CHAPTER-I

Synthesis of Hydrazones
1.1. Introduction:

A hydrazone is a class of organic compounds with the structure \( R_1R_2C=\text{NNH}_2 \). They are related to ketones and aldehydes by the replacement of the oxygen with the NNH\(_2\) functional group. They are formed usually by the action of hydrazine on ketones or aldehydes.\(^2,3\) Hydrazones are used not only to characterize aldehydes and ketones by derivatization with appropriate hydrazines,\(^4\) but they have also emerged as important synthons for several organic transformations\(^5\) the most remarkable being the Fischer indole synthesis.\(^6\) Hydrazones are of interest also because of their importance in analytical chemistry, medicine and industry. Especially, isonicotinhydrazide and its N-isopropyl acylhydrazone have been used as effective drugs in curing human tuberculosis in the past few years.\(^7\) They have been studied as chelating ligands for spectroscopic and fluorometric determination of trace elements.\(^8\) The chelation of several classes of aryl and hetaryl hydrazones with metals, especially iron\(^9\), has lead to their study as antiproliferative active agents against tumor cells.\(^10\) Recently some hydrazones have been found useful in treating sexual dysfunction.\(^11\) These compounds have interesting biological properties such as Anti-mycobacterial,\(^12\) Antimicrobial,\(^13-15\) Anti-tuberculosis,\(^16\) Anti-tumors,\(^17\) Anti-inflammatory,\(^18,19\) Anti-malarial,\(^20\) Anti-convulsants,\(^21\) and Anticancer-Anti HIV.\(^22\)

Hydrazones contain two connected nitrogen atoms of different nature and a C-N double bond that is conjugated with a lone electron pair of the terminal nitrogen atom. These structural fragments are mainly responsible for the physical and chemical properties of hydrazones. Both nitrogen atoms of the hydrazone group are nucleophilic, although the amino type nitrogen is more reactive. The carbon atom of hydrazone group has both electrophilic and nucleophilic character.\(^23\) Due to the capability to react with electropilic and nucleophilic reagents, hydrazones are widely used in organic synthesis, especially for the preparation of heterocyclic compounds. It is worth mentioning the synthesis of indoles according to the Fischer reaction,\(^24\) the synthesis of 4-thiazolidin-4-ones,\(^25\) the synthesis of azetidines \(^26\) by [2+2] cycloaddition and different syntheses of various five-membered heterocyclic compounds by 1,3-dipolar cycloaddition of azomethine imines\(^27\) that are formed by a 1,2-\(\text{H}\)-shift.

In past few years a library of 156 acylhydrazones was designed in order to evaluate the potential of this class of compounds as antimalerials and to study more detail the structure-activity relationship. In these, three acylhydrazones Fe chelators i.e. salicylaldehyde isonicotinoyl hydrazone (SIH), 2-hydroxy-1-naphthylaldehyde m-fluorobenzoyl hydrazone
(HNFBH) and pyridoxal isonicotinoyl hydrazone (PIH) show excellent antimalarial activity.\textsuperscript{28} As these compounds were orally effective and inexpensive.

\[
\text{SIH} \quad \text{HNFBH} \quad \text{PIH}
\]

Nowadays, substituted pyrazole-5-carbohydrazide hydrazone showed good inhibitory effects on the growth of A549 lung cancer cells.\textsuperscript{29}

\[
\text{Substituted 1H-pyrazole-5-carbohydrazide hydrazone}
\]

1.1.1 Review of literature:
A vast number of methods reported in the literatures for the synthesis of hydrazones due to their potent biological and material properties. This section summarized some of the important synthesis of hydrazones and their methods.

**Savini approach (1995)\textsuperscript{30}**
Savini et al. reported a number of pyruvic carboxaldehyde 2-quinolyhydrazones from 2-hydrazinoquinoline and pyruvic acid in methanol under reflux condition. All compounds evaluated for antitumourals activity.
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Vicini approach (2002)\textsuperscript{31}
Vicini et al. reported a series of hydrazones from cyclic and and acyclic 1,2-benzisothiazole hydrazides. The reaction was carried out in presence of HCl and EtOH. All compounds are assayed for antimicrobial and QSAR investigation.

Rollas approach (2002)\textsuperscript{32}
Rollas et al. synthesized a series of hydrazide hydrazones from 4-fluorobenzoic acid hydrazide and appropriate aldehydes in presence of ethanol. All compounds are assayed for antimicrobial activity.

Scheme 1. (a) CH\textsubscript{3}COCOOR; (b) CH\textsubscript{3}COCHO

Scheme 2. General scheme for synthesis of 1,2-benzisothiazole hydrazones.

Scheme 3. Synthesis of hydrazide hydrazones
Synthesis of hydrazones

Cunha approach (2002)\textsuperscript{33}

Cunha et al. reported synthesis and pharmacological evaluation of new N-heterocyclic functionalized N-acylhydrazone compounds (NAH), belonging to the N-substituted-phenylimidazolyl-4-acylhydrazone.

\begin{align*}
\text{Scheme 4.} \quad & \text{(a) NaCN, MnO}_2, \text{MeOH; (b) NH}_3\text{NH}_2\text{H}_2\text{O}, \text{EtOH, reflux; (c) ArCHO, EtOH, HCl, reflux} \\
\end{align*}

Savini approach (2004)\textsuperscript{34}

A series of 3- and 5-methylthiophene-2-carboxaldehyde α-(N)-heterocyclic hydrazones were synthesized from α-(N)-heterocyclic hydrazones and 3- and 5-methylthiophene-2-carboxaldehyde in EtOH. All compounds were evaluated to in vitro investigation of their anti-cancer, anti-HIV and their anti-nicrobial activity.

\begin{align*}
\text{Scheme 5.} \quad & \text{Synthetic pathway of heterocyclohydrazones} \\
\end{align*}

Metwally approach (2006)\textsuperscript{35}

A new series of 2-arylquinoline-4-carboxalic acid hydride-hydrazone was synthesized using an appropriate synthetic route. The synthesis of target compounds was carried out as the versatile pfitzinger reaction\textsuperscript{36} was utilized to synthesis the starting 2-arylquinoline-4-carboxylic acids (15) in satisfactory yield by reacting substituted isatin with α-methylketones in aqueous ethanol. The
Acids were subsequently treated with thionyl chloride in refluxing benzene to give the corresponding acid chlorides (16) which were used directly to prepare the hydrazides (17) through reaction with hydrazine hydrate in refluxing ethanol. The requisite hydrazones (18) were obtained by condensing the acid hydrazides (17) with the appropriate aldehydes in glacial acetic acid under reflux condition. In this protocol some compounds show good antibacterial and antifungal activity at concentration of 100 µg/ML.

Scheme 6. Synthesis route for target compounds. (a) NaOH, aq EtOH; (b) SOCl₂, dry benzene; (c) NH₂NH₂H₂O, EtOH; (d) substituted benzaldehyde HOAc

**Bedia approach (2006)**

A series of hydrazide-hydrazones, based on a series of 4-substituted benzoic acid, were synthesized, and their structures elucidated and screened for the antituberculosis activity.

Scheme 7. Synthetic pathway for hydrazide-hydrazones (a) NaOH; (b) NH₂NH₂, CH₃OH; (c) RCHO, C₂H₅OH

**Sondhi approach (2006)**

Sondhi et al. reported a series of hydrazones by condensing acetylpuridine/indol-3-carboxaldehyde with sulfonylhydrazides in microwave irradiation under solvent free condition. All compounds were tested for anti-inflammatory and analgesic activity.
Melnyk approach (2006)\textsuperscript{39}

Melnyk et al. reported a library of acylhydrazone iron chelators from substituted salicylaldehyde and tested for antimalarial activity. Some compounds shown good antimalarial activity.

Varma approach (2007)\textsuperscript{40}

Varma et al. reported an environmentally benign aqueous protocol for the synthesis of cyclic, bicyclic and heterocyclic hydrazones using polystyrene sulfonic acid as a catalyst. This simple reaction efficiently reported in water under microwave irradiation.

Naimi-Jamal approach (2007)\textsuperscript{41}

Naimi-Jamal et al. synthesized phenylhydrazones and 2,3-dinitrophenylhydrazones from aldehydes and ketones in a solvent free condition by using ball-mill method.
Leite approach (2008)$^{42}$

Leite et al. synthesized aryl hydrazones from aromatic aldehydes/ketones and hydrazines (semicarbazide, thiosemicarbazide and amio-gunadine) using aqueous medium under ultrasound irradiation. This protocol reported good to excellent yield of the products.

Xia approach (2008)$^{43}$

A series of novel 1-arylmethyl-3-aryl-1$H$-pyrazole-5-carbohydrazide hydrazone derivatives were synthesized and the effect of all the compounds on A549 cell growth was investigated.

Filho approach (2009)$^{44}$

The substituted 3-(4-substituted-aryl)-1,2,4-oxadiazolyl-N-acylhydrazones (23) were prepared from arylamidoximes. After the cyclocondensation reaction of between arylamidoximes and methyloxalyl chloridr under reflux in dry THF, the intermediate bearing an 1,2,4-oxadiazole ring
Synthesis of hydrazones

(21) were obtained and then converted into carbohydrazides (22) by reaction with hydrazine hydrate in ethanol at 0°C.

\[
\begin{align*}
\text{Scheme 14} & \quad \text{Synthesis route for target compounds} \\
& \quad \text{(a) THF, reflux; (b) NH}_3\text{NH}_2\text{H}_2\text{O, EtOH, } 0^\circ\text{C; (c) PhCHO, H}_2\text{SO}_4, \\
& \quad \text{EtOH, rt}
\end{align*}
\]

**Liu approach (2009)**

Liu et al. reported a series of ribavirin hydrazones by the condensation of ribavirin hydrazone with benzaldehyde or acetophenone derivatives. In this biological evaluation showed that one compound inhibits the growth of A549 cells at µM

\[
\begin{align*}
\text{Scheme 15} & \quad \text{Synthesis of ribavirin hydrazones} \\
& \quad \text{(a) bis(4-nitrophenyl)hydrogen phosphate; (b) MeOH, NH}_3, 25^\circ\text{C; (c) Hydrazine hydrate, EtOH; (d) HOAc, EtOH}
\end{align*}
\]

**Zheng approach (2009)**

Zheng et al. synthesized a series of novel 3-aryl-1-(4-tert-butylbenzyl)-1H-pyrazole-5-carbohydrazide hydrazone derivatives and effects of all the compounds on A549 cell growth were investigated.
Mogilaiah approach (2010)⁴⁷
In this protocol Mogilaiah et al. described PTSA catalyzed efficient synthesis of arylidenehydrazides under solvent free condition.

Ajani approach (2010)⁴⁸
Ajani et al. synthesized a various 2-quinoxalinnone-3-hydrazone derivatives by using microwave irradiation technique. The reaction was carried out in presence of ethanol. All compounds evaluated for their antimicrobial activity in that some compounds show good antimicrobial activity.
1.1.2 Present work:

1.1.2.1 Objective

To design and conduct chemical reactions with “green” experimental protocol is an enormous challenge that chemists have to confront to improve the quality of the environment for present and future generations. Target areas for achieving this goal are the exploration of alternative reaction conditions and reaction media to accomplish the desired chemical transformations with minimized by-products or waste, and elimination of the use of conventional organic solvents, wherever possible. Traditional chemical syntheses or transformations generally require volatile and often hazardous organic solvents as reaction media to facilitate mass and heat transfer, and to isolate and purify desired product from reaction mixtures. Over the past several years, chemists have been aware of the environmental implications of their chemistry. Nowadays, they are trying to develop new synthetic methods, reaction conditions, and uses of chemicals that reduce risks to humans and the environment. Organic solvents are high on the list of damaging chemicals because they are employed in huge amounts and are usually volatile liquids that are difficult to store.

In recent years, solid-state organic reactions have caused great interest. They have many advantages such as high efficiency and selectivity, easy separation and purification, and mild reaction conditions and benefit industry as well as the environment. Many articles about solid-state reactions with grinding have been reported, such as the Grignard reaction, Aldol condensations and other reactions.

Hydrazones are of interest also because of their importance in analytical chemistry, medicine and industry. Due to their wide range of applications these compounds have received a great deal of attention in concentration with their synthesis. Thus, in this chapter, firstly we report synthesis of novel hydrazones derived from 4,5-diazafluorene-9-hydrazone in acetic acid as a catalyst by grinding method. Secondly we report synthesis of hydrazones derived from substituted phenyl hydrazine under solvent and catalytically free condition. Synthesis of organic compounds by grinding method has the advantages of shorter time, higher yield, mild reaction condition as well as being environmentally friendly. Thus grinding method comes under the title of green chemistry. Theses synthesized hydrazones are also assayed for antibacterial (Escherichia coli, Staphylococcus aureus, Bacillus subtilis, and Klebsiella pneumoniae) activities by disc diffusion method.
1.1.3. Result and Discussion

1.1.3.1 Chemistry

The study was started by evaluating the efficiency of grinding in the reaction between 4,5-diazafluoren-9-hydrazone (Dzdfh) (73) and 4-bromobenzaldehyde (Scheme 1.1) in solid state to obtain the hydrazone 75a under the reaction conditions as described in the Table no. 1. Initially, the mixture was grounded in mortar with a pestle at room temperature under neat conditions. However, the results demonstrated the need of a catalyst, since the starting material was recovered (Table 1, entry 1). Thus, we chose four catalysts (PTSA, HOAc, ZnCl$_2$, SnCl$_2$) to be analyzed in this condensation reaction. The starting materials were mostly recovered in presence of PTSA (Table 1, entry 2, 3, 4), but at high mole % of PTSA, better yield of the product was obtained (Table 1, entry 5, 6).

![Scheme 1.1 Synthesis of 5-{(2E)-(4-bromobenzylidene)hydrazinylidene}-5$H$-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine; Reaction conditions: (i) KMnO$_4$, Water, Reflux; (ii) NH$_2$NH$_2$H$_2$O, EtOH, grinding; (iii) AcOH, grinding](image)

The reaction failed in the presence of ZnCl$_2$ and starting materials were recovered (Table 1, entry 12, 13, 14, 15, 16). Thus, we found HOAc, an inexpensive and common organic chemical which was used an efficient catalyst for the reaction. HOAc was used in 20 mol % to 40 mol % which hastened yield improvement and completion of the reaction in 3 min (Table 1, entry 7, 8). For evaluating the amount of catalyst, HOAc was employed in 60, 80 and 100 mol % for 3 min, however there was no large effect on yield of the product (Table 1, entry 9, 10, 11). This reaction also failed when we used SnCl$_2$ as a catalyst at 60, 80, and 100 mol % (Table 1, entry 19, 20, 21), but it gave moderate yield of the product at 20 and 40 mol % (Table 1, entry 17, 18).
Synthesis of hydrazones

Table 1. Optimization for synthesis of 75a

<table>
<thead>
<tr>
<th>Entry</th>
<th>Catalyst</th>
<th>Catalyst amount (mol %)</th>
<th>Time (min)</th>
<th>Yield a (%)</th>
</tr>
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<td>Neat</td>
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<td>6</td>
<td>— b</td>
</tr>
<tr>
<td>2</td>
<td>PTSA</td>
<td>20</td>
<td>3</td>
<td>45 c</td>
</tr>
<tr>
<td>3</td>
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<td>45 c</td>
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<tr>
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<td>3</td>
<td>50</td>
</tr>
<tr>
<td>19</td>
<td>SnCl₂</td>
<td>60</td>
<td>3</td>
<td>— b</td>
</tr>
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<tr>
<td>21</td>
<td>SnCl₂</td>
<td>100</td>
<td>3</td>
<td>— b</td>
</tr>
</tbody>
</table>

a Yield of isolated product; b The starting material was recovered; c The starting material were mostly recovered.

The IR spectra of 75a showed absorption at 1640.42, 1612.32 and 1595.72 cm⁻¹ correspondence to C=N/C=C, CH=N respectively. The ¹H NMR spectrum of 75a showed singlet of one proton at δ 8.60 correspondence to CH=N. The MASS spectrum of 75a showed m/z at 363.21 (MH⁺).

The generality of the reaction was authenticated by the use of aromatic aldehydes containing electron-donating groups or electron-withdrawing groups. As shown in Table 2, aldehydes containing electron-donating or electron withdrawing groups reacted well to give corresponding hydrazones (75a-75o) in high yield. This finding demonstrated no influence of the electronic nature of the substituent on the reaction time or yield.
Table 2. Synthesis of hydrazones from Dzdfh and aromatic aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dzdfh</th>
<th>Aldehydes</th>
<th>Products 75a-o</th>
<th>Grinding</th>
<th>EtOH reflux</th>
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<tbody>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield (%)</td>
</tr>
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<td>CHO</td>
<td>75a</td>
<td>3</td>
<td>92</td>
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<tr>
<td>2</td>
<td>73</td>
<td>CHO</td>
<td>75b</td>
<td>3</td>
<td>90</td>
</tr>
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<td>75c</td>
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<td>75d</td>
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<tr>
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<td>75e</td>
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<td>73</td>
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<td>75f</td>
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</tr>
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<td>7</td>
<td>73</td>
<td><img src="image1.png" alt="Chemical Structure" /></td>
<td><img src="image2.png" alt="Chemical Structure" /></td>
<td>3</td>
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<td><img src="image3.png" alt="Chemical Structure" /></td>
<td><img src="image4.png" alt="Chemical Structure" /></td>
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</tr>
<tr>
<td>9</td>
<td>73</td>
<td><img src="image5.png" alt="Chemical Structure" /></td>
<td><img src="image6.png" alt="Chemical Structure" /></td>
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<tr>
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<td><img src="image7.png" alt="Chemical Structure" /></td>
<td><img src="image8.png" alt="Chemical Structure" /></td>
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<tr>
<td>11</td>
<td>73</td>
<td><img src="image9.png" alt="Chemical Structure" /></td>
<td><img src="image10.png" alt="Chemical Structure" /></td>
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<tr>
<td>12</td>
<td>73</td>
<td><img src="image11.png" alt="Chemical Structure" /></td>
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<tr>
<td>13</td>
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<td><img src="image14.png" alt="Chemical Structure" /></td>
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<td>90</td>
</tr>
</tbody>
</table>
In continuation of our studies on structure modifications we condensed 4,5-diazafluorene-9-hydrazone (73) with different substituted aromatic ketones (76) under same condition as described above (Scheme 1.2). The results demonstrated that varieties of ketones gave low yield as compared to aldehydes (Table 3).

\[ \text{Scheme 1.2 Synthesis of hydrazones from substituted aromatic ketones; Reaction condition (i) } \text{NH}_2\text{NH}_2\text{H}_2\text{O, grinding} \]

**Table 3. Synthesis of hydrazones from Dzdfh and aromatic ketones**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Dzdfh</th>
<th>Ketones 76(a-e)</th>
<th>Products (77 a-e)</th>
<th>grinding</th>
<th>EtOH reflux</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Time (min)</td>
<td>Yield(^a) (%)</td>
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<tr>
<td>1</td>
<td>73</td>
<td>NCHO</td>
<td>77a</td>
<td>3</td>
<td>85</td>
</tr>
</tbody>
</table>
The IR spectra of 77a showed absorption at 1659.43, 1616.24 and 1578.75 cm\(^{-1}\) correspondence to C=N/C=C respectively. The \(^1\)H NMR spectrum of 77a showed singlet of three proton at δ 2.56 correspondence to CH\(_3\). The MASS spectrum of 77a showed m/z at 299.27 (MH\(^+\)).

In order to evaluate the scope and limitations of this solvent free reaction, we compared this grinding process with conventional thermal heating, with ethanol reflux and an acetic acid as a catalyst. From Table no 2 and 3, it is possible to affirm that the grinding allowed the reaction to proceed in a shorter reaction time, furnishing better yields as compared to conventional thermal heating. A possible explanation for the shorter reaction time and better yield under solvent free condition is that the formation of liquid phase prior to the reaction, i.e., formation of a eutectic mixture with uniform distribution of the reactants brings the reacting species into proximity than does a solvent.\(^{57}\)
1.1.3.2 Anti-bacterial activity

The anti-bacterial activities of the newly synthesized compounds 75 a-o and 77 a-e were evaluated against various pathogenic (Gram-negative and Gram-positive) bacterial strains viz., *Escherichia coli* (E. coli), *Staphylococcus aureus* (S. aureus), *Bacillus subtilis* (B. subtilis) and *Klebsiella pneumonae* (K. pneumonae). The anti-bacterial activities were evaluated by the disc diffusion method. The solvent used for the preparation of compound solution (DMSO) did not show inhibition against the tested organisms (negative control)

**Table 4.** Anti-bacterial activities of the compounds 75a-o and 77a-e

<table>
<thead>
<tr>
<th>Compounds</th>
<th>E. coli (mm)</th>
<th>S. aureus (mm)</th>
<th>B. subtilius (mm)</th>
<th>K. pneumonia (mm)</th>
</tr>
</thead>
<tbody>
<tr>
<td>75a</td>
<td>—</td>
<td>—</td>
<td>10</td>
<td>—</td>
</tr>
<tr>
<td>75b</td>
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<td>75j</td>
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<tr>
<td>75k</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>75l</td>
<td>12</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>75m</td>
<td>8</td>
<td>9</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>75n</td>
<td>—</td>
<td>9</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>75o</td>
<td>9</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>77a</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>9</td>
</tr>
<tr>
<td>77b</td>
<td>10</td>
<td>—</td>
<td>—</td>
<td>—</td>
</tr>
<tr>
<td>77c</td>
<td>—</td>
<td>9</td>
<td>8</td>
<td>—</td>
</tr>
<tr>
<td>77d</td>
<td>9</td>
<td>—</td>
<td>9</td>
<td>10</td>
</tr>
<tr>
<td>77e</td>
<td>—</td>
<td>—</td>
<td>—</td>
<td>10</td>
</tr>
<tr>
<td>S1</td>
<td>14</td>
<td>12</td>
<td>13</td>
<td>14</td>
</tr>
<tr>
<td>S2</td>
<td>12</td>
<td>15</td>
<td>14</td>
<td>14</td>
</tr>
</tbody>
</table>

−: indicates bacteria are resistant to the compounds; S1: Cephotoxime used as standard drug at concentration of 10 µg/ml; S1: Tetracycline used as standard drug at concentration of 30 µg/ml; All compounds (75a-o and 77a-e) tested at concentration of 250 µg/ml
The results of anti-bacterial screening of all newly synthesized compounds are presented in Table no 4. Most of these tested compounds did not show any activity against *E. coli*, *S. aureus*, *B. subtilis* and *K. pneumoniae* with concentration of 250 µg/ml in DMSO. But, thiophene and 2-nitro derivative of hydrazones (75k and 75l) showed moderate activity (zone of inhibition up to 12 mm at concentration of 250 µg/ml) against *Escherichia coli*. Compounds 75b, 75c, and 75d (which bear 4-OH, 2,4 di-chloro, 4-chloro) showed moderate activity against *Klebsiella pneumoniae* (zone of inhibition up to 11 to 12 mm at concentration of 250 µg/ml).

In continuation of our studies on greener synthesis of hydrazones we condensed substituted phenyl hydrazine with different substituted aldehydes (Scheme 1.3) or ketones (Scheme 1.4) under catalytically and solvent free condition.

Phenyl hydrazine or substituted phenyl hydrazine’s (78) was grind with a variety of carbonyl compounds (79/81) (alkyl, aryl and heteroaryl) at room temperature in solvent free condition (scheme 1.3 and 1.4). All the reactions proceed to completion in just 2-6 min. at room temperature without any organic solvent or any added catalyst. The respective hydrazones could be isolated in excellent yields in all the cases (Table 5 and 6). The methodology tolerates both electron withdrawing and electron donating substituents on the phenylhydrazines. All the reactions when carried out in a molecular solvent such as methanol under similar conditions required 2 h for complete conversions.
Table 5. Synthesis of hydrazones from substituted phenyl hydrazine and various aldehydes

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenyl hydrazine</th>
<th>Aldehydes</th>
<th>Products (80a-m)</th>
<th>Time (min)</th>
<th>Yield (%)</th>
</tr>
</thead>
</table>
| 1     | \[
\begin{array}{c}
\text{NH} \\
\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{CH}_3 \\
\text{H}
\end{array}
\] | \[
\begin{array}{c}
\text{NH}_2 \\
\text{N}
\end{array}
\] | 3 | 90 |
| 2     | \[
\begin{array}{c}
\text{NH} \\
\text{NH}_2
\end{array}
\] | \[
\begin{array}{c}
\text{N} \\
\text{OH}
\end{array}
\] | \[
\begin{array}{c}
\text{NH} \\
\text{N}
\end{array}
\] | 5 | 92 |
| 3     | \[
\begin{array}{c}
\text{NH} \\
\text{NH}_2
\end{array}
\] | \[
\text{CH}_3
\] | \[
\text{CH}_3
\] | 3 | 95 |
| 4     | \[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{NH}_2
\end{array}
\] | \[
\text{CH}_3
\] | \[
\text{O}_2\text{N}
\] | 5 | 91 |
| 5     | \[
\begin{array}{c}
\text{O}_2\text{N} \\
\text{NH}_2
\end{array}
\] | \[
\text{C}_6\text{H}_5
\] | \[
\text{O}_2\text{N}
\] | 5 | 93 |
| 6     | \[
\begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\] | \[
\text{CH}_3
\] | \[
\text{Cl}
\] | 3 | 92 |
| 7     | \[
\begin{array}{c}
\text{Cl} \\
\text{NH}_2
\end{array}
\] | \[
\text{C}_6\text{H}_5
\] | \[
\text{Cl}
\] | 5 | 91 |
Table 6. Synthesis of hydrazones from substituted phenyl hydrazine and various ketones

<table>
<thead>
<tr>
<th>Entry</th>
<th>Phenyl hydrazine</th>
<th>Ketones</th>
<th>Products (82a-l)</th>
<th>Time (min)</th>
<th>Yield(^a) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>[\text{Phenyl hydrazine}]</td>
<td>[\text{Ketones}]</td>
<td>[\text{Products (82a-l)}]</td>
<td>5</td>
<td>91</td>
</tr>
<tr>
<td>2</td>
<td>[\text{Phenyl hydrazine}]</td>
<td>[\text{Ketones}]</td>
<td>[\text{Products (82a-l)}]</td>
<td>4</td>
<td>94</td>
</tr>
</tbody>
</table>

\(^a\) Yield of isolated product
Synthesis of hydrazones

3

4

5

6

7

8

9

10

11
1.1.3.3 Conclusion:

A number of novel hydrazones were synthesized under solvent free condition. This protocol furnishes the products very quickly, simplifies the work-up and does not harm the environment. In this protocol, there is no influence of the electronic nature of the substituent on the reaction time or yield but ketones gives low yield as compared to aldehydes. The antibacterial screening results reveal that the compounds that bear 4-OH, 2,4 di-chloro, 4-chloro, thiophene and 2-nitro substituents showed moderate anti-bacterial activities i.e. 75b, 75c, 75d, 75k and 75l.

In another case, we have developed an efficient, solvent free synthesis of hydrazones at ambient conditions in near quantitative yields by using mechanochemistry. Excellent isolated yield, high reaction rate. Absence of organic solvent and any acid or base catalyst makes this an environment friendly methodology amenable for scale up.

1.1.4 Experimental:

1.1.4.1 General procedure for the synthesis of 4,5-diazafluoren-9-one (72)

The 4,5-diazafluoren-9-one was synthesized using method reported in the literature (Deshpande et al., 2005).58

1.1.4.2 General procedure for the synthesis of 4,5-diazafluoren-9-hydrazone (73)

A mixture of 4,5-diazafluoren-9-one (1mmol) and hydrazine hydrate (1.1mmol) was crushed in mortar with a pestle at room temperature and acetic acid (20 mol%) was added and crushed then the progress of reaction was monitored by TLC. After completion of reaction (3 min) the crude product was washed with water, dried and purified by column chromatography.

1.1.4.3 General procedure for the synthesis of hydrazones on grinding (75a-o/77a-e)

A mixture of 4,5-diazafluoren-9-hydrazone (1mmol) and aldehyde/ketone (1mmol) was
crushed in mortar with a pestle at room temperature and acetic acid (20 mol%) was added and crushed then the progress of reaction was monitored by TLC. After completion of reaction (3 min) the crude product was washed with water, dried and purified by column chromatography using 20% methanol in benzene as eluent.

1.1.4.4 General procedure for the synthesis of hydrazones on ethanol reflux (75a-o/77a-e)

A mixture of 4,5-diazafluoren-9-hydrazone (1mmol), aldehyde/ketone (1mmol) and acetic acid (20 mol%) was refluxed in ethanol and progress of reaction was monitored by TLC. Having completed the reaction, the resulting reaction mixture was cooled at -20°C then filtered and washed with cold ethanol three times. It was finally dried under vacuum at 40°C to give desire product.

1.1.4.5 General procedure for the synthesis of hydrazones (80a-m/82a-l)

A mixture of Phenyl hydrazine or substituted phenyl hydrazine’s (1mmol) and aldehyde/ketone (1mmol) was crushed in mortar with a pestle at room temperature. The progress of reaction was monitored by TLC. After completion of reaction (2-5 min) the crude product was purified by column chromatography using 25% methanol in benzene as eluent.

1.1.4.6 Antimicrobial activity assay procedure

Disc diffusion method

The antimicrobial activity of newly synthesized compounds was evaluated using the disc diffusion method as per the guidelines of the National Committee for Clinical Laboratory Standards [NCCLS, 1997]. Briefly, a 24/48 hours old culture of selected bacteria was mixed with sterile physiological saline (0.85%) and the turbidity was adjusted to the standard inoculum of McFarland scale 0.5 (~106 colony forming units (CFU) per milliliter). Petri plates containing 20 mL of Nutrient Agar (NA, Hi-Media) were used for all the bacteria tested. The inoculums was spread on the surface of the solidified media and Whatman no. 1 filter paper discs (6 mm in diameter) were impregnated with the test compound (20 μL/disc) and placed on the plates. Cefotaxime (10 μg/disc, Hi-Media) and Tetracycline (30 μg/disc, Hi-Media) were used as positive controls for bacteria. A paper disc impregnated with dimethylsulfoxide (DMSO) was used as negative control. Plates inoculated with the bacteria were incubated for 24 hours at 37°C. The inhibition zone diameters were measured in millimeters. All the tests were performed in
triplicate and the average was considered for final reading.

1.1.5 Spectral data:

General experimental method
Melting points of the synthesized compounds were determined in open-glass capillaries on a stuart-SMP10 melting point apparatus and are uncorrected. IR absorption spectra were recorded on a Perkin Elmer 1650 FTIR using KBr pellets in the range of 4000-450 cm\(^{-1}\). \(^1\)H-NMRs were recorded on a Bruker spectrometer operating at 300 MHz. The \(^1\)H-NMR chemical shifts are reported as parts per million (ppm) downfield from TMS (Me\(_4\)Si) used as an internal standard. The \(^{13}\)C NMR spectra were recorded at 50 MHz; chemical shifts (δ scale) are reported in parts per million (ppm). Mass spectra were recorded on LCQ ion trap mass spectrometer. Purity of the compounds were checked by thin layer chromatography (TLC) on Merck silica gel 60 F254 pre-coated sheets in benzene/methanol mixture and spots were developed using iodine vapor as visualizing agents.

\[5-[(2\ E)-(4-bromobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine\]

IR: (KBr, cm\(^{-1}\)) \(\nu\) 3044.65 (Ar-H), 1640.42, 1612.32 (C=N=C=C), 1595.72 (CH=N), 1509.63 (C=N-N), 1464.45 (C=N=C=C), 557.22 (C-Br);

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), δ: 8.74 (2H, m), 8.60 (1H, s, CH=N), 8.57 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.22 (1H, dd, J = 7.8 Hz, 1.5 Hz), 7.90 (2H, d, J = 8.1 Hz, bromobenzylidene), 7.78 (2H, d, J = 8.1 Hz, bromobenzylidene), 7.34 (2H, m)

MS: (ES) Found [Calcd.]: m/z 363.21 [363.17] (MH\(^+\)); mp: 238

\[4-[(E)-(5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridin-5-ylidenehydrazinylidene)methyl]phenol\]
Synthesis of hydrazones

**IR:** (KBr, cm⁻¹) ν 3439.5 (O-H), 3046.31 (Ar-H), 1640.23, 1607.12 (C=N/C=C), 1561.31 (CH=N), 1555.10 (C=N-N), 1458 (C=N/C=C)

**¹H NMR:** (DMSO-d⁶, 300 MHz), δ: 8.85 (1H, d, J = 7.5 Hz), 8.60 (2H, m), 8.35 (1H, s, CH=N), 8.22 (1H, d, J = 7.5 Hz), 7.70 (2H, d, J = 7.7 Hz, phenol), 7.32 (2H m), 7.10 (1H, s, -OH) 6.82 (2H, d, J = 7.7 Hz, phenol)

**MS:** (ES) Found [Calcd.]: m/z 300.12 [300.31] (MH⁺); **mp:** > 300

5-[(2E)-(2,4-dichlorobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

![Structure of 5-[(2E)-(2,4-dichlorobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine]

**IR** (KBr, cm⁻¹) v 3046.10 (Ar-H), 1640.17, 1610.46 (C=N/C=C), 1597.12 (CH=N), 1507.31 (C=N-N), 1466.54 (C=N/C=C), 787.11, 754.49 (C-Cl)

**¹H NMR:** (CDCl₃, 300 MHz), δ: 8.71 (2H, m), 8.61 (1H, s, CH=N), 8.58 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.20 (1H, dd, J = 7.8 Hz, 1.5 Hz), 7.85 (2H, d, J = 8.0 Hz, chlorobenzylidene), 7.61 (2H, d, J = 8.0 Hz, chlorobenzylidene), 7.31 (2H, m)

**MS:** (ES) Found [Calcd.]: m/z 318.75 [318.71] (MH⁺), 319.70 (MH⁺²); **mp:** 240

5-[(2E)-(4-chlorobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

![Structure of 5-[(2E)-(4-chlorobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine]

**IR** (KBr, cm⁻¹) v 3038.16 (Ar-H), 1647.36, 1620.56 (C=N/C=C), 1598.64 (CH=N), 1511.45 (C=N-N), 1469.23 (C=N/C=C), 790.11, 757.51 (C-Cl)

**¹H NMR:** (CDCl₃, 300 MHz), δ: 8.72 (2H, m), 8.61 (1H, s, CH=N), 8.58 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.20 (1H, dd, J = 7.8 Hz, 1.5 Hz), 7.85 (2H, d, J = 8.0 Hz, chlorobenzylidene), 7.61 (2H, d, J = 8.0 Hz, chlorobenzylidene), 7.31 (2H, m)

**MS:** (ES) Found [Calcd.]: m/z 318.75 [318.71] (MH⁺), 319.70 (MH⁺²); **mp:** 240
Synthesis of hydrazones

5-[(2E)-(4-nitrobenzylidene)hydrazinylidene]-5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm⁻¹) ν 3149.51 (Ar-H), 1632.67, 1607.04 (C=N/C=C), 1560.47 (CH=N), 1520.34 (C=N-N), 1483.44 (C=N/C=C), 1378.94 (NO₂)

¹H NMR: (DMSO-d⁶, 300 MHz), δ: 8.79 (2H, m), 8.61 (1H, s, CH=N), 8.59 (1H, dd, J = 7.7 Hz, 1.5 Hz), 8.25 (1H, dd, J = 7.7 Hz, 1.5 Hz), 8.01 (2H, d, J = 8.3 Hz, nitrobenzylidene), 7.85 (2H, d, J = 8.3 Hz, nitrobenzylidene), 7.36 (2H, m)

MS: (ES) Found [Calcd.]: m/z 329.19 [329.31] (MH⁺); mp: > 300

N,N-dimethyl-4-[(E)-(5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridin-5-ylidenehydrazinylidene)methyl]aniline

IR: (KBr, cm⁻¹) ν 3059.92, 3026.65 (Ar-H), 1601.04 (C=N/C=C), 1493.03, 1452.37 (C=N/C=C), 1181.94 (C-N)

¹H NMR: (CDCl₃, 300 MHz), δ: 9.02 (1H, d, J = 7.8 Hz), 8.80 (2H, m), 8.65 (1H, s, CH=N), 8.28 (1H, d, J = 7.8 Hz), 7.85 (2H, d, J = 7.7 Hz, aniline), 7.38 (2H, m), 6.72 (2H, d, J = 7.7 Hz, aniline), 3.11 (6H, s, 2xCH₃)

MS: (ES) Found [Calcd.]: m/z 328.1 [327.38] (MH⁺), 329.1 (MH⁺⁺); mp: 189

5-[(2E)-(3-nitrobenzylidene)hydrazinylidene]-5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm⁻¹) ν 3059.92, 3026.65 (Ar-H), 1601.04 (C=N/C=C), 1493.03, 1452.37 (C=N/C=C), 1181.94 (C-N)

¹H NMR: (CDCl₃, 300 MHz), δ: 9.02 (1H, d, J = 7.8 Hz), 8.80 (2H, m), 8.65 (1H, s, CH=N), 8.28 (1H, d, J = 7.8 Hz), 7.85 (2H, d, J = 7.7 Hz, aniline), 7.38 (2H, m), 6.72 (2H, d, J = 7.7 Hz, aniline), 3.11 (6H, s, 2xCH₃)

MS: (ES) Found [Calcd.]: m/z 328.1 [327.38] (MH⁺), 329.1 (MH⁺⁺); mp: 189
Synthesis of hydrazones

IR: (KBr, cm$^{-1}$) v 3148.45 (Ar-H), 1633.47, 1607.15 (C=N/C=C), 1564.56 (CH=N), 1521.30 (C=N-N), 1482.43 (C=N/C=C), 1377.90 (NO$_2$)

$^1$H NMR: (CDCl$_3$, 300 MHz), δ: 8.81 (2H, m), 8.74 (1H, s, nitrobenzylidene), 8.68 (1H, s, CH=N), 8.62 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.38 (1H, dd, J = 7.8 Hz, 1.0 Hz, nitrobenzylidene), 8.30 (1H, dd, J = 7.8 Hz, 1.5 Hz), 8.12 (1H, dd, J = 7.8 Hz, 1.0 Hz, nitrobenzylidene), 7.82 (1H, ddd, J= 8.0 Hz, 7.5 Hz, 1.0 Hz, nitrobenzylidene), 7.30 (2H, m)

MS: (ES) Found [Calcd.]: m/z 329.31 [329.35] (MH$^+$); mp: 232


IR: (KBr, cm$^{-1}$) v 3436.45 (O-H), 3044.72 (Ar-H), 1642.32, 1609.22 (C=N/C=C), 1560.36 (CH=N), 1557.07 (C=N-N), 1456.21 (C=N/C=C)

$^1$H NMR: (CDCl$_3$, 300 MHz), δ: 8.78 (2H, m), 8.64 (1H, d, J = 7.8 Hz), 8.35 (1H, s, CH=N), 8.20 (1H, d, J = 7.8 Hz), 7.30 (2H, m), 7.21 (1H, dd, J = 7.4 Hz, 1.2 Hz, phenol), 7.11 (1H, s, -OH), 6.98 (1H, s, phenol), 6.67 (1H, dd, J = 7.4 Hz, 1.2 Hz, phenol), 4.12 (3H, s, CH$_3$)

MS: (ES) Found [Calcd.]: m/z 330.34 [330.36] (MH$^+$); mp: 212

5-[(2E)-benzylidenehydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm$^{-1}$) v 3048.79 (Ar-H), 1630.08 (C=N/C=C), 1562.49 (CH=N), 1543.62 (C=N-N), 1484.89 (C=N/C=C);

$^1$H NMR: (CDCl$_3$, 300 MHz), δ: 8.81- 8.74 (3H, m), 8.67 (1H, s, CH=N), 8.25 (1H, dd, J= 8.7 Hz, 1.2 Hz), 7.94 (2H, m, benzylidene), 7.55 (3H, m, benzylidene), 7.37 (2H, m)

MS: (ES) Found [Calcd.]: m/z 284 [284.31] (MH$^+$); mp: 182
Synthesis of hydrazones


IR:  (KBr, cm\(^{-1}\)) \(\nu\) 3049.79 (Ar-H), 2226.78 (CN), 1632.97, 1604.36 (C=N/C=C), 1562.08 (CH=N), 1500.38 (C=N-N), 1397.40 (C=N/C=C), 1165.28 (C-N);

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), \(\delta\): 8.77 (2H, m), 8.65 (1H, s, CH=N), 8.62 (1H, dd, \(J = 7.8\) Hz, 1.5 Hz), 8.24 (1H, dd, \(J = 7.8\) Hz, 1.5 Hz), 8.04 (2H, d, \(J = 8.1\) Hz, benzonitrile), 7.83 (2H, d, \(J = 8.1\) Hz, benzonitrile), 7.37 (2H, m)

MS: (ES) Found [Calcd.]: m/z 309.25 [309.32] (MH\(^+\)); mp: 266

5-[(2E)-(thiophen-2-ylmethylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

IR:  (KBr, cm\(^{-1}\)) \(\nu\) 3161.59 (Ar-H), 1626.01, 1605.94 (C=N/C=C), 1566.57 (CH=N), 1512.80 (C=N-N), 1020 (C-S)

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), \(\delta\): 8.89 (1H, dd, \(J = 7.8\) Hz, 1.5 Hz), 8.85 (1H, s, CH=N), 8.75 (2H, m), 8.23 (1H, dd, \(J = 7.8\) Hz, 1.5 Hz), 7.62 (1H, d, \(J = 5.1\) Hz, thiophen), 7.57 (1H, d, \(J = 3.9\) Hz, thiophen), 7.37 (2H, m), 7.20 (1H, m, thiophen)

MS: (ES) Found [Calcd.]: m/z 291.1 [290.34] (MH\(^+\)), 292.1 (MH\(^+\)); mp: 125

5-[(2E)-(2-nitrobenzylidene)hydrazinylidene]-5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

IR:  (KBr, cm\(^{-1}\)) \(\nu\) 3114.24 (Ar-H), 1628.63, 1603.83 (C=N/C=C), 1578.28 (CH=N), 1507.27 (C=N-N), 1471.36 (C=N/C=C), 1340.54 (NO\(_2\))
Synthesis of hydrazones

\[ ^1H \text{NMR:} \] \((\text{CDCl}_3, 300 \text{ MHz})\), \(\delta: 9.12\ (1\text{H}, \text{s, CH=N}), 8.77\ (2\text{H}, \text{m}), 8.60\ (1\text{H}, \text{dd, J = 7.8 Hz, 1.0 Hz}), 8.32\ (1\text{H}, \text{dd, J= 7.5 Hz, 1.0 Hz, nitrobenzylidene}), 8.27\ (1\text{H}, \text{dd, J= 7.8 Hz, 1.0 Hz}), 8.14\ (1\text{H}, \text{dd, J= 8.1 Hz, 1.0 Hz, nitrobenzylidene}), 7.83\ (1\text{H}, \text{dd, J= 7.5 Hz, 7.5 Hz, 1.0 Hz, nitrobenzylidene}), 7.71\ (1\text{H}, \text{dd, J= 8.1 Hz, 7.5 Hz, 1.0 Hz, nitrobenzylidene}), 7.40\ (1\text{H}, \text{m}), 7.33\ (1\text{H}, \text{m})\)

**MS:** (ES) Found [Calcd.]: \(m/z\ 329.24 \ [329.31\] (MH\(^+\)); \textbf{mp:} 222

5-[(2\text{E})-(2-chlorobenzylidene)hydrazinylidene]-5\text{H}-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

**IR:** (KBr, cm\(^{-1}\)) \(\nu 3047.16\ (\text{Ar-H}), 1642.09, 1611.64\ (\text{C=N/C=C}), 1595.12\ (\text{CH=N}), 1507.78\ (\text{C=N-N}), 1467.93\ (\text{C=N/C=C}), 752.65\ (\text{C-Cl})

\[ ^1H \text{NMR:} \] \((\text{CDCl}_3, 300 \text{ MHz})\), \(\delta: 8.90\ (1\text{H}, \text{s, CH=N}), 8.70\ (2\text{H}, \text{m}), 8.54\ (1\text{H}, \text{dd, J = 7.8 Hz, 1.2 Hz}), 8.16\ (1\text{H}, \text{dd, J= 7.8 Hz, 1.2 Hz}), 7.92\ (1\text{H}, \text{dd, J= 7.4 Hz, 1.0 Hz, chlorobenzylidene}), 7.68\ (1\text{H}, \text{dd, J= 8.0 Hz, 1.0 Hz, chlorobenzylidene}), 7.48\ (1\text{H}, \text{dd, J= 7.5 Hz, 7.5 Hz, 1.2 Hz, chlorobenzylidene}), 7.38\ (2\text{H}, \text{m}), 7.30\ (1\text{H}, \text{dd, J= 8.0 Hz, 7.4 Hz, 1.0 Hz, chlorobenzylidene})\)

**MS:** (ES) Found [Calcd.]: \(m/z\ 318.75 \ [318.78\] (MH\(^+\)); \textbf{mp:} 125

5-[(2\text{E})-(pyridin-2-ylmethylidene)hydrazinylidene]-5\text{H}-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine

**IR:** (KBr, cm\(^{-1}\)) \(\nu 3124.35\ (\text{Ar-H}), 1647.85, 1607.23\ (\text{C=N/C=C}), 1572.34\ (\text{CH=N}), 1561.44\ (\text{C=N-N}), 1445.98\ (\text{C=N/C=C}), 1223.47, 1130\ (\text{C-N})

\[ ^1H \text{NMR:} \] \((\text{CDCl}_3, 300 \text{ MHz})\), \(\delta: 8.72-8.78\ (3\text{H}, \text{m}), 8.66\ (1\text{H}, \text{s, CH=N}), 8.61\ (1\text{H}, \text{dd, J = 7.8 Hz, 1.5 Hz}), 8.22-8.27\ (2\text{H}, \text{m, pyridin}), 7.91\ (1\text{H}, \text{dd, J = 7.8 Hz, 7.8 Hz, 1.5 Hz, pyridin}), 7.45\ (1\text{H}, \text{m, pyridin}), 7.35\ (2\text{H}, \text{m})\)

**MS:** (ES) Found [Calcd.]: \(m/z\ 285.19 \ [285.30\] (MH\(^+\)); \textbf{mp:} 190
Synthesis of hydrazones

5-[(2E)-(4-methoxybenzylidene)hydrazinylidene]-5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm\(^{-1}\)) \(\nu\) 3134.54 (Ar-H), 1648.35, 1607.64 (C=N/C=C), 1537.77 (CH=N), 1502.73 (C=N-N), 1488.21 (C=N/C=C), 1072.35 (C-O)

\(^1\)H NMR: (DMSO-d\(_6\), 300 MHz), \(\delta\): 8.80 (1H, d, J = 7.8 Hz), 8.64 (2H, m), 8.37 (1H, s, CH=N), 8.26 (1H, d, J = 7.8 Hz), 7.75 (2H, d, J = 7.7 Hz, methoxybenzylidene), 7.30 (2H m), 6.80 (2H, d, J = 7.7 Hz, methoxybenzylidene), 3.92 (3H, s, -CH\(_3\))

MS: (ES) Found [Calcd.]: m/z 314.34 [314.30] (MH\(^+\)); mp: 145

5-[(2E)-[1-(pyridin-2-yl)ethylidene]hydrazinylidene]-5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm\(^{-1}\)) \(\nu\) 3153.76 (Ar-H), 1659.43, 1616.24 (C=N/C=C), 1578.75 (CH=N), 1561.23 (C=N-N), 1438.45 (C=N/C=C), 1133.37 (C-N)

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), \(\delta\): 8.78 (1H, dd, J = 7.8 Hz, 1.2 Hz), 8.71-8.74 (2H, m), 8.22-8.34 (2H, m, pyridin & 1H, pyrido-pyridine), 7.89 (1H, ddd, J = 7.5 Hz, 7.5 Hz, 1.5 Hz, pyridin), 7.36-7.45 (2H, m), 7.24 (1H, m, pyridine), 2.56 (3H, s, -CH\(_3\))

MS: (ES) Found [Calcd.]: m/z 299.27 [299.32] (MH\(^+\)); mp: 162

5-[(2E)-(1-phenylethylidene)hydrazinylidene]-5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridine

IR: (KBr, cm\(^{-1}\)) \(\nu\) 3096.26 (Ar-H), 1648.04, 1596.21 (C=N/C=C), 1578.56 (CH=N), 1562.79 (C=N-N), 1491.50, 1400.04 (C=N/C=C)
**Synthesis of hydrazones**

\(^1\text{H NMR:}\) (CDCl\(_3\), 300 MHz), \(\delta: 8.74\) (2H, m), 8.37 (1H, dd, \(J = 8.7\) Hz, 1 Hz), 8.28 (1H, dd, \(J = 8.7\) Hz, 1 Hz), 8.02 (2H, m, phenyl), 7.52 (3H, m, phenyl), 7.38 (1H, m), 7.25 (1H, m), 2.49 (3H, s, -CH\(_3\))

**MS:** (ES) Found [Calcd.]: m/z 298.26 [298.34] (MH\(^+\)); **mp:** 192

\(5,5'\)-hydrazine-1,2-diylidenebis(5\(H\)-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridine)

\[\text{IR: } (\text{KBr, cm}^{-1}) \nu 3062 (\text{Ar-H}), 1630.12, 1608.64 (\text{C}=N/\text{C}=\text{C}), 1585.31 (\text{CH}=\text{N}), 1560.42 (\text{C}=\text{N}-\text{N}), 1410.46 (\text{C}=\text{N}/\text{C}=\text{C}) 734\]

\(^1\text{H NMR:}\) (CDCl\(_3\), 300 MHz), \(\delta: 8.80\) (2H, d), 8.78 (2H, d), 8.54 (2H, d), 8.36 (2H, d), 7.48 (2H, dd, \(J = 7.8\) Hz, 1.0 Hz), 7.30 (2H, dd, \(J = 7.8\) Hz, 1.0 Hz)

**MS:** (ES) Found [Calcd.]: m/z 360.37 [360.40] (MH\(^+\)); **mp:** > 300

\(4\)-methyl-2-\((1\text{E})-1-(5\text{H}-\text{pyrido}[3',2':4,5]\text{cyclopenta}[1,2-b]\text{pyridin}-5\text{-ylidenehydrazinylidene})\text{ethyl}\)phenol

\[\text{IR: } (\text{KBr, cm}^{-1}) \nu 3421.70 (\text{O-H}), 3082.24 (\text{Ar-H}), 1681.19, 1629.78 (\text{C}=\text{N}/\text{C}=\text{C}), 1564.83 (\text{CH}=\text{N}), 1530.27 (\text{C}=\text{N}-\text{N}), 1353.56 (\text{C}=\text{N}/\text{C}=\text{C}), 1094.75 (\text{C-O})\]

\(^1\text{H NMR:}\) (CDCl\(_3\), 300 MHz), \(\delta: 8.81\) (2H, m), 8.60 (1H, d, \(J = 7.8\) Hz), 8.24 (1H, d, \(J = 7.8\) Hz), 7.38 (1H, s, phenol), 7.31 (2H, m), 7.10 (1H, s, -OH), 6.98 (1H, dd, \(J = 7.8\) Hz, 1 Hz, phenol), 6.64 (1H, dd, \(J = 7.8\) Hz, 1 Hz, phenol), 2.48 (3H, s, CH\(_3\)), 2.21 (3H, s, CH\(_3\))

**MS:** (ES) Found [Calcd.]: m/z 328.36 [328.38] (MH\(^+\)); **mp:** 116
Synthesis of hydrazones

2-[(1E)-1-(5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridin-5-ylidenehydrazinylidene)ethyl]phenol

IR: (KBr, cm\(^{-1}\)) v 3415.02 (O-H), 3031.41 (Ar-H), 1630.58 (C=N/C=C), 1593.97 (CH=N), 1562.85 (C=N-N), 1400.53 (C=N/C=C), 1084.13 (C-O)

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), δ: 8.75 (2H, m), 8.43 (1H, dd, J = 9 Hz, 1.2 Hz), 8.26 (1H, dd, J = 9 Hz, 1.2 Hz), 7.65 (1H, dd, J = 9 Hz, 1.2 Hz, phenol), 7.45 (2H, m), 7.29 (1H, m, phenol), 7.13 (1H, s, OH) 6.96-7.09 (2H, m, phenol), 2.61 (3H, s, CH\(_3\))

MS: (ES) Found [Calcd.]: m/z 314 [314.34] (MH\(^+\)); mp: 226

1-hexylidene-2-phenyl hydrazine

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), δ: 7.59 (s, 1H), 7.34 (d, 4H), 7.03-7.08 (m, 1H), 6.45-6.48 (t, 1H), 2.22-2.24 (q, 2H), 1.21-1.38 (m, 6H), 0.89 (t, 3H); 

\(^{13}\)C NMR: (CDCl\(_3\), 50 MHz,) δ: 143.72, 138.53, 128.9, 123.62, 115.25, 31.22, 31.09, 27.24, 23.16, 14.0;

Mass: (ES) Found [Calcd.]: m/z 190.10 [190.28] (MH\(^+\))

3-Methyl-1-phenyl-1H-pyrazol-5-(4\(H\))-1-ethylidene-2-phenylhydrazine

\(^1\)H NMR: (CDCl\(_3\), 300 MHz), δ 11.07 (1H, s), 7.52 (1H, t), 7.16-6.78 (10H, m), 7.03 (1H, s), 5.23 (1H, s)

\(^{13}\)C NMR: (CDCl\(_3\), 50 MHz,) δ: 168.29, 143.72, 140.77, 135.79, 129.21, 127.38, 123.62, 122.60, 115.25, 107.25;
Synthesis of hydrazones

**Mass:** (ES) Found [Calcd.]: m/z 278.14 [278.30] (MH$^+$)

1-benzylidene-2-phenyl hydrazine

\[
\text{H NMR: (CDCl}_3, 300 \text{ MHz), } \delta: 7.99 (s, 1H), 7.93 (d, 2H), 7.58 (t, 4H), 7.34 (d, 4H), 7.06 (m, 1H);
\]

13\text{C NMR: (CDCl}_3, 50 \text{ MHz), } \delta: 115.25, 123.62, 127.27, 128.37, 128.94, 134.61, 138.67, 143.72;

**Mass:** (ES) Found [Calcd.]: m/z 196.14 [196.24] (MH$^+$)

1-phenyl-2-(1-phenylethylidene)hydrazine

\[
\text{H NMR: (CDCl}_3, 300 \text{ MHz), } \delta: 7.94 (d, 2H), 7.87 (s, 1H), 7.56-7.51 (m, 3H), 7.34 (d, 4H), 7.06 (m, 1H), 2.95 (s, 3H)
\]

13\text{C NMR: (CDCl}_3, 50 \text{ MHz), } \delta: 15.53, 115.13, 123.94, 127.19, 128.08, 128.76, 128.99, 137.85, 143.54, 147.0;

**Mass:** (ES) Found [Calcd.]: m/z 210.21 [210.27] (MH$^+$)

1-(3-nitrophenyl)-2-(1-phenylethylidene)hydrazine

\[
\text{H NMR (CDCl}_3, 300 \text{ MHz), } \delta 11.24 (1H, s), 7.49-6.68 (m, 9H) 1.43 (3H, s);
\]

13\text{C NMR: (CDCl}_3, 50 \text{ MHz), } \delta: 15.45, 147, 143.59, 137.85, 128.99, 126.13, 115.91, 16.53;

**Mass:** (ES) Found [Calcd.]: m/z 255.10 [255.27] (MH$^+$)

1-(3-methylbutan-2-ylidene)-2-(3-nitrophenyl)hydrazine
Synthesis of hydrazones

$^1$H NMR: (CDCl$_3$, 300 MHz), $\delta$: 8.25 (s, 1H), 8.14-8.12 (d, 2H), 7.21-7.19 (d, 2H), 3.13 (m, 1H), 2.07 (s, 3H), 0.93 (d, 6H);

$^{13}$C NMR: (CDCl$_3$, 50 MHz) $\delta$: 16.64, 19.86, 35.90, 115.91, 126.13, 143.59, 150.45, 157.41;

Mass: (ES) Found [Calcd.]: m/z 221.10 [221.25] (MH$^+$)

1-(3-chlorophenyl)-2-(1-phenylethylidene)hydrazine

$^1$H NMR: (CDCl$_3$, 300 MHz), $\delta$: 11.04 (1H, s), 7.38-6.54 (m, 9H) 1.21 (3H, s);

$^{13}$C NMR: (CDCl$_3$, 50 MHz) $\delta$: 147, 147.37, 137.85, 130.15, 128.90, 127.19, 116.02, 15.33;

Mass: (ES) Found [Calcd.]: m/z 246.64 [244.71] (MH$^+$)

1-(3-chlorophenyl)-2-(3-methylbutane-2-ylidene)hydrazine

$^1$H NMR: (CDCl$_3$, 300 MHz), $\delta$: 10.90 (1H, s), 7.48-6.69 (m, 4H) 1.40 (3H, s), 1.21 (1H, m) 0.90 (6H, d);

$^{13}$C NMR: (CDCl$_3$, 50 MHz) $\delta$: 157.41, 142.37, 130.15, 128.90, 116.02, 35.90, 19.86, 16.64;

Mass: (ES) Found [Calcd.]: m/z 212.60 [210.70] (MH$^+$)
1.1.6 Spectra’s

1.1.6.1 Spectra’s of 4-\{(E)-(5H-pyrido[3',2':4,5]cyclopenta[1,2-b]pyridin-5-ylidenehydrazinylidene) methyl\}benzonitrile (75j)
1.1.6.2 Spectra’s of 5-\[(2E)-(thiophen-2-ylmethylidene)hydrazinylidene\]-5H- pyrido [3',2':4,5] cyclopenta[1,2-\textit{b}]pyridine (75k)
1.1.6.3 Spectra’s of \( N,N\text{-dimethyl-4-}[(E)-(5H\text{-pyrido}[3',2':4,5]\text{cyclopenta}[1,2-b]\text{pyridin-5 ylidenehydrazinylidene})methyl]aniline \) (75f)
1.1.6.4 Spectra’s of 5-[(2E)-benzylidenehydrazinylidene]-5H-pyrido [3′,2′:4,5] cyclopenta [1,2-b]pyridine (75i)
Synthesis of hydrazones
1.1.6.5 Spectra’s of 5-[(2E)-(1-phenylethylidene)hydrazinylidene]-5H-pyrido [3',2':4,5] cyclopenta [1,2-b]pyridine (77b)
1.1.6.6 Spectra’s of 4-methyl-2-[(1E)-1-(5H-pyrido[3′,2′:4,5]cyclopenta[1,2-b]pyridin-5-ylidenehydrazinylidene)ethyl]phenol (77d)
Synthesis of hydrazones
1.1.6.7 Spectra’s of 4-methyl-2-[(1\textit{E})-1-(5H-pyrido[3’,2’:4,5]cyclopenta[1,2-\textit{b}]pyridin-5-ylidenehydrazinylidene)ethyl]phenol (77e)
Synthesis of hydrazones

1.1.6.8 Spectra’s of 1-benzylidene-2-phenyl hydrazine (80c)
Synthesis of hydrazones
1.1.6.9 Spectra’s of 1-phenyl-2-(1-phenylethylidene)hydrazine (82a)
1.1.6.10 Spectra’s of 1-(3-methylbutan-2-yldiene)-2-(3-nitrophenyl)hydrazine (82g)
Synthesis of hydrazones
1.1.7 References:

Synthesis of hydrazones