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LiBr-CATALYZED ONE-POT SYNTHESES OF DIHYDROPYRANO [2, 3-*c*] PYRAZOLES

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ABSTRACT
A new facile, greenand efficient protocol was developed for synthesis of Dihydropyrano [2,3-c] pyrazolesusing LiBr as an efficient, eco-friendly catalyst.Compared to other methods, this new method consistently has advantages, including excellent yields, short reaction time, mild reaction conditionsand reusability of catalyst.The synthesized Dihydropyrano [2,3-c] pyrazoleswere analyzed for ADME properties.

Keywords: Dihydropyrano [2,3-c] pyrazoles;LiBr; Green protocol, ADME properties.

INTRODUCTION
In pharmaceutical industries solvents play an important role for organic transformation and production of active pharmaceutical ingredient (API) have a direct impact on the environment because of its large volume consumption, limited recovery due to volatile nature and residual disposal problem. According to the regulatory agencies and international conference for harmonization (ICH) guideline there are limitation to use the class-1 and class-2 solvents in pharmaceutical product due to hazardous, toxic and carcinogenic nature. It has been recommended to use the class-3 solvent particularly for manufacturing of drug intermediate and finished product.[1]Therefore, replacing of such conventional solvents, with more environmentally benign media is one of the important tasks to meet the current Green Chemistry requirement, and a subject of significant academic and commercial interest.[2] By focusing on current demand of green chemistry, a variety of unconventional solvents, such as water,[3] ionic liquids,[4] polyethylene glycol,[5]supercritical fluids[6] and fluorousmedia[7] have been extensively used and studied well. Although the use of these solvents has certain limitations, such as the incompatibility of reactive reagents or substrates in water, high prices and insufficient data about the toxicity and bio-compatibility for ionic liquids, the requirement of sophisticated equipment for supercritical fluids. Therefore, the search of alternative and eco-friendly reaction media for organic transformation has become the considerable interest of researchers.

Lithium bromide is a stable, relatively safe and readily available low-cost reagent having unique mild Lewis acid properties. It has a wide variety of utility in different chemical transformations including Biginelli condensation, Knoevenagel condensation, Ehrlich-Sachs reaction, Friedel-Crafts reaction, rearrangement of epoxides and preparation of acylals and xanthenes.[8]In most of these reported reactions, LiBr is almost neutral[9] and also does not form any corrosive or harsh by-products during aqueous workup, unlike strong and expensive catalysts. However, there are no examples of use of lithium bromide as catalyst for synthesis of pyrano-pyrazole derivatives

In the current scenario of global warming issues, regulatory agencies and pollution control authorities are having a serious concern, about the waste disposal and air pollution generated by chemical and pharmaceutical industries. Due to the huge demand of fine chemicals, drug intermediate and drug molecule. It is necessary to develop the cost effective, robust and eco-friendly processto develop MCRs. To minimize the waste generation, operational simplicity and atom economy is a great interest of scientific community in recentyears. Therefore,there is a need to design a synthetic route for organic transformation using three or more components in one-pot operation with minimum waste generation. One-pot synthesis MCRs often take shorter reaction time, minimum utilities, use of energy and manpower with consistent higher product yields,compare to multi-step synthesis.[10]MCRs constitute large series of structurally related drug-like molecules, leads to identification and optimization in drug discovery program. Considering these advantages, over the multi-step synthesis, the design of new MCRs with environmental friendly method is a bigchallenge to the scientific community at the forefront area of green chemistry.[11]

As per green chemistry protocol transformation of organic reactions in aqueous media is a big challenging and attractive taskas water is an environmentally benign solvent. Water is abundant in nature, easily available, cheap, and user friendly andsustainability of exothermic reactions.Synthesisof organic reaction in aqueous media offer more benefit like, rate determining, faster reaction and products insolubility, which help for the product isolation in pure form by simple filtration which is more advantageous and beneficial over conventional organic solvents.

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In the class of heterocyclic molecules, multifunctional4*H*-pyran and their derivatives are important class of which composed most important core of various natural products[12]and photochromic materials.[13] Due to their wide range of biological potency such as antimicrobial,[14]antiproliferative,[15]anticancer,[16]and antioxidant properties.[17]It can be used to cure neurological disorder like Alzheimer's disease,Huntington's disease, neurodegenerative disease Parkinson's disease schizophrenia, and treatment of, including amyotrophic lateral sclerosis, AIDS associated dementia, Down syndrome and myoclonus.[18]Multifuctionalized 4*H*-Pyran derivatives also shows potential calcium channel antagonists properties, which are structurally similar to biologically active 1,4-dihydropyridines.[19]The nitrile functionality in 4*H*-pyran derivatives is important synthon, for the synthesis of different bioactive heterocyclic compounds such as pyranopyrazoles, lactones, pyridones, 1,4-dihydropyridines and aminopyrimidines.[20]In organic chemistry, Pyrazole is an important heterocyclic analogue which plays a vital role in many pharmaceutical and agrochemical drugs molecules and intermediates.

In medicinal chemistry and drug designing, Dihydropyrano [2,3-*c*]pyrazoles is became the first choice of researchers and scientistdue to its potential biological activity, and therefore become the interesting template for medicinal chemistry research. Most class of these compounds, are well known forantioxidant,[21]antimicrobial,[22] insecticidal,[23]molluscicidal,[24] analgesic,[25]anti-inflammatory agents[26] and some of their analogues act as vasodilators, hypotensive,[27]hypoglycemic and anticancer agents.[28]They are also potential inhibitors of human Chk1 kinase.[29]Furthermore, they play a significant role as crucial synthetic intermediates.[30]

Thus, considering the differentpotential therapeutic activity of pyrano [2,3-*c*]pyrazoles, heterocyclic compounds, various methodologies for synthesis of Dihydropyrano[2,3-*c*]pyrazoleshave been reported in the literature.These reportedmethodologies have shown good results in many instances.However, some of synthetic strategies have limitations interms of using metal catalyst, expensive reagents, long reaction time,environmental hazard solvents, harsh reaction conditions, tedious workupprocedure, unsatisfactory yield and use of homogeneouscatalyst which are difficult in separation from reaction mixture.In spite of many reported methods for the synthesis of Dihydropyrano[2,3-*c*]pyrazole derivatives, the development of a new synthetic strategy using easily accessible catalyst and mildand sustainable reaction condition still demand a lot of attention.

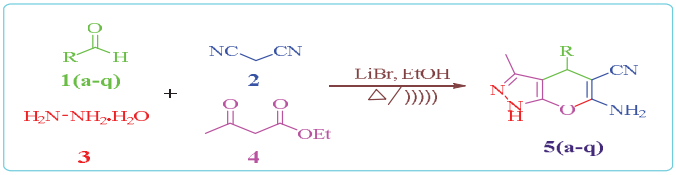
Recently, four-component reactions of aldehydes, 1,3-dicarbonyl compounds, malononitrile, and hydrazine have been developed for the synthesis of pyranopyrazoles usingtriphenylphosphine,[31]urea,[32]ionic liquid,[33]water containinga catalytic amount of piperidine,[34]CTACl,[35]heteropolyacids,[36]microwave,[37] piperazine,[38]*N*-methylmorpholine,[39]L-proline,[40] alumina,[41]per-6-amino-β-cyclodextrin,[42]sodium benzoate,[43]amberlyst A21,[44]glycine,[45]imidazole,[46] and I_2[47]Although thesemethods are quite satisfactory, some of them suffer from the absenceof green chemistry and have been associated with severalshortcomings, such as the use of volatile and hazardous organicsolvents, low yields, extended reaction time, high temperature andtedious procedure for the preparation of catalysts. Thus, thedevelopmentof general, economically and environmentally benignsynthetic methodologies for these heterocycles is highly desirable.

OBJECTIVE

Considering the significance of heterocyclic compounds likeDihydropyrano[2,3-*c*]pyrazoles derivatives in pharmaceutical and medicinal fields, the development of simple, eco-friendly and low cost protocol for the synthesis of this molecules is still the great interest of scientific community and researchers. Hence, with this inspiration we thought to develop new and efficient route for the synthesis of Dihydropyrano [2,3-*c*]pyrazolesusing LiBr as an efficient, eco-friendly catalystunder environmentally friendly conditions.

PRESENT WORK

A facile, economic, green and environmentally being protocol, was developed for one-pot multicomponent cyclocondensation of aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate (**Scheme1**). Successful implementation of LiBras a catalyst for an efficient and rapid synthesis of pyrano [2,3-*c*]pyrazole derivatives has been described. Higher product yields with shorter reaction time, reusable and economical catalytic system, and consistent performance on large scale make this synthetic strategy an attractive one(**Scheme 1**).



Scheme-1: Synthesis of pyrano [2,3-c]pyrazole derivatives.

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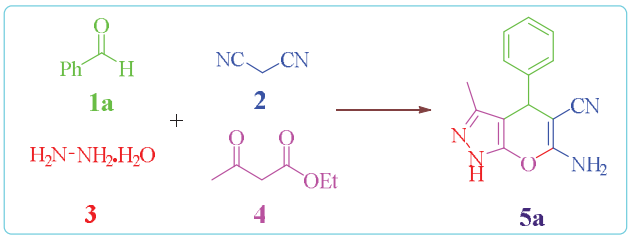
RESULTS AND DISCUSSION

In search of an efficient catalyst and the best experimental reaction conditions, initially we carried out the reaction between benzaldehyde **(1)** (1 mmol), malononitrile **(2)** (1 mmol), hydrazine hydrate**(3a)** (1 mmol) and ethyl acetoacetate**(4)** (1 mmol) has been considered as a model reaction.



Scheme-2: Standard model reaction

Initially when the reaction was carried out in absence of the catalyst, the product formed in trace amount (**Table1**, entry 1). During the initial study, various acid catalysts were screened, owing to theirwidespread catalytic applications in organic synthesis.For this purpose, we tried various Lewis acid catalyst like $AlCl_3$, $FeCl_3$, $ZnCl_2$afforded the product in 57, 59and 60% yields respectively(**Table1**, entries 2-4).Then we decided to use bromides of alkali metals like LiBr, NaBr, KBr and CsBr. It was observed that when NaBr, KBr and CsBr used as a catalyst, the rate of the reaction very small and product obtained in lower yield (**Table1**, **entry6-8**). In comparison,lithium bromide proved to be an excellent catalyst, furnishing the product inexcellent yield (**Table1**, **entry5**) and therefore was chosen as a catalyst of choicefor further optimization studies.

Tabl-1: Effect of catalyst[a]

Entry	Catalyst	Time (Min)	Yield[b] (%)
1	-	180	Trace
2	$AlCl_3$	120	57
3	$FeCl_3$	120	59
4	$ZnCl_2$	120	60
5	LiBr	30	95
6	NaBr	120	55
7	KBr	120	52
8	CsBr	120	50

[a]**Reaction conditions**: Aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethylacetoacetate (1 mmol) and catalyst in 5 mL Ethanol at 60°C. [b]Isolated yield.

Therefore, to accomplish this goal and considering the significance of green chemistry concept, to check the effect of temperature, model reaction was carried out initially at neat condition for appropriate time. But, formation of the desired product was not observed (**Table 2**, **entries 1**). In subsequent optimization experiments, efforts were directed towards the use polar protic and polar aprotic solvent at different temperatures. To our surprise, reaction in aqueous media at reflux conditions proceed towards the desired product in 40 %yield (**Table 2**, **entry 2**). Similarly, reaction carried out in polar aprotic solvents like acetonitrile, tetrahydrofuran, dimethyl sulfoxide and DMF, product formed in 42, 45, 46 and 48%respectively**(Table 2**, **Entry 3-6)**.Further, reaction carried out in polar protic solvents like IPA, Methanol and ethanol, product formed in 70, 75 and 95% yield respectively (**Table 2**, Entry 7-9). Among the tested solvents, ethanol was superior over the othersolvents in terms of both product yield and reaction time (**Table 2**, entry 9). Furthermore, reaction carried out in EtOH:H_2O mixture (**Table 2**, Entry 12) and ethanol at different temperature and found out that at 60°C product formed in excellent yield (**Table 2**, Entry 10). Therefore, from this study we found that, ethanol at 60°Cwas the best suitable solvent to carried out reaction with excellent yield.

Table-2: Screening of solvent[a]

Entry	Solvent	Temp (°C)	Time (Min)	Yield[b] (%)
1	Neat	100	180	Trace
2	Water	Reflux	180	40
3	CH_3CN	Reflux	180	42
4	THF	Reflux	180	45
5	DMSO	Reflux	180	46

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6	DMF	Reflux	180	48
7	IPA	Reflux	120	70
8	Methanol	Reflux	60	75
9	Ethanol	Reflux	30	95
10	Ethanol	60	30	95
11	Ethanol	40	60	85
12	EtOH:H_2O	Reflux	60	80
[a]**Reaction conditions**: Aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethylacetoacetate (1 mmol) and LiBr (20mol%) in 5 mL Solvent. [b]Isolated yield.				

To determine the appropriate concentration of the catalystLiBr, we investigated the model reaction at different concentrationsof LiBr such as 5, 10, 15, 20 and 25 mol%. Theproduct formed in 60, 72, 85, 95 and 95% yields respectively(**Table3**, entries 1-5). As increase in concentration of catalyst from 20 to 25 mol% does not increase the yield of product. This indicates that 20 mol% of LiBr is sufficient forthe reaction by considering yield of product(**Table3**, entry 4).

Table-3: Optimization of Catalyst[a]

Entry	LiBr (mol%)	Time (Min)	Yield[b] (%)
1	5	60	60
2	10	60	72
3	15	60	85
4	20	30	95
5	25	30	95
[a]**Reaction conditions**: Aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethylacetoacetate (1 mmol) and catalyst in 5 mL Ethanol at 60°C. [b]Isolated yield.			

Before proceeding towards the actual experimental part, a thorough analysis of the mechanistic path leading to the formation of the desired pyrano [2, 3-*c*] pyrazole system was performed. This detailed study revealed that the first two steps involved in the reaction path i.e. formation of Knoevenagel condensation product **A** and pyrazolone**B** can be achieved either under solvent-free condition or using water as a reaction medium, that even in the absence of catalyst. The only challenge was to achieve the desired product **C** by cycloaddition of **A** and **B** (**Figure 1**).

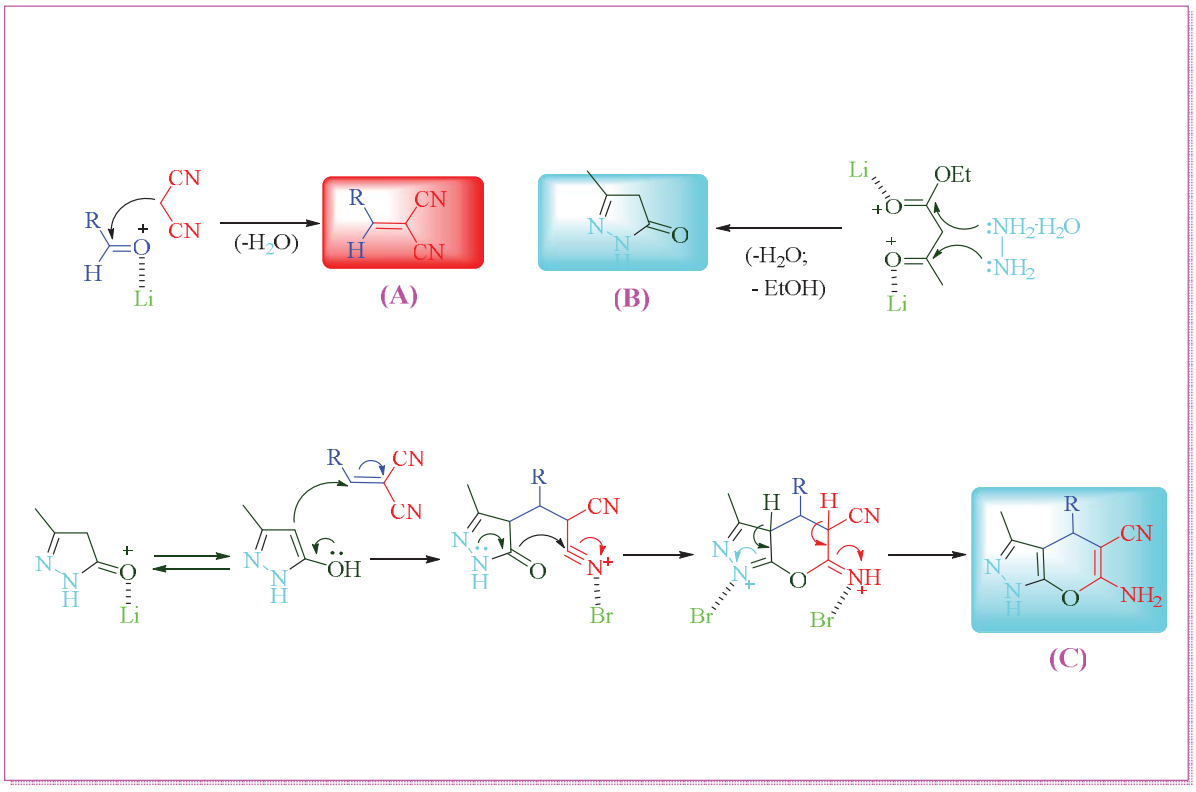

Figure-1: Proposed mechanism for LiBr catalyzed synthesis of pyrano [2,3-*c*]pyrazoles.

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Reason behind the success of LiBr bringing the reaction in its favor may be the small size of lithium cation which interact effectively with small negative charged atoms like oxygen. Lithium bromide is a salt of small cation and large anion. They can't interact effectively, though crystal lattice is quite easy to break. Indeed, lithium cation has the highest hydration energy of all alkali metal cations. Altogether, it means, that in solvents with oxygen atoms (alcohols, esters, acetone) lithium cation effectively bounds to solvent molecules, leaving crystal lattice, and bromide has to follow, resulting in some solubility of lithium bromide in solvents with negatively charged oxygen and to lesser extent, nitrogen (for example pyridine). Diagrammatic representation depicting plausible mechanism for LiBr catalyzed synthesis of pyrano [2,3-*c*]pyrazoles is rationalized with the help of **Figure 1**.

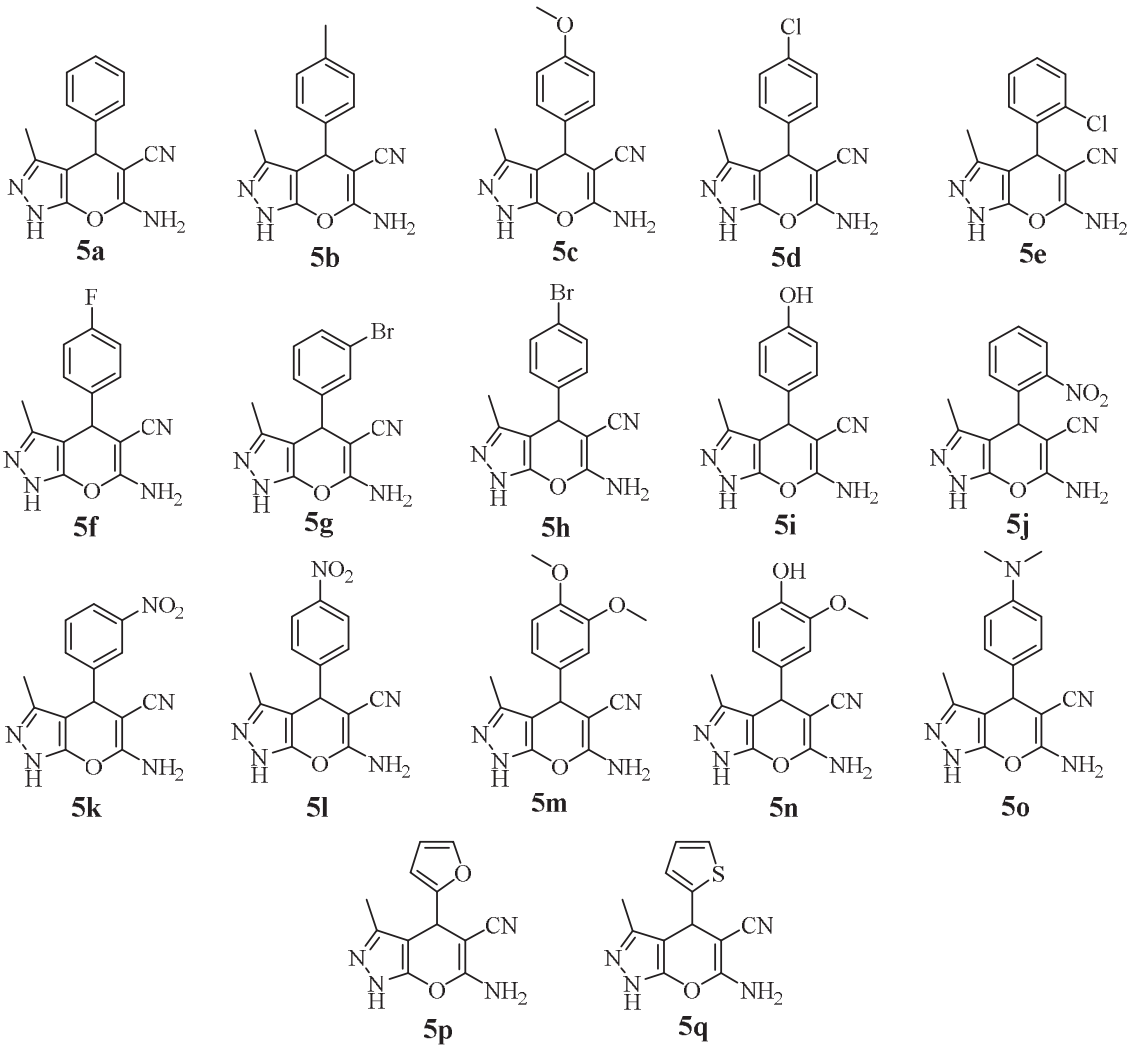

Figure-2: Structures of Dihydropyrano [2,3-*c*]pyrazole derivatives 5(a-q)

Considering the application of ultrasound to promote various organic transformations,we next attempted to carry out the model reaction using optimized reactionconditions under ultrasound irradiation at 30 °C with a view to explore whetherthe reaction could be expedited and the product yield enhanced. It was observed thatultrasonic irradiation led to relatively higher yield and significantly reduced reactiontime as compared with the conventional method. It is presumed that the efficiencywhen using ultrasound irradiation is due to the cavitation phenomenon, throughwhich energy is transmitted more efficiently to the substrates compared with theconventional method. Thus, ultrasonic irradiation was found to have a beneficialeffect on the synthesis of dihydropyrano [2,3-*c*]pyrazolederivatives, being superior to theconventional method in terms of yield, reaction time, simplicity, and safety.

To demonstrate the efficiency and the applicability of the developed method, reaction was performed with variety of electronically divergent aryl aldehydes under optimized reaction conditions and no obvious electronic effects of the substituent present on the aromatic ring of aldehyde was observed, affording the products in each case with excellent yields. Structures of the all the synthesized compounds shown in **Figure2**.

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Table-4: Synthesis of dihydropyrano [2,3-*c*]pyrazolederivatives5a-q

Compound	Ultrasound method[a]		Conventional method[b]		Melting point (°C)[d]
	Time (Min)	Yield (%)[c]	Time (Min)	Yield (%)[c]	
5a	15	95	30	95	241-243
5b	15	92	35	92	208-210
5c	20	94	35	94	207-209
5d	20	90	40	90	231-233
5e	25	92	45	92	143-144
5f	15	93	35	93	231-233
5g	15	87	30	87	179-180
5h	15	91	30	91	175-177
5i	20	93	40	93	221-223
5j	20	93	35	93	223-224
5k	20	88	40	88	192-195
5l	20	89	40	89	250-252
5m	20	84	45	84	190-191
5n	20	86	35	86	233-235
5o	25	90	45	90	165-168
5p	25	91	45	91	235-238
5q	25	89	45	89	234-237

[a]Aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethylacetoacetate (1 mmol) and LiBr (20mol%) in 5 mL Ethanol under ultrasound irradiation
[b]Aldehyde (1 mmol), malononitrile (1 mmol), hydrazine hydrate (1 mmol) and ethylacetoacetate (1 mmol) and LiBr (20mol%) in 5 mL Ethanol under conventional heating.
[c]Isolated yields; [d]Melting points match with literature values.

COMPUTATIONAL STUDY

*In*silicon ADME prediction

A computational study of all the synthesized Dihydropyrano [2,3-*c*]pyrazole derivatives **5**(**a-q**) was performed for prediction of ADME properties and the value obtained is presented in **Table 5**. It is observed that, the compounds exhibited a good % ABS (% absorption) ranging from 62.92to 78.73%. Furthermore, none of the compounds violated Lipinski's rule of five (miLog*P* ≤ 5). A molecule likely to be developed as an orally active drug candidate should show no more than one violation of the following four criteria: miLog*P* (octanol-water partition coefficient) ≤ 5, molecular weight ≤ 500, number of hydrogen bond acceptors ≤ 10 and number of hydrogen bond donors ≤ 5.[48] The larger the value of the drug likeness model score, the higher is also probability that the particular molecule will be active. All the tested compounds followed the criteria for orally active drug and therefore, these compounds may have a good potential for eventual development as oral agents.

Table-5: Pharmacokinetic parameters important for good oral bioavailability

Comp-ounds	% ABS	TPSA (A^2)	n-ROTB	MV	MW	Mi Log*P*	n-ON	n-OHNH	Lipinski violation	Drug-likeness model score
Rule	-	-	-	-	< 500	≤ 5	< 10	< 5	≤ 1	-
5a	78.73	87.73	1	223.38	252.28	1.44	5	3	0	-0.16
5b	78.73	87.73	1	239.94	266.30	1.89	5	3	0	-0.26
5c	75.54	96.97	2	248.92	282.30	1.50	6	3	0	0.05
5d	78.73	87.73	1	236.91	286.72	2.12	5	3	0	0.29
5e	78.73	87.73	1	236.91	286.72	2.07	5	3	0	0.19
5f	78.73	87.73	1	228.31	270.27	1.61	5	3	0	0.13
5g	78.73	87.73	1	241.26	331.17	2.23	5	3	0	-0.23
5h	78.73	87.73	1	241.26	331.17	2.25	5	3	0	-0.06
5i	71.75	107.96	1	231.40	268.28	0.96	6	4	0	0.24
5j	62.92	133.56	2	246.71	297.27	1.35	8	3	0	-0.22
5k	62.92	133.56	2	246.71	297.27	1.38	8	3	0	-0.11
5l	62.92	133.56	2	246.71	297.27	1.40	8	3	0	-0.18
5m	72.36	106.20	3	274.47	312.33	1.09	7	3	0	0.43

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5n	68.56	117.19	2	256.94	298.30	0.78	7	4	0	0.51
5o	77.62	90.97	2	269.28	295.35	1.55	6	3	0	-0.25
5p	74.20	100.87	1	204.95	242.24	0.70	6	3	0	-0.23
5q	78.73	87.73	1	214.09	258.31	1.34	5	3	0	-0.11

EXPERIMENTAL

General Methods

All the reagents and solvents used for the synthesis were purchased from Sigma Aldrich, Spectrochem and Molychem and were used as such without further purification. The melting points of all compounds were determined on a Toshniwal apparatus and are uncorrected. IR spectra were recorded on a Shimadzu FTIR-8400S spectrophotometer using KBr pellets. ^{1}H and ^{13}C NMR spectra were recorded in DMSO-d_6 using TMS as an internal standard on a Bruker spectrophotometer, respectively. Mass spectra of representative compounds were recorded on JEOL SX-102 spectrometer at 70 eV. Elemental microanalyses were carried out on a Carlo Erba1108 CHN analyzer. Thin layer chromatography was performed on pre-coated silica gel 60 F_{254} aluminium sheets (E. Merck, Germany) using various solvents systems and spots were identified by UV light and Iodine.

General procedure for the synthesis Dihydropyrano[2,3-c]pyrazoles5(a-q)

Conventional method

A mixture of aromatic aldehyde**1(a-q)**(1 mmol), malononitrile **(2)** (1 mmol), hydrazine hydrate**3** (1 mmol), ethyl acetoacetate **(4)** (1 mmol)andLiBr (20mol%)in ethanol (5 mL) were taken in a 50 mL round-bottomed flask. The resulting mixture was stirred at 60°C for a period as indicated in **Table4**. After completion of the reaction (monitored by TLC), the reaction mixture poured on ice. Solid obtained was collected by simple filtration and washed successively with warm water. The crude product was purified by crystallization from ethanol. The products **5(a-q)** were confirmed by comparing the physical and spectral data with those of the reported compounds.

Ultrasound method

A mixture of aromatic aldehyde**1(a-q)**(1 mmol), malononitrile **(2)** (1 mmol), hydrazine hydrate**3** (1 mmol), ethyl acetoacetate **(4)** (1 mmol)and LiBr (20mol%) in ethanol (5 mL) were taken in a 50 mL round-bottomed flask. The reaction flask was placed in the ultrasonic cleaner bath with the surface of reactants slightly lower than the water level and irradiated at 30°C for the period of time indicated in **Table 4**. After completion of the reaction (monitored by TLC), the reaction mixture poured on ice. Solid obtained was collected by simple filtration and washed successively with warm water. The crude product was purified by crystallization from ethanol. The products **5(a-q)** were confirmed by comparing the physical and spectral data with those of the reported compounds.

Spectral data

6-amino-3-methyl-4-phenyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5a): IR (KBr) *v* cm^{-1}: 3321, 3398 (NH_2), 2193 (C≡N), 1654 (C=C).^{1}H NMR (400 MHz, DMSO-d_6) *δ ppm*: 2.06 (s,3H, CH_3), 4.59 (s, 1H, CH), 5.48 (s, 1H, NH), 7.23-7.47 (m,5H, Ar-H), 10.48 (bs, 2H, NH_2). ^{13}C NMR (400 MHz, DMSO-d_6) *δ ppm*: 159.50, 157.02, 153.85, 134.85, 134.69, 127.38, 119.71, 96.54, 94.70, 57.77, 53.77, 34.74, 8.82. Mass (LC-MS) *m/z*: 251.2 (M^-).

Elemental analysis for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N, 22.21. Found: C, 66.57; H, 4.63; N, 22.13.

6-Amino-4-(4-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (***5b***): ^{1}H NMR (400 MHz, DMSO-d_6) δ 1.76 (s, 3H, -CH_3), 3.71 (s, 3H, -OCH_3), 4.51 (s, 1H), 6.79 (s, 2H, -NH_2), 6.84 (d, 2H, *J* = 8.0 Hz), 7.04 (d, 2H, *J* = 8.0 Hz), 12.04 (s, 1H, -NH). ^{13}C NMR (50 MHz, DMSO-d_6+$CDCl_3$) δ.8.8, 34.7, 53.8, 57.7, 94.7, 96.5, 112.5, 119.7, 127.4, 134.7, 134.8, 153.8, 157.0, 159.5. Mass (ES-MS) m/z 283.2 (M^+).

6-amino-4-(4-chlorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5d): Yellow solid, IR (KBr):3484.11, 3346.76, 3231.27, 2228.22 cm^{-1}, ^{1}H NMR (300 MHz, DMSO): δ 1.77 (s, 3H, CH_3), 4.67 (s, 1H, -CH), 6.55 (bs, 2H, -NH_2), 7.35-7.37 (dd, 2H, Ar-H, J = 6.0 Hz), 8.09-8.12(dd, 2H, Ar-H, J = 9.0 Hz), 11.95 (s, 1H, -NH),^{13}C NMR (75 MHz,$CDCl_3$): δ 10.21, 36.33, 97.37, 120.99, 128.67, 129.54, 131.96, 135.99, 143.47, 155.19, 161.27; Elemental Anal: C, (55.36%); H, (4.65%); N, (23.06%), Calcd. For $C_{14}H_{11}ClN_4O$:C, (55.39%); H, (4.62%); N, (23.09%).

6-Amino-4-(4-fluorophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5f):White powder; ^{1}H NMR (300 MHz, DMSO-d_6): δ= 1.79 (s, 3H), 4.64 (s, 1H), 6.92 (s, 2H), 7.10-7.30 (m, 4H), 12.13 (s, 1H);^{13}C NMR (75 MHz, DMSO-dd): δ= 9.78, 35.47, 38.69, 38.96, 39.24, 45.01, 49.29, 57.07, 97.53, 115.07, 115.36, 120.77, 129.33, 129.43, 135.67, 140.68, 140.72, 154.72, 159.37, 160.85. IR (neat):1395, 1491, 1591, 2198, 3090, 3226. MS (ESI):m/z= 271.1 $(M+H)^+$.

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6-amino-4-(4-bromophenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5h): Yellow solid, IR (KBr): 3486.37, 3431.74, 3271.99, 2193.51 cm^{-1},^{1}H NMR (200 MHz, DMSO): δ 1.82 (s, 3H, -CH_3), 4.56 (s, 1H, CH), 6.57 (bs, 2H, -NH_2), 7.10-7.14 (dd, 2H, Ar-H, J = 12.0 Hz), 7.42-7.46 (dd, 2H, Ar-H, J = 12.0 Hz), 11.96 (s, 1H, -NH), ^{13}C NMR (50MHz, DMSO):δ =9.75, 36.93, 57.07, 96.75, 119.85, 120.52, 120.52, 129.39, 131.08, 136.52, 143.33, 154.71 and 160.77; Elemental Anal: C, (50.77%); H, (3.35%); N, (16.92%), Calcd. For $C_{14}H_{11}BrN_4O$: C, (50.76%); H, (3.38%); N, (16.95%).

6-amino-4-(4-hydroxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5i): Yellow solid; IR (KBr): 3459.99, 3253.86, 3126.13, 2223.29 cm^{-1}, ^{1}H NMR (200 MHz, DMSO): δ 1.81 (s, 3H, -CH_3), 4.44 (s, 1H, -CH), 6.48 (bs, 2H, -NH_2), 6.71 (dd, 2H, Ar-H), 6.94(dd, 2H, Ar-H), 9.06 (bs, 1H, -OH),11.88 (s, 1H, -NH), Elemental Anal: C, (58.94%); H, (5.30%); N, (24.55%), Calcd. For$C_{14}H_{12}N_4O_2$: C, (58.92%); H, (5.31%); N, (24.58%),

6-amino-3-methyl-4-(4-nitrophenyl)-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5l): Yellow solid; IR (KBr): 3386.61, 3307.11, 3177.13, 2189.52, 1643.37cm^{-1}, ^{1}H NMR (300 MHz, DMSO): δ 1.76 (s,3H, -CH_3), 4.65 (s, 1H, -CH), 6.35 (bs, 2H, -NH_2), 7.33-7.36 (dd, 2H, Ar-H, J = 9.0 Hz), 8.08-8.11 (dd, 2H, Ar-H J = 9.0 Hz), 11.90 (s, 1H, -NH), ^{13}C NMR (75 MHz,$CDCl_3$): δ 10.16, 36.73, 58.01, 96.39, 120.49, 123.88, 128.73, 136.43, 146.88, 151.22, 155.18, 161.17,Elemental Anal: C(53.50%); H, (4.49%); N, (26.74%),Calcd. For $C_{14}H_{11}N_5O_3$: C, (53.50%), H, (4.49%); N, (26.74%).

6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5m): Yellow solid, IR (KBr):3413.28, 3350.11, 3176.29, 2186.78 cm^{-1};^{1}H NMR (300 MHz, DMSO): δ 1.76 (s, 3H, -CH_3), 3.71 (s, 6H, (OCH_3)$_3$), 4.45 (s, 1H, -CH), 6.37 (bs, 2H, -NH_2), 6.75-6.78 (dd, 2H, Ar-H, J = 9.0 Hz), 7.02-7.04 (dd, 2H, Ar-H), 11.84 (s, 1H, -NH), Elemental Anal: C, (58.35%); H, (5.81%); N, (21.26%), Calcd. For$C_{16}H_{16}N_4O_3$: C, (58.37%); H, (5.84%); N, (21.25%).

6-amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5n): Yellow solid, IR (KBr): 3490.79, 3413.72, 3275.81, 2195.64 cm^{-1}, ^{1}H NMR (200 MHz, DMSO): δ 1.85 (s, 3H, -CH_3), 3.79 (s, 3H, -OCH_3), 4.47 (s, 1H, -CH), 6.18 (bs, 2H, -NH_2), 6.66 (m, 2H, Ar-H), 7.86 (s, 1H, Ar-H), 8.46 (bs, 1H, -OH), 11.82 (s, 1H, -NH),^{13}C NMR (50MHz, DMSO):δ = 9.34, 9.78, 10.53, 26.15, 44.56, 53.37, 56.42, 62.08, 63.70, 68.39, 81.24, 86.18, 97.46, 110.90, 114.92, 119.74, 120.73, 134.91, 136.54, 140.13, 145.01, 147.17, 151.02, 154.79, 180.42, 186.13, 193.02, 196.73, 202.20, 211.13; Elemental Anal: C, (57.13%); H, (5.43%); N, (22.21%), Calcd. For $C_{15}H_{14}N_4O_3$: C, (57.16%); H, (5.42%); N, (22.19%).

6-amino-4-(4-(dimethylamino)phenyl)-3-methyl-1,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile (5o): Yellow solid, IR (KBr):3441.70, 3142.41, 2173.69cm^{-1}, ^{1}H NMR (300 MHz, DMSO): δ 1.78 (s,3H, -CH_3), 2.86 (s, 6H, -($N(CH_3)_2$), 4.41 (s, 1H, -CH), 6.01-6.62 (m, 4H, Ar-H, -NH_2), 6.94-6.97 (dd, 2H, Ar-H, J = 9.0 Hz), 8.08-8.11 (dd, 2H, Ar-H, J = 9.0 Hz), 11.91 (s, 1H, NH), ^{13}C NMR (75 MHz,$CDCl_3$)(Fig. 4.13): δ 10.22, 35.97, 58.83, 98.43, 112.61, 121.34, 128.37, 132.30, 135.91, 149.56, 155.26, 160.95, Elemental Anal: C, (61.52%); H, (6.45%); N, (26.90%), Calculated. For $C_{16}H_{17}N_5O$: C, (61.52%); H, (6.45%); N, (26.90%).

COMPUTATIONAL STUDY

ADME Properties

The success of a drug is determined not only by good efficacy but also by an acceptable ADME (absorption, distribution, metabolism and excretion) profile. In the present study, we have calculated molecular volume (MV), molecular weight (MW), logarithm of partition coefficient (miLog*P*), number of hydrogen bond acceptors (n-ON), number of hydrogen bonds donors (n-OHNH), topological polar surface area (TPSA), number of rotatable bonds (n-ROTB) and Lipinski's rule of five[49] using Molinspiration online property calculation toolkit.[50] Absorption (% ABS) was calculated by: % ABS = 109-(0.345×TPSA)[51] Drug-likeness model score (a collective property of physic-chemical properties, pharmacokinetics and pharmacodynamics of a compound is represented by a numerical value) was computed by MolSoft[52] software.

CONCLUSION

In summary, a facile, economic, echo friendly and green protocol developed for one-pot multicomponent cyclo-condensation of aldehydes, malononitrile, hydrazine hydrate and ethyl acetoacetate is established. Application of LiBras a catalyst for the synthesis of pyrano [2, 3-*c*] pyrazoleshas been exploited first time. The reaction conditions are mild accepting several functional groups present in the molecules and all reactions proceed under essentially neutral conditions, thus reducing the possibility of many unwanted side reactions. In addition, present method offers marked improvements with regard to product yield, reaction time, and greenness of procedure, avoiding hazardous organic solvents/toxic catalysts and provides a better, clean and practical alternative route of synthesis to the existing protocols.The synthesized Dihydropyrano [2,3-*c*] pyrazoleswere evaluated for ADME properties.

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