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

Urja D. Nimbalkar [1], Julio A. Seijas Vazquez [2], Maria Pilar Vazquez [2] and Anna Pratima G. Nikalje[3] *

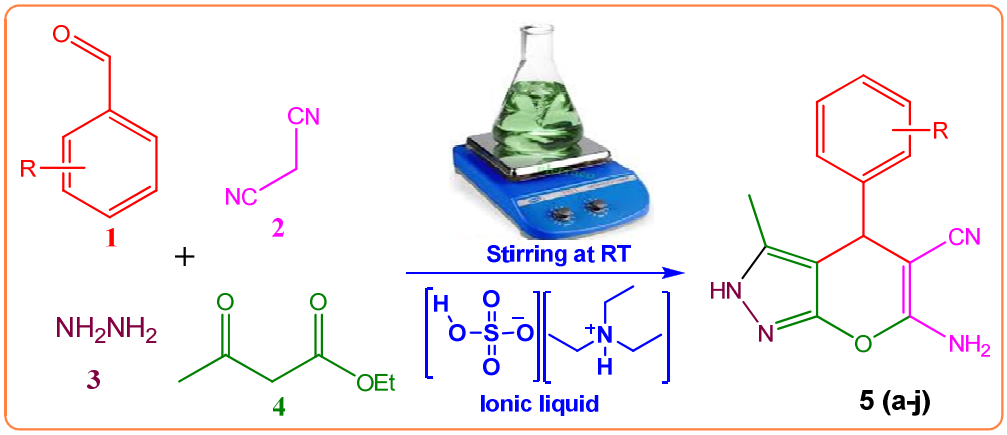
[1] Maulana Azad P. G. and Research Centre, Dr.RafiqZakaria Campus, RauzaBaug, Aurangabad 431001, India; urjasatish@gmail.com

[2] Departamento de QuímicaOrgánica, Facultad de Ciencias, Universidad of Santiago De Compostela, Alfonso X el Sabio, Lugo 27002, Spain; julioa.seijas@usc.es

[3] Y. B. Chavan College of Pharmacy, Dr.RafiqZakaria Campus, RauzaBaug, Aurangabad 431001, India;

* Correspondence: annapratimanikalje@gmail.com; Tel.: +91-916-892-9111

Graphical Abstract:



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

Urja D. Nimbalkar [1], Julio A. Seijas Vazquez [2], Maria Pilar Vazquez [2] and Anna Pratima G. Nikalje[3] *

[1] Maulana Azad P. G. and Research Centre, Dr.RafiqZakaria Campus, RauzaBaug, Aurangabad 431001, India; urjasatish@gmail.com

[2]Departamento de QuímicaOrgánica, Facultad de Ciencias, Universidad of Santiago De Compostela, Alfonso X el Sabio, Lugo 27002, Spain; julioa.seijas@usc.es

[3] Y. B. Chavan College of Pharmacy, Dr.RafiqZakaria Campus, RauzaBaug, Aurangabad 431001, India;

* Correspondence: annapratimanikalje@gmail.com; Tel.: +91-916-892-9111.

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[Et_3NH] [HSO_4] 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 ofsynthetic 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' refers 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)[Et_3NH][HSO_4] triethyl ammonium sulphate 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.

Introduction:

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. Multi-component reactions contribute to the needs of an eco-friendly methods of synthesis of simple and complex building blocks 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].So Multicomponent reactions gain an outstanding position in medicinal and organic chemistry by 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]

In organic synthesis green chemistry is now a days acting as boon with the use of deliberately important solvents so called a '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. [8,9]. Hence acting as very excellent catalysts, as well as solvents, for many organic transformations[10] Acidic Bronsted Ionic Liquids (ABILs) are of special importance, because they simultaneously possess proton acidity and the characteristic properties of ionic liquids. ABILs offer environmental 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]. 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. $[Et_3NH][HSO_4]$ ionic liquid posses advantages as non-toxic, inexpensive ,easy preparation with readily available starting reactants . [12,13].

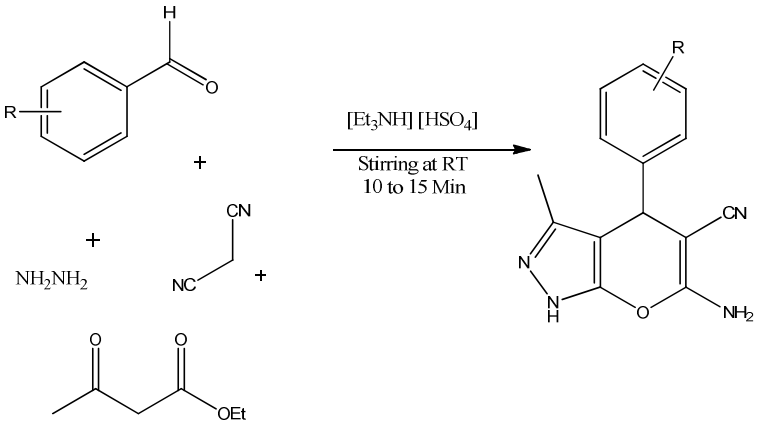
Organic chemist are always looking for the synthesis of new moiety with some biological effect, Pyrano[2,3-c]pyrazoles are such recently synthesised scaffold with numerous biological activity [14] including anticancer–antitumor,[15] antimicrobial[16] anti-inflammatory[17]analgesic[18] inhibitors of human chk1 kinase[19].Molluscicidal and insecticidal activity [20]also acting as potent pharmaceutical constituents and biodegradable agrochemicals.[21,22,23].Due to the broad spectrum of important biological activity associated with Pyrano[2,3-c]pyrazoles we planned to synthesize this moiety by multicomponent,one pot cyclocondensation of aromatic substituted aldehydes, malononitrile, ethyl acetoacetate, and hydrazine hydrate .

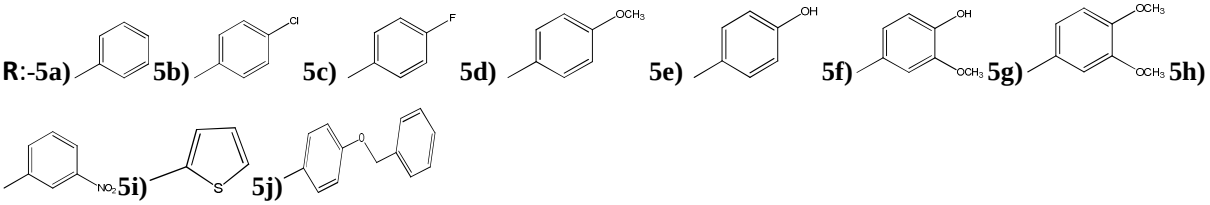
Synthesis of dihydropyrano[2,3-F]pyrazoles can be achived by various methodology with several catalyst are reported in literature including use of Piperazine[24]piperidine[25]N-methylmorpholine[26] hetero-polyacids[27] glycine[28]per-6-amino-b-cyclodextrin[29] Mg/Al hydrotalcite[30]nanosized magnesium 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 as a catalyst .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 moiety in early period has given us an idea to work on the ionic liquid containing triethyl amine as catalyst therefore we selected very efficient Acidic Bronsted Ionic Liquid (ABIL), Triethyl ammonium Sulphate $[Et_3NH][HSO_4]$ [39] as catalyst for present synthesis. This ionic liquid posses significant characteristics such as, cost effective, non-toxic, catalyst as well as solvent for many organic transformations giving 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 using 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.

Results and discussion:





SchemeI. Synthesis of 6-amino-4-substituted-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitriles(5a-5j)

Table1 Physical characterization of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

Compound	R	Yield(%)	Mp$^{(oC)}$
5a	-Ph	88	240-242
5b	4-Cl-Ph	94	228-230
5c	4-F-Ph	92	172-174
5d	4-OCH_3	94	205-207
5e	4-OH	88	219-221
5f	4-OH-3-OMe-Ph	85	232-234
5g	3,4-$(OMe)_2$-Ph	87	185-187
5h	3-NO_2	88	188-190
5i	2-thiophenyl	89	222-224
5j	4-benzyloxy-Ph	88	212-214

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 .

Table 2 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-methylpyridiniumtosylate)	75	62
3	DES(At 80^0C)	20	92
4	$[Et_3NH][HSO_4]$ (At RT)	15	94

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 appropriateconcentration of the catalyst and solvent $[Et_3NH][HSO_4]$, we investigated the model reaction atdifferent concentrations of $[Et_3NH][HSO_4]$, 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 forthe reaction by considering the product yield.

Table 3 Effect of ionic liquid 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

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 reactionmixture was quenched with ice crystals and extracted with ethyl acetate. Theresidual ionic liquid was washed with diethyl ether, dried under vacuum at 60and reused for subsequent reactions. The recovered ionic liquid could be used for four times without much loss of catalytic activity.

Table 4 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

With extreme high literature survey of all available method of multi component one pot cyclo condensation synthesis of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile herein as far as our genuine knowledge first time we are introducing the use of this green medium i.e. Acid Bronsted

Ionic Liquid [Et_3NH] [HSO_4]as solvent and catalyst in 20mol% at room temperature in 10 to 15 minutes with excellent yield up to 94%.

Material &Methods:

General Information

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) usingpre-coated silica gel F254 aluminum TLC sheets (Merck) and the spots were visualized by UV lightand 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 (δppm) were referred to internal TMSfor ^{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.

Synthesis of [Et_3NH][HSO_4]:98 % solutionof Sulphuric acid (1.96 g, 0.02 mol) in water was dropped into triethylamine (2.02 g, 0.02 mol) with stirring at 60^{0}C for 1 h. After the addition,the reaction mixture was stirred for another 1 h at 70 ^{0}C. The water molecule wasremoved by heating the residue at 80–90^{0}C under a high vacuum until the weightof 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] 20mol% and then the reaction mass was stirred at room temperature. Progress of the reaction was monitored by TLC (ethyl acetate: n-hexane 1:9). After 15 min of stirring, the reaction mixture was cooled to room temperature. 125 Then, it 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.An important feature of this method is that both electron-releasing and withdrawing groups give excellent yields.

5a) 6-amino-3-methyl-4-phenyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

Yield 88%, mp240-242^{0}C: IR (KBr *ν*max, cm-1): 3429 (N–H), 3122 (Ar–H), 2936 (C–H), 2208 (C-N), 1598 (C=N), 1152 and 1215 (C–O–C); ^{1}H NMR (400 MHz, DMSO-*d6*): δ ppm 1.86 (s, 3H, –CH_3), 4.51 (s, 1H,–CH–),6.99–7.76 (m, 5H, Ar–H) 8.45 (s, 2H, –NH_2), and 12.02 (s, 1H, –NH); ^{13}C NMR (100 MHz, DMSO-*d6*): δ ppm8.85, 34.69, 150 57.67, 94.69, 96.48, 112.57, 119.69, 127.35, 134.73, 134.79, 153.84, 151 157.23 and 159.45; MS (ESI) m/z:252.10 (100.0%), 253.10 (16.6%), 254.11 (1.3%)Elemental Analysis Calculated for $C_{14}H_{12}N_4O$: C, 66.65; H, 4.79; N,22.21; Found C, 66.67; H, 4.75; N, 22.21

5b) 6-amino-4-(4-chlorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 94%, mp228-230^{0}C; IR(KBr *v*max, cm^{-1}): 3380(N–H), 3281, (Ar–H), 2193(C-H)2208 (C-N), 1598 (C=N), 1152 and 1215 (C–O–C),744(C-Cl); ^{1}H NMR(400 MHz, DMSO-*d6*): δ ppm 1.80 (s, 3H, –CH_3);4.58 (s, 1H, –CH–); 7.68-7.73(m, 4H, Ar–H);8.2(s, 2H, –NH_2);12.06(s, 1H, –NH);^{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; MS (ESI)m/z: 286.06 (100.0%), 288.06 (32.2%), 287.07 (15.3%), Elemental Analysis Calculated for: $C_{14}H_{11}ClN_4O$ C, 58.65; H, 3.87; N, 19.54; Found: C, 58.61; H, 3.82; N, 19.50

5c) 6-amino-4-(4-fluorophenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 92%, mp 172-174^{0}C; IR(KBr *v*max, cm^{-1}): 3388(N–H); 3280 (Ar–H); 3055(C-H);2222 (C-N), 1640 (CN), 1160 and 1220 (C–O–C);^{1}H NMR(400 MHz, DMSO-*d6*):δ ppm1.92 (s, 3H,-CH_3);4.60 (s, 1H,-CH-); 7.12-7.21(m,4H,Ar-H)7.88(s,2H,-NH_2);12.04(s,1H,–NH)^{13}CNMR(100MHz,DMSO-*d6*):δppm13.13,25.5,59.2,113.4,117.3,115.4,130.6,139.1,159.9,163.7,176.1; MS (ESI) m/z : 270.09 (100.0%), 271.10 (15.3%), 271.09 (1.5%), Elemental Analysis Calculated for:$C_{14}H_{11}FN_4O$Elemental Analysis: C, 62.22; H, 4.10; N, 20.73; Found:C, 62.22; H, 4.10; N, 20.73

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

Yield 94%, mp203-207^{0}C; IR(KBr *v*max,cm^{-1}): 3483(NH),3280(Ar–H),2930(C-H),2208(C-N),1598 (C=N),1450(C-OCH_3), 1152 and 1215 (C–O–C); ^{1}H NMR(400 MHz, DMSO-*d6*):δ ppm1.79 (s, 3H,-CH_3); 3.74 (s, 3H,-OCH_3); 4.51 (s, 1H,-CH-); 6.80-7.0 (m, 4H,Ar-H); 8.2 (s,2H,-NH_2); 12.0 (s,1H,-NH); ^{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; MS (ESI) m/z :282.11 (100.0%), 283.12 (16.5%), 284.12 (1.7%), Elemental Analysis Calculated for: $C_{15}H_{14}N_4O_2$:C, 63.82; H, 5.00; N, 19.85; Found:C, 63.78; H, 5.05; N, 19.82

5e) 6-amino-4-(4-hydroxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 88%, mp 219 to 221^{0}C; IR(KBr *v*max, cm^{-1}): 3470(NH),3270(Ar–H),2940(C-H),2198(C-N),1600 (C=N), 1145 and 1200 (C–O–C); ^{1}H NMR(400 MHz, DMSO-*d6*): δ ppm 2.00 (s, 3H,-CH_3); 4.46 (s,1H,-CH-); 5.44 (s 1H,-OH); 6.33 -7.06 (m,4H,Ar-H); 8.52 (s,2H,-NH_2); 11.90 (s,1H,-NH);^{13}C NMR(100 MHz, DMSO-*d6*): δ ppm 12.0; 25.0; 59.0; 113.6; 119.5; 127.0;130.2; 141.5; 143.8; 155.4; 163.5; 179.1; MS (ESI) m/z : 268.10 (100.0%), 269.10 (15.4%), 270.10 (1.7%), (%): Elemental Analysis Calculated for:$C_{14}H_{12}N_4O_2$: C, 62.68; H, 4.51; N, 20.88; Found:C, 62.70; H, 4.48; N, 20.87;

5f) 6-amino-4-(4-hydroxy-3-methoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 85%, mp 232 to234^{0}C; IR(KBr *v*max, cm^{-1}):3583(NH),3180(Ar–H),2830(C-H),2308(C-N),1590 (C=N),1440(C-OCH_3), 1200 and 1222(C–O–C);^{1}H NMR(400 MHz, DMSO-*d6*): δ ppm 2.00 (s, 3H,CH_3); 3.80(s,3H,-OCH_3)4.46 (s,1H,-CH-); 5.44 (s,1H,-OH); 6.33-7.06 (m,3H,Ar-H); 8.50 (s,2H,-NH_2); 11.95(s,1H,-NH);^{13}C NMR(100 MHz, DMSO-*d6*): δ ppm 12.0; 25.0; 59.0; 113.6; 119.5; 127.0;130.2; 141.5; 143.8; 155.4; 163.5; 179.1; MS (ESI) m/z : 298.11 (100.0%), 299.11 (16.5%), 300.11 (2.1%), Elemental Analysis Calculated for:$C_{15}H_{14}N_4O_3$: C, 60.40; H, 4.73; N, 18.78; Found:C, 60.38; H, 4.70; N, 18.75

5g) 6-amino-4-(3,4-dimethoxyphenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 87%, mp 185 to 187^{0}C; IR(KBr *v*max, cm^{-1}): 3500(NH),3190(Ar–H),2850(C-H),2318(C-N),1580 (C=N),1400(C-OCH_3), 1190 and 1225(C–O–C);^{1}H NMR(400 MHz, DMSO-*d6*):δ ppm 2.07 (s, 3H,CH_3); 3.70 (s, 6H,(-OCH_3)$_2$); 4.61 (s,1H,-CH-); 6.80-7.16 (m,3H,Ar-H); 7.52 (s,2H,-NH_2); 11.99 (s,1H,-NH);^{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;

MS (ESI) m/z:312.12 (100.0%), 313.13 (17.6%), 314.13 (2.1%), Elemental Analysis Calculated for: $C_{16}H_{16}N_4O_3$: C, 61.53; H, 5.16; N, 17.94;Found:C, 61.50; H, 5.12; N, 17.92

5h) 6-amino-3-methyl-4-(4-nitrophenyl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 88%,mp188-190^{0}C; IR (KBr *v*max, cm^{-1}):): 3365 (N–H), 3222 (Ar–H), 2936 (C–H), 2208 (C-N), 1598 (C=N),1345(NO2),1152 and 1215 (C–O–C);^{1}HNMR(400 MHz, DMSO-*d6*): δ ppm 2.03 (s,3H,CH_3); 4.75 (s,1H,-CH-); 7.54-8.65 (m, 4H,Ar-H); 8.45 (s,2H,-NH_2); 11.88 (s,1H,-NH);^{13}C NMR(100 MHz, DMSO-*d6*): δ ppm 11.9; 26.3; 71.4; 112.4; 121.3; 127.6; 129.6; 133.1;135.2; 141.6; 147.2; 151.4; 154.0; 160.1; MS (ESI) m/z : 297.09 (100.0%), 298.09 (15.4%), 299.09 (2.0%),Elemental Analysis Calculated for:$C_{14}H_{11}N_5O_3$: C, 56.56; H, 3.73; N, 23.56; Found:C, 56.58; H, 3.70; N, 23.52

5i) 6-amino-3-methyl-4-(thiophen-2-yl)-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 89%, mp 222 to 224^{0}C; IR (KBrνmax, cm^{-1}): 3359(NH),2191(thiophene ring),1647(C-N),1600(C=N)1145-1014(-C-O-C-),^{1}HNMR(400MHz,DMSO-*d6*):δppm1.92(s,3H,-CH_3);4.91(s,1H,-CH-);6.40-7.45(m,3H,thiophene);8.59(s,2H,-NH_2)12.11 (s,1H,-NH);^{13}C NMR(100 MHz, DMSO-*d6*): δ ppm 8.4,30.2; 56.4; 95.9; 119.2;. 123.1; 124.8; 134.5; 148.0; 152.9; 159.2; MS (ESI) m/z :258.06 (100.0%), 259.06 (13.9%), 260.05 (4.5%), Elemental Analysis Calculated for: $C_{12}H_{10}N_4OS$: C, 55.80; H, 3.90; N, 21.69; Found:C,55.82; H, 3.88; N, 21.72

5j) 6-amino-4-(4-(benzyloxy)phenyl)-3-methyl-2,4-dihydropyrano[2,3-c]pyrazole-5-carbonitrile

Yield 88%, mp 212 to 214^{0}C; IR(KBrνmax, cm^{-1}):3483.78 (NH), 3255.25 (C-H), 2208 (C-N), 1598 (C=N), 1152 and 1215 (C–O–C),^{1}HNMR(400 MHz, DMSO-*d6*): δ ppm 1.93 (s,3H,-CH_3);4.75(s,1H,-CH-);5.14(s,2H,-CH_2-);6.38-7.47(m,9H,Ar-H);8.12(s,2H,-NH_2);11.88(s,1H,-NH);^{13}CNMR(100MHz,DMSO-*d6*):δppm13.3,25.5,59.2,70.8,113.4,114.3,117.3,127.1,127.3,127.6,128.9,139.1,156.0,163.7,176.8;MS (ESI) m/z : 358.14 (100.0%), 359.15 (23.0%), 360.15 (2.9%),Elemental Analysis Calculated for: $C_{21}H_{18}N_4O_2$: C, 70.38; H, 5.06; N, 15.63; Found:C, 70.40; H, 5.10; N, 15.70

4. 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[Et3NH][HSO4] 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 Mrs.Fatima Rafiq Zakaria, Chairman, Maulana Azad Educational Trust, Dr. Maqdoom Farooqui, Principal, Maulana Azad Postgraduate and Research Centre, Aurangabad and Dr. Zahid Zaheer, Principal, Y. B. Chavan College of Pharmacy, RafiqZakaria Campus, Aurangabad 431 001 (M.S.),India for providing the laboratory facility.

Author Contributions: U.D.N. research student, A.P.G.N. research guide, J.A.S.V. and M.P.V. co-operated for spectral analysis.

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-prolinecatalyzedassembly of densely functionalized 4H-pyrano[2,3-c]pyrazoles and bispyrazolylpropanoates from simple, acyclicstarting 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. Syn lett. 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: Chemoselectivecatalyst for the transesterification of beta-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., YewareA. Sarkar D.Shingate B.B. Facile synthesis of 1,3-thiazolidin-4-ones as antitubercularagentsBioorganic& Medicinal Chemistry Letters 26 (2016) 1704–1708

[13] ShaikhM.H. SubhedarD.D.Khan F.A.K.Sangshetti J.N. Shingate B.B [Et3NH][HSO4]-catalyzed one-pot, solvent-free synthesis and biological evaluation of a-aminophosphonates Res ChemIntermed (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. Synthesisand insecticidal activity of some new pyranopyrazoles, pyrazolopyranopyrimidines, andpyrazolopyranopyridines. 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 annulatedpyrazolo-pyrido (or pyrano) pyrimidine, pyrazolopyridine and pyranopyrazolederivatives. 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 noveldihydropyrano[2,3-c]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-carbonitriles

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]pyrazolescatalyzed 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 inethanol, ACS Sustainable Chem. Eng. 1 (2013) 440–447.

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

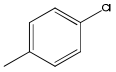
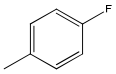
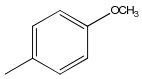
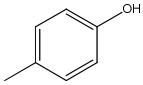
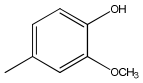
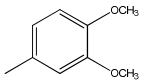
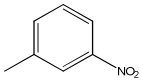
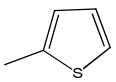
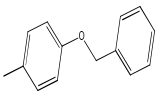
[37] Junek, H.; Aigner, H. Chem. Ber. 1973, 106, 914.

[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;

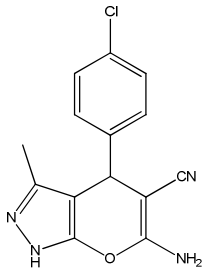
[39] a) Jiang, H.; Wang, C.; Li, H.; Wang, Y. Green Chem. 2006, 8, 1076; (b) Ganeshpure, P. A.; George, G.; Das, J. J. Mol. Catal. A: Chem. 2008, 279,182; (c)Wang, C.; Guo, L.; Li, H.; Wang, Y.; Weng, J.; Wu, L. Green Chem. 2006, 8, 603;(d) Weng, J.; Wang, C.; Li, H.; Wang, Y. Green Chem. 2006, 8, 96(e) 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

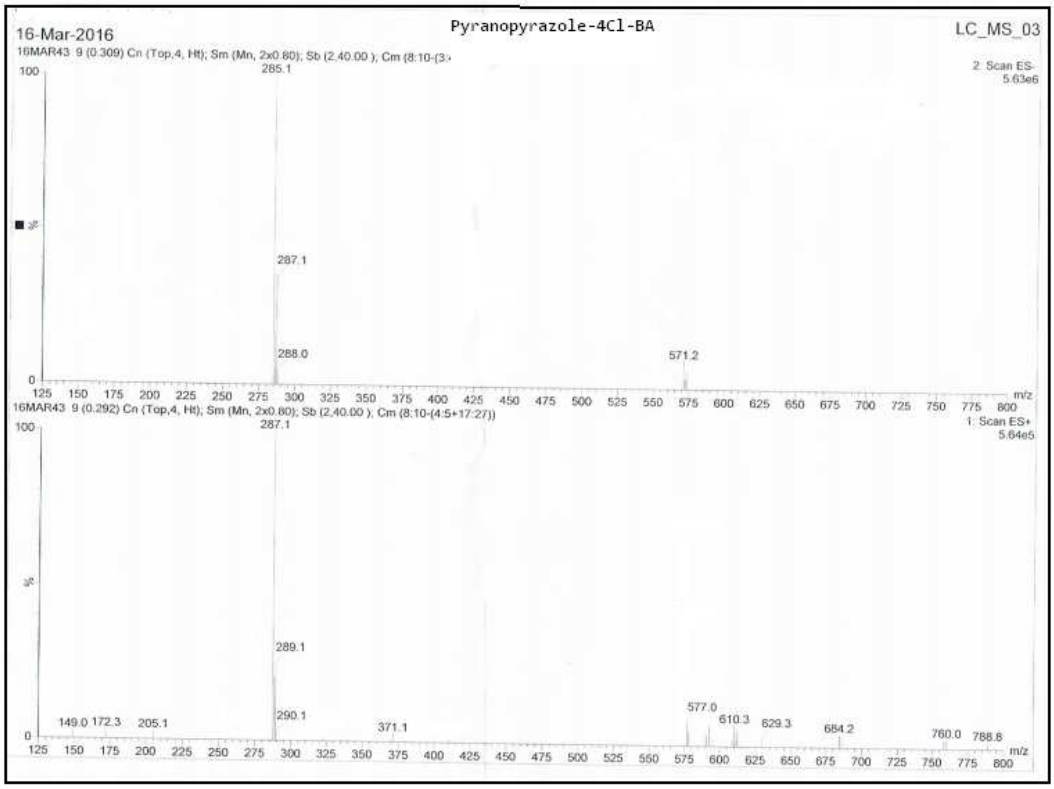
SUPPLIMENTRY DATA

Table1 Physical characterization of 6-amino-4-(substituted phenyl)-3-methyl-2,4-dihydropyrano[2,3-c] pyrazole-5-carbonitrile

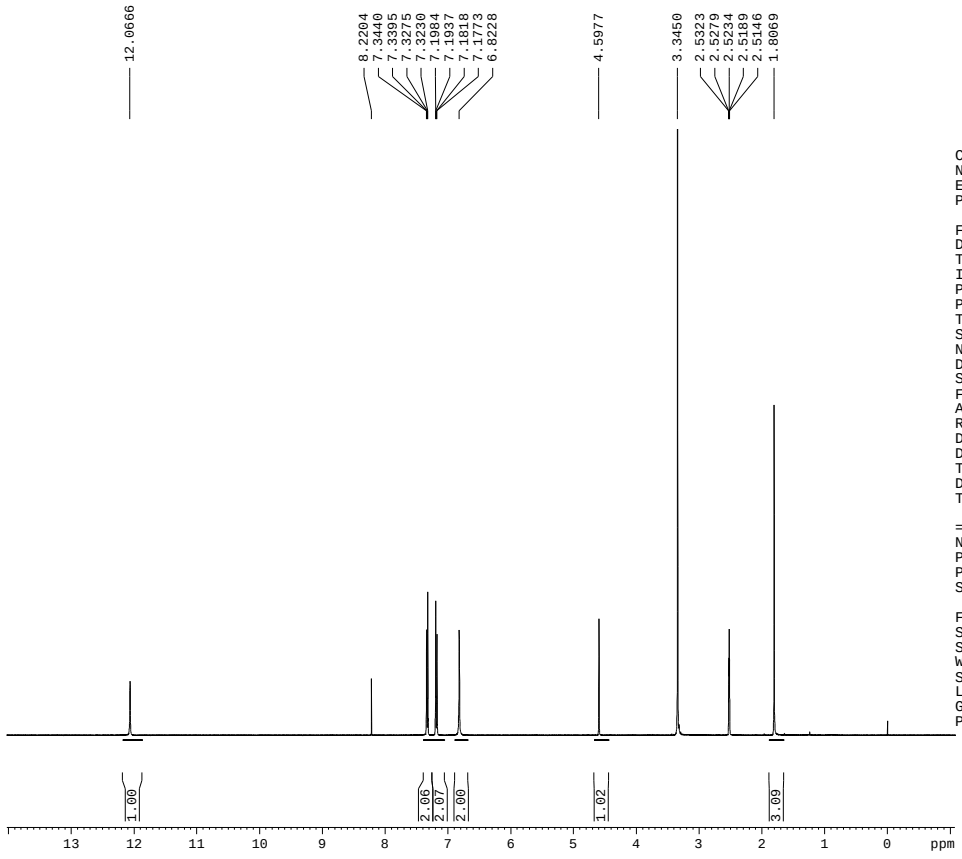
Derivatives	R	(Mol. wt)	Yield (%)	m.p. (^{o}C)	Analysis (%) Found [calculated] C H N
a		252.10	88	240-242	C,66.65; H, 4.79; N,22.21 [C,66.67; H, 4.75; N, 22.21]
b		286.06	94	228-230	C,58.65; H, 3.87; N, 19.54 [C,58.61; H, 3.82; N, 19.50]
c		270.09	92	172-174	C,62.22; H, 4.10; N, 20.73 [C, 62.22; H, 4.10; 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]

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





5C

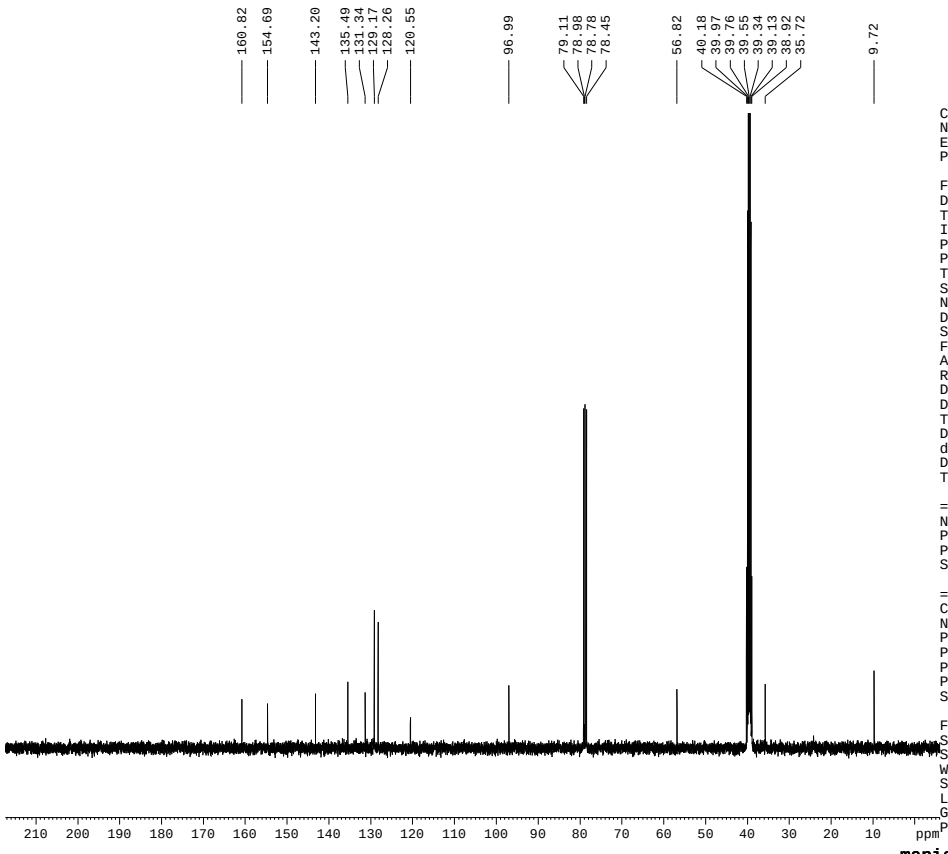


BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

```
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

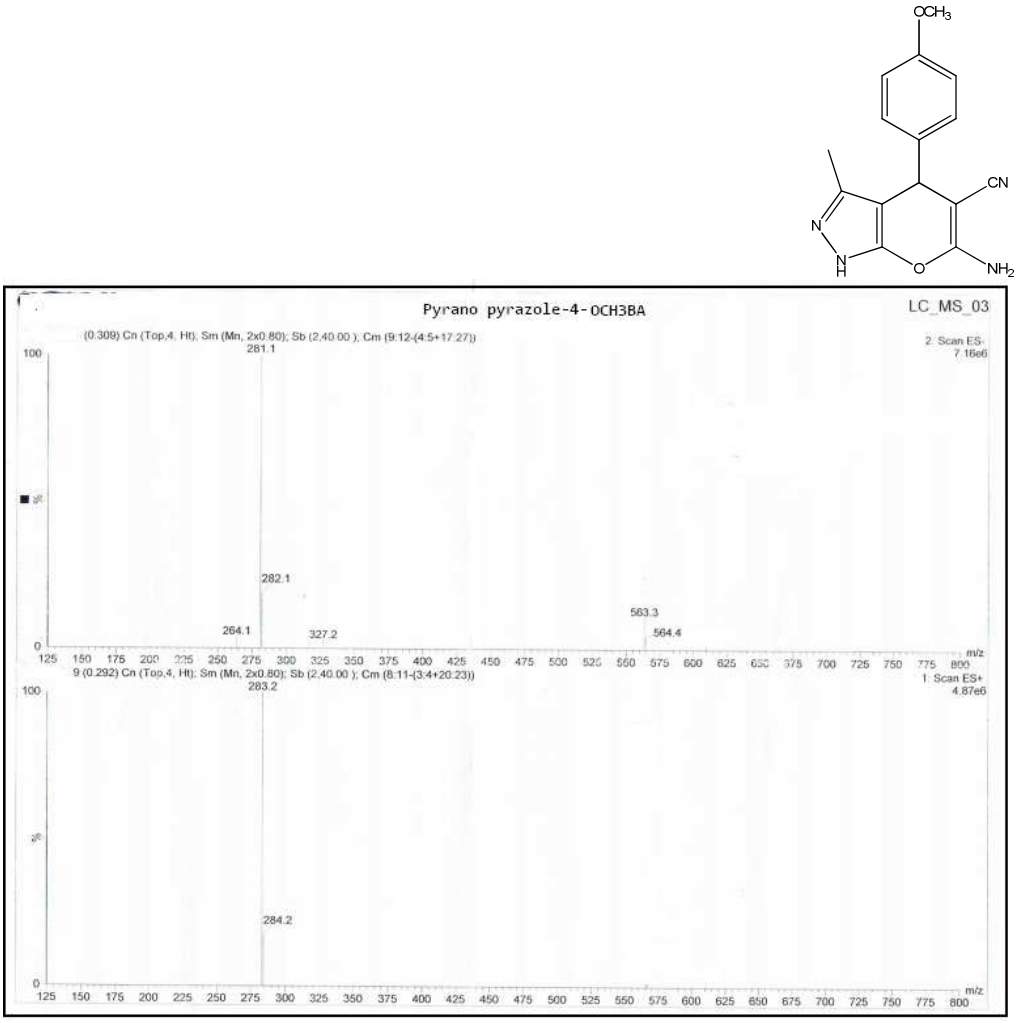
5C



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

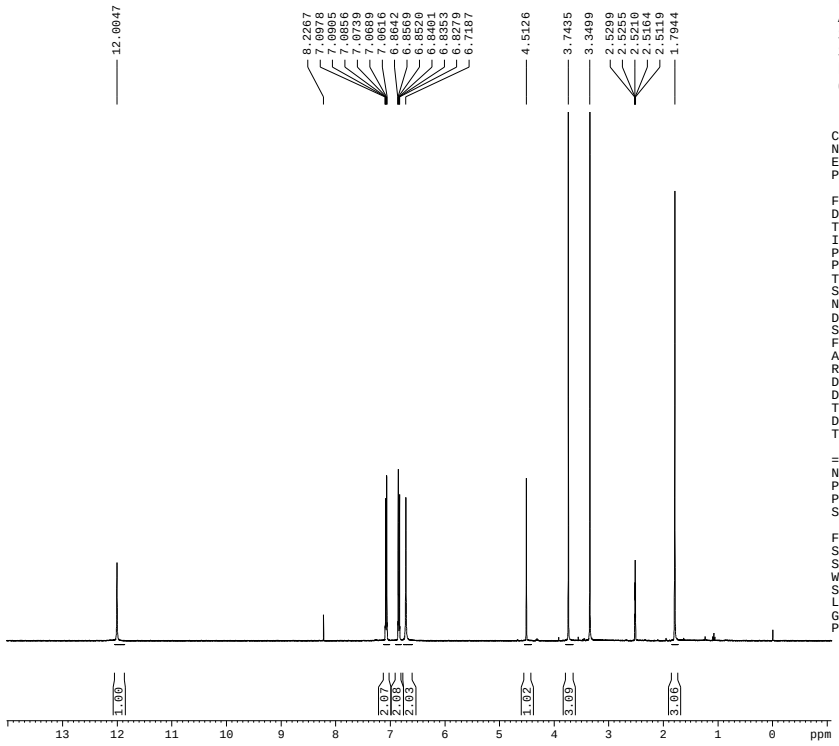
```
Current Data Parameters
NAME          Apr25-2016
EXPNO                571
PROCNO                 1

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

5d



BRUKER
AVANCE II 400 NMR
Spectrometer
SAIF
Panjab University
Chandigarh

Current Data Parameters
NAME Apr25-2016
EXPNO 580
PROCNO 1

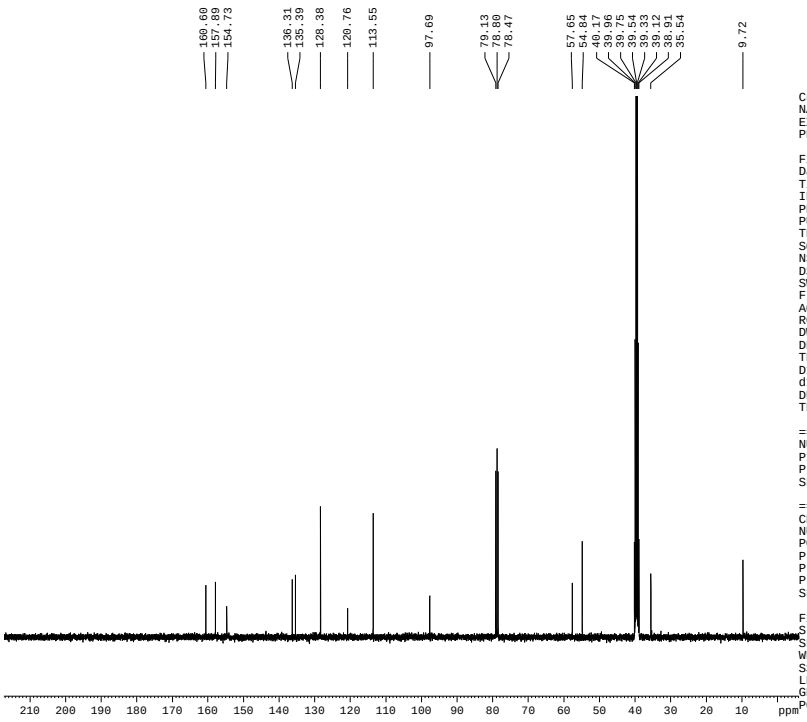
F2 - Acquisition Parameters
Date_ 20160426
Time 3.27
INSTRUM spect
PROBHD 5 mm PABBO BB-
PULPROG zg30
TD 65536
SOLVENT DMSO
NS 8
DS 2
SWH 12019.230 Hz
FIDRES 0.183399 Hz
AQ 2.7263477 sec
RG 322
DW 41.600 usec
DE 6.00 usec
TE 294.7 K
D1 1.00000000 sec
TD0 1

======== 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

5d



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