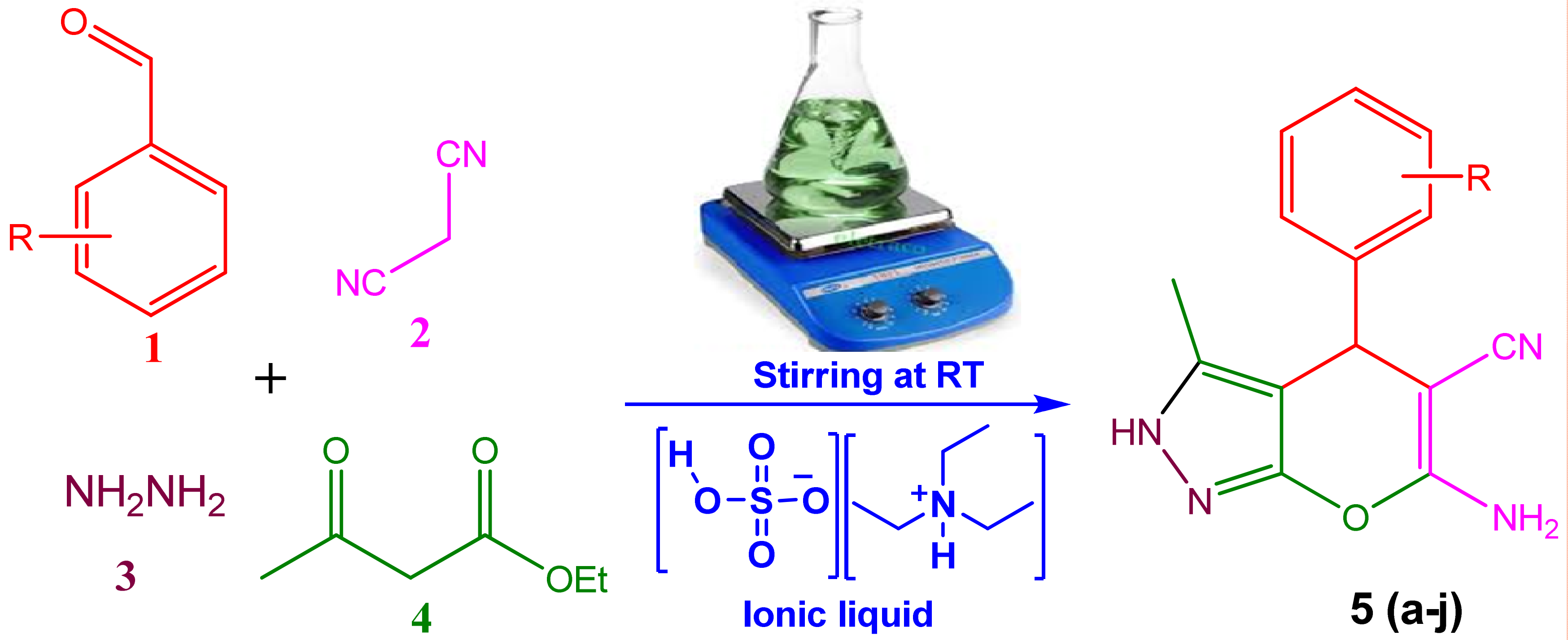
Ionic liquid [Et_3NH] [HSO_4]-catalyzed Multi component Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile.

Presented By
Dr. Anna Pratima G. Nikalje* Ms Urja D. Nimbalkar
Dr.Julio A. Seijas, Dr. Maria Pilar Vazquez Tato
***annapratimanikalje@gmail.com**

Department of Pharmaceutical Chemistry,
Dr. Rafiq Zakaria Campus,
Y. B. Chavan College of Pharmacy,
Aurangabad. MS. India

Y. B. CHAVAN
COLLEGE OF PHARMACY
AURANGABAD

Graphical Abstract:



Ionic liquid [Et_3NH] [HSO_4]-catalysed Multicomponent Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile.

Abstract: A series of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitriles(5a-5j) as a potent anticancer agent were synthesized via one-pot, four-component condensation reaction of aryl aldehydes, ethyl acetoacetate, malononitrile, and hydrazine hydrate in solvent-free conditions using ionic liquid [Et3NH] [HSO4] as an efficient, eco-friendly and reusable catalyst. The Multicomponent coupling reactions (MCRs) indicate a highly appreciated synthetic tool for the establishment of novel and complex molecular scaffold with a minimum number of synthetic steps with the advantage like shorter reaction times, lower costs, high degrees of atom economy etc. With the literature survey it is found that dihydropyrano[2,3-c]pyrazole derivatives possess very important biological activities, including anticancer, antiinflammatory, antimicrobial, inhibitors of human Chk1 kinase, molluscicidal, and insecticidal activities. The solvent used in conventional organic synthesis are suffered by many disadvantage like environmental hazards, toxicity, volatile nature, expensive etc. A new term ‘designer solvents’ referring to Ionic liquids because of their adjustable physical and chemical properties with the change in selected cationic and anionic combination. Ionic liquids have become a promising alternative media for various chemical processes due to their properties including good solvating capability, negligible vapour pressure, non-inflammability, ease of recyclability, controlled miscibility and high thermal stability. Herein we are introducing first time the use of acidic Bronsted ionic liquid(ABILs) [Et3NH][HSO4] triethylaminesulphate for the synthesis of biologically important scaffold 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile,the synthesised derivatives subjected to anticancer activity. Compared to other methods, this new method consistently has advantages, including excellent yields, a short reaction time, mild reaction conditions and catalyst reusability.

Keywords: Ionic liquid, Solvent free, Multicomponent Synthesis, Dihydropyrano[2,3-c]pyrazoles.

CONTENTS:

INTRODUCTION

- Multicomponent reactions gain an outstanding position in medicinal and organic chemistry with the implementation of principles of green chemistry. In modern era, academicians and industrialist are looking for green protocols for the synthesis of chemical processes to conquer eco-friendliness [3]To replace conventional media or solvents used for organic synthesis is very essential as they shows some side effects including toxicity, flammable and volatile nature so research is progressing in finding alternative greener media for commonly used organic synthesis [4],research and development of room-temperature ionic liquids are acting as best replacement to conventional media with the advantages such as chemo selectivity and facile condensation reactions [5,6,7]
- Ionic liquids have become a promising alternative media for various chemical processes due to their properties including good solvating capability, negligible vapour pressure, non-inflammability, ease of recyclability, controlled miscibility and high thermal stability. [8,9]. So Triethyl Ammonium Sulphate is acting as very excellent catalysts, as well as solvents, for many organic transformations[10] In particular, acidic Bronsted ionic liquids (ABILs) are of special importance, because they simultaneously possess proton acidity and the characteristic properties of ionic liquids ABILs offer environmentally friendly catalyst properties due to the combination of the advantages of liquid acids and solid acids, such as uniform acid sites, stability in water and air, easy separation and reusability. [11].

Cyclocondensation of aromatic substituted aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate to obtain dihydropyrano[2,3-F]pyrazoles can be achieved by various methodology including several catalyst Piperazine[24] piperidine[25]N-methylmorpholine[26] hetero- polyacids[27] glycine[28]per-6-amino-b-cyclodextrin[29] Mg/Al hydrotalcite[30]nanosized magnesium oxide[31] L-proline [32] ϒ-alumina [33] sodium benzoate [34] and amberlyst A21 [35] CTACl [36]

Junek and Aigner[37] first time introduced the synthesis of pyrano[2,3-c]pyrazole derivatives from 3-methyl-1- phenylpyrazolin-5-one and tetracyanoethylene in the presence of triethylamine .Sharanin and sharanina [38]also reported synthesis of 6-amino-4-aryl-3-methyl-2,4-dihydropyrano[2,3-c]pyrazoles using triethylamine, The use of Triethyl amine for the synthesis of pyranopyrazole moeity in early period has given an idea to work on the ionic liquid containing triethyl amine as one component so here we have selected very efficient Acidic Bronsted Ionic Liquid (ABIL), Triethyl ammonium Sulphate $[Et_3NH][HSO_4]$[39] which posses significant properties including, cost effective, non-toxic, catalyst as well as solvent for many organic transformations with excellent yield. Herein we are reporting synthesis of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles5(a-j) with excellent yield at room temperature with Ionic liquid $[Et_3NH][HSO_4]$ as catalyst as well as solvent and introducing one more novel green chemistry protocol in the list of methods of synthesis for pyrano[2,3-c]pyrazole derivatives as important biologically active scaffold.

NEED OF STUDY:

- Ionic liquids have become a promising alternative media for various chemical processes due to their properties including good solvating capability, negligible vapour pressure, non-inflammability, ease of recyclability, controlled miscibility and high thermal stability. [8,9].
- In recent times, the value of Acidic Bronsted Ionic Liquid (ABIL), mainly [Et_3NH][HSO_4] has acknowledged as a catalyst and solvent of choice for organic transformation with excellent yield and beneficial as non-toxic nature, inexpensive ,easy preparation methods and from readily available laboratory chemicals. [12,13].
- In modern synthetic organic chemistry, Multi-component reactions have been established as efficient and prominent tool assisting the reaction of three or more components in one pot to give new ‘‘drug-like’’ molecules with the essential parts of all the initial reactants. MCR offering significant advantages such as variety of convergent synthesis of complex organic compounds, facile mechanism, atom economy, low cost, shorter reaction and workup time , easy purification processes, and minimum wastage [1,2]
- Organic chemist are always looking for the synthesis of new moiety with some biological effect, Pyrano[2,3-c]pyrazoles are such recently synthesised and proven to show numerous biological activity [14] including anticancer–antitumor,[15] antimicrobial[16] anti-inflammatory[17]analgesic[18] inhibitors of human chk1 kinase[19]. Molluscicidal and insecticidal activity [20] also acting as potent pharmaceutical constituents and biodegradable agrochemicals.[21,22,23]

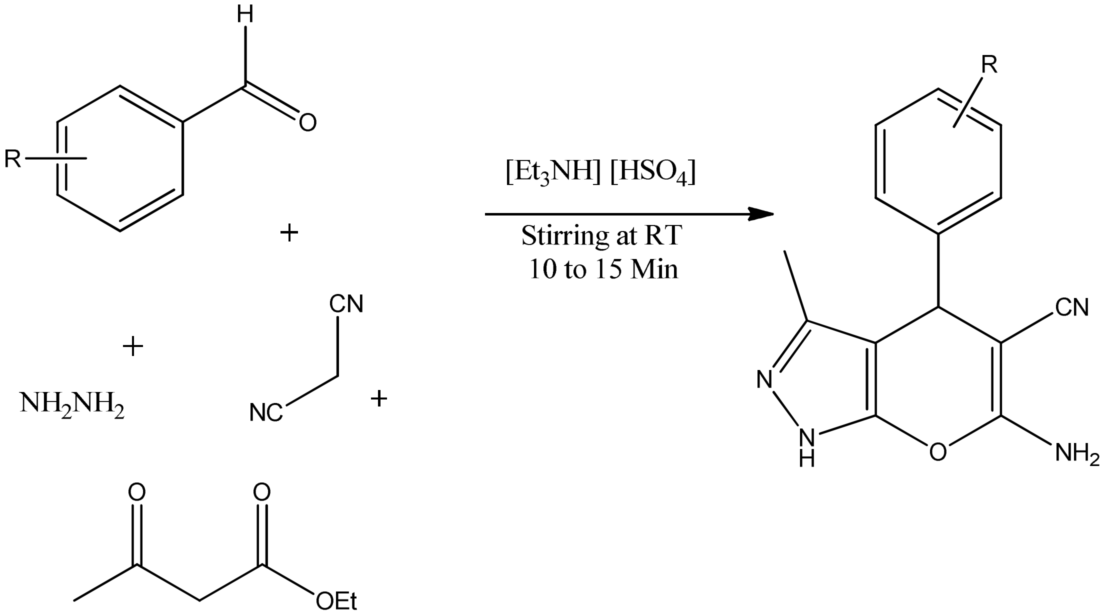
OBJECTIVE OF STUDY

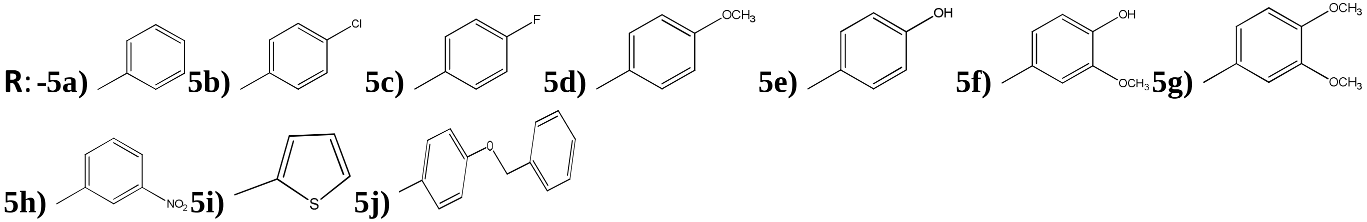
- To design and synthesize 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles(5a-5j) by using green solvent as wel as catalyst i.e Acid Bronsted Ionic Liquid [Et_3NH][HSO_4] in 20 mol% at ambient room temperature in 10 to 15 minutes with excellent yield upto 94%
- To conduct physicochemical characterization of all ten synthesized compounds**.**
- To confirm the structures of synthesized compounds by analytical and spectral techniques such as TLC, FT-IR, ES-MS, ^{1}H NMR and ^{13}C NMR .
- To determine anticancer activity of the synthesised compounds.

MATERIAL AND METHOD:

- All the chemicals used for synthesis were procured from Merck (Mumbai, Maharashtra, India), Sigma (Mumbai), HiMedia (Mumbai) or Qualigens (Mumbai) and used without further purification. The progress of each reaction was monitored by ascending thin layer chromatography (TLC) using pre-coated silica gel F254 aluminum TLC sheets (Merck) and the spots were visualized by UV light and iodine vapors. Elemental analyses (C, H, and N) were done with a FLASHEA 112 Shimadzu' analyzer (Mumbai) and all analyses were consistent (within 0.4%) with theoretical values. Infrared (IR) spectra were recorded on a PS 4000 FTIR (JASCO, Tokyo, Japan) using KBr pellets. ^{1}H-(400MHz) and ^{13}C-NMR (100 MHz) spectra were recorded on a BRUKER AVANCE 400NMR spectrometer (Bruker, Billerica, MA, USA) fitted with an Aspect 3000 computer and all the chemical shifts (δ ppm) were referred to internal TMS for ^{1}H and DMSO-*d*6 for^{13}C-NMR. ^{1}H-NMR data are reported in the order of chemical shift, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; br, broad; br s, broad singlet; m, multiplet and/ or multiple resonance), number of protons. A Micro TOF-Q-II (Bruker Daltonics, Billerica, MA, USA with electron spray ionization (ESI) was used to obtain the HRMS data.

SCHEME OF SYNTHESIS

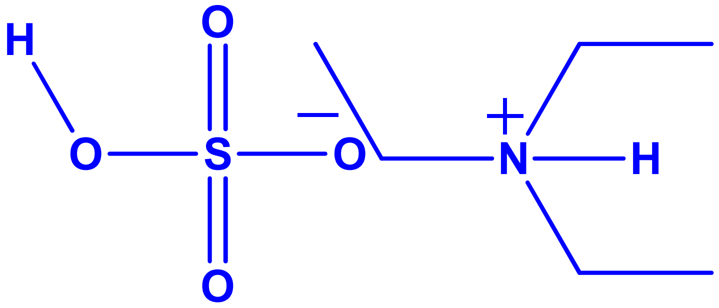




EXPERIMENTAL:

Synthesis of Ionic Lquid[Et_3NH][HSO_4]as Solvent and Catalyst:

- 98 % solution of Sulphuric acid (1.96 g, 0.02 mol) in water was dropped into triethylamine (2.02 g, 0.02 mol) with stirring at 60^0C for 1 h. After the addition, the reaction mixture was stirred for another 1 h at 70 ^{0}C. The water molecule was removed by heating the residue at 80–90^0C under a high vacuum until the weight of the residue remained constant.



Synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile:

- A mixture of substituted aromatic benzaldehyde (1) (1mmol), malononitrile (2) (1 mmol), hydrazine hydrate (3) (1mmol), and ethyl acetoacetate (4) (1 mmol) was added in $[Et_3NH]$ $[HSO_4]$ 20 mol% and then the reaction mass was stirred at room temperature. Progress of the reaction was monitored by TLC (ethyl acetate: n-hexane 1:9). Then, product was extracted using ethylacetate. The reaction mixture was quenched with crushed ice and extracted with ethyl acetate.
- The solvent was evaporated under reduced pressure to afford the corresponding crude compounds. The obtained crude compounds were recrystallized using ethanol.

Table 1 Physical characterization of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

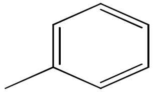
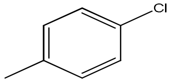
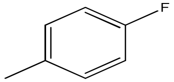
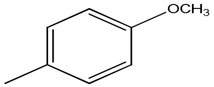
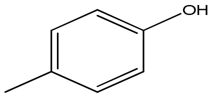
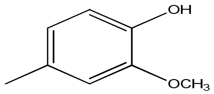
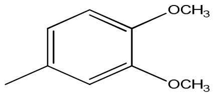
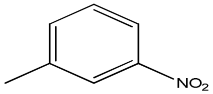
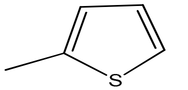
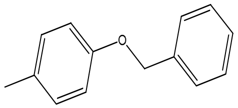
Derivatives	R	(Mol. wt)	Yield (%)	m.p. (ºC)	Analysis (%) Found [calcul
					C H N
a		252.10	88	240-242	C,66.65; H, 4.79; N,22.21 [C,66.67; H, 4.75; N, 22.21]
b		286.06	94	228-230	C,58.65; H, 3.87; N, 19.54 [C,58.61; H, 3.82; N, 19.50]
c		270.09	92	172-174	C,62.22; H, 4.10; N, 20.73 [C, 62.22; H, 4.10; N, 20.73]
d		282.11	94	205-207	C,63.82; H, 5.00; N, 19.85 [C, 63.78; H, 5.05; N, 19.82]
e		268.10	88	219-221	C,62.68; H, 4.51; N, 20.88 [C,62.70; H, 4.48; N, 20.87]
f		298.11	85	232-234	C,60.40; H, 4.73; N, 18.78 [C,60.38; H, 4.70; N, 18.75]
g		312.12	87	185-187	C,61.53; H, 5.16; N, 17.94 [C,61.50; H, 5.12; N, 17.92]
h		297.09	88	188-190	C,56.56; H, 3.73; N, 23.56 [C,56.58; H, 3.70; N, 23.52]
i		258.06	89	222-224	C,55.80; H, 3.90; N, 21.69 [C,55.82; H, 3.88; N, 21.72]
j		358.14	88	212-214	C,70.38; H, 5.06; N, 15.63 [C,70.40; H, 5.10; N, 15.70]

TABLE 2 SCREENING OF REACTION MEDIA FOR THE SYNTHESIS OF COMPOUND 5A-5J

Herein we also compared the reported ionic liquid with other three solvent as comparison for the synthesis of dihydropyrano[2,3-c]pyrazole in which [Et_3NH][HSO_4] provided better results in terms of high yield and a solvent-free protocol, and the reaction was carried out at room temperature and so we find it most significant method of synthesis .

Table2 Screening of reaction media for the synthesis of compound 5a-5j

Entry	**Solvent**	**Time in minutes**	**Yield(%)**
1	PEG	60	72
2	Ionic liquid (N-methylpyridinium tosylate)	75	62
3	DES(At 80^{0}C)	20	92
4	[Et_3NH][HSO_4] (At RT)	15	94

TABLE 3: EFFECT OF IONIC LIQUID CONCENTRATION ON REACTION TIME AND YIELD

All the final compounds (5a-5j) were synthesised following the procedure depicted in **scheme I**. Synthesis is carried out in one pot by adding all the reactant at a time with equimolar ratio as substituted aromatic aldehyde(1mmol),malononitrile(1mmol),hydrazine hydrate(1mmol)and ethyl acetoacetate(1mmol) initially, the reaction was carried out in the absence of the catalyst; no product is obtained so catalyst is added increasing amount to determine the appropriate concentration of the catalyst and solvent $[Et_3NH][HSO_4]$, we investigated the model reaction at different concentrations of [Et3NH][HSO4], such as 0,5, 10, 15, 20 and 25 mol%. The dihydropyrano[2,3-c]pyrazole formed in 0,50,65,70,94 and 85 % yields, respectively (Table 2).The increase in concentration of catalyst from 20 to 25 mol% does not increase the yield of product. This indicates that 20 mol% of $[Et_3NH]$ $[HSO_4]$ is sufficient for the reaction by considering the product yield.

Table3 Effect of ionic liquid as a catalyst concentration on reaction time and yield

Entry	**$[Et_3NH][HSO_4]$ mol%**	**Time in minutes**	**Yield(%)**
1	-	60	00
2	5	50	50
3	10	45	65
4	15	15	70
5	20	10	94
6	25	10	85

TABLE 4: REUSABILITY OF IONIC LIQUID FOR MODEL REACTION

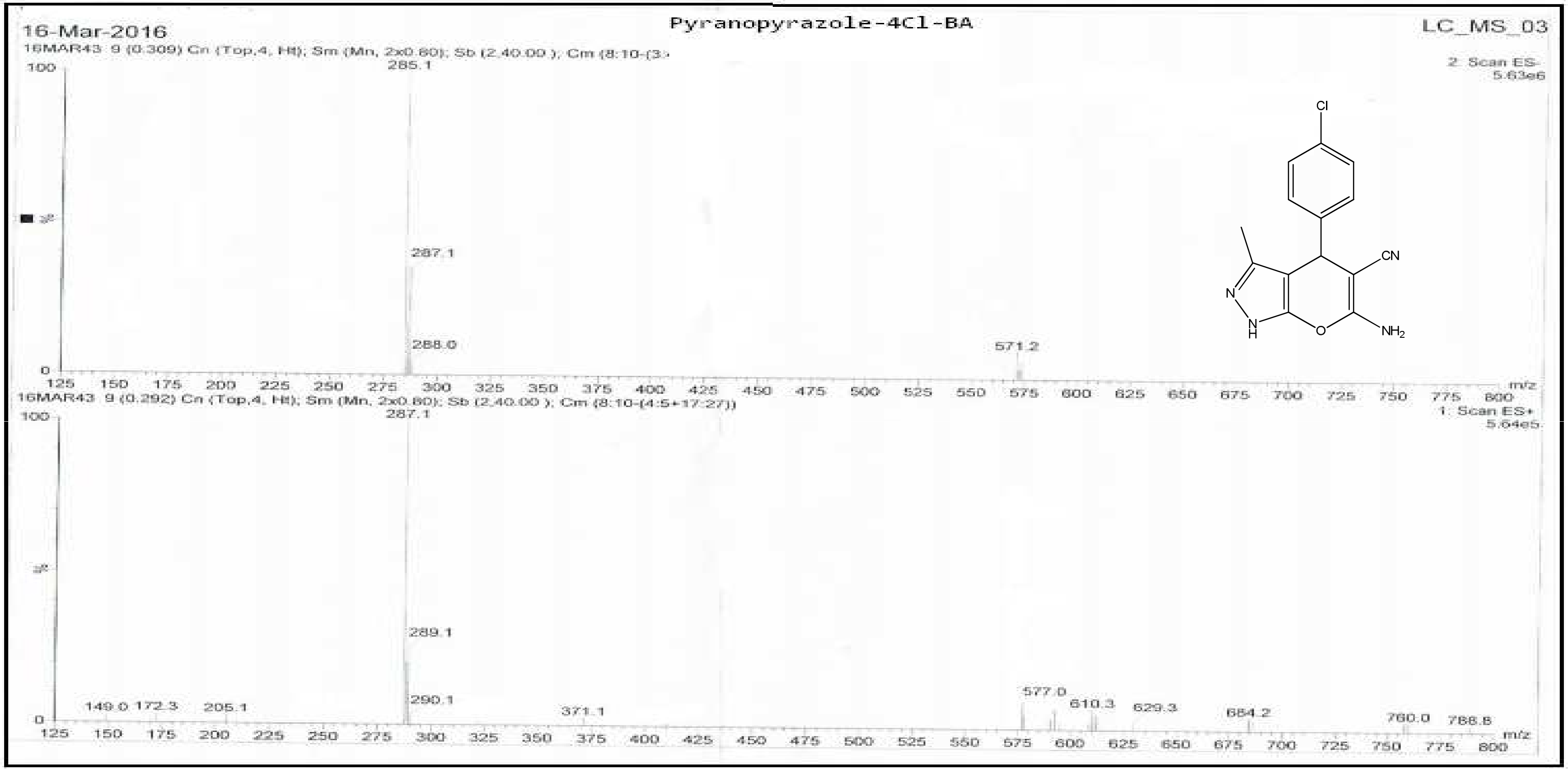
We have also statistically reported the recyclability of the ionic liquid [Et_3NH][HSO_4] in Table 4. After the completion of the reaction, the reaction mixture was quenched with ice crystals and extracted with ethyl acetate. The residual ionic liquid was washed with diethyl ether, dried under vacuum at 60 and reused for subsequent reactions. The recovered ionic liquid could be used for four times without much loss of catalytic activity.

Table4 Reusability of ionic liquid for model reaction

Entry	Run	Time in min	Yield in%
1	1	15	94
2	2	15	82
3	3	15	78
4	4	15	75

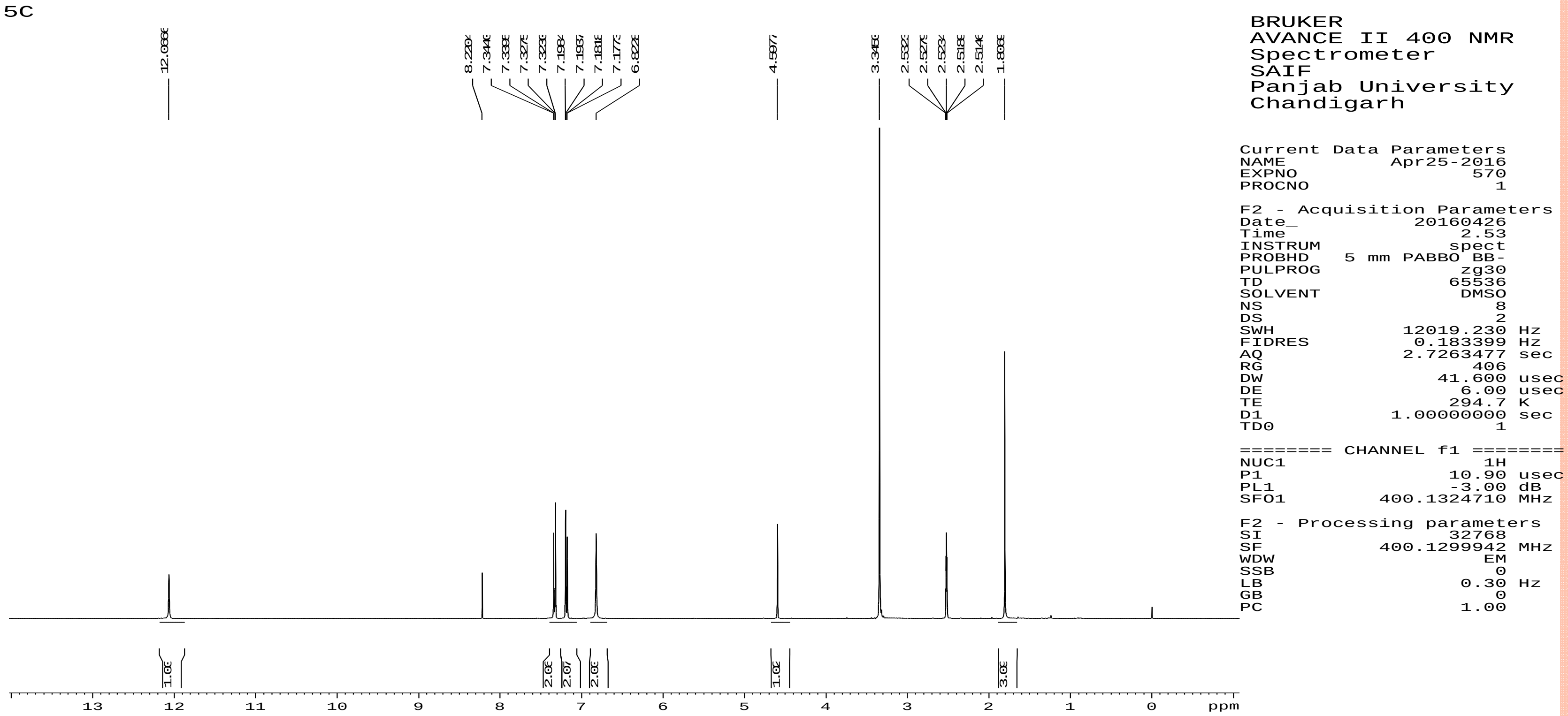
So we get excellent yield upto 94% of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile with green solvent i.e acid Bronsted ionic liquid and catalyst [Et_3NH][HSO_4] in 20 mol% at ambient room temperature in 10 to 15 minutes.

5B) 6-AMINO-4-(4-CHLOROPHENYL)-3-METHYL-2,4-DIHYDROPYRANO[2,3-C]PYRAZOLE-5-CARBONITRILE:MASS SPECTRA



Sr. No.	Fragmentation	m/z
1	M+	286.06
2	M+1	287.1
3	M-1	285.1

^{1}H NMR SPECTRA: 5B) 6-AMINO-4-(4-CHLOROPHENYL)-3-METHYL-2,4-DIHYDROPYRANO[2,3-C]PYRAZOLE-5-CARBONITRILE:MASS SPECTRA



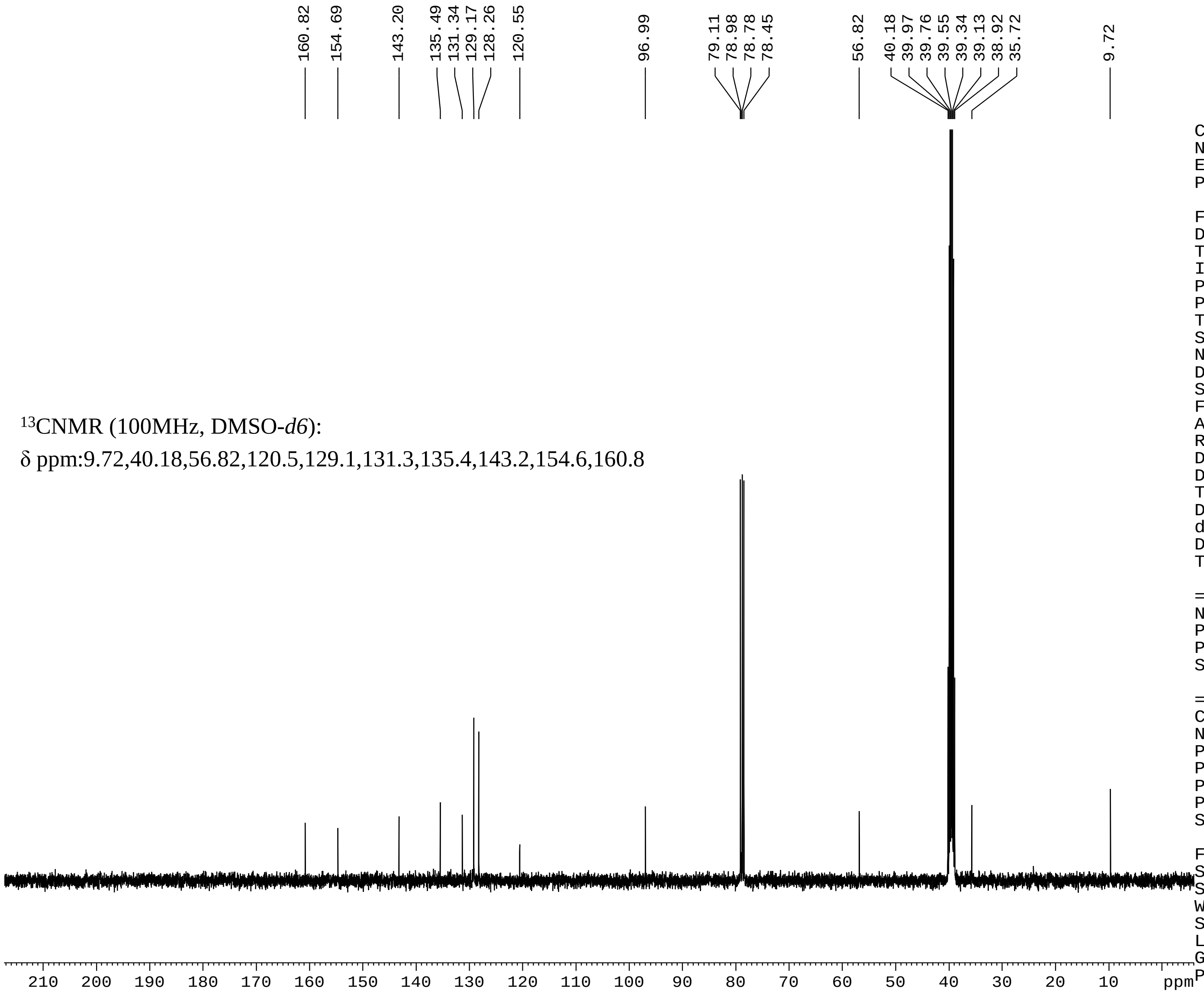
```
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME             Apr25-2016
EXPNO                   570
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160426
Time                   2.53
INSTRUM               spect
PROBHD     5 mm PABBO BB-
PULPROG                zg30
TD                    65536
SOLVENT                DMSO
NS                        8
DS                        2
SWH               12019.230 Hz
FIDRES             0.183399 Hz
AQ                2.7263477 sec
RG                      406
DW                   41.600 usec
DE                     6.00 usec
TE                    294.7 K
D1               1.00000000 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                     1H
P1                    10.90 usec
PL1                   -3.00 dB
SFO1            400.1324710 MHz

F2 - Processing parameters
SI                    32768
SF              400.1299942 MHz
WDW                      EM
SSB                       0
LB                     0.30 Hz
GB                        0
PC                     1.00
```

manishkumarmanu1986@gmail.com

Sr. No.	δ Values (ppm)	Multiplicity	No. of proton	Group
1	1.80	s	3H	-CH_3
2	4.58	s	1H	-CH-
3	7.68-7.73	m	4H	Ar-H
4	8.2	s	2H	-NH2
5	12.6	s	1H	-NH

^{13}C NMR Spectra:5b) 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile:Mass Spectra

5C



^{13}CNMR (100MHz, DMSO-*d6*):

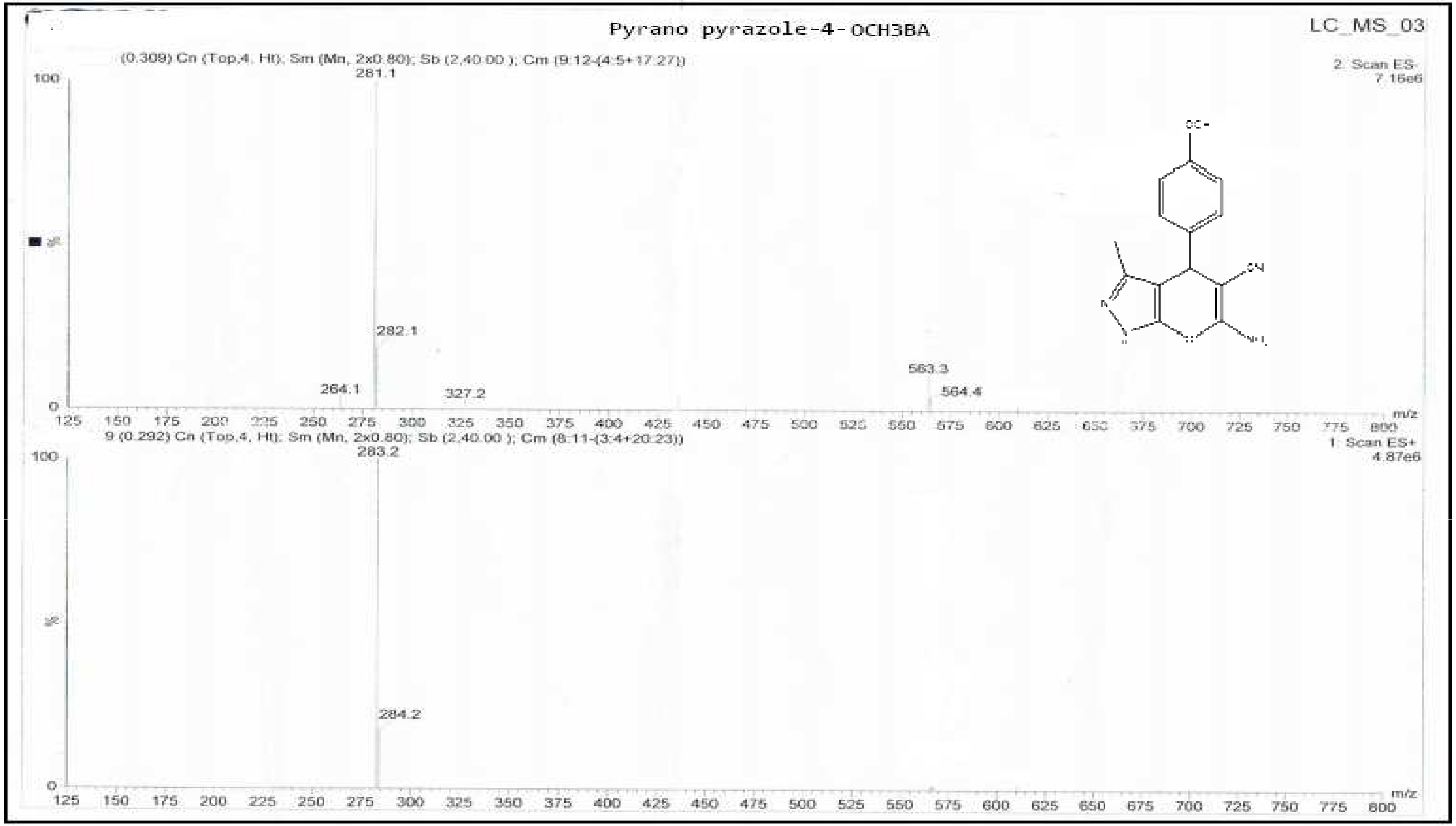
δ ppm:9.72,40.18,56.82,120.5,129.1,131.3,135.4,143.2,154.6,160.8

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME             Apr25-2016
EXPNO                   571
PROCNO                    1

F2 - Acquisition Parameters
Date_              20160426
Time                   3.22
INSTRUM               spect
PROBHD    5 mm PABBO BB-
PULPROG             zgpg30
TD                    65536
SOLVENT                DMSO
NS                      512
DS                        4
SWH               29761.904 Hz
FIDRES             0.454131 Hz
AQ                1.1010548 sec
RG                     1620
DW                   16.800 usec
DE                     6.00 usec
TE                    295.1 K
D1               2.00000000 sec
d11              0.03000000 sec
DELTA            1.89999998 sec
TD0                       1

======== CHANNEL f1 ========
NUC1                    13C
P1                     9.60 usec
PL1                   -2.00 dB
SFO1            100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2             waltz16
NUC2                     1H
PCPD2                 80.00 usec
PL2                   -3.00 dB
PL12                  14.31 dB
PL13                  18.00 dB
SFO2            400.1316005 MHz

F2 - Processing parameters
SI                    32768
SF              100.6128193 MHz
WDW                      EM
SSB                       0
LB                     1.00 Hz
GB                        0
PC                     1.40
```

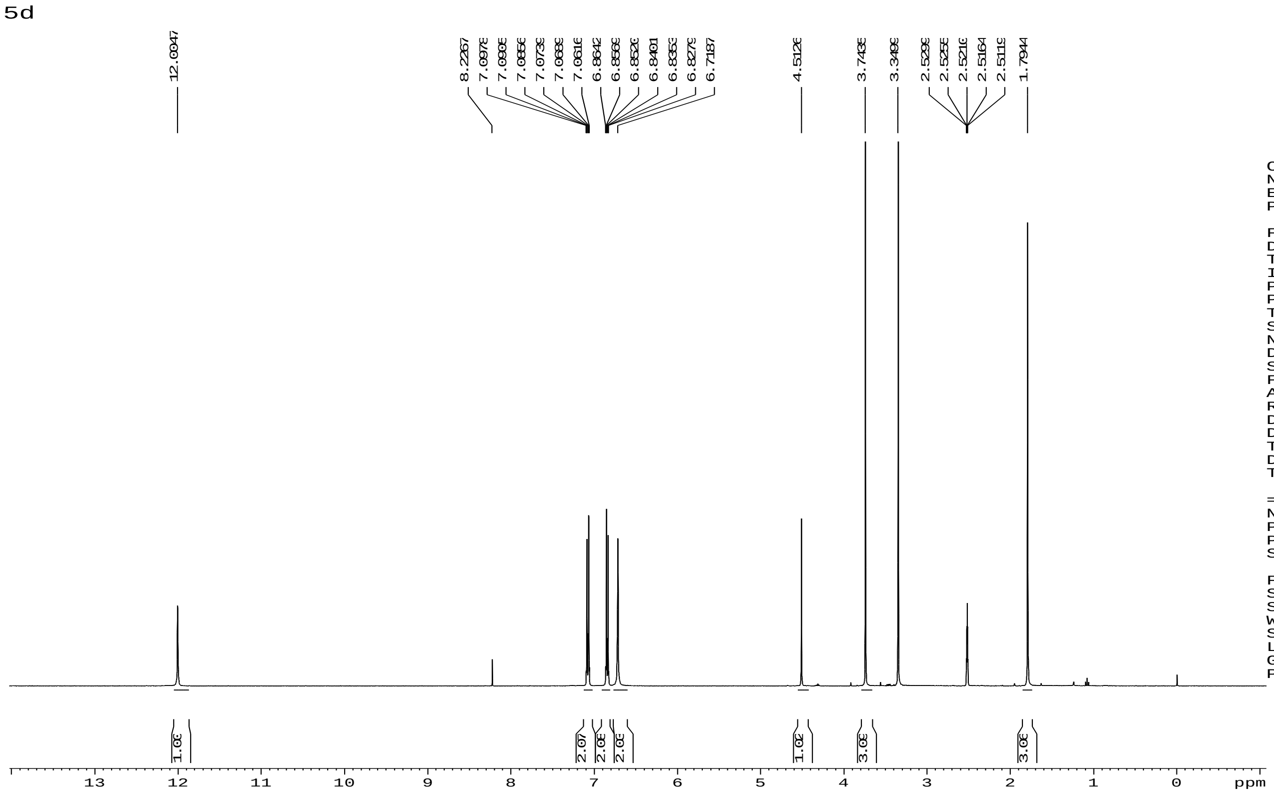
manishkumarmanu1986@gmail.com

Mass Spectra:5d) 6-amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile



Sr. No.	Fragmentation	m/z
1	M+	282.11
2	M+1	283.2
3	M-1	281.1

1H Spectra:5d) 6-amino-4-(4-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile



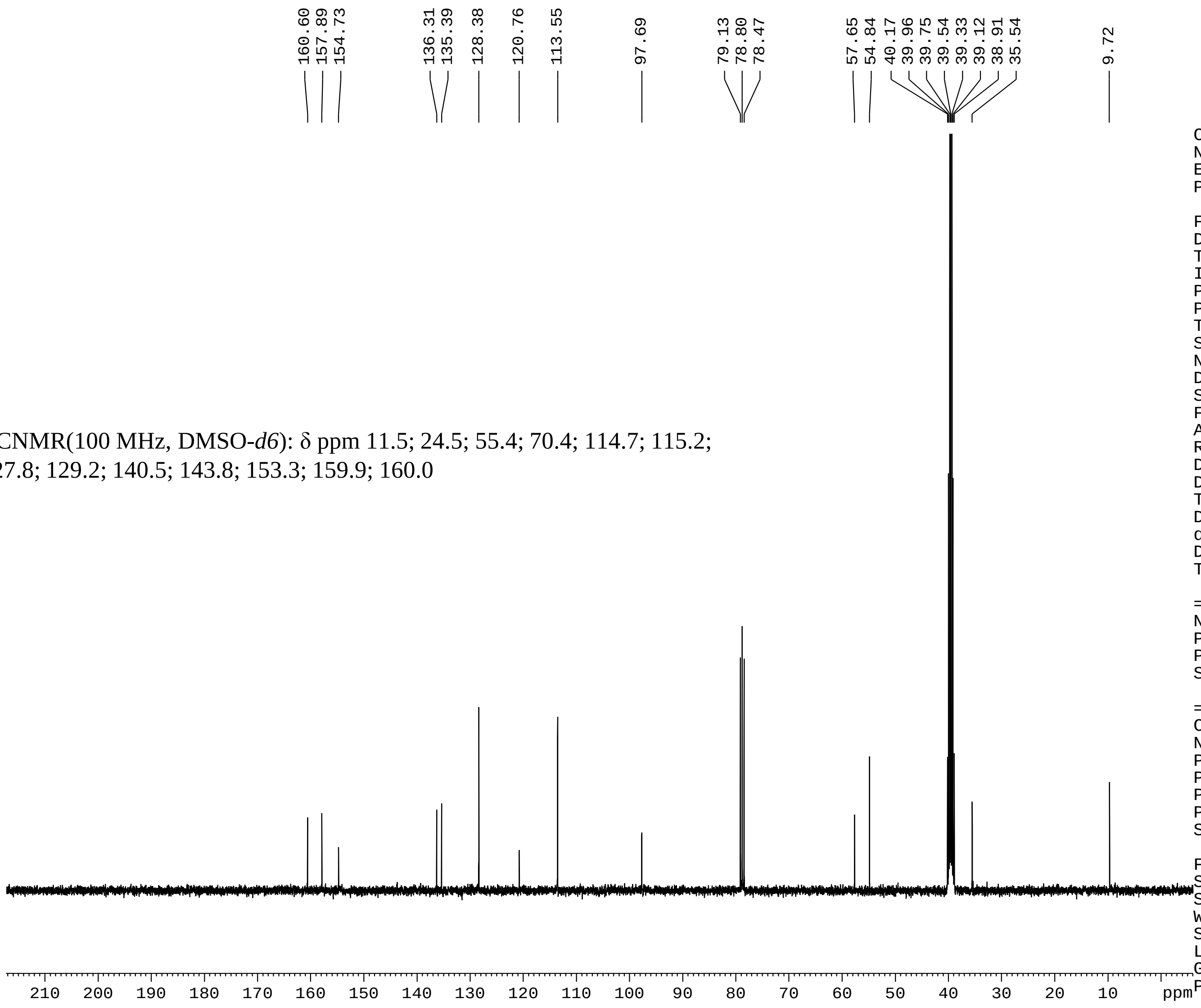
```
BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME              Apr25-2016
EXPNO                    580
PROCNO                     1

F2 - Acquisition Parameters
Date_               20160426
Time                    3.27
INSTRUM                spect
PROBHD     5 mm PABBO BB-
PULPROG                 zg30
TD                     65536
SOLVENT                 DMSO
NS                         8
DS                         2
SWH             12019.230 Hz
FIDRES           0.183399 Hz
AQ              2.7263477 sec
RG                       322
DW                41.600 usec
DE                  6.00 usec
TE                  294.7 K
D1             1.00000000 sec
TD0                        1

======== CHANNEL f1 ========
NUC1                      1H
P1                10.90 usec
PL1                -3.00 dB
SFO1         400.1324710 MHz

F2 - Processing parameters
SI                     32768
SF           400.1299952 MHz
WDW                       EM
SSB                        0
LB                   0.30 Hz
GB                         0
PC                      1.00
```

manishkumarmanu1986@gmail.com

Sr. No.	δ Values (ppm)	Multiplicity	No. of proton	Group
1	1.79	s	3H	$-CH_3$
2	3.74	s	3H	-O-CH3-
3	4.51	s	1H	-CH-
4	6.80-7.0	m	4H	Ar-H
5	8.2	s	2H	-NH2
6	12.0	s	1H	-NH

^{13}C NMR SPECTRA:5D) 6-AMINO-4-(4-METHOXYPHENYL)-3-METHYL-2,4-DIHYDROPYRANO[2,3-C]PYRAZOLE-5-CARBONITRILE

5d



^{13}CNMR(100 MHz, DMSO-*d6*): δ ppm 11.5; 24.5; 55.4; 70.4; 114.7; 115.2; 127.8; 129.2; 140.5; 143.8; 153.3; 159.9; 160.0

BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
Current Data Parameters
NAME            Apr25-2016
EXPNO                  581
PROCNO                   1

F2 - Acquisition Parameters
Date_             20160426
Time                  3.55
INSTRUM              spect
PROBHD   5 mm PABBO BB-
PULPROG            zgpg30
TD                   65536
SOLVENT               DMSO
NS                     512
DS                       4
SWH              29761.904 Hz
FIDRES            0.454131 Hz
AQ               1.1010548 sec
RG                    1030
DW                  16.800 usec
DE                    6.00 usec
TE                   295.0 K
D1              2.00000000 sec
d11             0.03000000 sec
DELTA           1.89999998 sec
TD0                      1

======== CHANNEL f1 ========
NUC1                   13C
P1                    9.60 usec
PL1                  -2.00 dB
SFO1           100.6228298 MHz

======== CHANNEL f2 ========
CPDPRG2            waltz16
NUC2                    1H
PCPD2                80.00 usec
PL2                  -3.00 dB
PL12                 14.31 dB
PL13                 18.00 dB
SFO2           400.1316005 MHz

F2 - Processing parameters
SI                   32768
SF             100.6128193 MHz
WDW                     EM
SSB                      0
LB                    1.00 Hz
GB                       0
PC                    1.40
```

manishkumarmanu1986@gmail.com

RESULTS AND DISCUSSION:

- With immense literature survey on all available method of multicomponent one pot cyclocondensation synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile having broad spectrum of biological activity,herein we are introducing the use of green medium i.e Acid Bronsted Ionic Liquid $[Et_3NH]$ $[HSO_4]$ as solvent and catalyst in 20 mol% first time for the synthesis of pyrano[2,3-c] pyrazole by stirring at ambient room temperature in very short reaction time 10 to 15 minutes with excellent yield up to 94%.

CONCLUSION:

In conclusion we have tried to developed an efficient, greener and prompt synthetic protocol for substituted dihydropyrano[2,3-F]pyrazoles via one pot cyclocondensation of various aromatic aldehydes, ethyl acetoacetate, hydrazine hydrate, and malononitrile by using[Et_3NH][HSO_4] catalyst. This technique overcomes some of the problems associated with excessive or wasteful refluxing procedure. Remarkable advantages of this synthetic strategy are reaction performs at ambient room temperature in very less reaction time with nontoxic and economically viable catalyst by avoiding the use of solvent and lastly shortened work-up procedure. As far our knowledge this is the first report on the use of [Et_3NH] [HSO_4] catalyst for the syntheses of substituted dihydropyrano[2,3-F]pyrazoles.

Acknowledgments:

- The authors are thankful to Fatima Rafiq Zakaria, Chairman, Maulana Azad Educational
- Trust, Maqdoom Farooqui, Principal, Maulana Azad Postgraduate and Research Centre, Aurangabad and
- Zahid Zaheer, Principal, Y. B. Chavan College of Pharmacy, Rafiq Zakaria Campus, Aurangabad 431 001 (M.S.),India for providing the laboratory facility.

REFERENCES:

- [1] Gu Y. Multicomponent reactions in unconventional solvents: state of the art. Green Chem 2012;14(8):2091–128.
- [2] Prasanna P, Perumal S, Mene´ndez JC. Chemodivergent,multicomponent domino reactions in aqueous media: L-prolinecatalyzed assembly of densely functionalized 4H-pyrano[2,3-c]pyrazoles and bispyrazolyl propanoates from simple, acyclic starting materials. Green Chem 2013;15(5):1292–9.
- [3]. Hailes, H. C. Reaction solvent selection: The potential of water as a solvent for organic transformations. Org. Process Res. Dev. 2007, 11, 114-120.
- [4] El-Tamany, E. S.; El-Shahed, F. A.; Mohamed, B. H. Synthesis and biological activity of some pyrazole derivatives. J. Serb. Chem. Soc.1999, 64, 9-18
- [5]. (a) Peng, J.; Deng, Y. Ionic liquid-catalysed Biginelli reaction under solvent free conditions. Tetrahedron Lett. 2001, 42, 5917; (b) Chowdari, N. S.; Ramachary, D. B.; Bardas, III; Carlos, F. Organocatalysis in ionic liquids: Highly efficient L-proline-catalysed direct asymmetric Mannich reactions involving ketone and aldehyde nucleophiles. Synlett. 2003, 1906; (c) Wang, B.; Gu, Y.; Luo, C.; Yang, T.; Yang, L.; Suo, J. Pyrole synthesis in ionic liquids by Paal–Knorr condensation under mild conditions. Tetrahedron Lett. 2004, 45, 3417.
- [6]. Bo, W.; Ming, Y. L.; Shuan, S. J. Ionic liquid–regulated sulfamic acid: Chemoselective catalyst for the transesterification of b-ketoesters. Tetrahedron Lett. 2003, 44, 5037.
- [7]. Gordon, C. M. New developments in catalysis using ionic liquids. Appl. Catal. A 2001, 222, 101.

- [8]. Z. Lei, C. Dai, B. Chen, Chem. Rev. 114, 1289 (2014)
- [9] M.V. Fedorov, A.A. Kornyshev, Chem. Rev. 114, 2978 (2014)006, 339, 456-460.
- [10]. Z.N. Siddiqui, K. Khan, ACS Sustain. Chem. Eng. 2, 1187 (2014). (reference cited their in)
- [11].X.X. Han, H. Du, C.T. Hung, L.L. Liu, P.H. Wu, D.H. Ren, S.J. Huang, S.B. Liu, Green Chem. 17, 499 (2015)
- [12].Subhedar D.D.Shaikh M.H. Arkile M.A., Yeware A.Sarkar D.Shingate B.B. Facile synthesis of 1,3-thiazolidin-4-ones as antitubercular agentsBioorganic & Medicinal Chemistry Letters 26 (2016) 1704–1708
- [13].Shaikh M.H. Subhedar D.D.Khan F.A.K. Sangshetti J.N. Shingate B.B [Et3NH][HSO4]-catalyzed one-pot, solvent-free synthesis and biological evaluation of a-amino phosphonates Res Chem Intermed (2016) 42:5115–5131
- [14]. (a) Elguero, J.; Goya, P.; Jagerovic, N.; Silva, A. M. S. Targets Heterocycl. Syst.2002, 6, 52; (b) Singh, S. K.; Reddy, P. G.; Rao, K. S.; Lohray, B. B.; Misra, P.;Rajjak, S. A.; Rao, Y. K.; Venkatewarlu, A. Bioorg. Med. Chem. Lett. 2004, 14, 499–504.
- [15]. Wang, J. L.; Liu, D.; Zheng, Z. J.; Shan, S.; Han, X.; Srinivasula, S. M.; Croce, C.M.; Alnemri, E. S.; Huang, Z. Proc. Natl. Acad. Sci. U.S.A. 2000, 97, 7124;
- [16]. El-Tamany, E. H.; El-Shahed, F. A.; Mohamed, B. H. J. Serb. Chem. Soc. 1999, 64, 9;
- [17].M.E.A. Zaki, H.A. Saliman, O.A. Hickal, A.E. Rashad, Pyrazolopyranopyrimi- 297 dines as a class of anti-inflammatory agents, J. Biosci. 61 (2006) 1–5; 298 (b) C.K. Sheng, J.H. Li, N. Hideo, Studies on heterocyclic compounds. 6 Synthesis 299 and analgesic and antiinflammatory activities of 3,4-dimethylpyrano[2,3-c]pyr- 300 azol-6-one derivatives, J. Med. Chem. 27 (1984) 539–544.

[18]. Kuo, S. C.; Huang, L. J.; Nakamura, H. J. Med. Chem. 1984, 27, 539;

[19]. Foloppe, N.; Fisher, L. M.; Howes, R.; Potter, A.; Robertson, A. G. S.; Surgenor, A.E. Bioorg. Med. Chem. 2006, 14, 4792.

[20] (a) Abdelrazek, F. M.; Metz, P.;Metwally, N. H.; El-Mahrouky, S. F. Arch. Pharm. 2006, 339, 456–460; (b) Abdelrazek, F. M.; Metz, P.; Kataeva, O.; Jaeger, A.; El-Mahrouky, S. F. Arch.Pharm. 2007, 340, 543–548 (c) Ismail, Z. H.; Aly, G. M.; El-Degwi, M. S.; Heiba, H. I.; Ghorab, M. M. Synthesis and insecticidal activity of some new pyranopyrazoles, pyrazolopyranopyrimidines, and pyrazolopyranopyridines. Egypt J. Biotech. 2003, 13, 73-82.

[21]. Sosnovskikh, V. Y.; Barabanov, M. A.; Usachev, B. I.; Irgashev, R. A.; Moshkin, V. S. Synthesis and some properties of 6-di(tri)fluoromethyl- and 5-di(tri)fluoroacetyl-3-methyl-1-phenylpyrano[2,3-c]pyrazol-4(1H)-ones. Russ. Chem. Bull., Int. Ed. 2005, 54, 2846-2850.

[22] El-Assiery, S. A.; Sayed, G. H.; Fouda, A. Synthesis of some new annulated pyrazolo-pyrido (or pyrano) pyrimidine, pyrazolopyridine and pyranopyrazole derivatives. Acta Pharm. 2004, 54, 143-150. [23]Rodinovskaya, L. A.; Gromova, A. V.; Shestopalov, A. M.; Nesterov, V. N. Synthesis of 6-amino-4-aryl-5-cyano-3-(3-cyanopyridin-2-ylthiomethyl)-2,4-dihydropyrano[2,3-c]pyrazoles and their hydrogenated analogs. Molecular structure of 6-amino-5-cyano-3-(3-cyano-4,6-dimethylpyridin-2-ylthiomethyl)-4-(2-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole. Russ. Chem. Bull., Int. Ed. 2003, 52, 2207-2213.

[24] Peng, Y.; Song, G.; Dou, R. Green Chem. 2006, 8, 573

[25]Vasuki, G.;Kumaravel, K. Tetrahedron Lett. 2008, 49, 5636

[26] F. Lehmann, S.L. Holm, M.S. Laufer, Three-component combinatorial synthesis of novel dihydropyrano[2,3-F]pyrazoles, J. Comb. Chem. 10 (2008) 364–367.

[27] M.M. Heravi, A. Ghods, F. Derikvand, K. Bakhtiari, F.F. Bammoharram, H14[NaP5W30O110] catalyzed one-pot three-component synthesis of dihydropyr- ano[2,3-c]pyrazole and pyrano[2,3-d]pyrimidine derivatives, J. Iran Chem. Soc. 7 (2010) 615–620

[28] M.B.M. Reddy, V.P. Jayashankara, M.A. Pasha, Glycine-catalyzed efficient synthesis of pyranopyrazoles via one-pot multicomponent reaction, Synth. Commun. 40 (2010) 2930–2934.

[29] K. Kanagaraj, K. Pitchumani, Solvent-free multicomponent synthesis of pyrano- pyrazoles: per-6-amino-b-cyclodextrin as a remarkable catalyst and host, Tetrahedron Lett. 51 (2010) 3312–3316

[30] S.D. Samant, N.R. Patil, S.W. Kshirsagar, Mg–Al Hydrotalcite as a first heterogeneous basic catalyst for the synthesis of 4H-pyrano[2,3-c]pyrazoles through a four-component reaction, Synth. Commun. 41 (2011) 1320–1325.

[31] M. Babaie, H. Sheibani, Nanosized magnesium oxide as a highly effective heterogeneous base catalyst for the rapid synthesis of pyranopyrazoles via a tandem four-component reaction, Arabian J. Chem. 4 (2011) 159–162.

[32] H. Mecadon, M.R. Rohman, I. Kharbangar, et al., L-Proline as an efficient catalyst for the multi-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4-dihydropyrano[2,3-F]pyrazole- 5-carbonitriles in water, Tetrahedron Lett. 52 (2011) 3228–3231.

[33] H. Mecadon, M.R. Rohman, M. Rajbangshi, B. Myrboh, g-Alumina as a recyclable catalyst for the four-component synthesis of 6-amino-4-alkyl/aryl-3-methyl-2,4- dihydropyrano[2,3-c]pyrazole-5-carb onitriles in aqueous medium, Tetrahedron Lett. 52 (2011) 2523–2525.

[34] H. Kiyani, H.A. Samimi, F. Ghorbani, S. Esmaieli, One-pot, four-component synthesis of pyrano[2,3-c]pyrazoles catalyzed by sodium benzoate in aqueous medium, Curr. Chem. Lett. 2 (2013) 197–206. 337

[35] M. Bihani, P.P. Bora, G. Bez, H. Askari, Amberlyst a21 catalyzed chromatography free method for multicomponent synthesis of dihydropyrano[2,3-F]pyrazoles in ethanol, ACS Sustainable Chem. Eng. 1 (2013) 440–447.

[36] Wu, M.; Feng, Q.; Wan, D.; Ma, J. Synth. Commun. 2013, 43, 1721;

[37] Junek, H.; Aigner, H. Chem. Ber. 1973, 106, 914.

[38] (a) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. Zh. Org. Khim. 1983, 19, 2609; (b) Sharanin, Y. A.; Sharanina, L. G.; Puzanova, V. V. J. Org. Chem. USSR 1983, 221;

[39] a) Jiang, H.; Wang, C.; Li, H.; Wang, Y. Green Chem. 2006, 8, 1076; (b) Ganeshpure, P. A.; George, G.; Das, J. J. Mol. Catal. A: Chem. 2008, 279,182; (c)Wang, C.; Guo, L.; Li, H.; Wang, Y.; Weng, J.; Wu, L. Green Chem. 2006, 8, 603;(d) Weng, J.; Wang, C.; Li, H.; Wang, Y. Green Chem. 2006, 8, 96(e) Wang, C.; Zhao, W.; Li, H.; Guo, L. Green Chem. 2009, 11, 843; (f) Rajendran, A.; Raghupathy, D.; Priyadarshini, M. Int. J. Chem. Technol.Res. 2011, 3, 298; (g)Kermani, E. T.; Khabazzadeh, H.; Jazinizadeh, T. J. Heterocycl. Chem. 2011, 48,
1192; (h) Suryawanshi, N. S.; Jain, P.; Singhal, M.; Khan, I. J. Appl. Chem. 2012, 1, 18; (i) Khabazzadeh, H.; Kermani, E. T.; Jazinizadeh, T. Arab. J. Chem. 2012, 5, 485; (j) Zhou, Z.; Deng, X. J. Mol. Catal. A: Chem. 2013, 367, 99; (k) Malla, A. M.; Parveen, M.; Ahmad, F.; Azaz, S.; Alam, M. RSC Adv. 2015, 5, 19552

Gracias !!