility and the necessity of using glycerol as a solvent, but have also contributed to the emergence of promising methods especially in the field of organic synthesis, catalysis, separations and materials chemistry. Now, we will show what glycerol as a solvent contributes to current chemistry.
5.1.4 **TWELVE PRINCIPAL OF GREEN CHEMISTRY:**

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<td><strong>1. Prevention</strong></td>
<td>It is better to prevent waste than to treat or clean up waste after it has been created.</td>
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<td><strong>2. Atom Economy</strong></td>
<td>Synthetic methods should be designed to maximise the incorporation of all materials used in the process into the final product.</td>
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<td><strong>3. Less Hazardous Chemical Synthesis</strong></td>
<td>Wherever practicable, synthetic methods should be designed to use and generate substances that possess little or no toxicity to people or the environment.</td>
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<td><strong>4. Designing Safer Chemicals</strong></td>
<td>Chemical products should be designed to effect their desired function while minimising unnecessary whenever possible and innocuous when used.</td>
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<td><strong>5. Safer Solvents and Auxiliaries</strong></td>
<td>The use of auxiliaries substances (e.g., solvents or separation agents) should be made unnecessary whenever possible and innocuous when used.</td>
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<td><strong>6. Design for Energy Efficiency</strong></td>
<td>Energy requirements of chemical processes should be recognised for their environmental and economic impacts and should be minimised. If possible, synthetic methods should be conducted at ambient temperature and pressure.</td>
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<td><strong>7. Use of Renewable Feedstocks</strong></td>
<td>A raw material or feedstock should be renewable rather than depleting whenever technically and economically practicable.</td>
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<td>8. Reduce Derivatives</td>
<td>Unnecessary derivatization (use of blocking groups, protection/de-protection, and temporary modification of physical/chemical processes) should be minimised or avoided if possible, because such steps require additional reagents and can generate waste.</td>
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<td>9. Catalysis</td>
<td>Catalytic reagents (as selective as possible) are superior to stoichiometric reagents.</td>
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<td>10. Design for Degradation</td>
<td>Chemical products should be designed so that at the end of their function they break down into innocuous degradation products and do not persist in the environment.</td>
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<td>11. Real-time Analysis for Pollution Prevention</td>
<td>Analytical methodologies need to be further developed to allow for real-time, in-process monitoring and control prior to the formation of hazardous substances.</td>
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<td>12. Inherently Safer Chemistry for Accident Prevention</td>
<td>Substances and the form of a substance used in a chemical process should be chosen to minimise the potential for chemical accidents, including releases, explosions, and fires.</td>
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5.1.5 REFERENCES:

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SECTION–I Synthesis of Quinoxaline

SECTION-II Synthesis of Benzoxazole and Benzimidazole
SECTION-I Synthesis of Quinoxaline

5.2.1 INTRODUCTION:

5.2.2 LITERATURE SURVEY:

5.2.2.1 General method for quinoxaline synthesis

5.2.3 OBJECTIVE OF THE WORK:

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5.2.5 EXPERIMENTAL:

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5.2.1 INTRODUCTION:

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Quinoxalines are well known and important N-containing heterocyclic compound, containing a ring complex made up of a benzene ring and a pyrazine ring, so called benzopyrazine. It is isomeric with quinazoline, phthalazine and cinnoline.¹

Figure 1

Quinoxaline derivatives display a broad spectrum of biological properties (Figure 2) ranging from DNA cleaving drugs,² antimicrobial and cancer drugs,³ to antibiotic⁴ and antitumor activity.⁵ Which have made them privileged structures in combinatorial drug discovery libraries.⁶ They have also found applications as dyes⁷ and building blocks in the synthesis of organic semiconductors,⁸ and they also serve as useful rigid subunits in macro cyclic receptors or molecular recognition⁹ and chemically controllable switches.¹⁰ Therefore, there are constantly new and innovative ideas being developed to access this important moiety.
Recently use of glycerol as a sustainable solvent for green chemistry has attracted more attention. These include Pd-catalyzed Heck and Suzuki cross-couplings, base- and acid- promoted condensations, catalytic hydrogenation, and asymmetrical hydrogenation. The peculiar physical and chemical properties of glycerol, such as polarity, low toxicity, biodegradability, high boiling point, and ready availability from renewable feedstocks, prompted us to extend its use as a green solvent in organic synthesis.

5.2.2 LITERATURE SURVEY:
5.2.2.1 General method for quinoxaline synthesis

A number of synthetic strategies have been developed for the preparation of substituted quinoxalines. By far, the most common method relies on the condensation of an aryl 1,2-diamine with a 1,2-dicarbonyl compound in refluxing ethanol or acetic acid for 2-12 h giving 34-85% yields.
Furthermore, there are several synthetic routes toward quinoxalines, including Bi-catalyzed oxidative coupling of epoxides with ene-1,2-diamines, heteroannulation of nitroketene N, S-aryliminoacetals with POCI₃, cyclization of α-arylimino oximes of α-dicarbonyl compounds, and from α-hydroxy ketones via a tandem oxidation process using Pd(OAc)₂ or RuCl₂-(PPh₃)₃-TEMPO as well as MnO₂. Most of the existing methodologies suffer from disadvantages such as use of volatile organic solvents, unsatisfactory product yields, critical product isolation procedures, expensive and detrimental metal precursors and harsh reaction conditions, which limit their use under the aspect of environmentally benign processes.

1) Coupling of epoxides and ene-1,2 diamines.

The oxidative coupling of epoxides and ene-1,2 diamines in the presence of Bi(0) and acid derivatives is an alternate procedure to access quinoxalines (Scheme 5.2). The reaction is fascinating since epoxides are generally not used to access quinoxalines although one method using cyano and sulfonyl epoxides has been reported.

2) Ammonium heptamolybdate tetrahydrate mediated synthesis of quinoxaline.
A. Hasaninejad et al have been reported the synthesis of quinoxalines from aryl 1,2-diamines and 1,2-diketones in the presence of ammonium heptamolybdate tetrahydrate in EtOH/H₂O (3/1) at room temperature (Scheme 5.3).¹⁶

![Scheme 5.3](image)

3) Polyethylene glycol (PEG-400) mediated synthesis of quinoxalines.

Lingaiah Nagarapu et al have been reported a Polyethylene glycol (PEG-400) mediated synthesis of quinoxalines (Scheme 5.4).¹⁷

![Scheme 5.4](image)

4) Gallium(III) triflate-catalyzed synthesis of quinoxaline.

Jing-Jing Cai et al have been reported a Gallium(III) triflate-catalyzed synthesis of quinoxaline derivatives (Scheme 5.5).¹⁸
5) **Molecular iodine as the catalyst for a one-pot synthesis of quinoxaline.**

Rajesh S. Bhosale et al also reported use of molecular iodine as the catalyst for a one-pot synthesis of quinoxaline derivatives at room temperature (Scheme 5.6).\(^{19}\)

![Scheme 5.5]

6) **Synthesis of quinoxaline under microwave irradiation.**

K. Padmavathy et al synthesis of quinoxalines, performed in two stages or as a one-pot reaction, starting from ketones via their \(\alpha\)-hydroxylimino ketone derivatives, and condensation of the latter with 1,2- diaminobenzene (Scheme 5.7).\(^{20}\)

![Scheme 5.6]

7) **Synthesis of quinoxaline using \(\beta\)-cyclodextrin.**

B. Madhav, S et al have been synthesized the various quinoxalines for the first time in the presence of \(\beta\)-cyclodextrin in water (Scheme 5.8).\(^{21}\)
8) Silica supported synthesis of quinoxaline.
Khodabakhsh Niknam et al reported the synthesis of The reaction of 3-mercaptopropylsilica (MPS) and chlorosulfonic acid in chloroform afforded silica bonded S-sulfonic acid (SBSSA), which was used as a catalyst for the room temperature synthesis of quinoxaline derivatives from 1,2-diamino compounds and 1,2-dicarbonyl compounds (Scheme 5.9).

9) Proline catalysed synthesis of quinoxaline.
Majid M. Heravi et al also have been reported the synthesis of quinoxaline Zn[(L)proline] was found to be an effective catalyst for the very fast synthesis of quinoxaline derivatives from the condensation of the o-phenylenediamines and 1,2-dicarbonyl compounds at room temperature (Scheme 5.10).
Limitations of Literature methods.

- Use of acid.
- Use of metals
- Create environmental issue
- Generate toxic waste

5.2.3 OBJECTIVE OF WORK:
The purpose of this study is to explore the scope and limitations of glycerol as an alternative green reaction medium. In this sense and due to our interest on green protocols correlated to the heterocyclic chemistry, we describe herein the use of glycerol as a green solvent for the preparation of quinoxaline via condensation reaction.

The previous survey illustrates biological significant of a variety of substituted quinoxaline which proved to possess wide range of biological activities.

On the light of these findings, the present work focuses on the synthesis of certain quinoxaline derivatives. Hence, a further investigation was adopted to predict the effect of changing the solvent.

5.2.4 DESIGN AND DEVELOPMENT:
Though there are many methods reported for synthesis of quinoxaline but most of the methods are having limitations as mentioned in above from environmental point of view. Therefore still there is broad scope for development of new green method for the quinoxaline synthesis, so to overcome above mentioned drawbacks. Efforts has
been done to develop a new green method for direct synthesis of quinoxaline which can overcome some of the limitations of existing methods in terms of safety, reaction time, yield, and cost of reagents.

Now, a day glycerol has played a prominent role in the ecological system as green solvent. We have tried to extend these green properties of glycerol solvent for the condensation of 1,2 diamine with 1,2 dicarbonyl compounds, and expected that it could be cyclised by glycerol and can able to give quinoxaline, without applying any use of acid or any catalyst.

Based on this aspect the model reaction was carried out by using o-phenylenediamine, and benzil in a glycerol, and reaction was monitored by TLC.

Reaction went to completion after 4 h. After completion of reaction, and work up, products containing a mixture of compounds were isolated. These compounds were separated by column chromatography & characterization were carried out by using IR and NMR techniques and their structure were elucidated as 2,3 diphenylquinoxaline. The isolated yield was 74% as shown in (Scheme 5.11).

So for our preliminary study, we had successfully developed a simple ecofreindly method for synthesis of quinoxaline, using very cheap and readily available solvent, i.e. glycerol. In proposed intensified process all the reaction conditions are feasible and mild from industrial point of view. All the reagents commercially available and conditions are easy to handle.

![Scheme 5.11](image-url)
5.2.5 **EXPERIMENTAL:**

*General procedure for synthesis of quinoxaline derivative:*

**Table 2, entry 1: 2,3-Diphenylquinoxaline**

To a stirred solution of *o*-phenylenediamine (0.9 mmol, 0.1 gm) in H₂O (2 mL), glycerol (5 ml) was added, and the reaction mixture was heated to 90°C followed by addition of benzil (0.9 mmol, 0.1 gm). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. When all the starting material had been consumed, the reaction was quenched with water (10 mL) and extracted with ethyl acetate (2 X 10 mL). The organic phase was separated and dried over anhydrous Na₂SO₄ and evaporated under reduced pressure to give crude product. The pure product was isolated by silica gel column chromatography using (EtOAc: hexane, 1:9); 0.19g (75%).

M. P. 127–128°C (Lit m.p: 127°C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 8.2 (m, 2H), 7.79 (m, 2H), 7.5 (m, 4H), 7.39 (m, 6H); IR (KBr) (cm⁻¹): 3055, 1541, 1345, 768, 729

**Table 2, Entry 2: 6-chloro-2,3-diphenylquinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to gave the product with 0.164g, (74%) as White solid; m.p. 124–126°C; ¹H NMR (60 MHz, CDCl₃): δ 8.19-8.15 (m, 1H, ArH), 8.14-8.07 (m, 1H, ArH), 7.74-7.67 (m, 1H, ArH), 7.55-7.40 (m, 4H, ArH), 7.42-7.30 (m, 6H, ArH); IR (KBr) vmax/cm⁻¹: 3060, 1544, 1350, 770

**Table 2, Entry 3: 6-nitro-2,3-diphenylquinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to gave the product with 0.177g, (83%) as yellow powder, m.p. 194-195°C; ¹H NMR (CDCl₃, 60 MHz): δ 9.08 (d, 1H), 8.53 (m, 1H), 8.30 (d, 1H),
7.55-7.58 (m, 4H), 7.35-7.44 (m, 6H); IR (KBr) v_max/cm⁻¹: 3439, 1614, 1520, 1397, 1340, 699.

**Table 2, Entry 4: 6-methyl-2,3-diphenylquinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol,) and the remaining procedure same as general procedure to gave the product with 0.152g, (63%) as white solid, m.p. 135-137°C, ¹H NMR (CDCl₃, 60 MHz): δ 8.07 (d, 1H), 7.96 (s,1H), 7.50-7.53 (m, 5H), 7.32-7.35 (m, 6H), 2.62 (s, 3H); IR (KBr) v_max/cm⁻¹: 3053, 1615, 1488, 1447, 1341, 670.

**Table 2, Entry 5: 2,3-bis(4-methoxyphenyl)quinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol,) and the remaining procedure same as general procedure to gave the product with 0.221g, (70%) as white solid, m.p. 148-150°C; ¹H NMR (CDCl₃, 60 MHz): δ 8.13 (m, 2H), 7.73 (m, 2H), 7.50 (d, 4H), 6.88 (d, 4H), 3.84 (s, 6H); IR (KBr) v_max/cm⁻¹: 2930, 2836, 1605, 1511, 1344, 1293, 1246, 1173, 833.

**Table 2, Entry 6: 2,3-bis(4-methoxyphenyl)- 6-chloroquinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol,) and the remaining procedure same as general procedure to gave the product with 0.190g, (72%) as Pale yellow solid, m.p. 150-151°C; ¹H NMR (CDCl₃): δ 3.90 (s, 6H), 6.79 (m, 4H), 7.48-7.57 (m, 4H), 7.72 (m, 1H), 8.10-8.16 (m, 2H); IR (KBr): V_max cm⁻¹ 3442, 3354, 3240, 2913, 1634, 1589, 1562.

**Table 2, Entry 7: 2,3-bis(4-methoxyphenyl)-6-nitroquinoxaline**

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol,) and the remaining procedure same as general procedure to gave the product with 0.189g, (75%) as yellow powder, m.p. 192-193°C; ¹HNMR (CDCl₃, 60 MHz) δ(ppm): 9.1 (d, 1H), 8.49 (m, 1H), 8.24 (d, 1H), 7.56 (m, 4H), 6.98 (d, 4H), 3.9 (s, 6H); IR (KBr) v_max (cm⁻¹): 2924, 1337, 1169, 1021, 835.
Table 2, Entry 8: 2,3-bis(4-methoxyphenyl)-6-methylquinoxaline

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to give the product with 0.215g, (74%) as White solid, m.p. 126-127°C; ¹H NMR (CDCl₃, 60 MHz): δ 8.00 (d, 1H), 7.90 (s, 1H), 7.46 - 7.56 (m, 5H), 6.87 (d, 4H), 3.83 (s, 6H), 2.59 (s, 3H); IR (KBr) νmax/cm⁻¹: 2925, 2835, 1606, 1343, 1292, 1248, 1175, 833

Table 2, Entry 9: 2,3-di-2-furylquinoxaline

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to give the product with 0.169g, (70%) as Pale brown solid, m.p.133-134°C; ¹H NMR (CDCl₃, 60 MHz): δ 8.12 (m, 2H), 7.72 (m, 2H), 7.61 (s, 2H), 6.66 (d, 2H), 6.55 (s, 2H); IR (KBr) νmax/cm⁻¹: 3103, 1566, 1484, 1397, 1328, 755

Table 2, Entry 10: 6-chloro-2,3-di-2-furylquinoxaline

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to give the product with 0.149g, (72%) as Brown solid, m.p.125-126°C; ¹H NMR (60 MHz, CDCl₃): δ 8.14-8.00 (m, 2H, ArH), 7.70-7.64 (m, 1H, ArH), 7.64-7.56 (s, 2H, furan-H), 6.72-6.50 (m, 4H, furan-H);IR (KBr): Vmax cm⁻¹ 3108, 1568, 1488, 1399, 1332, 755.

Table 2, Entry 11: 2,3-di-2-furyl-6-nitroquinoxaline

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as general procedure to give the product with 0.150g, (75%) as Orange solid, m.p. 165-166°C; ¹H NMR (CDCl₃, 60 MHz): δ 8.98 (d, 1H), 8.47 (m, 1H), 8.20 (d, 1H), 7.65-7.68 (m, 2H), 6.85 (m, 2H), 6.60-6.63 (m, 2H); IR (KBr) νmax/cm⁻¹: 3388, 1574, 1522, 1477, 1337, 749

Table 2, Entry 12: 2,3-di-2-furyl-6-methylquinoxaline

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H₂O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol.) and the remaining procedure same as
general procedure to gave the product with 0.146g, (65%) as Brown solid, m.p.116-117°C; \(^1\)H NMR (CDCl\(_3\), 60 MHz): \(\delta\) 8.01 (d, 1H), 7.91 (s, 1H), 7.56-7.61 (m, 3H), 6.55 ca. 6.62 (m, 4H), 2.58 (s, 3H); IR (KBr) \(v_{max}/\text{cm}^{-1}\): 3106, 2918, 1485, 1323, 747

Table 2, Entry 13: dibenzo(a,c)phenazine

To a stirred solution of opd (0.1g, 1 equiv., 0.93 mmol.), in glycerol:H\(_2\)O (5:2 mL) was added a benzil (0.1g, 1 equiv., 0.9 mmol,) and the remaining procedure same as general procedure to gave the product with 0.194g, (75%) as white powder, m.p.124-126°C; \(^1\)H NMR (60 MHz, CDCl\(_3\)) ppm \(\delta\) 7.51-7.66 (m, 6H), 8.10-8.13 (m, 2H), 8.33 (d, 2H), 9.18 (d, 2H); IR (KBr): \(V_{max}\) cm\(^{-1}\) 3351, 3228, 2900, 1630, 1578, 1559, 1410

5.2.6 RESULT AND DISCUSSION:

In a model condensation reaction, benzil and 1,2- diaminobenzene in glycerol were heated at 50°C, (Table 1, entry 2). The progress of the reaction was monitored by TLC. After completion of the reaction after 8 h, an aqueous work-up afforded 2,3-diphenylquinoxaline 2a (50% yield).

To optimise the reaction conditions to afford the desired quinoxoline in good yield, the same reaction was conducted at different temperature and it was observed that as slightly increasing temperature, the rate of reaction increases and good amount of yield was obtained at 90°C within 4 h (Table 1, entry 6). The reaction was
unsuccessful when carried out at room temperature, even after 24 h (Table 1, entry 1).

To evaluate the use of this procedure, a variety of substituted o-phenylenediamines were condensed with 1,2-disubstituted 1,2-dicarbonyl compounds. The results are shown in Table 2. It was observed that the starting materials were consumed after long reaction time as indicated by TLC analysis. Again the advantage of this protocol is, after the work-up procedure, glycerol is successfully recovered and reused for another reaction without affecting the yields.

Next, we also carried out the same reaction in glycerol–methanol mixture and recovered the desired product in the yield comparable to that obtained in glycerol–water system. Thus the glycerol–methanol is also a suitable solvent for this transformation. A variety of aldehydes were condensed with different 1,2 dicarbonyl compound and the results are summarised in Table 2.

Scheme 5.13

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Rxn. condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glycerol</td>
<td>R T</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Glycerol</td>
<td>50°C</td>
<td>8</td>
<td>50</td>
</tr>
<tr>
<td>3</td>
<td>Glycerol:H₂O</td>
<td>R T</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>4</td>
<td>Glycerol:H₂O</td>
<td>50°C</td>
<td>8</td>
<td>60</td>
</tr>
</tbody>
</table>
Table 2 Reaction of 1,2 diarylamines with 1,2 diketones in presence of glycerol

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2 Diaminobenzene</th>
<th>1,2 Diketone</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield %</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>( \text{NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} )</td>
<td>( \text{N} \text{N} \text{N} )</td>
<td>4</td>
<td>75</td>
</tr>
<tr>
<td>2</td>
<td>( \text{Cl-NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} )</td>
<td>( \text{Cl-N} \text{N} \text{Cl} )</td>
<td>5</td>
<td>74</td>
</tr>
<tr>
<td>3</td>
<td>( \text{O}_2\text{N-NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} )</td>
<td>( \text{O}_2\text{N-N} \text{N} \text{N} )</td>
<td>4</td>
<td>83</td>
</tr>
<tr>
<td>4</td>
<td>( \text{H}_3\text{C-NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} )</td>
<td>( \text{N} \text{O}_2\text{C-N} )</td>
<td>4</td>
<td>63</td>
</tr>
<tr>
<td>5</td>
<td>( \text{NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} \text{O} )</td>
<td>( \text{N} \text{N} \text{N} \text{N} \text{O} )</td>
<td>4</td>
<td>70</td>
</tr>
<tr>
<td>6</td>
<td>( \text{Cl-NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} \text{O} )</td>
<td>( \text{Cl-N} \text{O}_2\text{N-N} \text{N} )</td>
<td>6</td>
<td>72</td>
</tr>
<tr>
<td>7</td>
<td>( \text{O}_2\text{N-NH}_2 \text{NH}_2 )</td>
<td>( \text{O} \text{O} \text{O} \text{O} )</td>
<td>( \text{O}_2\text{N-N} \text{N} \text{N} \text{O} )</td>
<td>4</td>
<td>75</td>
</tr>
</tbody>
</table>
5.2.6.1 Mechanism of the reaction

*Reaction conditions: 1,2-diamine (1 equiv), 1,2-diketone (1 equiv). Isolated yields after column chromatography and structures were confirmed by comparison of m.p. with authentic materials.*
5.2.7 **SUMMARY AND CONCLUSION:**

The chemistry of heterocyclic compounds has been an interesting field of study for a long time. Quinoxalines are well known and important N-containing heterocyclic compound, containing a ring complex made up of a benzene ring and a pyrazine ring, so called benzopyrazine. A number of synthetic strategies have been developed for the preparation of substituted quinoxalines. Quinoxaline derivatives display a broad spectrum of biological properties ranging from DNA cleaving drugs, antimicrobial and cancer drugs, to antibiotic and antitumor activity. Which have made them privileged structures in combinatorial drug discovery libraries.

In summary, we have described an efficient protocol for preparing quinoxaline derivatives using glycerol as a solvent. The advantages of the present method lie in using economic and environmentally benign glycerol as solvent, no use of catalyst, mild reaction conditions, and good yields. This protocol suitable for large-scale synthesis, providing a valuable synthetic tool for industrial applications.
5.2.8 REFERENCES:


Development and Application of New Methodologies for Synthesis of Bioactive Molecules


5.2.9 SPECTRA:

Table 2, entry 1
Table 2, entry 1
Table 2, entry 4
Table 2, entry 4
Table 2, entry 3
Table 2, entry 3
Table 2, entry 13
Table 2, entry 13
SECTION-II Synthesis of Benzoxazole and Benzimidazole

5.2.1 INTRODUCTION:

5.2.2 LITERATURE SURVEY:

5.2.2.1 Synthesis of Benzoxazole

5.2.2.2 Synthesis of Benzimidazole

5.2.3 DESIGN AND DEVELOPMENT:

5.2.4 EXPERIMENTAL:

5.2.5 RESULT AND DISCUSSION:

5.2.5.1 Mechanism of the reactions.

5.2.6 SUMMERY AND CONCLUSION:

5.2.7 REFERENCES:

5.2.8 SPECTRA:
5.2.1 INTRODUCTION:

The main objective of the medicinal chemistry is to synthesize the compounds that show promising activity as therapeutic agents with lower toxicity. Benzoxazole and benzimidazole derivatives are very useful compound with well known biological activity.

Benzoxazoles\(^1\) and Benzimidazoles,\(^2\) are privileged organic compounds due to their recognition in biological and therapeutic activities (Figure 1). Recent medicinal chemistry applications of these heterocyclic compounds include 5-lipoxygenase inhibitor,\(^3\) poly(ADP-ribose)polymerase (PARP) inhibitor,\(^3\) factor Xa(FXa) inhibitor,\(^3\) histamine H1-receptor,\(^3\) 5-HT\(^3\)-receptor agonist\(^2,3\) HIV reverse transcriptase inhibitor L-697,695,\(^3\) anticancer agent NSC-693638,\(^3\) and orexin-1 receptor antagonist SB-334867\(^3\).

Other applications of these compounds include their use as anti-inflammatory,\(^4\) antimicrobial,\(^4\) antibacterial,\(^5\) and antiviral\(^6\) agents. So development of general methods for the synthesis of these compounds is thus highly relevant for drug discovery.
Figure 1 Examples of some biologically active compounds

Solvents are used daily in numerous industrial processes as reaction medium, in separation procedures, and as diluters. As solvents are responsible for a large part of the waste and pollution generated by chemical processes, a key factor to enabling a sustainable chemical process is solvent selection. Due to environmental concerns, safety considerations, reduction of costs, and the simplicity of the process, reactions using green solvents have drawn great attention in recent years.
5.2.2 LITERATURE SURVEY:

5.2.2.1 Synthesis of Benzoxazole

To date, three commonly used strategies for the synthesis of 2-substituted benzoxazoles have been developed. The first approach is through condensation of 2-aminophenols with carboxylic acids in the presence of a strong acid at high temperature. The drastic reaction conditions employed therein often cause low yields and side reactions. The second method is via the oxidative cyclization of phenolic Schiff bases promoted by various oxidants such as 2,3-dichloro-5,6-dicyanobenzoquinone, PhI(OAc)₂, ThClO₄, PCC, I₂, K₂S₂O₈, Pd(OAc)₂/O₂, HAuC₅l₄•H₂O/O₂, and activated carbon/ O₂. The third approach to 2-substituted benzoxazoles is the intramolecular cross-coupling of 2-bromoanilides promoted by copper(I)/(II), iron(III) complex, or copper(II) oxide nanoparticles. These coupling reactions usually proceed under mild conditions with wide substrate scope.

1) Iron-Catalyzed Intramolecular O-Arylation

Iron-catalyzed intramolecular O-arylation, which represents a practical and straightforward approach toward 2-aryl substituted benzoxazole derivatives (Scheme 5.1).

![Scheme 5.1]

2) Copper-Catalyzed Synthesis of Substituted Benzimidazoles, and Benzoxazoles
The synthesis of substituted benzimidazoles, and benzoxazoles is described via intramolecular cyclization of \( o \)-bromoaryl derivatives using copper (II) oxide nanoparticles in DMSO under air (Scheme 5.2).

\[ \text{Scheme 5.2} \]

3) Synthesis of 2-arylbenzoxazoles by oxidation with \( o \)-iodoxybenzoic acid (IBX)

The preparation of 2-arylbenzoxazoles has been developed based on the oxidation of phenolic Schiff bases with \( o \)-Iodoxybenzoic acid (IBX) (Scheme 5.3).\(^{13}\)

\[ \text{Scheme 5.3} \]

4) One-pot synthesis of 2-arylbenzoxazoles using hydrogen tetrachloroaurate as catalyst under oxygen atmosphere

One-pot synthesis of 2-arylbenzoxazoles, which were directly synthesized from 2-aminophenol and aldehydes catalyzed by hydrogen tetrachloroaurate (HAuCl\(_4\)·4H\(_2\)O)
under an oxygen atmosphere with anhydrous tetrahydrofuran (THF) as solvent or in solvent-free condition (Scheme 5.4).^{14}

![Scheme 5.4]

5) A Synthesis of 2-Substituted Benzoxazoles via RuCl₃·3H₂O Catalyzed Tandem Reactions in Ionic Liquid.

Synthesis of 2-substituted benzoxazoles through RuCl₃·3H₂O catalyzed, air oxidized tandem reactions of 2-aminophenols and aldehydes in [bmim]BF₄ was developed (Scheme 5.5).^{15}

![Scheme 5.5]

6) Phenylboronic acid catalyzed-cyanide promoted, one-pot synthesis of 2-(2-hydroxyphenyl)benzoxazole derivatives

phenylboronic acid catalyzed, cyanide promoted synthesis of 2-(2-hydroxyphenyl) benzoxazoles from salicylaldehydes and o-aminophenols is described (Scheme 5.6).^{16}

![Scheme 5.6]
5.2.2.2 Synthesis of Benzimidazole

Benzimidazoles have also been synthesized by a number of methods and using a variety of starting materials. The reported methods involved the condensation of o-phenylenediamine with different substituted aldehydes in the presence of various transition metal–triflate salts such as Sc(OTf)₃ or Yb(OTf)₃,¹⁷a,b sulphanic acid,¹⁷c H₂O₂–HCl,¹⁷d FeBr₃,¹⁷e KHSO₄¹⁷f and HfCl₄¹⁷g to afford benzimidazoles. However, these methods suffer from many drawbacks such as long reaction time, usage of expensive and corrosive reagent, high temperature with lesser yield products.

1) Copper- and Palladium-Catalyzed Intramolecular Aryl Guanidinylation.

The formation of 2-aminobenzimidazoles via intramolecular C-N bond formation between an aryl halide and a guanidine moiety can be achieved using either copper or palladium catalysis (Scheme 5.7).¹⁸

![Scheme 5.7](image)

2) Ionic liquid mediated synthesis.

A regioselective one-pot synthesis of 2-aryl benzimidazoles, benzoxazoles and benzthiazoles has been achieved in excellent isolated yields under ambient conditions using the ionic liquids, 1-butylimidazolium tetrafluoroborate ([Hbim]BF₄) and 1,3-di-n-butylimidazolium tetrafluoroborate ([bbim]BF₄) as reaction media and promoters (Scheme 5.8).¹⁹
3) **The synthesis of benzimidazoles using air as the oxidant.**

Direct one-step synthesis of various benzimidazoles from phenylenediamines and aldehydes is described using air as the oxidant (Scheme 5.9).²⁰

4) **Synthesis using polymer supported reagent.**

Synthesis of Benzimidazole and Benzo[a/(thia)zole Libraries through Polymer-Supported Hypervalent Iodine Reagent (Scheme 5.10).²¹

5) **β-Cyclodextrin-promoted synthesis of 2-phenylbenzimidazole in water using air as an oxidant.**
β-Cyclodextrin-promoted conversion of \( o \)-phenylenediamine and benzaldehyde to 2-phenylbenzimidazole is described using air as an oxidant (Scheme 5.11).\(^{22}\)

![Scheme 5.11]

6) **L-Proline catalyzed selective synthesis of 2-aryl-1-arylmethyl-1\(H\)-benzimidazole.**

L-Proline (10 mol \%) was found to be a versatile organocatalyst for the selective synthesis of 2-aryl-1-arylmethyl-1\(H\)benzimidazoles from a wide range of substituted \( o \)-phenylenediamines and aldehydes (Scheme 5.12).\(^ {23}\)

![Scheme 5.12]

7) **Microwave-Assisted Synthesis of Benzimidazoles, Benzoazoles, and Benzothiazoles from Resin-Bound Esters.**

Solid-phase synthesis of benzimidazoles, benzoazoles, and benzothiazoles libraries by microwave-assisted condensation of resin-bound esters with 1,2-phenylenediamines, 2-aminophenols, and 2-aminothiophenols was developed (Scheme 5.13).\(^ {24}\)
However, the major drawbacks of these protocols are use of specially made starting materials, expensive and/or toxic catalyst, and adverse impact on the environment due to the use of volatile organic solvents.

### 5.2.2 DESIGN AND DEVELOPMENT:

Honestly, the rationale of this study is to investigate the scope and limitations of glycerol as alternative green reaction medium. In this sense and due to our interest on green protocols correlated to the heterocyclic chemistry, we describe herein the use of glycerol as a green solvent for the preparation of benzoxazole, and benzimidazole via condensation reaction.

Intended, our preliminary condensation reaction studies, we carried out the reaction between 2-aminophenol and benzaldehyde using glycerol as a solvent to afford the desired benzoxazole (Scheme 5.14). A mixture of 2-aminophenol (1.0 mmol) and benzaldehyde (1.0 mmol) in aqueous glycerol was stirred at room temperature. Whereas the reaction using \( \text{\( o \)} \)-phenylenediamine instead of 2-aminophenol (Scheme 5.15). The reaction worked well using various substituted aldehydes furnishing the corresponding benzimidazoles.

![Scheme 5.13](image-url)
5.2.3 **EXPERIMENTAL:**

*General procedure for synthesis of benzoxazole derivative:*

**Table 2; entry 1:** 2-Phenylbenzoxazole

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of benzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 102-103°C (Lit\textsuperscript{25a} m.p: 102°C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 60 MHz) \( \delta \) (ppm): 8.32 (d, 2H), 7.86-7.79 (m, 1H), 7.67-7.53 (m, 4H), 7.44-7.36 (m, 2H); IR (KBr) (cm\textsuperscript{-1}): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

**Table 2; entry 2:** 2-p-Tolylbenzoxazole
To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-methyl benzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 114-115°C (Lit⁷ m.p: 118-119°C); ^1H NMR (CDCl₃, 60 MHz) δ (ppm): 8.5 (m, 2H), 7.76-7.73 (m, 1H), 7.55-7.52 (m, 1H), 7.33-7.28 (m, 4H), 2.40 (s, 3H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

Table 2; entry 3: 2-p-nitrobenzoxazole

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-nitro benzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 270-272°C (Lit⁸ m.p: 266-268°C); ^1H NMR (CDCl₃, 60 MHz) δ (ppm): 8.56-7.83 (m, 8H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

Table 2; entry 4: 2-p-Chlorobenzoxazole

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-chlorobenzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 150-152°C (Lit⁹ m.p: 147°C); ^1H NMR (CDCl₃, 60 MHz) δ (ppm): 8.08-8.12 (m, 2H), 7.61-7.71 (m, 1H), 7.52-7.46 (m, 1H), 7.44-7.39 (m, 2H), 7.31-7.25 (m, 2H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020, 900.

Table 2; entry 5: 2-p-Bromobenzoxazole
To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-bromo benzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 155-156°C (Lit¹⁰ m.p: 157-158°C);¹H NMR (CDCl₃, 60 MHz) δ (ppm): 8.16 (m, 2H), 7.84-7.78 (m, 1H), 7.75-7.68 (m, 2H), 7.66-7.59 (m, 1H), 7.45-7.37 (m, 2H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020, 600.

Table 2; entry 6: 2-(4-Methoxyphenyl)benzoxazole

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-methoxy benzaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 97-98°C (Lit⁶ m.p: 98°C);¹H NMR (CDCl₃, 60 MHz) δ (ppm): 8.2 (m, 2H), 7.74-7.71 (m, 1H), 7.55-7.52 (m, 1H), 7.33-7.28 (m, 2H), 7.01 (d, 2H), 3.86 (s, 3H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

Table 2; entry 7: 2-(Thien-2-yl)benzoxazole

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of thiophene-2-aldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 80-82°C (Lit⁶ m.p: 81-82°C);¹H NMR (CDCl₃, 60 MHz) δ (ppm): 7.9 (d, 1H), 7.74-7.71 (m, 1H), 7.55-7.52 (m, 2H), 7.34-7.31 (m, 2H), 7.17 (d, 1H); IR (KBr) (cm⁻¹): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

Table 2; entry 8: 2-(Furan-2-yl)benzoxazole
To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of furan-2-aldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 88-90°C (Lit\textsuperscript{11} m.p: 89-90°C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 60 MHz) δ (ppm): 7.75 (d, 1H), 7.66 (d, 1H), 7.55 (d, 1H), 7.38-7.33 (m, 2H), 7.27 (d, 1H) 6.60 (m, 1H); IR (KBr) (cm\textsuperscript{-1}): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

**Table 2; entry 9: 2-(1′-phenylethenyl)benzoxazole**

To a stirred solution of 2-aminophenol (0.1 gm, 0.92 mmol) in methanol (1 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of cinnamaldehyde (0.1 gm, 0.92 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 85-86°C (Lit\textsuperscript{12} m.p: 83-85°C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 60 MHz) δ (ppm): 8.6-7.82 (m, 8H), 7.58 (d, 1H), 7.42 (d, 1H); IR (KBr) (cm\textsuperscript{-1}): 3060, 2961, 1552, 1447, 1346, 1319, 1243, 1194, 1054, 1020.

**General procedure for synthesis of benzimidazole derivative:**

**Table 2, entry 10: 2-Phenylbenzimidazole**

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H\textsubscript{2}O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of benzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 294-295°C (Lit\textsuperscript{25b} m.p: 295°C); \textsuperscript{1}H NMR (CDCl\textsubscript{3}, 60 MHz) δ (ppm): 12.92 (s, 1H), 8.20 (d, Hz, 2H), 7.68 (d, Hz, 1H), 7.58-7.48 (m, 4H), 7.23 (d, 2H); IR (KBr) (cm\textsuperscript{-1}): 3421, 3296, 1587, 1512, 1338, 852, 744, 708
Table 2; entry 11: 2-(p-methylPhenyl)benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H₂O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-methyl benzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 268-270°C (Lit² m.p: 269-270°C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 12.90 (s, 1H), 8.00-8.08 (m, 2H), 7.60-7.20 (m, 6H), 2.30 (m, 3H); IR (KBr) (cm⁻¹): 3450, 3300, 1597, 1505, 1342, 850, 750, 690.

Table 2; entry 12: 2-(3-Nitrophenyl)-1H-benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H₂O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-nitro benzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 321-322°C (Lit³ m.p: 320 °C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 13.27 (bs, 1H), 8.36-8.41 (m, 4H), 7.7 (bs, 1H), 7.57 (bs, 1H), 7.23 (m, 2H); IR (KBr) (cm⁻¹): 3391, 3250, 1540, 1495, 1300, 856, 744, 708

Table 2; entry 13: 2-(4-Chlorophenyl)-1H-benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H₂O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-chlorobenzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 292-295°C (Lit³ m.p: 291°C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 12.5 (s, 1H), 8.20 (m, 2H), 8.10 (d, 1H), 7.6 (d, 2H), 7.3 (m, 2H), 7.10 (m, 2H); IR (KBr) (cm⁻¹): 3041, 1450, 1402, 1280, 965, 750
Table 2; entry 14: 2-(4-Bromophenyl)-1H-benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H$_2$O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-bromo benzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 296-298°C (Lit$^3$ m.p: 298°C); $^1$H NMR (CDCl$_3$, 60 MHz) δ (ppm): 12.9 (bs, 1H), 8.10 (d, 2H), 7.74 (d, 2H), 7.6 (m, 2H), 7.20 (m, 2H); IR (KBr) (cm$^{-1}$): 3466, 3396, 1639, 1594, 1312, 1274, 1084, 764

Table 2; entry 15: 2-(4-Methoxyphenyl)-1H-benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H$_2$O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of p-methoxy benzaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 225-226°C (Lit$^3$ m.p: 224°C); $^1$H NMR (CDCl$_3$, 60 MHz) δ (ppm): 12.7 (s, 1H), 8.00-8.08 (m, 2H), 7.20-7.6 (m, 6H), 3.81 (m, 3H); IR (KBr) (cm$^{-1}$): 3045, 1480, 1400, 1300, 1080, 985, 760

Table 2; entry 16: 2-(Furan-2-yl)-1H-benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H$_2$O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of furfuraldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 306-308°C (Lit$^4$ m.p: 310-312°C); $^1$H NMR (CDCl$_3$, 60 MHz) δ (ppm): 12.7 (bs, 1H), 7.94-7.93 (d, 1H), 7.58-7.54 (m, 2H), 7.21-7.18 (m, 2H), 6.74-6.72 (m, 2H); IR (KBr) (cm$^{-1}$): 3040, 1490, 1400, 1320, 1100, 980, 760

Table 2; entry 17: 2-(Thien-2-yl)-1H-benzimidazole
To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H₂O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of thiophene2-aldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 285-287°C (Lit⁴ m.p: 288°C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 12.7 (s, 1H), 7.85-7.83 (m, 1H), 7.73-7.69 (m, 1H), 7.57-7.53 (m, 1H), 6.82-7.03 (m, 3H); IR (KBr) (cm⁻¹): 3045, 1480, 1400, 1300, 1080, 985, 760

**Table 2; entry 18:** 2-(1'-phenylethenyl)benzimidazole

To a stirred solution of o-phenylenediamine (0.1 gm, 0.93 mmol) in H₂O (2 mL), glycerol (5 mL) was added and the reaction mixture was heated to 90°C, followed by addition of cinnamaldehyde (0.1 gm, 0.93 mmol). The reaction mixture was stirred vigorously at 90°C. The progress of reaction was monitored by TLC. After completion of reaction, the product was isolated as above procedure.

M.p. 201-203°C (Lit⁵ m.p: 202°C); ¹H NMR (CDCl₃, 60 MHz) δ (ppm): 12.7 (s, 1H), 7.65-7.8 (m, 3H), 7.47-7.69 (m, 2H), 7.41-7.46 (m, 2H), 7.33-7.39 (m, 1H), 7.24 (d, 1H), 7.16-7.21 (m, 2H); IR (KBr) (cm⁻¹): 3045, 1643, 1588, 1524, 1493, 1422, 1300, 1080, 985, 760 cm⁻¹

### 5.2.4 RESULT AND DISCUSSION:

For our initial condensation reaction studies, we carried out the reaction between 2-aminophenol and benzaldehyde using glycerol as a solvent to afford the desired benzoazole (Scheme 5.15). A mixture of 2-aminophenol (1.0 mmol) and benzaldehyde (1.0 mmol) in aqueous glycerol was stirred at room temperature. It was observed that the starting materials were consumed after long reaction time as indicated by TLC analysis.

To optimise the reaction conditions and to afford the desired benzoazole in good yield, the same reaction was conducted at different reaction temperature and it was
observed that as temperature increases, rate of reaction increases and good amount of yield was obtained at 90°C within 4 h (Table 1; entry 6). Again the advantage of this protocol is, after the work-up procedure, glycerol is successfully recovered and reused for another reaction without affecting the yields.

In order to study the effect of solvent on the rate of the reaction, we executed the same reaction in absence of water, but the yield of the product decreased drastically (Table 1, entry 2). Next, we also carried out the same reaction in glycerol: methanol mixture and recovered the desired product in the yield comparable to that obtained in glycerol: water system. Thus the glycerol: methanol is a suitable solvent for this transformation. A variety of aldehydes were condensed with 2-aminophenol and the results are summarised in Table 2.

![Scheme 5.15: Preparation of 2-arylbenzoxazole]

To expand the synthetic scope of this protocol, we carried out the reaction using o-phenylenediamine instead of 2-aminophenol (Scheme 5.16). The reaction worked well using various substituted aldehydes furnishing the corresponding benzimidazoles in moderate to good yields (Table 2; entries 10–18). In this case Glycerol:water system works well.

![Scheme 5.16: Preparation of 2-arylbenzimidazole]
To study the generality of this new protocol, a variety of aromatic and heterocyclic aldehydes with various substitution patterns were reacted with 2-aminophenol as well as \( \text{O-phenylenediamine} \) under the optimized conditions to give benzoxazoles and benzimidazoles respectively. As can be seen from Table 1, most of the substrates afforded good yields of the corresponding benzoxazoles and benzimidazoles. Heterocyclic aromatic aldehyde compounds were also suitable for this transformation (Table 1; entries 7, 8, 17, 18) giving moderate yield.

To the best of our knowledge, the dominant mechanism for production of 2-phenylbenzoxazole is the oxidative cyclization of phenolic Schiff bases, which are derived from the condensation of 2-aminophenols and aldehydes. The preparation of arylbenzoxazoles through the oxidative cyclization of phenolic Schiff bases may involve three steps. The first step is the condensation between aromatic aldehyde 1 and \( \text{o-aminophenol} \) 2 to form Schiff base 3. The second step is the five-membered-ring formation from 3 to 4. The third step is the cyclisation of 4 to arylbenzoxazole 5. In steps 1 and 3, water is produced, and in the presence of water, the equilibrium of the reaction moves backwards. Therefore, removing water and increasing the stability of 2 under oxidative condition would be beneficial to the reaction yield and hence the result of 2-aminophenol with aldehyde in a model reaction was good in methanol: glycerol system rather than glycerol: water system. In the reaction system, a Schiff base was generated from the condensation between \( \text{o-aminophenol} \) and aromatic aldehyde in glycerol.

If we accept the aforesaid mechanism, one can expect the general effect of electron donating and electron withdrawing groups on the feasibility of the reaction. In this regard, aromatic aldehydes bearing electron donating groups on the benzene ring should increase the yield of the reaction while electron withdrawing groups should have an inverse effect. As we expect, aromatic aldehydes with electron donating substituents and \( \text{p-halogenated aromatic aldehydes} \) afforded 2-phenylbenzoxazole and 2-phenylbenzimidazole, which furnished comparable yields of the desired products (Table 2, entries 2, 4-6, 11, 13-15). On the other hand, with electron-withdrawing substituents also give moderate yield of the corresponding 2-
phenylbenzoxazole and 2-phenylbenzimidazole were obtained (Table 2, entry 3, 12). In addition, we explored the scope of the reaction with heterocyclic aromatic aldehyde compounds, and it was also suitable for this transformation (Table 1; entries 7, 8, 17, 18) giving moderate yield.

Further investigation indicates that α, β unsaturated aldehydes are also suitable for this reaction (Table 1; entries 9, 16) without affecting the geometry of a double bond. In general, the aromatic aldehydes containing electron-donating substituent react faster giving better yield as compared to the aromatic aldehydes containing electron-withdrawing substituent.

Table 1. Reaction of OPD^a (1 eqiv.) or o-aminophenol^b (1 eqiv.) with benzaldehyde(1 eqv.) in glycerol at different rxn. conditions.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>Rxn. condition</th>
<th>Time (h)</th>
<th>Yield (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Glycerol</td>
<td>R T</td>
<td>24</td>
<td>NR</td>
</tr>
<tr>
<td>2</td>
<td>Glycerol</td>
<td>50^0C</td>
<td>8</td>
<td>50</td>
</tr>
</tbody>
</table>
Table 2. Reaction of \( o \)-aminophenol and 1,2-diaminobenzene with aldehydes in presence of glycerol\(^a\)

<table>
<thead>
<tr>
<th>Entry</th>
<th>1,2 Diaminobenzene</th>
<th>Aldehyde</th>
<th>Product</th>
<th>Time (h)</th>
<th>Yield (^b) %</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{Ph}
\end{align*}
\] | 4         | 80             |
| 2     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{CH}_3
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{CH}_3
\end{align*}
\] | 5         | 75             |
| 3     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{NO}_2
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{NO}_2
\end{align*}
\] | 6         | 60             |
| 4     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{Cl}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{Cl}
\end{align*}
\] | 4         | 65             |
| 5     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{Br}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{Br}
\end{align*}
\] | 4         | 75             |
| 6     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{OCH}_3
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{OCH}_3
\end{align*}
\] | 6         | 82             |
| 7     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{S}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{S}
\end{align*}
\] | 5         | 60             |
| 8     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{F}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{F}
\end{align*}
\] | 6         | 65             |
| 9     | \[
\begin{align*}
\text{Ph} & \text{NH}_2 \\
\text{O} & \text{H}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{CHO} \text{Ph}
\end{align*}
\] | \[
\begin{align*}
\text{Ph} & \text{N} \text{O} \\
\text{Ph} & \text{Ph}
\end{align*}
\] | 5         | 70             |

\(^a\) NR = no reaction
<table>
<thead>
<tr>
<th>No.</th>
<th>Reaction conditions</th>
<th>Isolated yields</th>
<th>Structures</th>
</tr>
</thead>
<tbody>
<tr>
<td>10</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>2</td>
<td>70</td>
</tr>
<tr>
<td>11</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>2</td>
<td>75</td>
</tr>
<tr>
<td>12</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>13</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>14</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>3</td>
<td>60</td>
</tr>
<tr>
<td>15</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>2</td>
<td>65</td>
</tr>
<tr>
<td>16</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>17</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>3</td>
<td>55</td>
</tr>
<tr>
<td>18</td>
<td>1,2-diamine (1 equiv), aldehydes (1 equiv).</td>
<td>3</td>
<td>55</td>
</tr>
</tbody>
</table>

*Reaction conditions: 1,2-diamine (1 equiv), aldehydes (1 equiv). Isolated yields after column chromatography and structures were confirmed by comparison of m.p. with authentic materials.

### 5.2.5.1 MECHANISMS:
Development and Application of New Methodologies for Synthesis of Bioactive Molecules

Figure xx

X = NH₂, OH

X = NH, O
5.2.5 **SUMMARY AND CONCLUSION:**

Furthermore, product isolation and recycling of glycerol were conveniently achieved by means of liquid–liquid phase extractions with ethyl acetate. These results not only demonstrated the necessity of using glycerol as a promoting medium for organic reactions, but also avoided the use of catalyst, thus simplifying the work-up procedure and consequently increasing the greenness of the synthetic method. Note that in the case of technical grade glycerol, the presence of residual free fatty acid salts may play the role of catalyst, thus allowing the reaction to proceed better than in neat water.

*Advantages of glycerol for this reaction include*

(i) The non-assistance of acid catalysts, which not only simplifies the work-up procedure and minimizes the generation of waste, but also allows the use of acid-sensitive substrates;

(ii) Easy separation of the reaction products; and

(iii) No volatile organic solvent was used.
5.2.6 REFERENCES:


Development and Application of New Methodologies for Synthesis of Bioactive Molecules


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*Journal of Molecular Catalysis A: Chemical* 2004, 214,155  
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5.2.7 **SPECTRA:**

Table 2, entry 2
Table 2, entry 2
Table 2, entry 3

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Table 2, entry 3
Table 2, entry 10
Table 2, entry 13
Table 2, entry 11