Synthesis and *in vitro* antimicrobial evaluation of 4*H*-pyrazolopyran, -benzopyran and naphthopyran derivatives of 1*H*-pyrazole

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Abstract

A new series of eight derivatives each of 4-pyrazolyl-4*H*-pyrazolopyran, -benzopyran and sixteen derivatives of naphthopyran has been synthesized by one-pot base-catalyzed cyclocondensation reactions of 1-phenyl-3-(het)aryl-pyrazole-4-carbaldehyde, malononitrile and substituted pyrazolin-5-ones or dimedone or naphthols respectively. All the synthesized compounds were subjected to *in vitro* antimicrobial screening against a panel of pathogenic strains of bacteria and fungi. Some of the compounds were found to be equipotent or more potent than commercial antibiotics against most of employed strains.

Keywords: 4*H*-Pyran, multi-component reaction, pyrazole-4-carbaldehyde, antimicrobial activity, MIC

Introduction

The 4*H*-Pyran nucleus is a fertile source of biologically important molecules possessing a wide spectrum of biological and pharmacological activities, such as antimicrobial,[1] antiviral,[2] mutagenicity,[3] antiproliferative,[4] sex pheromone,[5] antitumor,[6] cancer therapy[7] and central nervous system activity.[8] Some of these compounds are widely employed as cosmetics and pigments and as potential biodegradable agrochemicals.[9] Therefore, the synthesis of such compounds has attracted strong interest.

In recent years, 4-functionally substituted 1,3-diarylpyrazole derivatives have received considerable attention due to their wide range of useful biological properties, which include antimicrobial,[10-12] anti-inflammatory (COX-2 inhibitor and ulcerogenic activity),[11] antitubercular,[12] antitumor,[13,14] antiangiogenesis,[14] anti-parasitic[15] and antiviral activity.[16] A literature survey[17] revealed that a number of 4*H*-pyran derivatives have been synthesized using various aldehydes but not a single reference has been found where 1,3-diaryl pyrazole-4-carbaldehydes are used. Thus, in a view to obtain more biologically potent heterocyclic systems,

containing therapeutically active moieties pyran and pyrazole, and in continuation of our work[18] on biologically active heterocyclic compounds, we report herein the synthesis of some new substituted 4*H*-pyrazolopyran, -benzopyran and naphthopyran derivatives of pyrazole *via* a Multi-Component Reaction (MCR) approach. The constitutions of all the products were confirmed using elemental analysis, FT-IR, ^{1}H NMR and ^{13}C NMR spectroscopy. All synthesized compounds were screened for *in vitro* antimicrobial activity against eight human pathogens, of which three gram positive bacterial pathogens *Streptococcus pneumoniae, Clostridium tetani, Bacillus subtilis*, three gram negative bacterial pathogens *Salmonella typhi, Vibrio cholerae, Escherichia coli* and two fungal pathogens *Aspergillus fumigatus and Candida albicans*, using broth microdilution MIC (Minimum Inhibitory Concentration) method.[19]

Results and Discussion

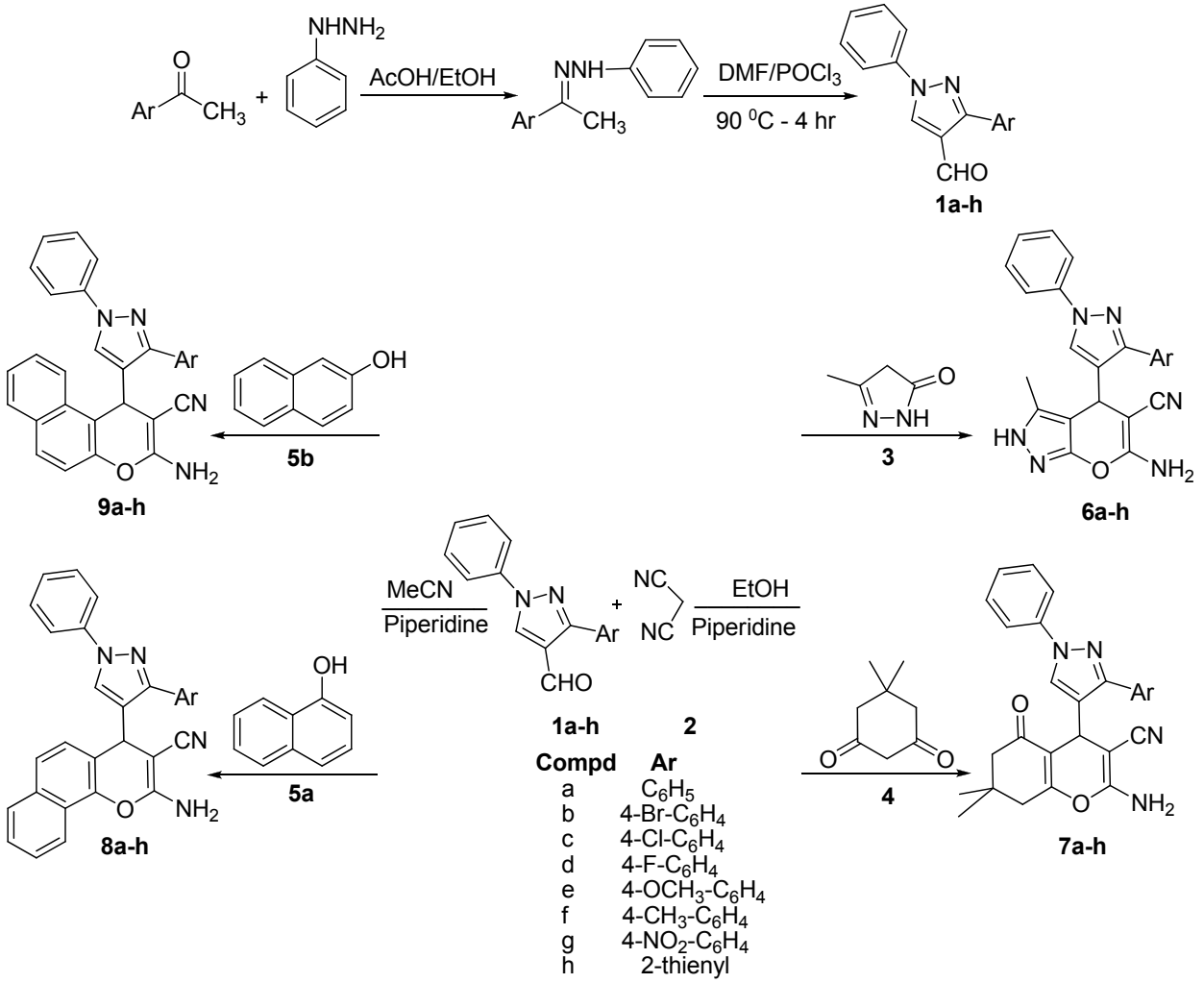
A series of 4-pyrazolyl-4*H*-pyrazolopyran **6a-h**, -benzopyran **7a-h** and naphthopyran **8a- h, 9a-h** derivatives has been synthesized by one-pot three-component cyclocondensation reaction of 1-phenyl-3-(het)aryl-pyrazole-4-carbaldehyde **1a-h**, malononitrile **2** and substituted pyrazolin-5-ones **3** or dimedone **4** or naphthols **5a-b** respectively, in the presence of piperidine as catalyst. The mixture refluxing under ethanol or acetonitrile gives moderate to good yield (50–76%) (Scheme 1). A mechanism for the formation of the pyran derivatives is outlined in Scheme 2. The reaction occurs *via* an *in situ* initial formation of the heterylidenenitrile, containing the electron-poor C=C double bond, from the Knoevenagel condensation between pyrazole-4-carbaldehyde and malononitrile by loss of water molecules. Finally, Michael addition of **3** or **4** or **5** to the initially formed unsaturated nitrile, i.e. nucleophilic attack of hydroxyl moiety to the cyano moiety affords cyclized pyran derivatives **6a-h, 7a-h, 8a-h** and **9a-h.**

The structures of all the new synthesized compounds were established by ^{1}H NMR, ^{13}C NMR and FT-IR spectral data and molecular weight of some selected compounds confirmed by mass spectrometry. NMR spectroscopy is especially useful to elucidate the structures of products i.e. ^{1}H NMR (DMSO-d_6) spectrum of **6a** exhibited a singlet peak at δ 4.59 for H4 and δ 6.91 ppm for NH_2 of the pyran ring. Aromatic protons of **6a** resonate as multiplets at around δ 6.98–7.96 ppm and a deshielded aromatic singlet at δ 8.31 ppm stands for H5 of pyrazole ring. A singlet at δ 1.79 ppm and δ 12.18 ppm stands for methyl and secondary amine of the fused pyrazole ring respectively. ^{13}C NMR of **6a** exhibited a distinctive signal at *δ* 10.4 ppm for methyl of fused pyrazole ring and *δ* 27.2 ppm for C4 of the pyran ring. All the aromatic carbons of **6a** showed signals around δ 114.5–151.2 ppm in the ^{13}C NMR spectra. Moreover, distinctive signals at δ 161.6 ppm for C2, δ 57.8 ppm for C3, δ 98.4 ppm for C5, δ 154.7 ppm for C6 and δ 120.9 ppm for CN of pyran ring in the ^{13}C NMR spectra confirms the structure **6a**.

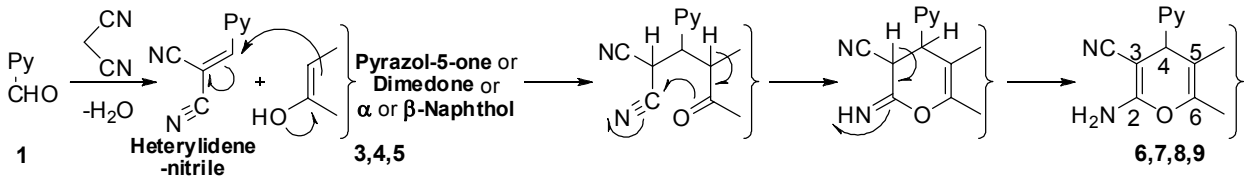
The IR spectrum of compound **6a** exhibited characteristic absorption bands at 3410 and 3385 cm^{-1} (asym. & sym. str.) for –NH_2 and 2210 cm^{-1} for -CN functional group respectively. The presence of band around 1220 cm^{-1} of cyclic ether linkage supports the formation of pyran

derivative **6a.** Further, the structure of selected compounds, **6e, 7e, 8f** and **9h** were confirmed by its mass spectral studies. The mass spectra detected the expected molecular ion signals corresponding to respective molecular formula of synthesized compounds. Mass spectra of compound **6e** gave molecular ion peak at 425.1 (M^++1) corresponding to molecular formula $C_{24}H_{20}N_6O_2$.

Similarly, all these compounds were characterized on the basis of spectral studies. All spectroscopic data have been given in experimental section. All the compounds were screened for their antibacterial and antifungal activity.



Scheme 1. Synthetic pathway for the compounds **6a-h, 7a-h, 8a-h** and **9a-h.**



Scheme 2. Plausible mechanistic pathway of the synthesis of pyran derivatives.

Antimicrobial screening

The *in vitro* antimicrobial activity of all the synthesized compounds was carried out by broth microdilution method.[19] Mueller Hinton broth was used as nutrient medium to grow and dilute the compound suspension for the test bacteria and Sabouraud Dextrose broth used for fungal nutrition. Inoculum size for test strain was adjusted to 10^8 $CFUmL^{-1}$ (Colony Forming Unit per milliliter) by comparing the turbidity. The strains employed for the activity were procured from (MTCC – Micro Type Culture Collection) Institute of Microbial Technology, Chandigarh.

The compounds **6a-h, 7a-h, 8a-h** and **9a-h** were screened for their antibacterial activity against *Bacillus subtilis* (MTCC 441), *Clostridium tetani* (MTCC 449), *Streptococcus pneumoniae* (MTCC 1936), *Escherichia coli* (MTCC 443), *Salmonella typhi* (MTCC 98) and *Vibrio cholerae* (MTCC 3906) as well as antifungal activity against *Aspergillus fumigatus* (MTCC 3008) and *Candida albicans* (MTCC 227). DMSO was used as vehicle to get desired concentration of compounds to test upon microbial strains. The lowest concentration, which showed no visible growth after spot subculture was considered as MIC for each compound. Ampicillin, chloramphenicol, ciprofloxacin, gentamicin and norfloxacin were used as standard antibacterial drugs, whereas griseofulvin and nystatin was used as standard antifungal drugs. The protocols were summarized in Table 1.

The examination of the data (Table 1) reveals that most of the compounds showed excellent antibacterial and antifungal activity when compared with ampicillin and griseofulvin. Against Gram positive pathogen *S. pneumoniae*, compounds **8b** and **9a** were found to be more efficient than chloramphenicol and ciprofloxacin where as, **8c** and **9h** were more potent, and **7f, 8g** and **9f** were found to exhibit comparable activity, to ampicillin. The compounds **9f** and **8g** possess comparable activity to ciprofloxacin, and **6a, 6d-g, 7b, 7f, 8a-b, 8d-e, 8h, 9c-d** and **9g-h** were found equally potent to ampicillin, towards *C. tetani*. The compounds **8b** and **9a** shows better activity where as, **9h** is equally active compared to ciprofloxacin and chloramphenicol and compounds **8c, 8g, 9f** shows better activity, and **6a-b, 6d, 7a, 7e-f, 8a, 8d-e, 8h, 9c-d** and **9g** found equally potent, to ampicillin, against *B. subtilis*.

Table 1. Antimicrobial activity of the compounds **6a-h, 7a-h, 8a-h** and **9a-h**

Compds	Minimum Inhibitory Concentration (MIC, μgmL^{-1})							
	Gram positive bacteria			Gram negative bacteria			Fungi	
	S. p. MTCC 1936	***C. t.*** MTCC 449	***B. s.*** MTCC 441	***S. t.*** MTCC 98	***V. c.*** MTCC 3906	***E. c.*** MTCC 443	***A. f.*** MTCC 3008	***C. a.*** MTCC 227
6a	250	**250**	**250**	200	500	200	>1000	**500**
6b	250	500	**250**	200	**100**	125	>1000	1000
6c	500	500	1000	250	500	200	500	**500**
6d	500	**250**	**200**	500	250	250	>1000	**250**
6e	250	**200**	500	250	250	200	>1000	500
6f	1000	**200**	1000	1000	250	500	1000	1000
6g	1000	**250**	500	1000	500	500	>1000	**500**
6h	500	500	500	250	500	250	1000	1000
7a	1000	100	**250**	150	150	250	>1000	1000
7b	500	**250**	1000	250	500	250	>1000	**500**
7c	500	500	500	500	1000	250	500	**500**
7d	1000	1000	1000	1000	500	500	1000	1000
7e	500	500	**250**	250	1000	250	500	**500**
7f	**100**	**250**	**250**	150	500	**100**	1000	1000
7g	500	500	500	500	500	250	500	**500**
7h	250	1000	500	250	1000	150	500	1000
8a	250	**200**	**250**	500	250	500	500	1000
8b	**25**	**250**	**25**	**25**	**25**	**62.5**	1000	**500**
8c	**62.5**	500	**62.5**	**100**	**62.5**	200	>1000	1000
8d	250	**250**	**250**	150	250	500	500	**500**
8e	250	**250**	**250**	200	250	250	>1000	1000
8f	500	500	500	250	500	125	>1000	>1000
8g	**100**	**100**	**100**	**62.5**	**100**	**100**	1000	1000
8h	200	**200**	**200**	250	200	**100**	500	**500**
9a	**25**	500	**25**	**50**	**25**	50	1000	1000
9b	500	500	500	500	500	500	500	**500**
9c	200	**200**	**200**	**62.5**	200	**100**	500	1000
9d	250	**250**	**250**	200	250	**100**	>1000	**500**
9e	500	500	500	150	500	125	>1000	1000
9f	**100**	**100**	**100**	**62.5**	**100**	250	500	**500**
9g	200	**200**	**200**	250	200	500	1000	**500**
9h	**50**	**250**	**50**	**25**	**50**	125	500	1000
Ampi.	**100**	**250**	**250**	**100**	**100**	**100**	-	-
Chlora.	**50**	**50**	**50**	**50**	**50**	**50**	-	-
Cipro.	**50**	**100**	**50**	**25**	**25**	**25**	-	-
Genta.	**0.5**	**5**	**1**	**5**	**5**	**0.05**	-	-
Grise.	-	-	-	-	-	-	**100**	**500**
Nyst.	-	-	-	-	-	-	**100**	**100**

Ampi.: Ampicillin, Chlora.: Chloramphenicol, Cipro.: Ciprofloxacin, Genta.: Gentamicin, Grise.: Griseofulvin, Nyst.: Nystatin

S. p.: Streptococcus pneumoniae, C. t.: Clostridium tetani, B. s.: Bacillus subtilis, S. t.: Salmonella typhi, V. c.: Vibrio cholerae, E. c.: Escherichia coli, A. f.: Aspergillus fumigatus, C. a.: Candida albicans

Towards Gram negative strain *S. typhi*, compounds **8b, 9h** and **9a** were equally active to ciprofloxacin and chloramphenicol where as, compounds **8g, 9c** and **9f** were found better active and **8c** is equally active than ampicillin. The Compounds **8b, 9a** and **9h** found equipotent to ciprofloxacin and chloramphenicol where as, compounds **6b, 8c, 8g** and **9f** are comparably active to ampicillin against *V. cholerae*. The compounds **8b** shows better, and **7f, 8g, 8h, 9c** and **9d** were found to exhibit comparable activity to ampicillin towards *E. coli*. The compounds **8b** and **8g** were highly active against all the the tested Gram positive and negative pathogens. The remaining compounds showed moderate to good activity to inhibit the growth of bacterial pathogens and are all less effective than ampicillin. Against fungal pathogen *C. albicans*, compound **6d** found better activity where as, **6a, 6c, 6g, 7b-c, 7e, 7g, 8b, 8d, 8h, 9b, 9d, 9f** and **9g** were found to be equipotent compared to griseofulvin. None of the tested compounds found to be potent against *A. fumigatus* compared to standard drugs.

Conclusion

A new series of substituted 4-pyrazolyl-4*H*-pyrazolopyran **6a-h**, -benzopyran **7a-h** and naphthopyran **8a-h, 9a-h** derivatives has been synthesized *via* an MCR approach and was characterized by elemental and spectral analysis. This synthetic strategy allows the construction of relatively complicated oxygen containing fused heterocyclic system as well as the introduction of various (hetero)aromatic substitutions into 4-position of pyran system. It can be concluded from antimicrobial screening (Table 1), against panel of human pathogens, that most of the synthesized naphthopyran derivatives **8a-h, 9a-h** was found to be highly active, compared to pyrazolopyran **6a-h** and benzopyran **7a-h**, against bacterial pathogens. Among them, compounds **8b**, **8g, 9a, 9f** and **9h** were found to be the most active against the microorganisms employed for antibacterial activity. Antifungal activity of the compounds shows that most of the compounds found to be potent against *C. albicans* compared to *A. fumigatus*. It is worth mentioning that minor change in molecular configuration of these compounds profoundly influences the activity.

Experimental Section

General. All the reagents were obtained commercially and used with further purification. Solvents used were of analytical grade. All melting points were taken in open capillaries and are uncorrected. Thin-layer chromatography (TLC, on aluminium plates coated with silica gel $60F_{254}$, 0.25 mm thickness, Merck) was used for monitoring the progress of all reactions, purity and homogeneity of the synthesized compounds; eluent-toluene:ethyl acetate::7:3. UV radiation and iodine were used as the visualizing agents. Elemental analysis (% C, H, N) was carried out by Perkin-Elmer 2400 series-II elemental analyzer at Sophisticated Instrumentation Centre for Applied Research & Training (SICART), Vallabh Vidyanagar and all compounds are within

±0.4% of theory specified. The IR spectra were recorded in KBr on a Perkin-Elmer Spectrum GX FT-IR Spectrophotometer and only the characteristic peaks are reported in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker Avance 400F (MHz) spectrometer using solvent peak as internal standard at 400 MHz and 100 MHz respectively. Chemical shifts are reported in parts per million (ppm). Mass spectra were scanned on a Shimadzu LCMS 2010 spectrometer. 1-Phenyl-3-(het)aryl-pyrazole-4-carbaldehydes **1a-h** were prepared by Vilsmeier-Haack reaction of acetophenone (het)arylhydrazones (Scheme 1).[20]

General procedure for the synthesis of 6-amino-4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 6a-h

3-Aryl-1-phenylpyrazole-4-carbaldehyde **1a-h** (30 mmol), malononitrile **2** (30 mmol), 3-methyl-2-pyrazolin-5-one **3** (30 mmol), ethanol (15 mL) and 3 drops of piperidine were charged in 100mL round bottom flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 3-4 hr. On completion of reaction, monitored by TLC (ethyl acetate:toluene::3:7), the reaction mixture was cooled to room temperature and the solid separated was filtered and washed with mixture of chloroform and methanol to obtain the pure compounds **6a-h.** Analytical and spectroscopic characterization data of the synthesized compounds **6a-h** are given below:

6-Amino-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 6a. Yield: 60 %. m.p. 209-211 °C. Anal.Calcd. for $C_{23}H_{18}N_6O$ (394.44 gm/mole): C 70.04, H 4.60, N 21.31 %. Found: C 69.87, H 4.42, N 21.54 %. IR (KBr, ν, cm^{-1}): 3410 & 3385, 3270 (asym. & sym. str. of $-NH_2$ and -NH- str.), 2210 (-C≡N str.), 1220 (asym. str. of cyclic ArC-O-C ether). ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.79 (s, 3H, CH_3), 4.59 (s, 1H, pyran H4), 6.91 (s, 2H, D_2O exch., NH_2), 6.98-7.96 (m, 10H, Ar-H), 8.31 (s, 1H, pyrazole H5), 12.18 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.4 (CH_3), 27.2 (pyran C4), 57.8 (pyran C3), 98.4 (pyran C5), 120.9 (CN), 114.5, 117.3, 124.8, 126.5, 127.3, 128.9, 129.5, 129.7, 131.3, 135.8, 140.1, 151.2 (Ar-C), 154.7 (pyran C6), 161.6 (pyran C2).

6-Amino-4-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano-[2,3-*c*]pyrazole-5-carbonitrile 6b. Yield: 58 %. m.p. 235-237 °C. Anal.Calcd. for $C_{23}H_{17}BrN_6O$ (473.33 gm/mole): C 58.36, H 3.62, N 17.76 %. Found: C 58.57, H 3.85, N 17.59 %. IR (KBr, ν, cm^{-1}): 3395 & 3360, 3285 (asym. & sym. str. of $-NH_2$ and -NH- str.), 2190 (-C≡N str.), 1235 (asym. str. of cyclic ArC-O-C ether). ^1H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.75 (s, 3H, CH_3), 4.78 (s, 1H, pyran H4), 6.80 (s, 2H, D_2O exch., NH_2), 7.01-8.08 (m, 9H, Ar-H), 8.39 (s, 1H, pyrazole H5), 11.97 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.3 (CH_3), 26.6 (pyran C4), 58.6 (pyran C3), 97.7 (pyran C5), 121.3 (CN), 114.3, 119.1, 123.3, 126.6, 126.9, 128.0, 129.4, 129.8, 131.2, 135.6, 140.0, 150.5 (Ar-C), 154.6 (pyran C6), 162.0 (pyran C2).

6-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile 6c. Yield: 61 %. m.p. 203-205 °C. Anal.Calcd. for $C_{23}H_{17}ClN_6O$ (428.88 gm/mole): C 64.41, H 4.00, N 19.60 %. Found: C 64.25, H 3.77, N 19.82 %. IR (KBr, ν,

cm^{-1}): 3410 & 3355, 3250 (asym. & sym. str. of -NH_2 and -NH- str.), 2200 (-C≡N str.), 1210 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.69 (s, 3H, CH_3), 4.60 (s, 1H, pyran H4), 6.94 (s, 2H, D_2O exch., NH_2), 6.99-7.94 (m, 9H, Ar-H), 8.35 (s, 1H, pyrazole H5), 12.36 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.2 (CH_3), 26.7 (pyran C4), 57.9 (pyran C3), 97.9 (pyran C5), 121.4 (CN), 113.6, 118.9, 125.0, 126.4, 127.4, 128.6, 129.3, 130.0, 130.4, 136.2, 140.1, 150.6 (Ar-C), 156.1 (pyran C6), 161.3 (pyran C2).

6-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 6d. Yield: 50 %. m.p. 229-231 °C. Anal.Calcd. for $C_{23}H_{17}FN_6O$ (412.43 gm/mole): C 66.98, H 4.16, N 20.38 %. Found: C 66.69, H 4.39, N 20.23 %. IR (KBr, ν, cm^{-1}): 3400 & 3370, 3285 (asym. & sym. str. of -NH_2 and -NH- str.), 2190 (-C≡N str.), 1255 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.80 (s, 3H, CH_3), 4.88 (s, 1H, pyran H4), 6.79 (s, 2H, D_2O exch., NH_2), 6.87-7.89 (m, 9H, Ar-H), 8.27 (s, 1H, pyrazole H5), 12.54 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 11.4 (CH_3), 27.4 (pyran C4), 58.5 (pyran C3), 98.3 (pyran C5), 120.9 (CN), 115.0, 117.4, 124.4, 126.2, 127.3, 128.8, 129.7, 130.1, 130.5, 135.5, 139.2, 150.9 (Ar-C), 155.4 (pyran C6), 160.8 (pyran C2).

6-Amino-4-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-3-methyl-2,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile 6e. Yield: 60 %. m.p. 215-217 °C. Anal.Calcd. for $C_{24}H_{20}N_6O_2$ (424.47 gm/mole): C 67.91, H 4.75, N 19.80 %. Found: C 67.79, H 4.49, N 20.07 %. IR (KBr, ν, cm^{-1}): 3405 & 3360, 3255 (asym. & sym. str. of -NH_2 and -NH- str.), 2205 (-C≡N str.), 1230 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.75 (s, 3H, CH_3), 3.79 (s, 3H, OCH_3), 4.85 (s, 1H, pyran H4), 6.82 (s, 2H, D_2O exch., NH_2), 6.96-7.91 (m, 9H, Ar-H), 8.45 (s, 1H, pyrazole H5), 12.01 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.2 (CH_3), 26.7 (pyran C4), 55.5 (OCH_3), 57.4 (pyran C3), 97.9 (pyran C5), 121.4 (CN), 114.1, 118.1, 124.5, 126.0, 126.4, 128.4, 129.9, 131.6, 135.9, 139.8, 151.3 (Ar-C), 154.9 (pyran C6), 159.4 (Ar<u>C</u>-OCH_3), 161.1 (pyran C2). MS: 425.1 (M^++1).

6-Amino-3-methyl-4-(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)-2,4-dihydropyrano [2,3-*c*]pyrazole-5-carbonitrile 6f. Yield: 58 %. m.p. 208-210 °C. Anal.Calcd. for $C_{24}H_{20}N_6O$ (408.47 gm/mole): C 70.57, H 4.94, N 20.58 %. Found: C 70.34, H 5.17, N 20.31 %. IR (KBr, ν, cm^{-1}): 3385 & 3345, 3270 (asym. & sym. str. of -NH_2 and -NH- str.), 2195 (-C≡N str.), 1250 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.79 (s, 3H, CH_3), 2.34 (s, 3H, tolyl-CH_3), 4.61 (s, 1H, pyran H4), 6.87 (s, 2H, D_2O exch., NH_2), 7.06-8.14 (m, 9H, Ar-H), 8.32 (s, 1H, pyrazole H5), 12.15 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.5 (CH_3), 20.9 (tolyl-CH_3), 27.3 (pyran C4), 57.8 (pyran C3), 98.2 (pyran C5), 120.8 (CN), 113.2, 118.4, 125.1, 126.8, 126.6, 128.1, 129.3, 129.9, 130.8, 136.1, 140.0, 150.8 (Ar-C), 154.8 (pyran C6), 161.4 (pyran C2).

6-Amino-3-methyl-4-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 6g. Yield: 55 %. m.p.190-192 °C. Anal.Calcd. for $C_{23}H_{17}N_7O_3$ (439.44 gm/mole): C 62.87, H 3.90, N 22.31 %. Found: C 63.05, H 3.74, N 22.09 %. IR (KBr, ν,

cm^{-1}): 3395 & 3350, 3195 (asym. & sym. str. of -NH_2 and -NH- str.), 2185 (-C≡N str.), 1245 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.76 (s, 3H, CH_3), 4.76 (s, 1H, pyran H4), 6.86 (s, 2H, D_2O exch., NH_2), 6.97-8.22 (m, 9H, Ar-H), 8.41 (s, 1H, pyrazole H5), 12.40 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 11.3 (CH_3), 26.8 (pyran C4), 59.0 (pyran C3), 97.9 (pyran C5), 120.8 (CN), 114.8, 117.8, 124.1, 126.1, 127.4, 128.9, 129.6, 129.7, 131.6, 136.2, 140.2, 151.1 (Ar-C), 156.1 (pyran C6), 160.9 (pyran C2).

6-Amino-3-methyl-4-(1-phenyl-3-(thien-2-yl)-1*H*-pyrazol-4-yl)-2,4-dihydropyrano[2,3-*c*]pyrazole-5-carbonitrile 6h. Yield: 57 %. m.p. 230-232 °C. Anal.Calcd. for $C_{21}H_{16}N_6OS$ (400.47 gm/mole): C 62.99, H 4.03, N 20.99 % Found: C 63.29, H 4.32, N 20.64 %. IR (KBr, ν, cm^{-1}): 3415 & 3380, 3200 (asym. & sym. str. of -NH_2 and -NH- str.), 2190 (-C≡N str.), 1220 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.72 (s, 3H, CH_3), 4.59 (s, 1H, pyran H4), 6.83 (s, 2H, D_2O exch., NH_2), 7.03-8.09 (m, 8H, Ar-H), 8.35 (s, 1H, pyrazole H5), 12.28 (s, 1H, D_2O exch., NH). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 10.2 (CH_3), 26.8 (pyran C4), 58.4 (pyran C3), 97.8 (pyran C5), 121.0 (CN), 114.9, 119.0, 124.4, 126.0, 126.3, 128.7, 129.7, 130.0, 131.9, 136.2, 139.9, 151.0 (Ar-C), 155.6 (pyran C6), 162.0 (pyran C2).

General procedure for the synthesis of 2-amino-4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7a-h

3-Aryl-1-phenylpyrazole-4-carbaldehyde **1a-h** (30 mmol), malononitrile **2** (30 mmol), 5,5-dimethyl-1,3-cyclohexanedione (dimedone) **4** (30 mmol), ethanol (15 mL) and 3 drops of piperidine were charged in 100mL round bottom flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 3-4 hr. On completion of reaction, monitored by TLC (ethyl acetate:toluene::3:7), the reaction mixture was cooled to room temperature and the solid separated was filtered, washed with mixture of chloroform and methanol and dried to obtain the pure compounds **7a-h.** Analytical and spectroscopic characterization data of the synthesized compounds **7a-h** are given below:

2-Amino-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7a. Yield: 69 %. m.p. 209-211 °C. Anal.Calcd. for $C_{27}H_{24}N_4O_2$ (436.52 gm/mole): C 74.29, H 5.54, N 12.84 %. Found: C 74.13, H 5.38, N 13.01 %. IR (KBr, ν, cm^{-1}): 3430 & 3300 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1680 (C=O str. of cyclic ketone), 1235 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.04 (s, 3H, CH_3), 1.11 (s, 3H, CH_3), 2.19-2.47 (4H, m, 2×CH_2), 4.43 (s, 1H, pyran H4), 6.88 (s, 2H, D_2O exch., NH_2), 6.96-7.91 (m, 10H, Ar-H), 8.31 (s, 1H, pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.6 (CH_3), 27.9 (CH_3), 28.5 (pyran C4), 32.5 ($\underline{C}(CH_3)_2$), 42.1 (CH_2), 51.2 ($\underline{C}H_2$-CO), 58.0 (pyran C3), 112.7 (pyran C5), 121.8 (CN), 114.3, 118.0, 125.3, 125.8, 126.9, 127.8, 128.8, 131.0, 136.1, 138.8, 151.1 (Ar-C), 157.9 (pyran C6), 163.1 (pyran C2), 196.1 (C=O).

2-Amino-4-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7b. Yield: 60 %. m.p. 227-229 °C. Anal.Calcd. for $C_{27}H_{23}BrN_4O_2$ (515.41 gm/mole): C 62.92, H 4.50, N 10.87 %. Found: C 62.78, H 4.66, N 10.71 %. IR (KBr, ν, cm^{-1}): 3420 & 3295 (asym. & sym. str. of $-NH_2$), 2210 (-C≡N str.), 1685 (C=O str. of cyclic ketone), 1255 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.97 (s, 3H, CH_3), 1.06 (s, 3H, CH_3), 2.15-2.50 (4H, m, 2×CH_2), 4.57 (s, 1H, pyran H4), 6.85 (s, 2H, D_2O exch., NH_2), 7.01-7.93 (m, 10H, Ar-H), 8.39 (s, 1H, pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.8 (CH_3), 27.7 (CH_3), 28.6 (pyran C4), 33.0 ($\underline{C}(CH_3)_2$), 41.8 (CH_2), 52.0 ($\underline{C}H_2$-CO), 57.7 (pyran C3), 113.9 (pyran C5), 120.3 (CN), 115.0, 117.8, 124.9, 125.4, 126.8, 128.2, 129.2, 130.9, 136.2, 139.1, 150.9 (Ar-C), 157.4 (pyran C6), 162.8 (pyran C2), 194.9 (C=O).

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7c. Yield: 63 %. m.p. 229-231 °C. Anal.Calcd. for $C_{27}H_{23}ClN_4O_2$ (470.96 gm/mole): C 68.86, H 4.92, N 11.90 %. Found: C 69.03, H 4.73, N 11.75 %. IR (KBr, ν, cm^{-1}): 3455 & 3290 (asym. & sym. str. of $-NH_2$), 2200 (-C≡N str.), 1680 (C=O str. of cyclic ketone), 1230 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.02 (s, 3H, CH_3), 1.10 (s, 3H, CH_3), 2.16-2.49 (4H, m, 2×CH_2), 4.47 (s, 1H, pyran 4H), 6.93 (s, 2H, D_2O exch., NH_2), 7.04-7.90 (m, 10H, Ar-H), 8.32 (s, 1H, pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.7 (CH_3), 27.9 (CH_3), 28.4 (pyran C4), 31.9 ($\underline{C}(CH_3)_2$), 40.6 (CH_2), 50.8 ($\underline{C}H_2$-CO), 57.3 (pyran C3), 115.0 (pyran C5), 121.5 (CN), 114.9, 118.3, 125.7, 126.0, 127.0, 128.6, 129.1, 130.6, 136.5, 139.3, 152.1 (Ar-C), 158.1 (pyran C6), 163.2 (pyran C2), 195.7 (C=O).

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7d. Yield: 65 %. m.p. 222-224 °C. Anal.Calcd. for $C_{27}H_{23}N_4FO_2$ (454.51 gm/mole): C 71.35, H 5.10, N 12.33 %. Found: C 71.21, H 4.94, N 12.45 %. IR (KBr, ν, cm^{-1}): 3435 & 3350 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.), 1690 (C=O str. of cyclic ketone), 1240 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.94 (s, 3H, CH_3), 1.03 (s, 3H, CH_3), 2.09-2.48 (4H, m, 2×CH_2), 4.55 (s, 1H, pyran H4), 6.84 (s, 2H, D_2O exch., NH_2), 7.20-7.90 (m, 10H, Ar-H), 8.27 (s, 1H, pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.6 (CH_3), 27.6 (CH_3), 28.6 (pyran C4), 32.4 ($\underline{C}(CH_3)_2$), 42.0 (CH_2), 51.5 ($\underline{C}H_2$-CO), 59.4 (pyran C3), 114.4 (pyran C5), 120.8 (CN), 115.1, 118.5, 126.2, 126.2, 127.2, 127.4, 128.6, 131.1, 136.2, 138.6, 150.9 (Ar-C), 157.9 (pyran C6), 162.7 (pyran C2), 194.8 (C=O).

2-Amino-4-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-7,7-dimethyl-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7e. Yield: 58 %. m.p. 216-217 °C. Anal.Calcd. for $C_{28}H_{26}N_4O_3$ (466.54 gm/mole): C 72.09, H 5.62, N 12.01 %. Found: C 71.91, H 5.88, N 11.84 %. IR (KBr, ν, cm^{-1}): 3400 & 3285 (asym. & sym. str. of -NH_2), 2195 (-C≡N str.), 1700 (C=O str. of cyclic ketone), 1235 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.97 (s, 3H, CH_3), 1.01 (s, 3H, CH_3), 2.11-2.43 (4H, m, 2×CH_2), 3.82 (s, 3H, OCH_3), 4.42 (s, 1H, pyran H4), 6.99 (s, 2H, D_2O exch., NH_2), 7.03-7.85 (m, 10H, Ar-H), 8.37 (s, 1H,

pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.8 (CH_3), 27.9 (CH_3), 28.4 (pyran C4), 32.1 ($\underline{C}(CH_3)_2$), 40.2 (CH_2), 50.6 ($\underline{C}H_2$-CO), 55.6 (OCH_3), 59.0 (pyran C3), 112.3 (pyran C5), 120.3 (CN), 114.1, 118.2, 126.3, 126.6, 127.8, 129.8, 130.2, 136.5, 139.9, 151.2 (Ar-C), 157.5 (pyran C6), 159.4 (Ar$\underline{C}$-OCH_3), 162.3 (pyran C2), 196.4 (C=O). MS: 467.2 (M^++1).

2-Amino-7,7-dimethyl-5-oxo-4-(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7f. Yield: 61 %. m.p. 207-209 °C. Anal.Calcd. for $C_{28}H_{26}N_4O_2$ (450.54 gm/mole): C 74.65, H 5.82, N 12.44 %. Found: C 74.76, H 5.95, N 12.19 %. IR (KBr, ν, cm^{-1}): 3425 & 3335 (asym. & sym. str. of -NH_2), 2205 (-C≡N str.), 1695 (C=O str. of cyclic ketone), 1250 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.02 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.17-2.45 (4H, m, 2×CH_2), 2.37 (s, 3H, tolyl-CH_3), 4.46 (s, 1H, pyran H4), 6.94 (s, 2H, D_2O exch., NH_2), 7.22-8.04 (m, 10H, Ar-H), 8.39 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.1 (tolyl-CH_3), 25.8 (CH_3), 27.7 (CH_3), 28.5 (pyran C4), 31.9 ($\underline{C}(CH_3)_2$), 40.7 (CH_2), 52.1 ($\underline{C}H_2$-CO), 56.5 (pyran C3), 113.4 (pyran C5), 120.6 (CN), 114.2, 118.0, 125.6, 126.7, 127.7, 128.5, 130.7, 131.3, 136.8, 138.4, 151.3, (Ar-C), 157.4 (pyran C6), 163.0 (pyran C2), 195.0 (C=O).

2-Amino-7,7-dimethyl-4-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-5-oxo-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7g. Yield: 64 %. m.p. 224-226 °C. Anal.Calcd. for $C_{27}H_{23}N_5O_4$ (481.51 gm/mole): C 67.35, H 4.82, N 14.54 %. Found: C 67.27, H 4.68, N 14.42 %. IR (KBr, ν, cm^{-1}): 3410 & 3320 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1690 (C=O str. of cyclic ketone), 1245 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 0.96 (s, 3H, CH_3), 1.04 (s, 3H, CH_3), 2.10-2.51 (4H, m, 2×CH_2), 4.52 (s, 1H, pyran H4), 6.90 (s, 2H, D_2O exch., NH_2), 7.29-8.01 (m, 10H, Ar-H), 8.29 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.7 (CH_3), 27.8 (CH_3), 28.5 (pyran C4), 32.7 ($\underline{C}(CH_3)_2$), 41.3 (CH_2), 52.0 ($\underline{C}H_2$-CO), 56.2 (pyran C3), 113.5 (pyran C5), 121.1 (CN), 114.9, 117.8, 126.0, 126.5, 127.4, 127.6, 129.7, 131.2, 136.0, 139.4, 152.0 (Ar-C), 158.0 (pyran C6), 162.9 (pyran C2), 197.1 (C=O).

2-Amino-7,7-dimethyl-5-oxo-4-(1-phenyl-3-(thien-2-yl)-1*H*-pyrazol-4-yl)-5,6,7,8-tetrahydro-4*H*-chromene-3-carbonitrile 7h. Yield: 66 %. m.p. 204-206 °C. Anal.Calcd. for $C_{25}H_{22}N_4O_2S$ (442.55 gm/mole): C 67.85, H 5.01, N 12.66 %. Found: C 67.60, H 5.24, N 12.47 %. IR (KBr, ν, cm^{-1}): 3430 & 3345 (asym. & sym. str. of -NH_2), 2195 (-C≡N str.), 1685 (C=O str. of cyclic ketone), 1240 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 1.03 (s, 3H, CH_3), 1.12 (s, 3H, CH_3), 2.18-2.42 (4H, m, 2×CH_2), 4.49 (s, 1H, pyran H4), 6.87 (s, 2H, D_2O exch., NH_2), 7.09-8.06 (m, 10H, Ar-H), 8.41 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 25.8 (CH_3), 27.7 (CH_3), 28.4 (pyran C4), 32.3 ($\underline{C}(CH_3)_2$), 42.0 (CH_2), 51.8 ($\underline{C}H_2$-CO), 58.0 (pyran C3), 115.1 (pyran C5), 121.4 (CN), 114.2, 118.2, 126.1, 126.3, 127.1, 128.3, 129.3, 130.9, 136.8, 139.2, 150.9 (Ar-C), 157.8 (pyran C6), 162.3 (pyran C2), 195.9 (C=O).

General procedure for the synthesis of 2-amino-4-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8a-h and 3-amino-1-(3-aryl-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9a-h

3-Aryl-1-phenylpyrazole-4-carbaldehyde **1a-h** (30 mmol), malononitrile **2** (30 mmol), 1- or 2-naphthol **5** (30 mmol), acetonitrile (MeCN) (15 mL) and 3 drops of piperidine were charged in 100mL round bottom flask with mechanical stirrer and condenser. The reaction mixture was slowly heated and refluxed for 3-4 hr. On completion of reaction, monitored by TLC (ethyl acetate:toluene::3:7), the reaction mixture was cooled to room temperature and the solid separated was filtered and washed with mixture of chloroform and methanol to obtain the pure compounds **8a-h** and **9a-h.** Analytical and spectroscopic characterization data of the synthesized compounds **8a-h** and **9a-h** are given below:

2-Amino-4-(1,3-diphenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8a. Yield: 73 %. m.p. 186-188 °C. Anal.Calcd. for $C_{29}H_{20}N_4O$ (440.51 gm/mole): C 79.07, H 4.58, N 12.72 %. Found: C 79.26, H 4.44, N 12.53 %. IR (KBr, ν, cm^{-1}): 3400 & 3295 (asym. & sym. str. of -NH_2), 2185 (-C≡N str.), 1245 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 4.97 (s, 1H, pyran H4), 6.91 (s, 2H, D_2O exch., NH_2), 7.04-8.29 (m, 16H, Ar-H), 8.31 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 30.4 (pyran C4), 56.7 (pyran C3), 115.9 (pyran C5), 120.9 (CN), 117.8, 118.8, 122.1, 123.3, 124.4, 125.5, 126.2, 126.3, 127.0, 127.3, 128.5, 128.6, 129.3, 129.4, 132.8, 134.1, 136.1, 139.1, 144.2 (Ar-C), 146.1 (pyran C6), 160.7 (pyran C2).

2-Amino-4-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8b. Yield: 69 %. m.p. 231-233 °C. Anal.Calcd. for $C_{29}H_{19}BrN_4O$ (519.40 gm/mole): C 67.06, H 3.69, N 10.79 %. Found: C 66.83, H 3.50, N 10.93 %. IR (KBr, ν, cm^{-1}): 3415 & 3305 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.), 1265 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.15 (s, 1H, pyran H4), 6.89 (s, 2H, D_2O exch, NH_2), 7.12-8.14 (m, 15H, Ar-H), 8.27 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 31.1 (pyran C4), 56.8 (pyran C3), 116.3 (pyran C5), 120.8 (CN), 118.0, 119.0, 123.0, 124.0, 125.7, 126.1, 126.4, 126.5, 127.5, 127.6, 128.2, 128.3, 129.2, 129.7, 131.1, 134.8, 137.8, 139.6, 144.3 (Ar-C), 147.0 (pyran C6), 160.8 (pyran C2).

2-Amino-4-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8c. Yield: 67 %. m.p. 200-202 °C. Anal.Calcd. for $C_{29}H_{19}ClN_4O$ (474.95 gm/mole): C 73.34, H 4.03, N 11.80 %. Found: C 73.22, H 3.86, N 11.99 %. IR (KBr, ν, cm^{-1}): 3405 & 3335 (asym. & sym. str. of -NH_2), 2180 (-C≡N str.), 1230 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.23 (s, 1H, pyran H4), 6.86 (s, 2H, D_2O exch., NH_2), 7.07-8.16 (m, 15H, Ar-H), 8.39 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 30.5 (pyran C4), 57.5 (pyran C3), 117.0 (pyran C5), 120.9 (CN), 118.7, 119.3, 122.9, 124.9, 125.4, 126.4, 126.7, 126.8, 127.8, 128.0, 128.1, 129.5, 129.6, 129.9, 131.7, 134.1, 137.6, 139.6, 143.0 (Ar-C), 148.9 (pyran C6), 161.4 (pyran C2).

2-Amino-4-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8d. Yield: 68 %. m.p. 204-205°C. Anal.Calcd. for $C_{29}H_{19}FN_4O$ (458.50 gm/mole): C

75.97, H 4.18, N 12.22 %. Found: C 76.20, H 4.37, N 12.15 %. IR (KBr, ν, cm^{-1}): 3455 & 3310 (asym. & sym. str. of -NH_2), 2195 (-C≡N str.), 1225 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.10 (s, 1H, pyran H4), 6.94 (s, 2H, D_2O exch., NH_2), 7.18-8.25 (m, 15H, Ar-H), 8.47 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 29.9 (pyran C4), 58.0 (pyran C3), 115.1 (pyran C5), 121.0 (CN), 117.4, 118.7, 123.2, 124.5, 125.3, 126.0, 126.3, 126.7, 127.1, 127.6, 128.6, 129.2, 129.4, 129.6, 130.0, 134.8, 136.6, 138.4, 144.7 (Ar-C), 150.2 (pyran C6), 160.8 (pyran C2).

2-Amino-4-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8e. Yield: 65 %. m.p. 239-241 °C. Anal.Calcd. for $C_{30}H_{22}N_4O_2$ (470.53 gm/mole): C 76.58, H 4.71, N 11.91 %. Found: C 76.43, H 4.40, N 12.16 %. IR (KBr, ν, cm^{-1}): 3400 & 3290 (asym. & sym. str. of -NH_2), 2205 (-C≡N str.), 1250 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 3.87 (s, 3H, OCH_3), 5.22 (s, 1H, pyran H4), 6.90 (s, 2H, D_2O exch., NH_2), 7.14-8.13 (m, 15H, Ar-H), 8.32 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 31.0 (pyran C4), 54.7 (OCH_3), 56.8 (pyran C3), 115.9 (pyran C5), 120.9 (CN), 117.2, 118.9, 123.9, 124.7, 125.1, 126.1, 126.5, 127.2, 127.8, 128.6, 128.8, 129.0, 129.8, 131.3, 134.7, 137.9, 139.7, 143.9 (Ar-C), 147.6 (pyran C6), 158.0 (Ar<u>C</u>-OCH_3), 162.0 (pyran C2).

2-Amino-4-(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8f. Yield: 63 %. m.p. 199-201 °C. Anal.Calcd. for $C_{30}H_{22}N_4O$ (454.53 gm/mole): C 79.28, H 4.88, N 12.33 %. Found: C 79.11, H 5.04, N 12.12 %. IR (KBr, ν, cm^{-1}): 3395 & 3320 (asym. & sym. str. of -NH_2), 2215 (-C≡N str.), 1215 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.31 (s, 3H, CH_3), 5.19 (s, 1H, pyran H4), 6.96 (s, 2H, D_2O exch., NH_2), 6.98-8.24 (m, 15H, Ar-H), 8.47 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.2 (CH_3), 31.2 (pyran C4), 56.5 (pyran C3), 117.9 (pyran C5), 121.0 (CN), 118.4, 121.2, 123.2, 124.2, 126.2, 126.3, 126.5, 127.0, 127.1, 128.0, 128.6, 128.9, 129.3, 129.9, 130.6, 133.2, 137.7, 139.8, 142.9 (Ar-C), 151.6 (pyran C6), 160.2 (pyran C2). MS: 455.1 (M^++1).

2-Amino-4-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8g. Yield: 65 %. m.p. 224-226 °C. Anal.Calcd. for $C_{29}H_{19}N_5O_3$ (485.51 gm/mole): C 71.74, H 3.95, N 14.43 %. Found: C 71.89, H 4.14, N 14.30 %. IR (KBr, ν, cm^{-1}): 3430 & 3315 (asym. & sym. str. of -NH_2), 2220 (-C≡N str.), 1260 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.36 (s, 1H, pyran H4), 6.87 (s, 2H, D_2O exch., NH_2), 7.02-8.17 (m, 10H, Ar-H), 8.21 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 31.2 (pyran C4), 58.1 (pyran C3), 115.9 (pyran C5), 121.1 (CN), 117.2, 118.6, 123.9, 124.1, 125.4, 126.4, 126.5, 126.9, 127.3, 127.5, 128.0, 128.2, 129.4, 129.6, 130.5, 133.3, 136.4, 139.3, 142.7 (Ar-C), 147.8 (pyran C6), 161.5 (pyran C2).

2-Amino-4-(1-phenyl-3-(thien-2-yl)-1*H*-pyrazol-4-yl)-4*H*-benzo[*h*]chromene-3-carbonitrile 8h. Yield: 60 %. m.p. 237-238 °C. Anal.Calcd. for $C_{27}H_{18}N_4OS$ (446.54 gm/mole): C 72.63, H 4.06, N 12.55 %. Found: C 72.35, H 3.90, N 12.70 %. IR (KBr, ν, cm^{-1}): 3435 & 3345 (asym. & sym. str. of -NH_2), 2185 (-C≡N str.), 1235 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400

MHz, DMSO-d_6) δ_H (ppm): 5.29 (s, 1H, pyran H4), 6.92 (s, 2H, D_2O exch., NH_2), 7.20-7.98 (m, 14H, Ar-H), 8.33 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 29.8 (pyran C4), 57.4 (pyran C3), 116.5 (pyran C5), 121.0 (CN), 117.3, 118.3, 122.4, 124.4, 125.0, 126.4, 126.8, 127.0, 127.2, 128.1, 128.5, 128.5, 129.3, 129.9, 130.2, 134.1, 137.5, 139.2, 142.5 (Ar-C), 150.3 (pyran C6), 161.4 (pyran C2).

3-Amino-1-(1,3-diphenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile (9a). Yield: 76 %. m.p. 255-257 °C. Anal.Calcd. for $C_{29}H_{20}N_4O$ (440.51 gm/mole): C 79.07, H 4.58, N 12.72 %. Found: C 79.18, H 4.41, N 12.81 %. IR (KBr, ν, cm^{-1}): 3450 & 3290 (asym. & sym. str. of -NH_2), 2180 (-C≡N str.), 1270 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.19 (s, 1H, pyran H4), 6.98 (s, 2H, D_2O exch., NH_2), 7.00-8.22 (m, 16H, Ar-H), 8.51 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 29.8 (pyran C4), 57.2 (pyran C3), 116.8 (pyran C5), 121.2 (CN), 117.1, 118.9, 122.7, 124.6, 125.6, 126.7, 126.9, 127.2, 127.2, 128.0, 128.5, 129.4, 129.5, 129.7, 130.9, 133.3, 137.4, 138.7, 144.5 (Ar-C), 147.7 (pyran C6), 160.7 (pyran C2).

3-Amino-1-(3-(4-bromophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9b. Yield: 58 %. m.p. 221-223 °C. Anal Anal.Calcd. for $C_{29}H_{19}BrN_4O$ (519.40 gm/mole): C 67.06, H 3.69, N 10.79 %. Found: C 66.93, H 3.80, N 10.97 %. IR (KBr, ν, cm^{-1}): 3425 & 3290 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1240 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.37 (s, 1H, pyran H4), 6.90 (s, 2H, D_2O exch., NH_2), 6.96-8.18 (m, 15H, Ar-H), 8.41 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 30.5 (pyran C4), 57.3 (pyran C3), 116.7 (pyran C5), 120.8 (CN), 117.2, 118.8, 123.0, 124.1, 125.0, 126.3, 126.6, 127.3, 127.7, 128.1, 128.6, 128.9, 129.4, 129.7, 131.6, 133.8, 136.2, 138.0, 143.8 (Ar-C), 148.5 (pyran C6), 162.0 (pyran C2).

3-Amino-1-(3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9c. Yield: 62 %. m.p. 210-212 °C. Anal.Calcd. for $C_{29}H_{19}ClN_4O$ (474.95 gm/mole): C 73.34, H 4.03, N 11.80 %. Found: C 73.58, H 3.92, N 11.93 %. IR (KBr, ν, cm^{-1}): 3455 & 3295 (asym. & sym. str. of -NH_2), 2190 (-C≡N str.), 1275 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.25 (s, 1H, pyran H4), 6.88 (s, 2H, D_2O exch., NH_2), 7.05-8.20 (m, 15H, Ar-H), 8.35 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 30.6 (pyran C4), 58.1 (pyran C3), 115.8 (pyran C5), 120.8 (CN), 117.8, 118.1, 122.3, 124.4, 125.9, 126.2, 126.4, 126.5, 127.6, 127.8, 128.7, 128.8, 129.2, 129.3, 131.7, 134.1, 137.2, 139.4, 144.6 (Ar-C), 148.4 (pyran C6), 160.8 (pyran C2).

3-Amino-1-(3-(4-fluorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9d. Yield: 65 %. m.p. 252-254 °C. Anal.Calcd. for $C_{29}H_{19}FN_4O$ (458.50 gm/mole): C 75.97, H 4.18, N 12.22 %. Found: C 76.09, H 4.06, N 12.10 %. IR (KBr, ν, cm^{-1}): 3400 & 3300 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1255 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.17 (s, 1H, pyran H4), 6.85 (s, 2H, D_2O exch., NH_2), 7.10-7.99 (m, 15H, Ar-H), 8.45 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 31.1 (pyran C4), 56.9 (pyran C3), 117.4 (pyran C5), 121.1 (CN), 118.0, 119.9, 123.4, 124.3, 125.4,

126.3, 126.7, 127.4, 127.5, 127.9, 128.1, 128.4, 129.3, 129.4, 130.8, 133.3, 136.4, 139.3, 143.1 (Ar-C), 149.6 (pyran C6), 161.3 (pyran C2).

3-Amino-1-(3-(4-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9e. Yield: 69 %. m.p. 194-195 °C. Anal.Calcd. for $C_{30}H_{22}N_4O_2$ (470.53 gm/mole): C 76.58, H 4.71, N 11.91 %. Found: C 76.67, H 4.56, N 12.03 %. IR (KBr, ν, cm^{-1}): 3415 & 3280 (asym. & sym. str. of -NH_2), 2195 (-C≡N str.), 1220 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 3.94 (s, 3H, OCH_3), 5.32 (s, 1H, pyran H4), 6.93 (s, 2H, D_2O exch., NH_2), 7.01-8.11 (m, 15H, Ar-H), 8.27 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 29.9 (pyran C4), 55.8 (OCH_3), 58.7 (pyran C3), 117.4 (pyran C5), 121.1 (CN), 118.3, 119.5, 123.2, 124.2, 125.5, 126.1, 126.3, 127.1, 127.6, 128.5, 128.7, 129.0, 129.6, 131.3, 133.3, 136.2, 138.0, 144.4 (Ar-C), 149.6 (pyran C6), 157.4 (Ar<u>C</u>-OCH_3), 161.3 (pyran C2).

3-Amino-1-(1-phenyl-3-(4-methylphenyl)-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9f. Yield: 62 %. m.p. 279-281 °C. Anal.Calcd. for $C_{30}H_{22}N_4O$ (454.53 gm/mole): C 79.28, H 4.88, N 12.33 %. Found: C 79.08, H 4.98, N 12.51 %. IR (KBr, ν, cm^{-1}): 3460 & 3310 (asym. & sym. str. of -NH_2), 2205 (-C≡N str.), 1235 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 2.37 (s, 3H, CH_3), 5.24 (s, 1H, pyran H4), 6.84 (s, 2H, D_2O exch., NH_2), 6.96-8.19 (m, 15H, Ar-H), 8.32 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 21.4 (CH_3), 29.4 (pyran C4), 57.2 (pyran C3), 116.7 (pyran C5), 120.9 (CN), 118.2, 119.0, 122.6, 123.1, 123.4, 124.2, 125.5, 126.1, 127.5, 128.1, 128.3, 129.1, 129.4, 129.8, 131.2, 134.1, 138.1, 139.7, 142.1 (Ar-C), 148.9 (pyran C6), 160.0 (pyran C2).

3-Amino-1-(3-(4-nitrophenyl)-1-phenyl-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9g. Yield: 60 %. m.p. 238-240 °C. Anal.Calcd. for $C_{29}H_{19}N_5O_3$ (485.51 gm/mole): C 71.74, H 3.95, N 14.43 %. Found: C 71.96, H 3.75, N 14.28 %. IR (KBr, ν, cm^{-1}): 3420 & 3295 (asym. & sym. str. of -NH_2), 2210 (-C≡N str.), 1230 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.41 (s, 1H, pyran H4), 6.97 (s, 2H, D_2O exch., NH_2), 7.05-8.21 (m, 15H, Ar-H), 8.42 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 30.7 (pyran C4), 56.8 (pyran C3), 116.3 (pyran C5), 121.2 (CN), 117.7, 118.9, 122.8, 123.1, 125.7, 126.2, 126.7, 127.6, 128.4, 128.6, 128.8, 129.1, 129.3, 129.9, 130.1, 134.9, 137.9, 139.1, 143.2 (Ar-C), 150.1 (pyran C6), 161.4 (pyran C2).

3-Amino-1-(1-phenyl-3-(thien-2-yl)-1*H*-pyrazol-4-yl)-1*H*-benzo[*f*]chromene-2-carbonitrile 9h. Yield: 63 %. m.p. 241-243 °C. Anal.Calcd. for $C_{27}H_{18}N_4OS$ (446.54 gm/mole): C 72.63, H 4.06, N 12.55 %. Found: C 72.97, H 3.95, N 12.67 %. IR (KBr, ν, cm^{-1}): 3405 & 3325 (asym. & sym. str. of -NH_2), 2200 (-C≡N str.), 1240 (asym. str. of cyclic ArC-O-C ether). ^{1}H NMR (400 MHz, DMSO-d_6) δ_H (ppm): 5.57 (s, 1H, pyran H4), 6.99 (s, 2H, D_2O exch., NH_2), 7.23-7.91 (m, 14H, Ar-H), 8.25 (pyrazole H5). ^{13}C NMR (100 MHz, DMSO-d_6) δ_C (ppm): 29.8 (pyran C4), 57.5 (pyran C3), 115.7 (pyran C5), 121.1 (CN), 117.5, 118.4, 123.3, 125.2, 126.6, 126.8, 127.1, 127.3, 127.4, 128.3, 128.8, 129.0, 129.8, 130.5, 131.2, 134.8, 137.4, 139.3, 144.7 (Ar-C), 146.6 (pyran C6), 160.2 (pyran C2). MS: 447.0 (M^++1).

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