Chapter 2
A clean, benign, catalyst free and Green Chemistry approach towards the synthesis of pyrano[2,3-c]pyrazoles and their biological evaluation

2.1 Introduction
Concerns about the environmental impact of the growth of human society have nowadays become ubiquitous and sustainability has emerged as a prior issue in every area of human activity. The chemical industry is a major player in human development and, unsurprisingly, an increased pressure has been put on chemists to develop sustainable processes. In this context, the concept of Green Chemistry has been defined as the design of chemical products and processes to reduce or eliminate the use and generation of hazardous substances and was developed in principles to guide the chemists in their search towards greenness [1].

In particular, the use of solvents is a constant source of worry since it gives rise to toxicity, hazard, pollution and waste treatment issues. Moreover, solvents generally account for the major source of the wasted mass of a given process or a synthetic pathway [2]. From a strict green chemistry point of view, the best answer to this problem would be to run the reactions under neat conditions, i.e. without any solvent. However, running a reaction in a solvent is often essential to facilitate mass and heat transfer. In addition, the appropriate choice of the solvent allows the reaction rates, the selectivities and the position of chemical equilibria to be acted upon [3].

Consequently, many efforts have been devoted to the finding of sustainable reaction media, and notably the use of water as solvent has attracted much interest in recent years [4-12]. Indeed, water offers many advantages because it is a cheap, readily available, non-toxic and non-flammable solvent, thus being very attractive from both an economical and an environmental point of view. At first sight, water appears as a poor solvent for organic transformations due to the low solubility of organic compounds in water and since it has long been considered as a contaminant.
But it is now well established that the unique structure and physicochemical properties of water lead to particular interactions like polarity, hydrogen bonding, hydrophobic effect and trans-phase interactions that might greatly influence the reaction course. However, running a reaction in water instead of an organic solvent does not necessarily improve the environmental impact of the synthetic sequence since many other parameters must be considered, such as atom efficiency, yield, workup and purification processes, for example.

The present review has a twin objective, aiming to show, through representative examples, not only the broad scope of reactions that can be conducted in water, but also that the use of water can lead to additional sustainability benefits which enhance the overall environmental impact of a given process.

2.2 Enhancement of reactivity and selectivity
Improving the rate and the selectivity of a reaction affects importantly its sustainability since it may allow shorter reaction time, lower temperature, lower catalytic loadings, better yields and easier purification. In fact, the emergence of the use of water as a solvent for organic reactions was probably impulsed by the work of Breslow in the 1980s on the substantial rate enhancement of Diels–Alder reactions conducted in water compared to in other organic solvents [13]. In these studies, he observed that the cycloaddition of butenone and cyclopentadiene was 740 times faster in water than in isooctane and that an increased selectivity could be obtained with water (endo/exo = 21.4) compared to the same reaction in cyclopentadiene (endo/exo = 3.85). It was all the more remarkable that the use of protic polar solvents like methanol or ethanol led to similar results to those obtained with hydrocarbon solvents. These observations were rationalized by the hydrophobic effect [14].

This property of water comes from the repulsive interactions between hydrophobic molecules and water, which leads to the formation of hydrophobic aggregates that allow reducing the contact surface between them. To maintain the network of hydrogen bonds (related to its high cohesive energy density), water wraps itself around these aggregates, thus acting as an internal pressure which accelerates reactions with negative activation volume, like Diels–Alder reactions. In some cases, the rate enhancements may also originate from interfacial interactions between the
Sharpless et al. recently defines as ‘‘on water’’ conditions using water as solvent for the reaction of water insoluble reactants [16]. In particular, his group reported a very demonstrative example of the acceleration of the reaction rate ‘‘on water’’ with the reaction of quadricyclane and dimethyl azodicarboxylate (Figure 2.1). The time to completion was measured in a broad variety of solvents and it clearly appeared that not only the dipolar effect and hydrogen bonding enhance the reaction rate (18 h in methanol compared to 36 h in DMSO, 72 h in dichloromethane or more than 120 h in toluene), but heterogeneity also played an important role in large rate acceleration with only a 10 min reaction time in water. In comparison, the reaction conducted under neat conditions requires 48 h to reach completion. Interestingly, when D2O is used as solvent, the reaction time increased to 45 min which may be due to a reduction of the hydrophobic effects and a higher viscosity that prevents a good mixing of the heterogeneous mixture [17].

Another impressive result on cycloaddition rate acceleration was reported by the group of Engberts in their study of the Diels–Alder reaction of cyclopentadiene and 3-aryl-1-(2-pyridyl)-2-propen-1-ones (Figure 2.2) [18]. They showed that the...
reaction carried out in water as solvent was 287-fold faster than the same reaction in acetonitrile.

In addition, they found that the reaction in water, combined with the use of Lewis acid and micellar catalysis, was accelerated by a factor of 1,800,000 compared to the reaction in acetonitrile.

Considering that reactions with negative activation volumes are likely to be accelerated in water, the group of Pirrung studied the influence of solvent on multicomponent transformations like Ugi and Passerini reactions [19, 20]. Indeed, as Multicomponent reactions consist of the reaction of three or more starting materials to
form a single product, they involve transition states resulting from the condensation of several molecules and are therefore predicted to have negative activation volumes. They initially studied the Passerini reaction of 3-methylbut-2-enoic acid, 3-methylbutanal and 2-isocyanato-2-methylpropane in several solvents (Figure 2.3). They reported that dichloromethane allowed the formation of the product with a 50% yield after 18 h, whereas no product was obtained in methanol and only a 15% yield was observed in dimethylformamide. In contrast, the use of water furnished the expected product quantitatively within 3.5 h. Moreover, the reaction could even be sped up by conducting the reaction in water containing additives that increase the hydrophobic effect, like lithium chloride (16-fold acceleration) or glucose (7-fold acceleration).

Examples of the improvement of reactivity in aqueous media for reactions involving free radicals have also begun to emerge recently since the strong oxygen–hydrogen bonds of water make it a very suitable solvent for these reactions [21]. For instance, Oshima and co-workers studied the metal free carbon–carbon bond formation through the iodine transfer cyclization of a-iodoacetates (Figure 2.4) [22].

In many organic solvents such as hexane, benzene, dichloromethane or tetrahydrofuran, the use of triethylborane as a radical initiator at room temperature could not afford the formation of the lactone. However, under the same conditions,
the product was obtained with a good 78% yield in water whereas low yields were obtained in other polar solvents such as acetonitrile, alcohols, dimethylformamide or dimethyl sulfoxide. Interestingly, these conditions were successfully applied to the formation of medium and large rings (up to 18-membered ring).

In some cases, water can improve the yield not only through the acceleration of the reaction but also because it eliminates or reduces side reactions. This concept was pertinently applied at the industrial level by Novartis for the synthesis of 1-substituted-4-cyano-1,2,3-triazoles from 2-chloroacrylonitrile and organic azides [23]. In this transformation, the 1,3-dipolar cycloaddition is followed by an aromatization which generates hydrogen chloride as a by-product and the main challenge is that 2-chloroacrylonitrile is known to polymerize under both acidic and basic conditions. In organic solvents (Figure 2.5), the hydrogen chloride released raises the acidity of the reaction mixture, thus favoring the polymerization of the olefin and decreasing the yield of the product, and high dilution or excess of this reagent has to be used in order to obtain good yields. In this context, the use of water turned out to be a very convenient and sustainable alternative since it enabled the reaction to take place in the organic phase while the generated hydrogen chloride was solubilized in the aqueous phase allowing minimization of the polymerization of the alkene.

Selectivity is also a very important parameter for sustainability since a non-selective transformation increases the environmental impact of a given organic reaction not only through the wasted mass of the by-products but also through the higher complexity of the purification steps.

<table>
<thead>
<tr>
<th>Solvent</th>
<th>Yields (%)</th>
</tr>
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<tbody>
<tr>
<td>n-Haptane</td>
<td>46</td>
</tr>
<tr>
<td>Toluene</td>
<td>51</td>
</tr>
<tr>
<td>Dimethylformamide</td>
<td>78</td>
</tr>
<tr>
<td>Ethanol</td>
<td>40</td>
</tr>
<tr>
<td>Neat</td>
<td>72</td>
</tr>
<tr>
<td>Water</td>
<td>98</td>
</tr>
</tbody>
</table>

![Figure 2.5 Beneficial use of water in the synthesis of triazole from azides and 2-chloroacrylonitrile.](image)
The nucleophilic opening of epoxides is a commonly used reaction in the synthesis of natural products and the selectivity of this reaction represents an important issue. The use of water as solvent in these reactions is being more and more described [24]. Recently, the group of Azizi reported that β-aminoalcohols could be synthesized in high yields from the reaction of epoxides and amines in water at room temperature (Figure 2.6) [25]. In most cases, a total regio- and stereoselectivity was obtained. In the case of styrene oxide however, both the regioisomers were formed but their yields and proportions were maximized in water compared to other organic solvents.

![Figure: 2.6 Formation of β-aminoalcohols through the ring opening of epoxides in water](image)

In 2005, the group of Kobayashi studied the asymmetric desymmetrization of meso-epoxides with amines catalyzed by a chiral scandium complex [26]. They showed that the reaction of aromatic epoxides with anilines led to a higher enantiomeric excess in water compared to dichloromethane or THF/water mixtures (Figure 2.6). In addition, the use of scandium tris(dodecylsulfate) instead of scandium triflate resulted in a better yield and enantiomeric excess, and these conditions were consequently successfully applied to a wide range of substrates, though the reaction is limited to aromatic amines.

In the field of organocatalysis, water is also being more and more investigated as a valuable solvent [27, 28], although its effects on the reaction mechanism are not necessarily well understood and still under study and discussion [29, 30]. In 2010, the group of Zhong reported a one-pot organocatalyzed synthesis of substituted tetrahydronaphthalene isoxazolidines (Figure 2.7) [31].
This transformation allowed the diastereo- and enantioselective formation of five stereogenic centers through a Michael addition/intramolecular [3+2] nitroene-olefin cycloaddition sequence.
During their optimization of the reaction conditions, the authors investigated several solvents and water afforded the best selectivities compared to hexane or dichloromethane (Figure 2.8). The use of a carboxylic acid as an additive was essential to obtain good conversions probably because it promoted both the enamine formation and the hydrolysis of the iminium ion to complete the catalytic cycle.

### 2.3 Workup improvement

Even though the use of water as the reaction medium in a given reaction is advantageous because of no toxicity and is hazardless, it does not necessarily allow us to eliminate organic solvents from the whole process. Indeed, the workup procedure, through extractions or chromatography purifications for instance, may be responsible for the consumption of a huge amount of solvent relative to the recovered mass of the product.

The group of Hayashi developed an efficient organocatalyst, combining both siloxy and tetrazole functional groups within a pyrrolidine scaffold, for the organocatalyzed asymmetric Mannich reaction of several ketones with dimethoxyacetaldehyde and p-anisidine (Figure 2.9) [32]. Practically, an aqueous solution of the aldehyde was used and no additional amount of water was necessary to obtain good yields and selectivities. This enables to charge directly the crude mixture on a silica gel column for chromatography, thus bypassing the extraction step.

![Figure 2.9 Extraction free organocatalyzed asymmetric Mannich reaction](image)

Luo and co-workers reported an aqueous asymmetric Michael addition between nitrostyrenes and cyclohexanone using a surfactant type chiral organocatalyst (Figure 2.10) [33]. They could run the reaction at room temperature without any...
additional additive and the adducts were obtained in high yields and selectivities. In general, no organic solvent was needed for the extraction since the isolation of the crude product was performed by filtration or phase separation.

![Aqueous asymmetric Michael addition catalyzed by a surfactant-type organocatalyst](image)

Figure 2.10 Aqueous asymmetric Michael addition catalyzed by a surfactant-type organocatalyst

Ideally, however, the use of chromatography purifications should be avoided. This requires not only a very efficient and selective reaction, but also a means to isolate the product from by-products or catalysts. When they developed a convenient copper(I)-catalyzed click glycosylation of alkynes to form unprotected neoglycoconjugates at room temperature in water, Vauzeilles and co-workers generated the active catalytic species with a mixture of copper(II) sulfate and sodium ascorbate (Figure 2.11) [34].

![Practical synthesis of unprotected neoglycoconjugates by click chemistry](image)

Figure 2.11 Practical synthesis of unprotected neoglycoconjugates by click chemistry

In order to separate the product from polar by-products (like the oxidation product of ascorbate), they used a catalytic amount of ortho-phenylenediamine which allowed the formation of quinoxaline derivatives from dehydroascorbate. These compounds, as well as copper complexes, were then easily removed by adsorption on
activated charcoal at the end of the reaction, and a simple filtration led to the pure product without the need for chromatography purification.

Since in most cases the organic product is hardly water soluble, efficient procedures for the organic solvent free purification of reactions conducted with water as solvent (provided that the reaction has reached completion) are the filtration or phase separation. In this context, the group of Butler showed that the 1,3-dipolar cycloaddition of phthalazinium-2-dicyanomethanide with various alkenes led to sparingly water soluble adducts which can be isolated from the reaction mixture by a simple filtration (Figure 2.12) [35]. In the case of N-arylmaleimides, the reaction can be conducted at room temperature since their slight solubility in water allows them to react with the dipolar starting material whereas the use of insoluble dipolarophiles (such as 4-chlorobenzylideneacetone) requires to run the reaction at their liquefaction temperature.

To demonstrate the value of water as solvent for the high throughput synthesis of molecules in a combinatorial chemistry approach, Pirrung and co-workers performed the Ugi reaction of two isonitriles, four aldehydes and four acids to obtain...
a library of 32 β-lactams (Figure 2.13) [19,20]. In most cases, the products were solid and could be collected by filtration as the only purification.

![Diagram](image)

Figure 2.14 Organic solvent free synthesis of a Diels–Alder adduct through asymmetric organocatalysis

During their development of an organocatalyzed asymmetric Diels–Alder reaction of α,β-unsaturated aldehydes and dienes using a chiral diarylprolinol silyl ether salt, the group of Hayashi showed that scaling up the reaction to a 20 mmol scale can avoid the use of organic solvents (Figure 2.14) [36]. Indeed, the water phase can be simply removed by decantation and distillation afforded the cycloadduct with excellent yields and selectivities.

### 2.4 Mild reaction conditions

From a Green Chemistry point of view, the development of mild reaction conditions is a key issue, not only because it can lead to safer processes, but also because less reactive reagents are generally more easily available, requiring less upstream synthetic procedures.

The group of Charette described the racemic and asymmetric transition metal-catalyzed cyclopropanation of various olefins in water [37]. However, this reaction involved the synthesis and subsequent use of potentially explosive ethyl diazoacetate. To address this issue, the same group described conditions allowing the in situ synthesis of the diazo compound, starting from glycine ethyl ester hydrochloride salt and adding sodium nitrite and sulfuric acid, which then reacted with the rhodium catalyst and styrene to lead to the expected cyclopropane in good yields and moderate selectivities (Figure 2.15). Moreover, this reaction was conducted successfully on a 3 g scale, enabling a cheap, secured and straightforward access to cyclopropane moieties.
In the field of copper(I)-catalyzed alkyne azide 1,3-dipolar cycloaddition (CuAAC), Perica’s and co-workers described a highly active copper complex (prepared in four steps from readily available substrates), catalyzing azide-alkyne couplings in water at room temperature with catalyst loading of 0.5 mol% [38]. In addition, they were able to conduct the same reaction but starting from the brominated starting material through the in situ formation of the azide (Figure 2.16), thus avoiding the manipulation and storage of organic azides.

Reduction of double bonds is a widely used methodology in synthesis either for the introduction of chiral centers in organic molecules or for functional group interconversion. However, this methodology often involves the use of hazardous hydrogen gas and pressure reaction vessels and, lately, transfer hydrogenation has emerged as a safer alternative [39]. Interestingly, the use of water as solvent in transfer hydrogenation has recently gained interest [40]. For example, the group of Xiao described in 2006 very mild conditions for the efficient and chemoselective iridium-catalyzed reduction of aldehydes to alcohols in water (Figure 2.17) [41].
particular, they showed that the reaction tolerated many functional groups like halogens, olefins or nitro, and did not require an inert atmosphere with catalyst loading as low as 0.002 mol%. A TOF of 1 32 000 h⁻¹ was even achieved for the reduction of benzaldehyde.

![Figure 2.17 Aqueous transfer hydrogenation of aldehydes](image)

The nucleophilic addition of acetylides to electrophiles is also a powerful transformation, allowing us to access compounds that can be further converted into a wide range of products.

![Figure 2.18 Synthesis of propargylamines in water by the A³ coupling](image)

However, these reactions often require stoichiometric highly basic reagents (and thus protecting groups) and/or anhydrous and inert conditions. Recently, milder conditions have been reported to conduct some of these transformations, in which water holds a particular place [42]. For instance, the group of Li showed that the
three-component coupling of an aldehyde, an amine and an alkyne (A³ coupling) could be carried out in water using commercially available gold or silver catalysts (Figure 2.18). In addition, they were able to develop an asymmetric version of this reaction in water using a combination of copper(I) triflate and pybox as a catalytic system which led to high yields and good enantioselectivities (Figure 2.18) [43].

Organoboron reagents are particularly attractive compounds because they are stable, easy to handle and have a low toxicity. In particular, they have been widely used in cross-coupling reactions (Suzuki–Miyaura coupling). The use of water as the sole solvent in this reaction is therefore an attractive challenge. In 2005, the group of Buchwald described the synthesis of a new sulfonated ligand which was found to form a highly active complex for the aqueous Suzuki–Miyaura coupling of aryl chlorides with boronic acids (Figure 2.19) [44]. In many cases, the reaction could be conducted at room temperature and low catalyst loadings could be used (0.1–0.5 mol%). Interestingly, a broad scope of aryl chlorides or boronic acids with different functional groups reacted under these conditions without the need of any protecting groups.

A very straightforward and atom-economic strategy for the formation of carbon–carbon bonds is the direct coupling of two carbon–hydrogen bonds under oxidative conditions (cross-dehydrogenative coupling) [45]. This methodology allows the use of readily available substrates, thus by-passing the functionalization /defunctionalization steps and shortening the synthetic paths. However, in order to obtain a substantial gain in the environmental impact with these reactions, the choice
of oxidant is crucial, and in particular the use of clean and inexpensive molecular oxygen is highly desirable.

2.5 Key findings from the literature survey

Green chemistry is a multifaceted and complex challenge. Though complete greenness may be difficult to reach, it is a goal chemists must aim at, through the improvement of several aspects and parameters of a given reaction, from the synthesis and availability of its reactants and reagents, to the separation and purification of the product. In this context, the use of water as solvent features many benefits: not only because water itself is innocuous, but also it can potentially improve reactivities and selectivities, simplify the workup procedures, enable the recycling of the catalyst and allow mild reaction conditions and protecting group free synthesis. In addition, development of organic chemistry in water can lead to uncommon reactivities and reverse selectivities compared to organic solvents, thus complementing the organic chemists’ synthetic toolbox.

Moreover, the emergence of this field is also crucial for novel applications and developments in biology and bioorganic chemistry, leading to rich research opportunities. Studying chemistry in water is also an interesting way to gain insights into the biosynthesis of natural products and then to learn how Nature does chemistry and, ultimately, to which extent we can mimic it.

2.6 Reported synthetic strategies

2.6.1 Three-component synthesis of Dihydropyrano[2,3-c]pyrazoles

Laufer et al. [46] have synthesized 1,4-dihydropyrano[2,3-c]pyrazoles (Figure 2.20) with various substituents at the 1-, 3-, and 4-position. Given the large number of commercially available aldehydes and the easy access to hydrazines and β-keto esters, this method should be applicable to synthesis of libraries with high diversity.

The corresponding β-keto esters were synthesized either according to Yuasa and Tsuruta [47] or by deprotonation of esters and subsequent reaction with ethyl acetate. This second procedure (deprotonation of esters), described in a patent application for the synthesis of ethyl 3-oxo-3-(pyridin-4-yl)propanoate [48], is more advantageous because the reaction can be performed using ethyl acetate as both the
solvent and reagent without further purification. The reaction was performed at room temperature overnight, and nearly all products precipitated as discrete crystals.

\[
\begin{align*}
\text{R}_1&= \text{H}, \text{CH}_3, \text{C}_6\text{H}_5, 4\text{-OCH}_3\text{-C}_6\text{H}_4, -\text{CH}_2\text{-C}_6\text{H}_5 \\
\text{R}_2&= \text{CH}_3, \text{C}_3\text{H}_7, \text{C}_6\text{H}_5, 4\text{-F}\text{-C}_6\text{H}_4, -\text{CH}_2\text{-C}_6\text{H}_5, \text{pyridine} \\
\text{R}_3&= \text{C}_6\text{H}_5, 4\text{-F}\text{-C}_6\text{H}_4, 4\text{-OCH}_3\text{-C}_6\text{H}_4, 4\text{-Cl}\text{-C}_6\text{H}_4, 4\text{-OH}\text{-C}_6\text{H}_4, \\
&\quad 2\text{-Cl}\text{-5-NO}_2\text{-C}_6\text{H}_4, \text{pyridine}
\end{align*}
\]

Figure 2.20

2.6.2 Four-component pyrano[2,3-c]pyrazoles synthesis

Shestopalov et al. [49] demonstrated that a four-component reaction of aromatic aldehydes, malononitrile, \( \beta \)-ketoesters, and hydrazine hydrate successfully yields 6-aminopyrano[2,3-c]pyrazol-5-carbonitriles without the need of prior pyrazolin-5-ones isolation [50]. The multicomponent synthesis of pyranopyrazoles was carried out by simultaneously refluxing all four starting materials in ethanol for 15 min. in the presence of Et\(_3\)N (Scheme 2.20).

\[
\begin{align*}
\text{H}_2\text{N} &\quad \text{H}_2\text{O} \\
\text{NH}_2 &\quad \text{CHO} \\
&\quad *\text{H}_2\text{O} \\
\text{EtOH}, \text{Et}_3\text{N}, \text{reflux}, 15 \text{ min.}
\end{align*}
\]

Figure 2.21

They showed that aromatic aldehydes with electron-withdrawing, electron-donating, withdrawing and donating groups, as well as napthaldehydes and heteroaromatic aldehydes can be successfully reacted with \( \beta \)-ketoesters, malononitrile, and hydrazine hydrate to yield final pyrano[2,3-c]pyrazoles with high regio-selectivity.
2.6.3 1,4-dihydropyrano[2,3-c]pyrazoles synthesis in aqueous media

Shi et al. [51] report one-pot synthesis of 1,4-dihydropyrano[2,3-c]pyrazole derivatives by three-component reaction in aqueous media. When aromatic aldehydes, malononitrile, 3-methyl-1-phenyl-2-pyrazolin-5-one, and triethylbenzylammonium chloride (TEBA) were stirred at 90 °C for 6-10 h in water, the products were obtained in good yields (Figure 2.22).

![Figure 2.22](image)

The three-component reaction of aromatic aldehydes, malononitrile, and 3-methyl-1-phenyl-2-pyrazolin-5-one to 6-amino-5-cyano-4-aryl-1,4-dihydropyrano[2,3-c]pyrazoles has been efficiently performed in aqueous media. The easy purification of products by simple crystallization, and the use of water as solvent combined with the exploitation of the multicomponent strategy open to this process suggest good prospects for its industrial applicability.

2.6.4 Base-catalyzed route of Dihydropyrazolo[3,4-b]pyrans

2.6.4.1 By using Ammonium acetate

Li et al. [52] reported the preparation of 2H,4H-dihydropyrazolo[3,4-b]pyrans from the reaction of 4-Arylidene-3-methyl-1-phenyl-5-pyrazolones and β-ketoester using ammonium acetate as a catalyst (Figure 2.23).

![Figure 2.23](image)

R = C₆H₅, p-CH₃C₆H₄, p-CH₃OC₆H₄, p-NO₂C₆H₄, p-BrC₆H₄, o-CH₃C₆H₄, o-FC₆H₄, m-ClC₆H₄, o-OHC₆H₄
Ammonium acetate has been used widely as a base or a catalyst in Biginelli reactions [53, 54], Hantzsch reactions [55] and other reactions [56, 57]. With this aim in view, they applied the ammonium acetate to this reaction. Treatment of 3-methyl-1-phenyl-4-phenylidene-5-pyrazolone with 1 equiv. of ammonium acetate followed by β-ketoester in ethanol at room temperature for 2 h gave the corresponding 1,4,5,6-tetrahydropyrazolo[3,4-b]pyrans.

2.6.4.2 By using TEA
Mixing equimolecular amounts of ethyl acetoacetate with hydrazine hydrate, benzaldehyde and malononitrile has produced corresponding pyranopyrazoles (Figure 2.24). This same product could be obtained in almost the same yield by reacting 3-amino-2-pyrazoline-5-one and arylidenemalononitriles in ethanol in the presence of chitosan or, as originally reported, in the presence of piperidine. Despite the recently claimed isolation of Michael adduct, this could not be repeated even when the reaction was conducted at room temperature for a short period. Only either unchanged starting materials or cyclic products were isolated. It is of value to report that after an induction period the reaction is exothermic and temperature control is somewhat difficult.

The reaction of compound 4-(p-Methylphenylaminomethylidene)-1-phenyl-3,5-pyrazolidinedione with active nitriles and cyclic ketones, namely malononitrile, cyanoacetamide, cyanothioacetamide, cyanoacetic hydrazide, 1-phenyl-3,5-pyrazolidinedione, 3-methyl-1-phenyl-5-pyrazolone, cyclopentanone, cyclohexanone
and cycloheptanone in the presence of a catalytic amount of triethylamine gave pyrano[2,3-c]pyrazole derivatives (Figure 2.25) [58]. The reaction pathway of such compound was assumed to follow a preliminary formation of carbanion of the active methylene reagent, which was added to the double bond followed by a nucleophilic attack of the NH group at the CN, CO, and CS groups with the elimination of a water molecule in the case of cyanoacetamide and a H₂S molecule in the case of cyanothioacetamide [59].

Here, 4-(p-Methylphenylaminomethylidine)-1-phenyl-3,5-pyrazolidinedione was prepared from the reaction of 1-phenylpyrazolidine-3,5-dione with ethyl orthoformate and p-toluidine in boiling dimethylformamide.

2.6.4.3 Synthesis of spiro-dihydropyrazolo[3,4-b]pyrans

Figure 2.25

Figure 2.26
Evans et al. [60] describe a three-component condensation in which substituted piperidin-4-ones have been used in place of aromatic aldehydes to synthesize a new spiro heterocyclic system. They report that the base-catalyzed reaction of substituted piperidin-4-ones, pyrazol-5-ones, and malononitrile proceeds in ethanol at 20 °C with the formation of substituted 6-amino-5-cyanospiro-4-(piperidine-4’)-2H,4H-dihydropyrazolo[3,4-b]pyrans (Figure 2.26).

Three-component condensation of 4-piperidinones, 5-pyrazolones, and malononitrile proceeds chemically and electrochemically and is a convenient one-step means of synthesis of substituted 6-amino-5-cyanospiro-4-(piperidine-4’)-2H,4H-dihydropyrazolo[3,4-b]pyrans. The electrochemical reactions proceed under milder conditions and with yields 12-15% greater than those of the reactions catalyzed by chemical bases.

### 2.6.4.4 Dihydropyrazolopyrans from 1H-indole-2,3-dione

Aly H. Atta [61] reported the synthesis of a new series of compounds containing both the two moieties is likely to result in the formation of some interesting bioactive compounds. The one-pot reaction of 1H-indole-2,3-dione, 3-methyl-1-phenyl-2-pyrazolin-5-one, and active methylenes, namely malononitrile, ethyl cyanoacetate, pyrazolone, and acetyl acetone afforded the products. These products can be obtained via reaction of 3-[3-methyl-5-oxo-1-phenyl-1,5-dihydro-pyrazol-(4Z)-ylidene]-1,3-dihydro-indol-2-one with the corresponding active methylenes (Figure 2.27).

![Figure 2.27](image)

### 2.6.4.5 Pyrazolopyrans from pyrazole-aldehydes

Thumar and Patel [62] reported a series of 4-pyrazolyl-4H-pyrazolopyran derivatives by one-pot three-component cyclocondensation reaction of 1-phenyl-3-(het)aryl-pyrazole-4-carbaldehyde, malononitrile and substituted pyrazolin-5-ones in the
presence of piperidine as catalyst. The mixture refluxing under ethanol or acetonitrile gives pyran derivatives (Figure 2.28).

The reaction occurs via an in situ initial formation of the heterylidenenitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between pyrazole-4-carbaldehyde and malononitrile by loss of water molecules. Finally, Michael addition into the initially formed unsaturated nitrile, i.e. nucleophilic attack of hydroxyl moiety to the cyano moiety affords cyclized pyran derivatives.

2.6.4.6 Pyranopyrazoles by using heteropolyacid as a catalyst

Heravi et al. [63] reported facile method for the synthesis of 1,4-dihydropyrano[2,3-c] pyrazole derivatives via three-component one-pot condensation of 3-methyl-1-phenyl-1H-pyrazol-5(4H)-one, aldehydes and malononitrile in the presence of a catalytic amount of preyssler type heteropolyacid as a green and reusable catalyst in water or ethanol under refluxing conditions (Figure 2.29).

There has been considerable interest in the use of heteropolyacids as environmentally benign catalysts due to their unique properties such as high thermal stability, low cost, ease of preparation and recyclability. Numerous chemical reactions can occur in the presence of heteropolyacids [64]. Preyssler type heteropolyacid, $\text{H}_{14}\text{[NaP}_5\text{W}_{30}\text{O}_{110]}$, is remarkable owing to its exclusive physicochemical properties. These include strong Bronsted acidity, reversible transformations, solubility in polar and non-polar solvents, high hydrolytic and thermal stability, which are all essential in
catalytic processes. Preyssler polyanion, as a large anion, can provide many “sites” on the oval-shaped molecule that are likely to render the catalyst effective [65]. This heteropolyanion with [66] acidic protons, is an efficient “super acid” solid catalyst which can be used both in the homogeneous and heterogeneous phases [67].

![Figure 2.29](image)

**2.6.4.7 Synthesis of aminochromenes**

A four component Knoevenagel-Michael addition-cyclization sequence has been studied for the synthesis of dihydropyranopyrazole derivatives from hydrazine hydrate, a malonitrile, a β-ketoester, and an aldehyde or a ketone.

![Figure 2.30](image)
The reaction was described under catalyst- and solvent-free conditions [68] and using piperidine in ultrapure aqueous media [69], both at room temperature. But this methodology was intensively developed by Shestopalov and co-workers since they used a wide range of aldehydes, ketones, and \( \beta \)-ketoesters to form a series of these fused heterocyclic skeletons, even if substituted hydrazines were unreactive in this protocol [49].

More recently, an adaptation of this four-component transformation in water was proposed as a green combinatorial synthesis of novel aminochromene derivatives bearing an hydroxymethyl pyrazole functional group in the four-position, instead of a fused skeleton. In this unexpected transformation, 2-hydroxybenzaldehyde plays a crucial role by reacting selectively with malonitrile to form the chromene intermediate (Figure 2.30) [70].

2.6.4.8 Solvent-free multicomponent synthesis of pyranopyrazoles

The conventional synthesis of 2-amino-3-cyano-4\( H \)-pyrans use organic solvent, but these solvents make the workup procedure complicated and lead to poor yields of products [71]. In recent years, 2-amino-3-cyano-4\( H \)-pyrans have also been synthesized under microwave [72], with ultrasound irradiation [73], or in aqueous media [51, 74, 75]. Some two-component [76] and three-component [74] condensations have been introduced for the synthesis of 2-amino-3-cyano-4\( H \)-pyrans. Each of these methods has its own merit, with at least one of the limitations of low yields, long reaction time, effluent pollution, harsh reaction conditions, and tedious workup procedures. All of these reasons spur us to study the possibility of synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[\( b \)]pyrans and 6-amino-5-cyano-4-aryl-1,4-dihydro-pyran[2,3-\( c \)]pyrazoles under solvent-free conditions.

Li et al. [77] report a highly efficient procedure for the synthesis of 2-amino-3-cyano-4-aryl-7,7-dimethyl-5,6,7,8-tetrahydrobenzo[\( b \)]pyrans and 6-amino-5-cyano
Chapter 2 Pyrano[2,3-c]pyrazoles…

-4-aryl-1,4-dihydropyrano[2,3-c]pyrazoles via a one-pot grinding method under solvent-free conditions using an inexpensive and commercially available D,L-proline as catalyst (Figure 2.31 & 2.32).

In a typical general experimental procedure, aromatic aldehydes, malononitrile, dimedone [1,3-cyclohexanedione or 3-methyl-1-phenyl-2-pyrazolin-5-one], and a catalytic amount of D,L-proline are added to a mortar. The mixture is ground by mortar and pestle at room temperature for a period. The solid product is obtained from an intermediate melt and then is laid up at room temperature for 30 min. The mixture is transferred to ice water and then is filtered off. The crude products are purified by recrystallization by ethanol to afford the products in good yields.

A simple, green and efficient protocol is developed with per-6-amino-b-cyclodextrin (per-6-ABCD) which acts simultaneously as a supramolecular host and as an efficient solid base catalyst for the solvent-free syntheses of various dihydropyrano[2,3-c]pyrazole derivatives involving a four-component reaction (Figure 2.33).

Per-6-amino-b-cyclodextrin (per-6-ABCD) is used extensively as a supramolecular chiral host and as a base catalyst for Cu-catalyzed N-arylation [78] and for Michael addition of nitromethane to chalcones [79]. Kanagaraj and Pitchumani [80] have utilized per-6-ABCD as an excellent supramolecular host for
the synthesis of pyranopyrazole derivatives, in an efficient and ecofriendly four-component reaction protocol under solventfree conditions at room temperature. It is also interesting to note that the catalyst can be recovered and reused several times.

2.6.4.9 Syntheses of Polyfunctionalized Phenols Linked to Heterocycles

Boghdadie et al. [81] reported that, a solution of 4-(hydroxyl-3-methoxybenzylidine) malononitrile and 3-ethyl-1-phenyl-2-pyrazolin-5-one, in ethanol (50 ml) and two drops of piperidine was heated under reflux for 2 hours, cooled and poured onto water. The products were recrystallized from ethanol to give the corresponding compound 6-amino-3-ethyl-4-(4-hydroxy-3-methoxyphenyl)-1-phenyl-4H-pyrano[3,2-d]pyrazole-5-carbonitrile (Figure 2.34).

2.6.5 Benzopyran Derivatives

2.6.5.1 4H-benzo[b]pyrans using TBAB as a catalyst
Fard et al. [82] reported a highly efficient procedure for the preparation of 4H-benzo[b]pyrans and pyrano[2,3-d]pyrimidinones via a domino Knoevenagel cyclocondensation reaction using TBAB as a catalyst in water.

In a typical experimental procedure, a mixture of aromatic aldehyde, malononitrile, dimesdione or barbituric acid in water under reflux condition, was stirred in the presence of a catalytic amount of TBAB (10 mol%) to afford the 4H-benzo[b]pyrans and pyrano[2,3-d]pyrimidinones (Figure 2.35).

2.6.5.2 2-Imino-2H-chromene-3-carbonitrile using NaBH₄ as a catalyst

Rai et al. [83] have reported a synthesis (Figure 2.36) in ethanol using triethylamine to first get 2-Imino-2H-chromene-3-carbonitrile which they reduced using sodium borohydride in methanol to give the essential 2-Aminon-Cyanochromane derivative. The reaction mixture here has been conventionally refluxed for 3 h.

2.6.5.3 2-Amino-3-cyanochromene using MgO as a catalyst

Kumar et al. [84] have reported an environmentally benign synthetic process using Magnesium oxide as the catalyst and by process of grinding (Figure 2.37). This is the classical reaction where in a benzaldehyde or ketone has first been reacted with a malanionitile which has got an active hydrogen site, yielding the benzylidene malononitrile which when reacted to a 1,3-Diketo compound herein a meldurms acid afforded the 2-Amino-3-cyanochromene derivative the only difference than the classical methodology is that the reaction has been carried at room temperature and it is grinded which means there are absolutely no solvent which makes it a green process and which is also faster and gives a higher yield.
2.6.5.4 Benzopyrans using chitosan as a catalyst

Similarly, Al-Matar et al. [85] have synthesized many compounds of this class using chitosan as the catalyst (Figure 2.38).

2.6.5.5 Benzopyrans using piperidine as a catalyst

More so ever Al-Matar et al. [85] have also studied the formation of the exact product i.e. 2-Amino-3-cyano-7-hydroxy-4H-chromene instead of 5-hydroxy derivative when resorcinol is reacted with malanoniitrile using piperidine and ethanol. They have come out with this result using the Nuclear Overhauser Effect calculation from the proton NMR spectrum (Figure 2.39).
They have also prepared many such compounds using the same methodology but different starting materials as shown in Figure 2.40.

Naliyapara et al. [86] have extended this work using 4-Hydroxy coumarin as a starting product (Figure 2.41).
They have synthesized the spiro-compounds using the cyclic ketones to produce the desired results but failed to obtain the chromenes when the aryl ketones were used in the reaction. The reaction schemes followed are shown in Figure 2.42.

2.6.5.6 Benzopyrans using potassium carbonate as a catalyst

Kidwai et al. [87] has prepared the same class of the compounds using water as a solvent and potassium carbonate as the required base catalyst (Figure 2.43).

Such compounds were prepared using different starting materials as diverse kinds of aldehydes viz. Phenyl, Quinolyl, Indolyl and alkyl were reacted with malanonitrile in presence of saturated potassium carbonate solution and then microwave irradiation was induced upon the reaction mixture which afforded the 2-Amino-3-cyano-4-substituted phenyl-7-hydroxy-4H-chromene derivatives.

2.6.5.7 Ionic liquids as catalyst for the synthesis of benzopyrans
The synthesis of 4H-benzo[b]pyran derivatives has also been proposed by means of a basic ionic liquid-catalyzed three-component approach involving malononitrile, aromatic aldehydes and dimedone. The conventional method, requiring the use of refluxing DMF or acetic acid, lead to low yields and renders the isolation step troublesome. Other procedures have been described but all of them suffer at least from one limitation. Alternatively, it has been found that a small amount of N,N-dimethylaminoethylbenzyl-dimethylammonium chloride catalyzed a rapid and high yielding solvent-free transformation at 60 °C with a wide variation of the aldehyde partner (Figure 2.44) [88].

While, Peng and Song conducted this MCR in a mixture of catalytically active ionic liquid and water [89], and Lingaiah and co-workers reported the use of a heterogeneous strong basic Mg/La mixed oxide catalyst in methanol [90]. Compared to the utilization of more classical solvents and organic bases, these strategies combine advantages in efficiency such as shorter reaction times and higher yields, with ecological advantages in terms of recovery and reusability of the catalyst.

This approach has been extended to cyclic 1,3-dicarbonyls for the synthesis of tetrahydrobenzopyrane derivatives, also known as tetrahydrochromenes, which have attracted much attention due to their wide range of biological properties. Thus, a mixture of an aromatic aldehyde, dimedone, and malonitrile in aqueous media catalyzed either by (S)-proline [91] or tetramethylammonium hydroxide (TMAH) [92] gave the bicyclic heterocycle in excellent yields (Figure 2.45).
2.7 Aim of current work

Pyran and fused pyran derivatives have attached a great deal of interest due to their association with various kinds of biological properties. They have been reported for their antimicrobial [93-96], antiviral [97, 98], anticonvulsant [99], cytotoxic [100] and antigenotoxic [101] activities. The incorporation of another heterocyclic moiety in pyrans either in the form of a substituent or as a fused component changes its properties and converts it into an altogether new and important heterocyclic derivative.

Pyrazole have attracted particular interest over the last few decades due to use of such ring system as the core nucleus in various drugs. They are well-known for their activities such as antidiabetic [102], antipyretic [103], anti-inflammatory [104], anti-hypertensive [105], antitumour [106], peptide deformylase inhibitor [107], and antidepressant agents [108]. Considering the importance of pyran and pyrazole derivatives, it was thought worthwhile to synthesize new compounds incorporating both these moieties.

It is pertinent to mention that a large number of pyrazole fused and pyrazole substituted pyran derivatives are reported as biologically important compounds and their chemistry have received considerable attention of chemists in recent days [109-113]. Thus, pyranopyrazoles exhibit useful biological properties such as antimicrobial [114], insecticidal [115], and anti-inflammatory [116]. Furthermore Dihydropyrano[2,3-\textit{c}]pyrazoles showed molluscicidal activity [117, 118] and was identified as a screening hit for Chk1 kinase inhibitor [119].

Over the last years, the chemistry of dihydropyrano[2,3-\textit{c}]pyrazoles has received great interest. The first approach to synthesize these substances was undertaken by Otto [120], in which he initiated the reaction sequence by the base-catalyzed cyclization of 4-aryliden-5-pyrazolone. In a further report, this same group showed that weak bases can also be used for a Michael-type cyclization [121]. Extending the work of Otto, Klokol and colleagues performed the direct conversion of 3-methyl-3-pyrazolin-5-one with malononitrile in the presence of a weak base [122]. Recent methods for the synthesis of 1,4-dihydropyrano[2,3-\textit{c}]pyrazoles include synthesis in aqueous media [51], under microwave irradiation [72], and under solvent-free conditions [77, 123].
Thus, in view of the diverse therapeutic activity of pyran[2,3-c]pyrazoles, we report one-pot synthesis of pyran[2,3-c]pyrazole derivatives (YUG 101-140) by three-component reaction, a scaffold from which a diverse range of other biologically important New Chemical Entities (NCE’s) could be generated. A series of novel 1,4-dihydropyran[2,3-c]pyrazole derivatives (YUG 101-140) has been synthesized by one-pot three-component cyclocondensation reaction of aromatic aldehydes, malononitrile and substituted pyrazolin-5-ones. The mixture was stirred in ethanol/water (1:1, v/v) to give 1,4-dihydropyran[2,3-c]pyrazole derivatives. The products were characterized by FT-IR, mass, $^1$H NMR, $^{13}$C NMR spectroscopy and elemental analyses. The structure of representative compound was elucidated using single crystal X-ray diffraction method. The newly synthesized compounds were subjected to various biological activities viz., antimicrobial, antitubercular, anticancer and antiviral.
2.8 Reaction Scheme

Reagents & Conditions: (a) EtOH/Water (1:1, v/v), Stirring, 30 min.

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<th>M.W.</th>
<th>M.P. °C</th>
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### Chapter 2

#### Pyrano[2,3-c]pyrazoles

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<td>75</td>
<td>0.49</td>
<td>0.63</td>
<td></td>
</tr>
<tr>
<td>YUG-140</td>
<td>Ph 3,4,5-OCH₃</td>
<td>C₂₃H₂₄N₄O₄</td>
<td>446</td>
<td>174-176</td>
<td>80</td>
<td>0.50</td>
<td>0.68</td>
<td></td>
</tr>
</tbody>
</table>

2.9 Plausible Reaction Mechanism

The mechanism reaction occurs via an in situ initial formation of the arylidene of malononitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between aromatic aldehydes and malononitrile by loss of water molecules. Finally, Michael addition of pyrazolone to the initially formed unsaturated nitrile, i.e. nucleophilic attack of hydroxyl moiety to the cyano moiety affords cyclized pyran derivatives.
2.10 Experimental

2.10.1 Materials and Methods
Melting points were determined in open capillary tubes and are uncorrected. Formation of the compounds was routinely checked by TLC on silica gel-G plates of 0.5 mm thickness and spots were located by iodine. IR spectra were recorded on Shimadzu FT-IR-8400 instrument using KBr pellet method. Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. $^1$H NMR and $^{13}$C NMR was determined in DMSO-$d_6$ solution on a Bruker Ac 400 MHz spectrometer. Elemental analysis of the all the synthesized compounds was carried out on Elemental Vario EL III Carlo Erba 1108 model and the results are in agreements with the structures assigned.

2.10.2 Synthesis of 3-isopropyl-1H-pyrazol-5(4H)-one/3-isopropyl-1-phenyl-1H-pyrazol-5(4H)-one
Synthesis of 3-propyl-1H-pyrazol-5(4H)-one/3-propyl-1-phenyl-1H-pyrazol-5 (4H)-one was prepared by known literature method [122].

2.10.3 General procedure for the synthesis of 6-amino-4-(aryl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG -101 to 120)
A mixture of the malononitrile (0.01 mol), 3-propyl-1H-pyrazol-5(4H)-one (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in 8-10 mL of EtOH/H$_2$O (1:1) was stirred for 30 min. After completion of the reaction, the reaction mixture was filtered to give the solid products YUG-101 to 120, which were recrystallized from ethanol.

2.10.3.1 6-amino-1,4-dihydro-4-(4-methoxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-101)
Chapter 2

Yield: 70%; mp 168-171 °C; IR (cm⁻¹): 3514 (N-H stretching of free primary amine), 3254 (N-H stretching of pyrazole ring), 3093 (C-H stretching of aromatic ring), 2183 (C≡N stretching of the nitrile group), 1635 (C=N stretching of pyrazole ring), 1600 (N-H deformation pyrazole ring), 1188 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.68-0.72 (t, 3H, Hₐ), 1.21-1.35 (m, 2H, Hₙ), 2.04-2.22 (m, 2H, Hₜ), 3.76 (s, 1H, Hₜ), 4.50 (s, 3H, Hₜ), 6.22 (s, 2H, Hₜ), 6.79-6.82 (m, 2H, H₂₉, J = 11.56 Hz), 7.06-7.10 (m, 2H, H₂₉, J = 14.2 Hz), 11.84 (s, 1H, Hₙ); ¹³C NMR (DMSO-d₆) δ ppm: 13.15, 20.87, 26.32, 35.85, 54.73, 58.77, 97.10, 113.34, 120.62, 128.27, 136.19, 139.86, 154.68, 157.96, 160.31; MS: m/z 310; Anal. Calcd. for C₁₇H₁₈N₄O₂: C, 65.79; H, 5.85; N, 18.05. Found: C, 65.75; H, 5.81; N, 18.01%.

2.10.3.2 6-amino-1,4-dihydro-3-propyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-102)

Yield: 78%; mp 188-190 °C; IR (cm⁻¹): 3473 (N-H stretching of free primary amine), 3227 (N-H stretching of pyrazole ring), 3117 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1635 (C=N stretching of pyrazole ring), 1600 (N-H deformation pyrazole ring), 1188 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.67-0.71 (t, 3H, Hₐ), 1.18-1.36 (m, 2H, Hₙ), 2.02-2.24 (m, 2H, Hₜ), 2.30 (s, 1H, Hₜ), 4.50 (s, 3H, Hₜ), 6.40 (s, 2H, Hₜ), 7.01-7.09 (m, 2H, H₂₉, J = 16.92 Hz), 11.88 (s, 1H, Hₙ); ¹³C NMR (DMSO-d₆) δ ppm: 13.16, 20.60, 26.30, 30.46, 36.27, 58.27, 97.05, 120.64, 127.19, 128.65, 135.65, 139.75, 141.26, 154.68, 160.47; MS: m/z 294; Anal. Calcd. for C₁₇H₁₈N₄O: C, 69.37; H, 5.81; N, 19.03. Found: C, 69.33; H, 6.12; N, 18.99%.
2.10.3.3 6-amino-4-(4-fluorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-103)

Yield: 81%; mp 184-186 °C; IR (cm\(^{-1}\)): 3487 (N-H stretching of free primary amine), 3234 (N-H stretching of pyrazole ring), 3057 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1604 (N-H deformation pyrazole ring), 1182 (N-N deformation of pyrazole ring), 1049 (C-H in plane bending of aromatic ring), 826 (C-H out of plane bending for 1,4-disubstituted aromatic ring); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 0.67-0.71 (t, 3H, H\(_a\)), 1.18-1.36 (m, 2H, H\(_b\)), 2.03-2.22 (m, 2H, H\(_c\)), 4.56 (s, 1H, H\(_d\)), 6.40 (s, 3H, H\(_e\)), 6.98-7.03 (t, 2H, H\(_{ff'}\), \(J = 17.02\) Hz), 7.16-7.19 (m, 2H, H\(_{gg'}\), \(J = 13.84\) Hz), 11.92 (s, 1H, H\(_k\)); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) ppm: 13.13, 20.86, 26.30, 35.96, 58.05, 96.73, 114.63, 120.47, 128.93, 140.22, 154.63, 159.82, 160.48, 162.24; MS: \(m/z\) 298; Anal. Calcd. for C\(_{16}\)H\(_{15}\)FN\(_4\)O: C, 64.42; H, 5.07; N, 18.78. Found: C, 64.38; H, 5.03; N, 18.75%.

2.10.3.4 6-amino-4-(4-chlorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-104)

Yield: 72%; mp 188-190 °C; IR (cm\(^{-1}\)): 3475 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrazole ring), 3043 (C-H stretching of aromatic ring), 2195 (C≡N stretching of the nitrile group), 1635 (C=N stretching of pyrazole ring), 1599 (N-H deformation pyrazole ring), 1186 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring), 813 (C-H out of plane bending for 1,4-
disubstituted aromatic ring); $^1$H NMR (DMSO-$d_6$) $\delta$ ppm: 0.67-0.71 (t, 3H, $H_a$), 1.19-1.35 (m, 2H, $H_b$), 2.03-2.22 (m, 2H, $H_c$), 4.56 (s, 1H, $H_d$), 6.58 (s, 2H, $H_e$), 7.15-7.21 (m, 2H, $H_{ff'}$, $J = 14.40$ Hz), 7.27-7.30 (m, 2H, $H_{gg'}$, $J = 10.76$ Hz), 11.92 (s, 1H, $H_h$); $^{13}$C NMR (DMSO-$d_6$) $\delta$ ppm: 13.17, 20.88, 26.28, 36.08, 57.46, 96.49, 120.44, 128.10, 128.98, 131.57, 139.76, 143.21, 154.63, 160.62; MS: $m/z$ 314; Anal. Calcd. for C$_{16}$H$_{15}$ClN$_4$O: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.01; H, 4.70; N, 17.70%.

2.10.3.5 6-amino-1,4-dihydro-3-propyl-4-(pyridin-3-yl)pyrano[2,3-c]pyrazole-5-carbonitrile (YUG-105)

Yield: 69%; mp 180-183 ºC; IR (cm$^{-1}$): 3475 (N-H stretching of free primary amine), 3240 (N-H stretching of pyrazole ring), 3022 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1643 (C=N stretching of pyrazole ring), 1600 (N-H deformation pyrazole ring), 1184 (N-N deformation of pyrazole ring), 1051 (C-H in plane bending of aromatic ring); $^1$H NMR (DMSO-$d_6$) $\delta$ ppm: 0.68-0.72 (t, 3H, $H_a$), 1.24-1.37 (m, 2H, $H_b$), 2.06-2.22 (m, 2H, $H_c$), 4.63 (s, 1H, $H_d$), 6.20 (s, 2H, $H_e$), 7.30-7.32 (d, 1H, $H_f$, $J = 4.88$ Hz), 7.54-7.56 (d, 1H, $H_g$, $J = 7.6$ Hz), 8.47 (s, 2H, $H_h$) 11.93 (s, 1H, $H_i$); MS: $m/z$ 281; Anal. Calcd. for C$_{15}$H$_{15}$N$_5$O: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.01; H, 5.33; N, 24.87%.

2.10.3.6 6-amino-1,4-dihydro-4-(2-hydroxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-106)

Yield: 86%; mp 180-182 ºC; MS: $m/z$ 296; Anal. Calcd. for C$_{16}$H$_{16}$N$_4$O$_2$: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.81; H, 5.41; N, 18.89%.
2.10.3.7 6-amino-4-(3-chlorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-107)

Yield: 76%; mp 188-191 °C; IR (cm⁻¹): 3454 (N-H stretching of free primary amine), 3244 (N-H stretching of pyrazole ring), 3057 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1635 (C=N stretching of pyrazole ring), 1591 (N-H deformation pyrazole ring), 1184 (N-N deformation of pyrazole ring), 1051 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.67-0.71 (t, 3H, Hᵃ), 1.19-1.35 (m, 2H, Hᵇ), 2.09-2.20 (m, 2H, Hᶜ), 4.57 (s, 1H, Hᵈ), 6.61 (s, 2H, Hᵉ), 7.12-7.14 (t, 2H, Hᶠᶠ′, J = 8.16 Hz), 7.20-7.23 (m, 1H, Hᵍ), 7.27-7.31 (t, 1H, Hᵇ), 12.02 (s, 1H, Hⁱ); MS: m/z 314; Anal. Calcd. for C₁₆H₁₅ClN₄O: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.03; H, 4.76; N, 17.76%.

2.10.3.8 6-amino-4-(4-bromophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-108)

Yield: 80%; mp 218-220 °C; IR (cm⁻¹): 3471 (N-H stretching of free primary amine), 3223 (N-H stretching of pyrazole ring), 3039 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1633 (C=N stretching of pyrazole ring), 1600 (N-H deformation pyrazole ring), 1184 (N-N deformation of pyrazole ring), 1051 (C-H in plane bending of aromatic ring), 813 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.69-0.72 (t, 3H, Hᵃ), 1.21-1.38 (m, 2H, Hᵇ), 2.04-2.12 (m, 2H, Hᶜ), 4.54 (s, 1H, Hᵈ), 6.49 (s, 2H, Hᵉ), 7.08-7.12 (m, 2H, Hᶠᶠ′, J = 13.40 Hz), 7.41-7.44 (m, 2H, Hᵍᵍ′, J = 13.12 Hz), 11.96 (s, 1H, Hⁱ);
2.10.3.9 
6-amino-1,4-dihydro-4-(4-hydroxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-109)

Yield: 88%; mp 148-151 ºC; MS: m/z 296; Anal. Calcd. for C_{16}H_{16}N_{4}O_{2}: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.81; H, 5.41; N, 18.89%.

2.10.3.10 
6-amino-1,4-dihydro-4-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-110)

Yield: 77%; mp 198-200 ºC; IR (cm^{-1}): 3485 (N-H stretching of free primary amine), 3230 (N-H stretching of pyrazole ring), 3034 (C-H stretching of aromatic ring), 2195 (C≡N stretching of the nitrile group), 1631 (C=N stretching of pyrazole ring), 1599 (N-H deformation pyrazole ring), 1184 (N-N deformation of pyrazole ring), 1051 (C-H in plane bending of aromatic ring); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 0.66-0.70 (t, 3H, H\(_a\)), 1.17-1.33 (m, 2H, H\(_b\)), 2.04-2.21 (m, 2H, H\(_c\)), 4.55 (s, 1H, H\(_d\)), 6.12 (s, 2H, H\(_e\)), 7.16-7.22 (m, 3H, H\(_{f-h}\)), 7.26-7.30 (m, 2H, H\(_{ii-i}'\)), 11.88 (s, 1H, H\(_j\)); \(^{13}\)C NMR (DMSO-\(d_6\)) \(\delta\) ppm: 13.07, 20.81, 26.31, 36.65, 58.67, 96.87, 120.52, 126.48, 127.28, 127.98, 139.96, 143.95, 154.69, 160.42; MS: m/z 280; Anal. Calcd. for C\(_{16}\)H\(_{16}\)N\(_4\)O: C, 68.55; H, 5.75; N, 19.99. Found: C, 68.51; H, 5.72; N, 19.95%.
2.10.3.11 6-amino-1,4-dihydro-4-(3-hydroxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-111)

Yield: 79%; mp 208-210 ºC; MS: m/z 296; Anal. Calcd. for C_{16}H_{16}N_{4}O_{2}: C, 64.85; H, 5.44; N, 18.91. Found: C, 64.81; H, 5.41; N, 18.87%.

2.10.3.12 6-amino-4-(2,4-dichlorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-112)

Yield: 82%; mp 220-223 ºC; MS: m/z 348; Anal. Calcd. for C_{16}H_{14}Cl_{2}N_{4}O: C, 55.03; H, 4.04; N, 16.04. Found: C, 55.00; H, 4.01; N, 16.00%.

2.10.3.13 6-amino-4-(3-bromophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-113)

Yield: 72%; mp 194-196 ºC; MS: m/z 358; Anal. Calcd. for C_{16}H_{13}BrN_{4}O: C, 53.50; H, 4.21; N, 15.60. Found: C, 53.46; H, 4.18; N, 15.56%.
2.10.3.14 6-amino-4-(2-bromophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-114)

Yield: 81%; mp 230-232 ºC; MS: m/z 281; Anal. Calcd. for C_{15}H_{15}N_{5}O: C, 64.04; H, 5.37; N, 24.90. Found: C, 64.01; H, 5.33; N, 24.87%.

2.10.3.15 6-amino-4-(2-bromophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-115)

Yield: 86%; mp 270-273 ºC; IR (cm\(^{-1}\)): 3473 (N-H stretching of free primary amine), 3232 (N-H stretching of pyrazole ring), 3105 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1637 (C=N stretching of pyrazole ring), 1597 (N-H deformation pyrazole ring), 1184 (N-N deformation of pyrazole ring), 1053 (C-H in plane bending of aromatic ring); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 0.63-0.67 (t, 3H, \(H_a\)), 1.11-1.31 (m, 2H, \(H_b\)), 2.05-2.28 (m, 2H, \(H_c\)), 5.14 (s, 1H, \(H_d\)), 6.47 (s, 2H, \(H_e\)), 7.03-7.13 (m, 2H, \(H_{ff'}\)), 7.22-7.33 (m, 1H, \(H_g\)), 7.45-7.56 (m, 1H, \(H_h\)), 11.92 (s, 1H, \(H_j\)); MS: m/z 358; Anal. Calcd. for C_{16}H_{15}BrN_{4}O: C, 53.50; H, 4.21; N, 15.60. Found: C, 53.46; H, 4.18; N, 15.56%.
2.10.3.16 6-amino-4-(2,6-dichlorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-116)

Yield: 75%; mp 138-140 °C; IR (cm⁻¹): 3369 (N-H stretching of free primary amine), 3240 (N-H stretching of pyrazole ring), 3099 (C-H stretching of aromatic ring), 2187 (C≡N stretching of the nitrile group), 1653 (C=N stretching of pyrazole ring), 1606 (N-H deformation pyrazole ring), 1159 (N-N deformation of pyrazole ring), 1047 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-­d₆) δ ppm: 0.63-0.67 (t, 3H, Hₐ), 1.11-1.31 (m, 2H, Hₐ), 2.05-2.28 (m, 2H, Hₙ), 5.14 (s, 1H, Hₜ), 6.47 (s, 2H, Hₐ), 7.03-7.13 (m, 2H, Hₕ), 7.22-7.33 (m, 1H, Hₙ), 7.45-7.56 (m, 1H, Hₜ), 11.92 (s, 1H, Hₗ); MS: m/z 349; Anal. Calcd. for C₁₆H₁₄Cl₂N₄O: C, 55.03; H, 4.04; N, 16.04. Found: C, 55.00; H, 4.00; N, 16.00%.

2.10.3.17 6-amino-4-(2-chlorophenyl)-1,4-dihydro-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-117)

Yield: 79%; mp 185-187 °C; MS: m/z 314; Anal. Calcd. for C₁₆H₁₅ClN₄O: C, 61.05; H, 4.80; N, 17.80. Found: C, 61.01; H, 4.76; N, 17.76%.
2.10.3.18 6-amino-1,4-dihydro-4-(3,4-dimethoxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-118)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\text{NH} \\
\text{O} \\
\text{O} \\
\text{O} \\
\text{N}_{\text{H}} \\
\text{O}
\end{array}
\]

Yield: 83%; mp 188-190 °C; MS: \(m/z\) 340; Anal. Calcd. for \(C_{18}H_{20}N_4O_3\): C, 61.05; H, 4.80; N, 17.80. Found: C, 61.01; H, 4.76; N, 17.77%.

2.10.3.19 6-amino-1,4-dihydro-4-(2,5-dimethoxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-119)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{NH} \\
\text{CN} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Yield: 77%; mp 183-185 °C; MS: \(m/z\) 340; Anal. Calcd. for \(C_{18}H_{20}N_4O_3\): C, 61.05; H, 4.80; N, 17.80. Found: C, 61.01; H, 4.76; N, 17.77%.

2.10.3.20 6-amino-1,4-dihydro-4-(3,4,5-trimethoxyphenyl)-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-120)

\[
\begin{array}{c}
\text{O} \\
\text{N} \\
\text{CN} \\
\text{NH}_{\text{H}} \\
\text{O} \\
\text{O} \\
\text{O} \\
\end{array}
\]

Yield: 79%; mp 181-183 °C; MS: \(m/z\) 370; Anal. Calcd. for \(C_{19}H_{22}N_4O_4\): C, 61.61; H, 5.99; N, 15.13; Found: C, 61.58; H, 5.97; N, 15.08%.
2.10.4 General procedure for the synthesis of 6-amino-1,4-dihydro-3-isopropyl-4-(aryl)-1-phenylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG -121 to 140)

A mixture of the malononitrile (0.01 mol), 3-propyl-1-phenyl-1H-pyrazol-5(4H)-one (0.01 mol) and an appropriate aromatic aldehyde (0.01 mol) in 8-10 mL of EtOH/H₂O (1:1) was stirred for 30 min. After completion of the reaction, the reaction mixture was filtered to give the solid products YUG-121 to 140, which were recrystallized from ethanol.

2.10.4.1 6-amino-1,4-dihydro-4-(4-methoxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-121)

Yield: 85%; mp 145-148 °C; IR (cm⁻¹): 3400 (N-H stretching of free primary amine), 3026 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1629 (C=N stretching of pyrazole ring), 1176 (N-N deformation of pyrazole ring), 1070 (C-H in plane bending of aromatic ring), 812 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.93-1.00 (t, 3H, Hₐ), 1.23-1.44 (m, 2H, Hₗ), 2.02-2.18 (m, 2H, Hₖ), 3.76 (s, 3H, Hₜ), 4.58 (s, 1H, Hₑ), 6.85-6.85 (d, 2H, Hᵦ', J = 8.56 Hz), 6.99 (s, 2H, H₇), 7.14-7.16 (d, 2H, Hₕ′, J = 8.56 Hz), 7.26-7.35 (m, 1H, Hᵣ), 7.43-7.48 (m, 2H, Hₗ), 7.79-7.87 (dd, 2H, Hₘₖ, J = 7.84 Hz) 11.92 (s, 1H, Hᵣ); ¹³C NMR (DMSO-d₆) δ ppm: 13.57, 20.72, 28.93, 30.52, 36.36, 54.87, 54.87, 58.95, 98.16, 113.62, 119.88, 125.76, 128.62, 128.99, 135.67, 137.66, 143.72, 149.06, 158.20, 159.04; MS: m/z 386; Anal. Calcd. for C₂₃H₂₂N₄O₂: C, 71.48; H, 5.74; N, 14.50. Found: C, 71.44; H, 5.70; N, 14.46%.
2.10.4.2 6-amino-1,4-dihydro-1-phenyl-3-propyl-4-p-tolylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-122)

![Chemical structure of YUG-122]

Yield: 81%; mp 150-152 °C; MS: m/z 370; Anal. Calcd. for C_{23}H_{22}N_{4}O: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.53; H, 5.95; N, 15.08%.

2.10.4.3 6-amino-4-(4-fluorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-123)

![Chemical structure of YUG-123]

Yield: 77%; mp 151-153 °C; IR (cm\(^{-1}\)): 3454 (N-H stretching of free primary amine), 3061 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1660 (C=N stretching of pyrazole ring), 1126 (N-N deformation of pyrazole ring), 1068 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); \(^1\)H NMR (DMSO-d\(_6\)) \(\delta\) ppm: 0.74-0.77 (t, 3H, H\(_a\)), 1.24-1.42 (m, 2H, H\(_b\)), 2.03-2.19 (m, 2H, H\(_c\)), 4.67 (s, 1H, H\(_d\)), 7.07 (s, 2H, H\(_e\)), 7.09-7.11 (t, 2H, H\(_{ff'}\)), 7.26-7.30 (m, 3H, H\(_{gg'h}\)), 7.44-7.48 (t, 2H, H\(_{ii'}\)), 7.81-7.83 (t, 2H, H\(_{jj'}\)); \(^{13}\)C NMR (DMSO-d\(_6\)) \(\delta\) ppm: 13.52, 20.71, 28.93, 36.42, 58.51, 97.78, 115.12, 119.94, 125.81, 129.40, 137.63, 139.79, 143.79, 148.96, 159.18, 160.00, 162.43, 169.99; MS: m/z 374; Anal. Calcd. for C_{22}H_{19}F_{3}N_{4}O: C, 70.57; H, 5.11; N, 14.96. Found: C, 70.54; H, 5.08; N, 14.92%.
2.10.4.4 6-amino-4-(4-chlorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-124)

\[
\begin{align*}
\text{O} & \quad \text{N} \\
\text{N} & \quad \text{CN} \\
\text{NH}_2 \\
\text{H}_3\text{C} \\
\text{Cl} \\
a & b & c & d & e & f & g & h & i & j & k & l & m & n & o & p & q & r & s & t & u & v & w & x & y & z
\end{align*}
\]

Yield: 83%; mp 152-154 °C; IR (cm\(^{-1}\)): 3454 (N-H stretching of free primary amine), 3061 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1660 (C=N stretching of pyrazole ring), 1126 (N-N deformation of pyrazole ring), 1068 (C-H in plane bending of aromatic ring), 806 (C-H out of plane bending for 1,4-disubstituted aromatic ring); \(^1\)H NMR (DMSO-\(d_6\)) \(\delta\) ppm: 0.74-0.78 (t, 3H, H\(_a\)), 1.26-1.44 (m, 2H, H\(_b\)), 2.02-2.19 (m, 2H, H\(_c\)), 4.66 (s, 1H, H\(_d\)), 7.10 (s, 2H, H\(_e\)), 7.25-7.30 (t, 3H, H\(_{f-h}\)), 7.32-7.36 (t, 2H, H\(_{i-i'}\)), 7.40-7.48 (m, 2H, H\(_{j-j'}\)), 7.80-7.82 (d, 2H, H\(_{kk'}\), \(J = 8.00\) Hz); MS: \(m/z\) 370; Anal. Calcd. for C\(_{23}\)H\(_{22}\)N\(_4\)O: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.53; H, 5.95; N, 15.08%.

2.10.4.5 6-amino-1,4-dihydro-4-(4-nitrophenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-125)

\[
\begin{align*}
\text{NO}_2 \\
\text{H}_3\text{C} \\
\text{CN} \\
\text{O} \\
\text{NH}_2
\end{align*}
\]

Yield: 69%; mp 181-183 °C; MS: \(m/z\) 401; Anal. Calcd. for C\(_{22}\)H\(_{19}\)N\(_5\)O\(_3\): C, 65.83; H, 4.77; N, 17.45%. Found: C, 65.80; H, 4.73; N, 17.40%.
2.10.4.6 6-amino-1,4-dihydro-4-(3-nitrophenyl)-1-phenyl-3-propylpyrano[2,3-c]-pyrazole-5-carbonitrile (YUG-126)

Yield: 70%; mp 158-161 ºC; MS: m/z 401; Anal. Calcd. for C_{22}H_{19}N_{5}O_{3}: C, 65.83; H, 4.77; N, 17.45%; Found: C, 65.81; H, 4.74; N, 17.41%.

2.10.4.7 6-amino-4-(3-chlorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-127)

Yield: 80%; mp 167-168 ºC; IR (cm^{-1}): 3462 (N-H stretching of free primary amine), 3070 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1656 (C=N stretching of pyrazole ring), 1130 (N-N deformation of pyrazole ring), 1072 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-d6) δ ppm: 0.76-0.80 (t, 3H, H_a), 1.24-1.46 (m, 2H, H_b), 2.05-2.22 (m, 2H, H_c), 4.65 (s, 1H, H_d), 6.94 (s, 2H, H_e), 7.19-7.34 (m, 5H, H_f-j), 7.44-7.47 (t, 2H, H_kk'), 7.79-7.80 (d, 2H, H_ll', J = 8.36 Hz); MS: m/z 370; Anal. Calcd. for C_{23}H_{22}N_{4}O: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.53; H, 5.96; N, 15.08%.
2.10.4.8 6-amino-4-(4-bromophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-128)

Yield: 75%; mp 140-143 °C; IR (cm⁻¹): 3448 (N-H stretching of free primary amine), 3057 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1660 (C=N stretching of pyrazole ring), 1126 (N-N deformation of pyrazole ring), 1070 (C-H in plane bending of aromatic ring), 802 (C-H out of plane bending for 1,4-disubstituted aromatic ring); ¹H NMR (DMSO-δ₆) δ ppm: 0.74-0.78 (t, 3H, Hₐ), 1.23-1.44 (m, 2H, Hₐ), 2.02-2.18 (m, 2H, Hₐ), 4.66 (s, 1H, H_d), 7.13 (s, 2H, H_e), 7.19-7.24 (dd, 2H, H_ff'), 7.27-7.34 (m, 2H, H_gg'), 7.40-7.51 (m, 2H, H_hh'), 7.88-7.90 (d, 1H, H_j); MS: m/z 434; Anal. Calcd. for C₂₂H₁₉BrN₄O: C, 60.70; H, 4.40; N, 12.87. Found: C, 60.76; H, 4.36; N, 12.83%.

2.10.4.9 6-amino-1,4-dihydro-4-(4-hydroxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-129)

Yield: 88%; mp 174-176 °C; MS: m/z 372; Anal. Calcd. for C₂₂H₂₀N₄O₂: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.91; H, 5.37; N, 14.99%.
2.10.4.10 6-amino-1,4-dihydro-1,4-diphenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-130)

![Structure of YUG-130]

Yield: 73%; mp 219-221 °C; IR (cm⁻¹): 3462 (N-H stretching of free primary amine), 3070 (C-H stretching of aromatic ring), 2193 (C≡N stretching of the nitrile group), 1656 (C=N stretching of pyrazole ring), 1130 (N-N deformation of pyrazole ring), 1072 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.73-0.77 (t, 3H, Hₐ), 1.23-1.43 (m, 2H, Hₗ), 2.02-2.19 (m, 2H, Hₗ'), 4.62 (s, 1H, Hₖ), 6.88 (s, 2H, Hₖ'), 7.23-7.34 (m, 6H, Hₖ), 7.40-7.47 (m, 2H, Hₖ'), 7.79-7.81 (d, 2H, Hₖ′, J = 7.84 Hz); MS: m/z 356; Anal. Calcd. for C₂₂H₂₀N₄O: C, 74.14; H, 5.66; N, 15.72. Found: C, 74.10; H, 5.62; N, 15.68%.

2.10.4.11 6-amino-1,4-dihydro-4-(3-hydroxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-131)

![Structure of YUG-131]

Yield: 82%; mp 214-216 °C; MS: m/z 372; Anal. Calcd. for C₂₂H₂₀N₄O₂: C, 70.95; H, 5.41; N, 15.04. Found: C, 70.91; H, 5.37; N, 15.01%.
2.10.4.12 6-amino-4-(2,4-dichlorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-132)

Yield: 85%; mp 184-186 °C; IR (cm⁻¹): 3462 (N-H stretching of free primary amine), 2989 (C-H stretching of aromatic ring), 2196 (C≡N stretching of the nitrile group), 1660 (C=N stretching of pyrazole ring), 1128 (N-N deformation of pyrazole ring), 1068 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.73-0.77 (t, 3H, Hₐ), 1.21-1.42 (m, 2H, Hₖ), 2.03-2.19 (m, 2H, Hₐ), 5.17 (s, 1H, Hₐ), 7.23 (s, 2H, H₉), 7.28-7.38 (m, 3H, H₉, H₁₀), 7.45-7.52 (m, 3H, H₁₁), 7.79-7.81 (d, 2H, H₁₁, J = 7.76 Hz); ¹³C NMR (DMSO-d₆) δ ppm: 13.51, 20.91, 28.88, 30.55, 56.53, 96.81, 99.49, 119.35, 120.00, 125.99, 127.86, 128.70, 129.07, 132.26, 132.50, 133.00, 137.53, 144.18, 148.62, 159.76; MS: m/z 424; Anal. Calcd. for C₂₂H₁₈Cl₂N₄O: C, 62.13; H, 4.27; N, 13.17. Found: C, 62.09; H, 4.23; N, 13.13%.

2.10.4.13 6-amino-4-(3-bromophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-133)

Yield: 88%; mp 188-190 °C; MS: m/z 434; Anal. Calcd. for C₂₂H₁₉BrN₄O: C, 60.70; H, 4.40; N, 12.87. Found: C, 60.76; H, 4.36; N, 12.83%.
2.10.4.14 6-amino-1,4-dihydro-1-phenyl-3-propyl-4-(pyridin-2-yl)pyrano[2,3-c]pyrazole-5-carbonitrile (YUG-134)

\[
\text{\includegraphics[width=2cm]{image1.png}}
\]

Yield: 79%; mp 180-183 ºC; MS: \textit{m/z} 357; Anal. Calcd. for C_{21}H_{19}N_{5}O: C, 70.57; H, 5.36; N, 19.59. Found: C, 70.53; H, 5.32; N, 19.55%.

2.10.4.15 6-amino-4-(2-bromophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-135)

\[
\text{\includegraphics[width=2cm]{image2.png}}
\]

Yield: 87%; mp 180-182 ºC; MS: \textit{m/z} 435; Anal. Calcd. for C_{22}H_{19}BrN_{4}O: C, 60.70; H, 4.40; N, 12.87. Found: C, 60.76; H, 4.36; N, 12.83%.

2.10.4.16 6-amino-4-(2,6-dichlorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-136)

\[
\text{\includegraphics[width=2cm]{image3.png}}
\]
Yield: 80%; mp 188-191 ºC; IR (cm⁻¹): 3450 (N-H stretching of free primary amine), 3088 (C-H stretching of aromatic ring), 2198 (C≡N stretching of the nitrile group), 1662 (C=N stretching of pyrazole ring), 1134 (N-N deformation of pyrazole ring), 1068 (C-H in plane bending of aromatic ring); ¹H NMR (DMSO-d₆) δ ppm: 0.69-0.73 (t, 3H, Hₐ), 1.11-1.41 (m, 2H, Hₕ), 2.07-2.19 (m, 2H, Hₜ), 5.71 (s, 1H, H₉), 7.10 (s, 2H, H₂), 7.25-7.32 (m, 3H, H₃₋₅), 7.43-7.47 (m, 3H, H₇₋₉), 7.78-7.80 (d, 2H, H₁₁₋₁₂, J = 8.00 Hz); MS: m/z 424; Anal. Calcd. for C₂₂H₁₈Cl₂N₄O: C, 62.13; H, 4.27; N, 13.17. Found: C, 62.09; H, 4.23; N, 13.13%.

2.10.4.17 6-amino-4-(3-chlorophenyl)-1,4-dihydro-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-137)

Yield: 83%; mp 218-220 ºC; MS: m/z 370; Anal. Calcd. for C₂₃H₂₂N₄O: C, 74.57; H, 5.99; N, 15.12. Found: C, 74.53; H, 5.95; N, 15.08%.

2.10.4.18 6-amino-1,4-dihydro-4-(3,4-dimethoxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-138)

Yield: 79%; mp 148-151 ºC; MS: m/z 416; Anal. Calcd. for C₂₄H₂₄N₄O₃: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.18; H, 5.77; N, 13.41%.
2.10.4.19 6-amino-1,4-dihydro-4-(2,5-dimethoxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-139)

Yield: 75%; mp 140-143 °C; MS: m/z 416; Anal. Calcd. for C_{24}H_{24}N_{4}O_{3}: C, 69.21; H, 5.81; N, 13.45. Found: C, 69.18; H, 5.78; N, 13.41%.

2.10.4.20 6-amino-1,4-dihydro-4-(3,4,5-trimethoxyphenyl)-1-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-140)

Yield: 80%; mp 174-176 °C; MS: m/z 446; Anal. Calcd. for C_{25}H_{26}N_{4}O_{4}: C, 67.25; H, 5.87; N, 12.55. Found: C, 67.21; H, 5.83; N, 12.51%.
2.11 Spectral discussion

2.11.1 Mass spectral study
Mass spectra were recorded on Shimadzu GC-MS-QP-2010 model using Direct Injection Probe technique. Systematic fragmentation pattern was observed in mass spectral analysis. Molecular ion peak was observed in agreement with molecular weight of respective compound. Mass fragmentation pattern for a representative compound of each series is depicted below.

2.11.2 IR spectral study
IR spectra were recorded on Shimadzu FT-IR-8400 model using KBr pellet method. Various functional groups present in molecule were identified by characteristic frequency obtained for them. For pyrano[2,3-c]pyrazoles (YUG-101 to 140), confirmatory bands for primary amine (-NH₂) and nitrile (C≡N) stretching band was observed at 3473-3500 cm⁻¹. Another characteristic band for N-H deformation was observed at 1597-1610 cm⁻¹, which suggested the formation of pyranopyrazoles ring system.

2.11.3 \(^1\)H NMR spectral study
\(^1\)H NMR spectra were recorded in DMSO-\(d_6\) solution on a Bruker Ac 400 MHz spectrometer using TMS as an internal standard. Number of protons and their chemical shifts were found to support the structure of the synthesized compounds. \(^1\)H NMR spectra confirmed the structures of pyrano[2,3-c]pyrazoles (YUG-101 to 140) on the basis of following signals: singlet for primary amino group proton was observed at 6.12-7.23 \(\delta\) ppm and a singlet for the methine proton of pyran ring at 4.58-5.71 \(\delta\) ppm. The aromatic ring protons and \(J\) value were found to be in accordance with substitution pattern on phenyl ring.

2.11.4 \(^13\)C NMR spectral study
\(^13\)C NMR spectra were recorded in DMSO-\(d_6\) solution on a Bruker Ac 400 MHz spectrometer. Number of carbons and their chemical shifts were found to support the structure of the synthesized compounds. \(^13\)C NMR spectra confirmed the structures of pyrano[2,3-c]pyrazoles (YUG-101 to 140) on the basis of following signals: signal for chiral carbon of pyran ring was observed at 20-22 \(\delta\) ppm. Signal for carbon of
cyano group was observed at 110-120 δ ppm, indicates the involvement of malanoniitrile in cyclization process.
Chapter 2

Mass Spectrum of YUG-101

IR Spectrum of YUG-101
Chapter 2

Pyrano[2,3-c]pyrazoles…

\textbf{\textsuperscript{1}H NMR Spectrum of YUG-101}

\textbf{Expanded \textsuperscript{1}H NMR Spectrum of YUG-101}
Chapter 2 Pyrano[2,3-c]pyrazoles…

Expanded $^1$H NMR Spectrum of YUG-101

Expanded $^1$H NMR Spectrum of YUG-101
**13C NMR Spectrum of YUG-101**

**Mass Spectrum of YUG-102**
Chapter 2

Pyrano[2,3-c]pyrazoles...

IR Spectrum of YUG-102

1H NMR Spectrum of YUG-102
Chapter 2

Expanded $^1$H NMR Spectrum of YUG-102

Expanded $^1$H NMR Spectrum of YUG-102
Chapter 2

Pyrano[2,3-c]pyrazoles…

$^{13}$C NMR Spectrum of YUG-102

Mass Spectrum of YUG-103
IR Spectrum of YUG-103

$1^H$ NMR Spectrum of YUG-103
Expanded $^1$H NMR Spectrum of YUG-103

Expanded $^1$H NMR Spectrum of YUG-103
Chapter 2

Pyrano[2,3-c]pyrazoles...

\[\text{\^{13}C NMR Spectrum of YUG-103}\]

\[\text{Mass Spectrum of YUG-104}\]
Chapter 2

Pyrano[2,3-c]pyrazoles...

IR Spectrum of YUG-104

1H NMR Spectrum of YUG-104
Chapter 2

Expanded $^1$H NMR Spectrum of YUG-104

Expanded $^1$H NMR Spectrum of YUG-104
Chapter 2

Pyrano[2,3-c]pyrazoles...

$^{13}$C NMR Spectrum of YUG-104

Mass Spectrum of YUG-105
Chapter 2

IR Spectrum of YUG-105

1H NMR Spectrum of YUG-105
Expanded $^1$H NMR Spectrum of YUG-105

Expanded $^1$H NMR Spectrum of YUG-105
Chapter 2  Pyrano[2,3-c]pyrazoles…

Mass Spectrum of YUG-107

IR Spectrum of YUG-107
Chapter 2

Pyrano[2,3-c]pyrazoles...

$^1$H NMR Spectrum of YUG-107

Expanded $^1$H NMR Spectrum of YUG-107
Chapter 2

Expanded $^1H$ NMR Spectrum of YUG-107

Mass Spectrum of YUG-108
Chapter 2

Pyrano[2,3-c]pyrazoles...

IR Spectrum of YUG-108

\[ \text{YUG-108} \]

\[ \text{1H NMR Spectrum of YUG-108} \]
Chapter 2

Expanded $^1$H NMR Spectrum of YUG-108
Mass Spectrum of YUG-110

IR Spectrum of YUG-110
\textbf{Chapter 2}  \hspace{3cm} \textbf{Pyrano[2,3-c]pyrazoles…}

$^1\text{H NMR Spectrum of YUG-110}$

\includegraphics[width=\textwidth]{hnmr_spectrum_yug110}

\textbf{Expanded $^1\text{H NMR Spectrum of YUG-110}}$

\includegraphics[width=\textwidth]{expanded_hnmr_spectrum_yug110}
Chapter 2

Pyrano[2,3-c]pyrazoles...

Expanded $^1H$ NMR Spectrum of YUG-110

$^{13}C$ NMR Spectrum of YUG-110
Chapter 2                                                                                   Pyrano[2,3-c]pyrazoles…

Mass Spectrum of YUG-115

![Mass Spectrum of YUG-115](image1)

IR Spectrum of YUG-115

![IR Spectrum of YUG-115](image2)
Chapter 2

Pyrano[2,3-c]pyrazoles...

Expanded $^1$H NMR Spectrum of YUG-115

Mass Spectrum of YUG-116
Chapter 2  

Pyrano[2,3-c]pyrazoles...

**IR Spectrum of YUG-116**

![IR Spectrum of YUG-116](image)

**$^1$H NMR Spectrum of YUG-116**

![$^1$H NMR Spectrum of YUG-116](image)
Chapter 2

Expanded $^1$H NMR Spectrum of YUG-116

Expanded $^1$H NMR Spectrum of YUG-116
Chapter 2

Pyrano[2,3-c]pyrazoles

Mass Spectrum of YUG-121

IR Spectrum of YUG-121
Chapter 2

Pyrano[2,3-c]pyrazoles…

$^1$H NMR Spectrum of YUG-121

Expanded $^1$H NMR Spectrum of YUG-121
Chapter 2

Pyrano[2,3-c]pyrazoles...

Expanded $^1$H NMR Spectrum of YUG-121

$^{13}$C NMR Spectrum of YUG-121
Chapter 2

Pyrano[2,3-c]pyrazoles…

Mass Spectrum of YUG-123

IR Spectrum of YUG-123
Chapter 2

Pyrano[2,3-c]pyrazoles...

$^1$H NMR Spectrum of YUG-123

Expanded $^1$H NMR Spectrum of YUG-123

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Chapter 2

Expanded $^1$H NMR Spectrum of YUG-123

Mass Spectrum of YUG-124
Chapter 2

Pyrano[2,3-c]pyrazoles...

IR Spectrum of YUG-124

\[\text{YUG-124}\]

1H NMR Spectrum of YUG-124

\[\text{YUG-124}\]
Chapter 2  Pyrano[2,3-c]pyrazoles…

Mass Spectrum of YUG-127

IR Spectrum of YUG-127
\[ \text{1H NMR Spectrum of YUG-127} \]

![1H NMR Spectrum of YUG-127](image)

\[ \text{Expanded 1H NMR Spectrum of YUG-127} \]

![Expanded 1H NMR Spectrum of YUG-127](image)
Chapter 2

Pyrano[2,3-c]pyrazoles…

Expanded $^1$H NMR Spectrum of YUG-127

Mass Spectrum of YUG-128
Chapter 2

**IR Spectrum of YUG-128**

---

**$^1$H NMR Spectrum of YUG-128**

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Chapter 2

Expanded $^1$H NMR Spectrum of YUG-128

[Image of expanded $^1$H NMR spectrum of YUG-128]

Expanded $^1$H NMR Spectrum of YUG-128

[Image of expanded $^1$H NMR spectrum of YUG-128]
Chapter 2

Pyrano[2,3-c]pyrazoles...

Mass Spectrum of YUG-130

IR Spectrum of YUG-130
Chapter 2

Pyran[2,3-c]pyrazoles...

$^1$H NMR Spectrum of YUG-130

Expanded $^1$H NMR Spectrum of YUG-130
Expanded $^1$H NMR Spectrum of YUG-130

Mass Spectrum of YUG-132
**IR Spectrum of YUG-132**

![IR Spectrum of YUG-132](image)

**$^1$H NMR Spectrum of YUG-132**

![$^1$H NMR Spectrum of YUG-132](image)
Chapter 2  Pyrano[2,3-c]pyrazoles...

Expanded $^1$H NMR Spectrum of YUG-132

Expanded $^1$H NMR Spectrum of YUG-132
Chapter 2

Pyrano[2,3-c]pyrazoles

$^{13}$C NMR Spectrum of YUG-132

Mass Spectrum of YUG-133
IR Spectrum of YUG-133

1H NMR Spectrum of YUG-133
Chapter 2

Expanded $^1$H NMR Spectrum of YUG-133

Expanded $^1$H NMR Spectrum of YUG-133
Chapter 2

Pyrano[2,3-c]pyrazoles...

1H NMR Spectrum of YUG-136

Expanded 1H NMR Spectrum of YUG-136
Expanded $^1$H NMR Spectrum of YUG-136
Chapter 2

2.12 X-Ray Diffraction Study of pyrano[2,3-c]pyrazole

2.12.1 Single Crystal X-Ray Diffraction Analysis of 6-amino-1,4-dihydro-4-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile (YUG-110)

Single crystal X-ray diffraction is the most common experimental method for obtaining a detailed picture of a small molecule that allows resolution of individual atoms. It is performed by analyzing the diffraction of x-rays from an ordered array of many identical molecules. Many molecular substances, including proteins, polymers and other solidify into crystals under the proper conditions. When solidifying into the crystalline state, these individual molecules typically adapted as one of only a few possible orientations. A crystal is a three dimensional array of those molecules that are held together by Van der Waals and noncovalent bonding. The smallest representative unit of this crystal is referred to as the unit cell. Understanding the unit cell of these arrays simplifies the understanding of a crystal as a whole.

2.12.2 Procedure for the development of single crystal

In the present study, the pure, single spot (on TLC) compound was taken in ethanol and heated with stirring till it dissolved. A small quantity of charcoal was added for decolorizing. The solution was then heated to boiling and immediately filtered while hot in corkable 50 ml conical flask using Whatmann filter paper. The flask was corked and kept for several days. The crystals thus grown by thin film evaporation technique were isolated and washed with chilled methanol. The functional groups and proton and carbon framework of 6-amino-1,4-dihydro-4-phenyl-3-propylpyrano[2,3-c]pyrazole-5-carbonitrile was supported by IR, ^1^H NMR, ^13^C NMR and Mass Spectral studies.

2.12.3 Single Crystal X-ray Diffraction and Structure Determination

X-ray single-crystal data was collected using Mo Kα radiation (λ=0.71073 Å) radiation on a SMART APEX diffractometer equipped with CCD area detector. Data collection, data reduction and structure solution/refinement were carried out using the software package of SMART APEX. Table 1 shows the unit cell parameters and other crystallographic details. All the structures were solved by direct method and refined in a routine manner. In most of the cases, nonhydrogen atoms were treated
anisotropically. Whenever possible, the hydrogen atoms were located on a difference Fourier map and refined. In other cases, the hydrogen atoms were geometrically fixed. CCDC no. 893155 contains the supplementary crystallographic data for this article. These data can be obtained from www.ccdc.cam.ac.uk/conts/retrieving.html free of charge (or from the Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB21EZ, UK; fax: (+44) 1223-336-033; or deposit@ccdc.cam.ac.uk).
2.12.3.1 ORTEP diagram of the organic compound with atom numbering scheme
(40% probability factor for the thermal ellipsoids)
2.12.3.2 Crystal data and structure refinement

Table 1

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### 2.12.3.5 Atomic coordinates and equivalent thermal parameters of the non-hydrogen atoms

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### 2.12.3.6 Hydrogen-bonding geometry (Å)

**Table 5**

<table>
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<th>D-H</th>
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*Note: D-H and H-A distances are essentially standard values and are not derived from the experiment.*
2.13 Biological evaluation

2.13.1 Antimicrobial evaluation

All the synthesized compounds (YUG-101 to YUG-140) were tested for their antibacterial and antifungal activity (MIC) *in vitro* by broth dilution method [124, 125] with two Gram-positive bacteria *Staphylococcus aureus* MTCC-96, *Streptococcus pyogenes* MTCC 443, two Gram-negative bacteria *Escherichia coli* MTCC 442, *Pseudomonas aeruginosa* MTCC 441 and three fungal strains *Candida albicans* MTCC 227, *Aspergillus Niger* MTCC 282, *Aspergillus clavatus* MTCC 1323 taking ampicillin, chloramphenicol, ciprofloxacin, norfloxacin, nystatin, and greseofulvin as standard drugs. The standard strains were procured from the Microbial Type Culture Collection (MTCC) and Gene Bank, Institute of Microbial Technology, Chandigarh, India.

The minimal inhibitory concentration (MIC) values for all the newly synthesized compounds, defined as the lowest concentration of the compound preventing the visible growth, were determined by using microdilution broth method according to NCCLS standards [124]. Serial dilutions of the test compounds and reference drugs were prepared in Mueller-Hinton agar. Drugs (10 mg) were dissolved in dimethylsulfoxide (DMSO, 1 mL). Further progressive dilutions with melted Mueller-Hinton agar were performed to obtain the required concentrations. In primary screening 1000 μg mL⁻¹, 500 μg mL⁻¹ and 250 μg mL⁻¹ concentrations of the synthesized drugs were taken. The active synthesized drugs found in this primary screening were further tested in a second set of dilution at 200 μg mL⁻¹, 100 μg mL⁻¹, 50 μg mL⁻¹, 25 μg mL⁻¹, 12.5 μg mL⁻¹, and 6.25 μg mL⁻¹ concentration against all microorganisms. The tubes were inoculated with 10⁸ cfu mL⁻¹ (colony forming unit/mL) and incubated at 37 °C for 24 h. The MIC was the lowest concentration of the tested compound that yields no visible growth (turbidity) on the plate. To ensure that the solvent had no effect on the bacterial growth, a control was performed with the test medium supplemented with DMSO at the same dilutions as used in the experiments and it was observed that DMSO had no effect on the microorganisms in the concentrations studied.

The results obtained from antimicrobial susceptibility testing are depicted in Table 1.
Table 1. Antibacterial and antifungal activity of synthesized compounds YUG-101 to 140

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<th>Gram-negative</th>
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2.13.2 Antimycobacterial, anticancer and antiviral evaluation

Antimycobacterial, anticancer and antiviral screening of all the newly synthesized compounds YUG-101 to YUG-140 is currently under investigation and results are awaited.
2.14 References and Notes:


Chapter 2

[42] Li, C.-J. *Accounts of Chemical Research* 2010, 43, 581.


Chapter 2


Chapter 2 Pyrano[2,3-c]pyrazoles…


Chapter 2

Pyrano[2,3-c]pyrazoles...


