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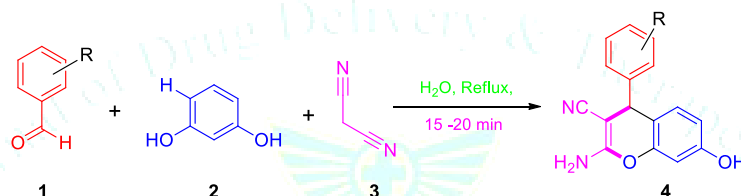
Research Article

A Benign Synthesis of 2-Amino-3-Cyano-4*H*-Benzopyrans via Domino Reaction

S. Silambarasan ^{*a}, A. Jamal Abdul Nasser ^a^a Department of Chemistry, Jamal Mohamed College, Tiruchirappalli 620020, Tamil Nadu, India.

ABSTRACT

A green and operationally simple approach domino reaction has been developed for the synthesis of 2-amino-3-cyano-4*H*-chromene derivatives from aromatic aldehydes, resorcinol and malononitrile in aqueous medium. This work represents the first example of catalyst free and organic solvents free multi-component reactions for the synthesis of pharmaceutically important chromene derivatives. The structures of the synthesized compounds were confirmed by ¹H NMR, ¹³C NMR, IR, Mass and single crystal XRD.



Keywords: Benzopyrans, malononitrile, Michael addition reaction, domino reaction, water mediated synthesis.

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*Address for Correspondence:

S. Silambarasan, Department of Chemistry, Jamal Mohamed College, Tiruchirappalli 620020, Tamil Nadu, India.

INTRODUCTION

Chromene (benzopyran) is a heterocyclic ring system in which a benzene ring and a pyran ring are fused together. The chromene nucleus containing natural alkaloids are anthocyanins, tocopherols and flavonoids. Moreover, a variety of natural and synthetic chromene derivatives has an important biological and pharmacological applications, such as antimicrobial, [1] anti-inflammatory, [2] antiproliferative, [3] antioxidant, [4] herbicidal, analgesic and anticonvulsant, [5] antitubercular, [6] anticoagulant, estrogenic antispasmodic, [7] TNF- α inhibitor effects and activities, [8] as well as inhibitor of diabetes-induced vascular dysfunction.[9] Moreover 7-Hydroxy-6-methoxy-

4*H*-chromene **A** (Fig. 1) is an example of naturally occurring 4*H*-chromene, which was obtained from the flowers of *Wisteria sinensis* and is one of their fragrance components.[10] Among different types of chromene systems, 2-amino-4*H*-chromenes have been reported to exhibit highly useful proapoptotic properties for the treatment of a wide range of cancer ailments.[11] In cancer chemotherapy, 2-amino-4*H*-chromene **B** was marked for drug development due to its high inhibition of tumor-associated Bcl-2 proteins.[12] A modified 4*H*-chromene structure **C** was able to induce apoptosis (programmed cell death) in several cancer cell lines.[13]

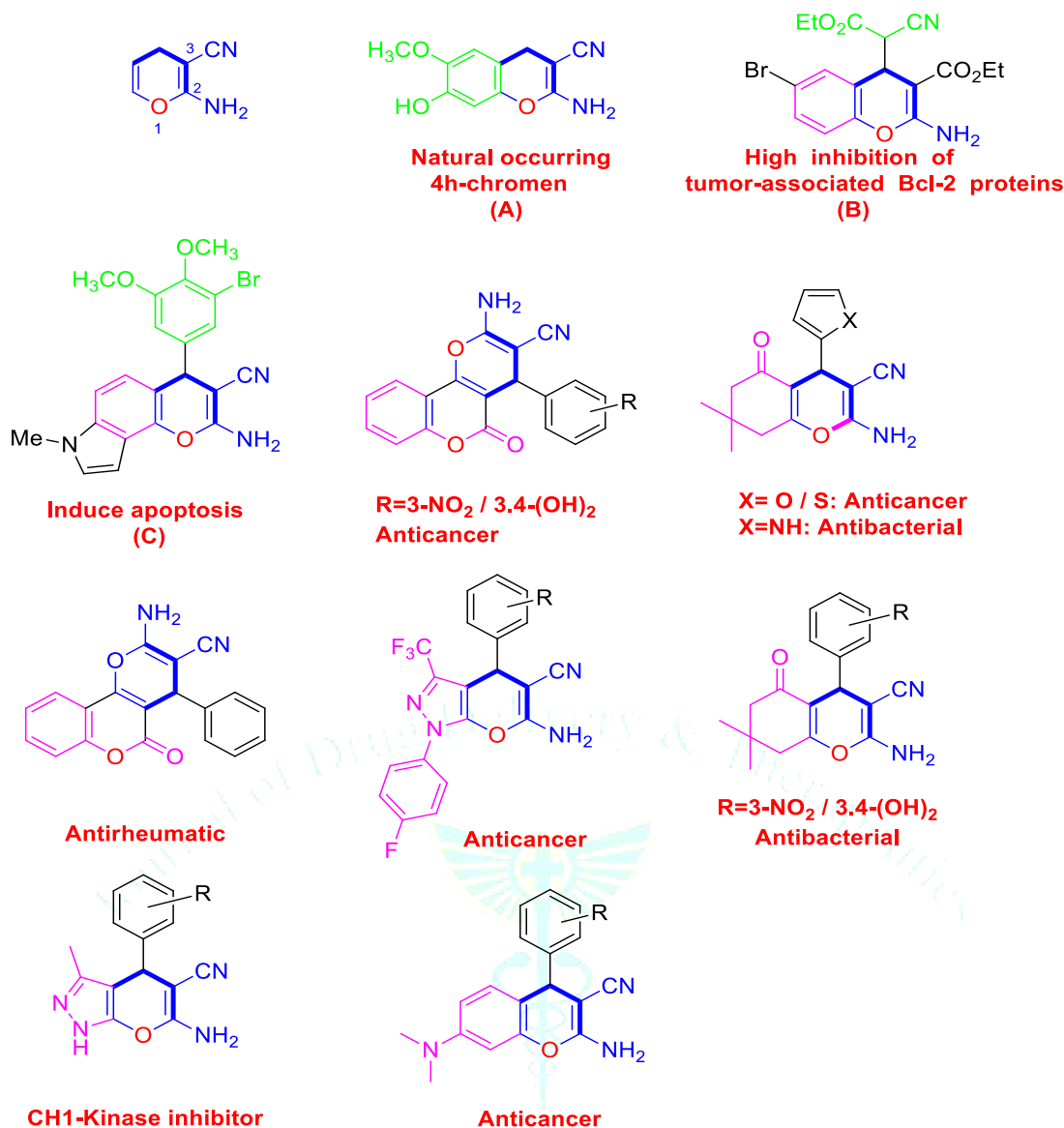


Figure 1: Structure of some biologically important 2-amino-3-cyano- 4H-chromenes

The biological records of these privileged motifs prompted us to develop an atom-economical, one pot, mild and greener method for the synthesis of chromene derivatives. Many synthetic procedures have appeared in the literature for the synthesis of 2-amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile; these generally utilize the homogeneous, heterogeneous catalysts and acid/base mediated harsh reaction conditions. Therefore, a new synthetic route associated with environmentally friendly reaction condition is highly desirable. One of the most important progresses to combine economic aspects with the environmental concerns is the use of green protocol techniques which has provided simple and efficient synthetic methods of great promise. The elimination of toxic organic solvent in the reaction medium, shorter reaction time, straightforward work-up, and providing good to excellent yields with stoichiometric amounts of reactants are apparent advantages that distinguish the green chemical methods from others techniques such as microwave or ultrasound irradiation.[14,15] In the present work, we describe the synthesis of 2-amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile derivatives *via* multi-component domino reaction in aqueous medium using aromatic aldehyde, resorcinol and malononitrile.

RESULTS AND DISCUSSION

Initially, multicomponent domino reaction of malononitrile, aryl aldehyde and resorcinol was chosen as the model reaction. The effect of various reaction parameters such as the influence of solvent, formation of hydrogen bond and the effect of temperature were studied to optimize the reaction conditions (Table 1). It is important to note that K₂CO₃ and Na₂CO₃ with a molar ratio of 0.1 was found to be the catalyst for the three component reaction of malononitrile, aryl aldehyde and resorcinol affording a considerable yield of the desired product. Moreover in the absence of catalyst a significant product formation was observed under reflux condition (Table 1, entry 14).

The solvent temperature plays an important role in the reactivity (Table 1). We have investigated the effect of various protic, aprotic and non-polar solvents on the three component reaction of resorcinol, aryl aldehyde and malononitrile (Table 1, entry 1-14). In non-polar solvents such as 1,4-dioxane and Toluene, the yield of the reaction was found to be very low (10-20%) (Table 1, entry 5,6,11,12). Whereas in the case of polar aprotic solvents such as THF, acetonitrile, the yield of the reaction was found to be low (8-15%) (Table 1, entry 3,4,9,10). In the case of

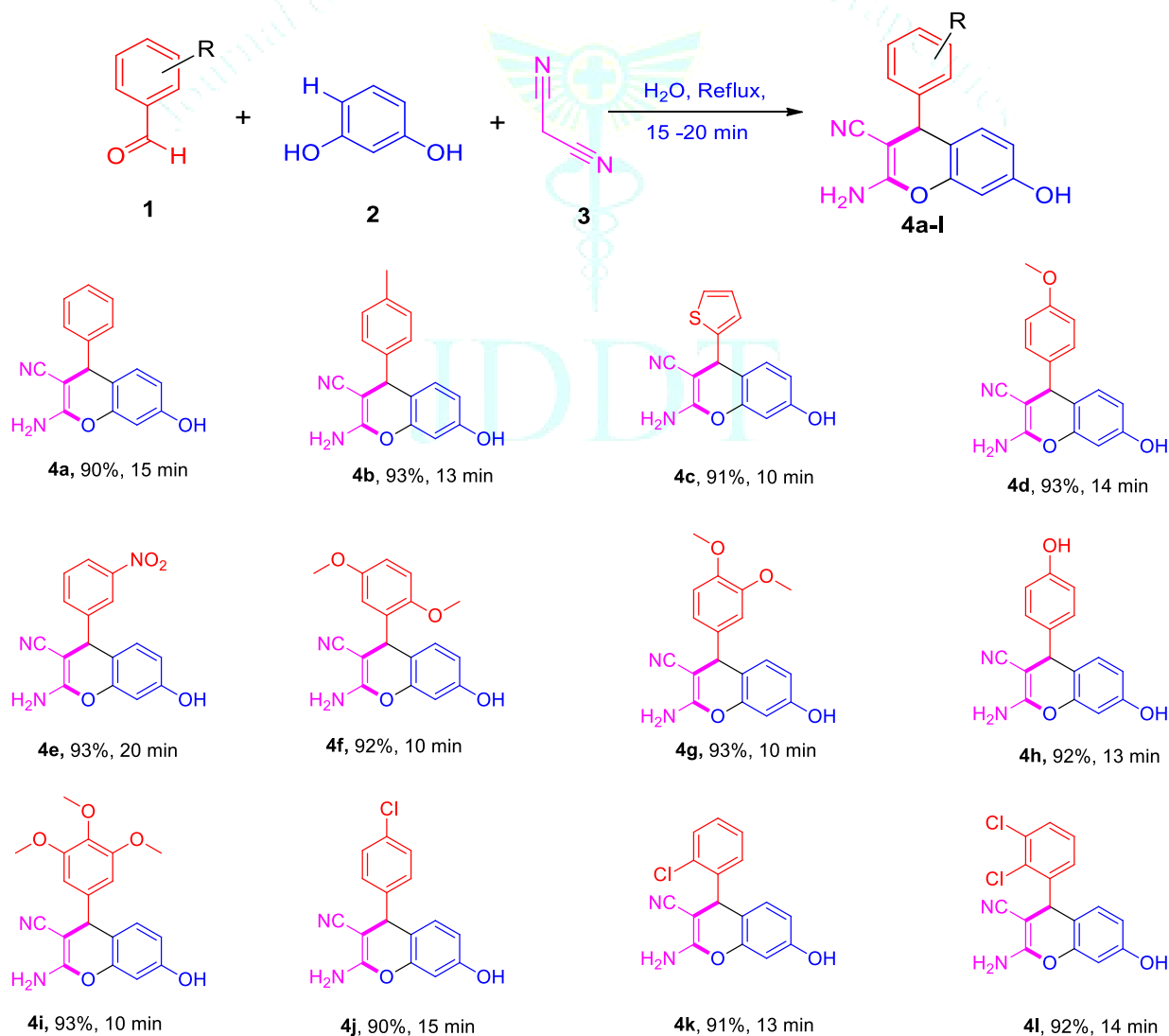
polar protic solvents such as ethanol and methanol (Table 1, entry 1,2,7,8), the yield of the desired product was considerable (50-65%). Further increase in the reaction temperature to reflux makes the reaction almost quantitative (Table 1, entry 14). From Table 1, it is clear that water was the best choice as solvent.

We examined the substrate scope of substituted benzaldehydes (**1a-1l**) under optimized reaction condition for the synthesis of chromene derivatives (**4a-4l**). All the electron donating and electron withdrawing aldehydes are compatible with optimized reaction condition afforded the excellent yield 80-93%.

Table 1 Optimization of reaction conditions

Entry	base	solvent (1 equiv)	Temp (°C)	Time (min)	Yield 4a (%)
1	Na ₂ CO ₃	EtOH	60	30	50
2	"	MeOH	50	30	55
3	"	THF	50	30	10
4	"	Acetonitrile	60	30	8
5	"	Dioxane	60	30	15
6	"	Toluene	80	30	10
7	K ₂ CO ₃	EtOH	60	30	60
8	"	MeOH	50	30	65
9	"	THF	50	30	15
10	"	Acetonitrile	60	30	10
11	"	Dioxane	60	30	20
12	"	Toluene	80	30	12
13	-	H ₂ O	60	30	50
14	-	H ₂ O	reflux	15-20	80-93

Scheme 1 Synthesis of 2-amino-3-cyano-4*H*-chromenes derivatives (**4a-l**)



Single-crystal X-Ray study

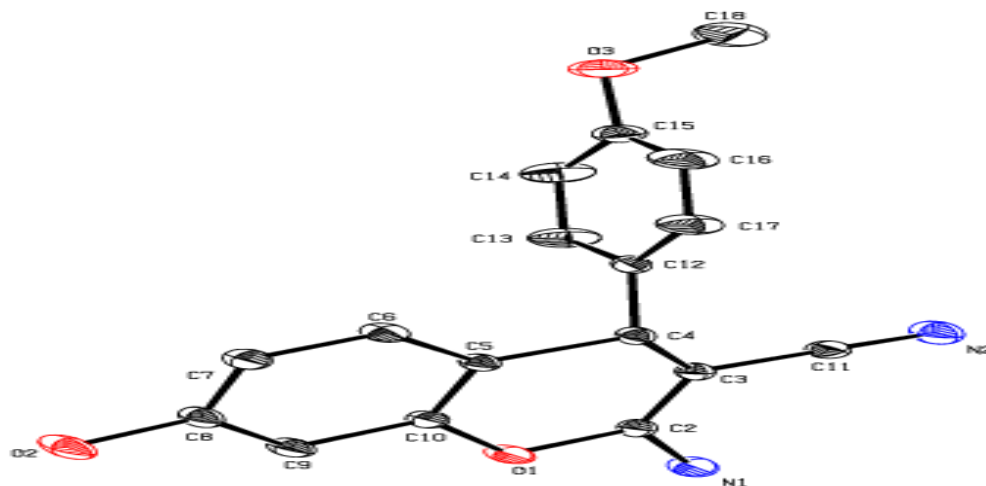
Refinement: Crystal data collection and structure refinement details are summarized in **Table 2**

Table 2. Crystallographic data for **4d** and **4k**

Compound	4d	4k
Identification code	mrb-4	mrb-12
Empirical formula	C ₁₇ H ₁₁ N ₂ O ₃	C ₁₆ H ₁₁ ClN ₂ O ₂
Formula weight	287.30	270.31
Temperature	293(2) K	296(2) K
Wavelength	0.71073 Å	0.71073 Å
Crystal system	Triclinic,	Monoclinic,
Space group	P1	P21/n
Unit cell dimensions	a = 6.2316(3) Å α = 116.255(2)° b = 11.0207(6) Å β = 90.099(2)° c = 11.8732(6) Å γ = 96.165(2)°	a = 6.6658(3) Å α = 90° b = 30.1600(16) Å β = 106.088(2)° c = 7.2193(4) Å γ = 90°
Volume	725.95(6) Å ³	1394.53(12) Å ³
Z, Density (calculated)	2, 1.314 Mg/m ³	4, 1.287 Mg/m ³
Absorption coefficient	0.086 mm ⁻¹	0.078 mm ⁻¹
F(000)	298	568
Crystal size	0.20 x 0.22 x 0.20 mm	0.15 x 0.10 x 0.10 mm
Theta range for data collection	3.72 to 36.41°	1.35 to 26.70°
Index ranges	-10 ≤ h ≤ 10, -18 ≤ k ≤ 18, -19 ≤ l ≤ 19	-6 ≤ h ≤ 8, -38 ≤ k ≤ 38, -9 ≤ l ≤ 8
Reflections collected	31554 / 6513 [R(int) = 0.0402]	21899 / 2942 [R(int) = 0.0335]
Completeness to theta =		99.70%, 25.000°
Refinement method	91.8 %, 24.998°	Full-matrix least-squares on F ²
Data / restraints / parameters	Full-matrix least-squares on F ²	2942 / 0 / 191
Goodness-of-fit on F ²		1.111
Final R indices [I > 2σ(I)]	6513 / 2 / 209	R1 = 0.0407, wR2 = 0.1070
R indices (all data)	1.072	R1 = 0.0684, wR2 = 0.1384
Largest diff. peak and hole		0.319 and -0.210 e. Å ⁻³
	R1 = 0.1496, wR2 = 0.3302 R1 = 0.1990, wR2 = 0.3606 1.069 and -0.760 e. Å ⁻³	

The X-ray diffraction analysis reveals that the benzopyran ring of the compound **4d**, C₁₇H₁₁N₂O₃, is planar [maximum deviation = 0.080 (2) Å] and the methoxyphenyl ring is also in planar conformation. The benzopyran derivative is almost perpendicular to the methoxyphenyl ring [dihedral angle = 88.75 (5)°]. The *ORTEP* plot of the molecule is shown in Fig.2. The methoxyphenyl substituted benzopyran compound crystallise in triclinic P1 space group. In the structure, the benzopyran and methoxyphenyl rings are planar. The benzopyran ring makes a dihedral angle of

90.857 (5)° with the methoxyphenyl ring and confirms the fact that the two moieties are in axial orientation. The orientation of the benzopyran and methoxyphenyl rings also confirmed from the torsion angle values of [C3—C4—C12—C13=] 75.6 (2)° & [C3—C4—C12—C17=] -105.3 (2)°, respectively. In the benzopyran moiety, the attached carbonitrile, amino and hydroxy groups lie in a same plane, with the maximum deviation of atom N2[-0.055 (2) Å]. The sum of the bond angles around atom N1 of the pyran ring is in accordance with sp² hybridization state[360°]

Figure 2: ORTEP diagram of **4d**

The benzopyran ring of the compound **4k**, $C_{16}H_{11}N_2O_2Cl$, is planar [maximum deviation = 0.079 (2) Å] and the chlorophenyl ring is also in planar conformation. The benzopyran derivative is almost perpendicular to the chlorophenyl ring [dihedral angle = 86.85 (6)°]. The ORTEP plot of the molecule is shown in Fig.3. The chlorophenyl substituted benzopyran compound crystallise in monoclinic P2 1/c space group. In the structure, the benzopyran and chlorophenyl rings are planar. The benzopyran ring makes a dihedral angle of 86.85 (6)° with the chlorophenyl ring and confirms the fact that the two moieties are in axial

orientation. The chlorophenyl moiety is also planar with the maximum deviation noted for atom CL12 as -0.040 (1) Å. The orientation of the benzopyran and chlorophenyl rings also confirmed from the torsion angle values of [C3—C4—C11—C12=] 76.5 (2)° & [C3—C4—C11—C16=] -100.4 (2)°, respectively. In the benzopyran moiety, the attached carbonitrile, amino and hydroxy groups lie in a same plane, with the maximum deviation of atom N2[-0.053 (2) Å]. The sum of the bond angles around atom N1 of the pyran ring is in accordance with sp^2 hybridization state [360°].

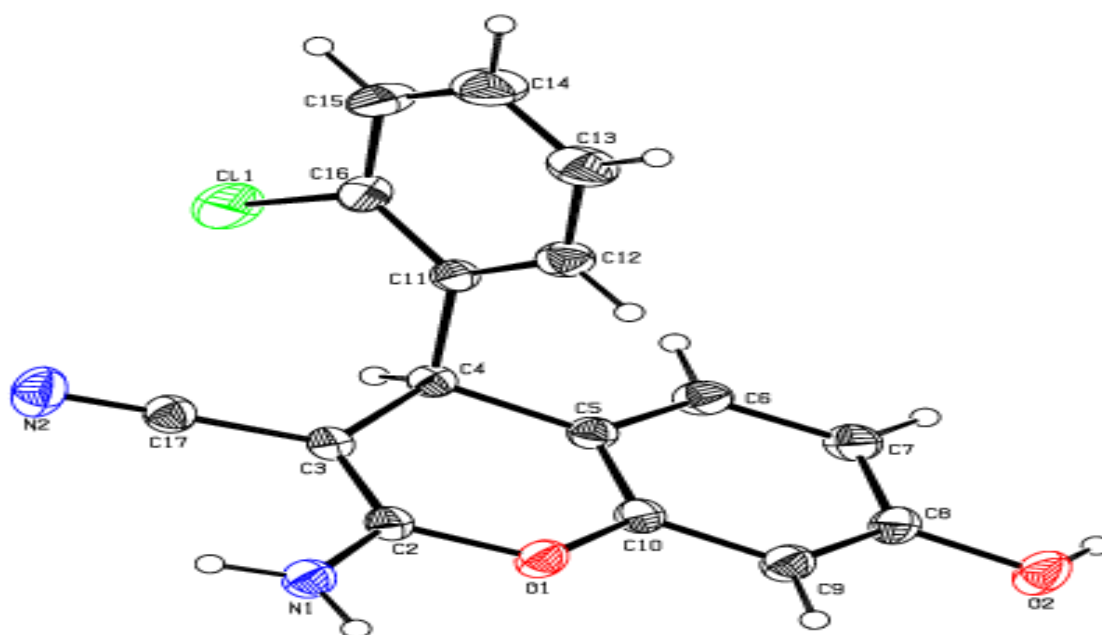


Figure 3: ORTEP diagram of **4k**

Experimental

All the chemicals used were purchased from Merck AnalaR grade and purified wherever necessary using the standard purification method. The purity of compounds were checked by TLC using silica gel-G plate and visualized by iodine vapours. The melting points were recorded in open capillary tube and uncorrected. The FT-IR spectra were recorded in SHIMADZU FT-IR Affinity-I spectrometer using KBr pellets and Perkinealmer. The 1H -NMR and ^{13}C -NMR spectra were obtained in DMSO- d_6 on BRUKER 300 MHz and 500MHz instrument with TMS as an internal standard and the chemical shift values are presented in ppm. The mass spectra were taken on SHIMADZU GC-MS QP 2010 spectrometer operating at an ionization potential of 70eV.

General experimental procedure for the Synthesis of 2-amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile

To a stirred solution of substituted benzaldehyde (0.05 mol) in water was added resorcinol (0.05 mol) and malononitrile (0.05 mol) at room temperature and refluxed for 15 - 20 minutes. The progress of the reaction was monitored by thin layer chromatography using silica gel-G plates. The reaction mixture was cooled and allowed to 30 minutes. The precipitated solid was filtered at suction pump. The crude solid obtained was recrystallized by methanol.

2-Amino-7-hydroxy-4-phenyl-4H-chromene-3-carbonitrile **4a**

IR: (KBr cm^{-1}) 3425 (OH), 3332, 3219 (NH_2), 2193(CN), 1651 (C=C Vinyl nitrile) 1587 (C=C Aromatic), 1H NMR (300 MHz DMSO - d_6): δ_H 4.63 (s, 1H), 6.43 (d, $J=2.4$, 1H), 6.48-6.52 (m, 1H) 6.81 (d, $J=8.7$, 1H), 6.89 (s, 2H) 7.16-7.22(m, 3H), 7.29 (t, $J=6.9$, 2H), 9.74 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6): δ_C 56.22, 102.15, 112.36, 113.71, 120.68, 126.61, 127.35, 128.56, 129.90, 146.35, 148.82, 157.06, 161.23.

2-Amino-7-hydroxy-4-(p-tolyl)-4H-chromene-3-carbonitrile **4b**

IR: (KBr cm^{-1}) 3410(OH), 3340, 3230 (NH_2), 2181(CN), 1641 (C=C Vinyl nitrile) 1587 (C=C Aromatic), 1H NMR (300 MHz): δ_H 2.24 (s, 3H), 4.58 (s, 1H), 6.44 (d, $J=2.1$, 1H), 6.48-6.52 (m, 1H), 6.78(d, $J=8.4$, 1H), 6.86 (s, 2H), 7.04-7.12 (m, 4H), 9.72 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6): δ_C 20.55, 56.39, 102.12, 112.31,113.87,120.70, 127.28, 129.10, 135.68, 143.40,148.78, 156.99, 160.14.

2-Amino-7-hydroxy-4-(thiophen-2-yl)-4H-chromene-3-carbonitrile **4c**

IR: (KBr cm^{-1}) 3421(OH), 3332, 3219 (NH_2), 2193(CN), 1654 (C=C Vinyl nitrile) 1589 (C=C Aromatic), 1H NMR (300 MHz DMSO - d_6): δ_H 4.9 (s, 1H), 6.40 (d, $J=2.4$, 1H), 6.52-6.56 (m, 1H), 6.91-6.94 (m, 1H), 6.97 (t, $J=3.6$, 2H), 6.99 (s, 2H), 7.34-

7.36 (m, 1H), 9.77 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 56.39, 102.15, 112.37, 113.49, 120.50, 124.00, 125.02, 126.72, 129.85, 148.51, 151.48, 157.30, 160.28.

2-Amino-7-hydroxy-4-(4-methoxyphenyl)-4H-chromene-3-carbonitrile 4d

IR: (KBr cm^{-1}) 3415(OH), 3334, 3221 (NH_2), 2187(CN), 1655 (C=C Vinyl nitrile) 1587 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 3.71 (s, 3H), 4.58 (s, 1H), 6.42 (d, $J=2.1$, 1H), 6.48-6.52 (m, 1H), 6.85-7.13 (m, 6H), 9.71 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 54.96, 56.56, 102.09, 112.30, 113.88, 114.03, 120.72, 128.41, 129.91, 130.13, 138.46, 148.73, 156.94, 157.93, 160.05.

2-Amino-7-hydroxy-4-(3-nitrophenyl)-4H-chromene-3-carbonitrile 4e

IR: (KBr cm^{-1}) 3450(OH), 3334, 3221 (NH_2), 2190(CN), 1658 (C=C Vinyl nitrile) 1587 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 4.96 (s, 1H), 6.52 (d, $J=2.4$ Hz, 1H), 5.5-5.58 (m, 1H), 6.87 (d, $J=8.4$ Hz, 1H), 7.11 (s, 2H), 7.63-7.72 (m, 2H), 8.08-8.14 (m, 2H), 9.87 (s, 1H); ^{13}C NMR (300 MHz DMSO- d_6); δ_c 55.31, 112.49, 112.66, 120.40, 121.74, 121.82, 129.96, 130.27, 134.27, 147.89, 148.53, 148.88.

2-Amino-4-(2,5-dimethoxyphenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4f

IR: (KBr cm^{-1}) 3406(OH), 3338, 3223 (NH_2), 2187(CN), 1657 (C=C Vinyl nitrile) 1503 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 3.63 (s, 3H), 3.71 (s, 3H), 4.93 (s, 3H), 6.39 (d, $J=2.0$ Hz, 1H), 6.46-6.48 (m, 1H), 6.53 (d, $J=3.0$ Hz, 1H), 6.73-6.76 (m, 1H), 6.82 (s, 2H), 6.84 (d, $J=8.5$ Hz, 1H), 6.90 (d, $J=9.0$ Hz, 1H), 9.67 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 55.56, 55.66, 56.71, 102.56, 111.98, 112.65, 113.26, 114.25, 115.54, 121.24, 129.69, 135.78, 149.57, 151.06, 153.75, 157.39, 161.41.

2-Amino-4-(3,4-dimethoxyphenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4g

IR: (KBr cm^{-1}) 3435(OH), 3332, 3233 (NH_2), 3070(CH-Ar), 2135(CH-Aliphatic), 2194 (CN), 1643 (C=C Vinyl nitrile) 1571 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 3.84 (s, 3H), 3.98 (s, 3H), 4.59 (s, 1H), 6.42 (d, $J=2.4$ Hz, 1H), 6.50-6.52 (m, 1H), 6.67-6.70 (m, 1H), 6.80 (d, $J=1.8$ Hz, 1H), 6.83 (s, 2H), 6.86-6.90 (m, 2H), 9.71 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 54.66, 55.40, 56.38, 102.08, 111.18, 112.27, 113.91, 115.80, 121.46, 125.97, 129.88, 138.84, 147.53, 148.23, 150.30, 156.93, 160.14, 161.24, 165.85.

2-Amino-7-hydroxy-4-(4-hydroxyphenyl)-4H-chromene-3-carbonitrile 4h

IR: (KBr cm^{-1}) 3481(OH), 3354, 3254 (NH_2), 2193 (CN), 1652 (C=C Vinyl nitrile) 1588 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 4.49 (s, 1H), 3.98 (s, 3H), 4.49 (s, 1H), 6.39 (s, 1H), 6.47 (d, $J=8.5$ Hz, 1H), 6.67 (d, $J=8$ Hz, 2H), 6.67 (s, 1H),

6.78 (s, 2H), 6.95 (d, $J=8.5$ Hz, 2H), 9.28 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 57.23, 102.53, 112.73, 114.78, 115.68, 121.24, 128.83, 130.36, 137.27, 149.22, 156.50, 157.33, 160.51.

2-Amino-7-hydroxy-4-(3,4,5-trimethoxyphenyl)-4H-chromene-3-carbonitrile 4i

IR: (KBr cm^{-1}) 3410(OH), 3333, 3222 (NH_2), 3073(CH-Ar), 2945(CH-Aliphatic), 2194 (CN), 1658 (C=C Vinyl nitrile) 1592 (C=C Aromatic), ^1H NMR (300 MHz DMSO - d_6): δ_H 3.62 (s, 3H), 3.71 (s, 6H), 4.58 (s, 1H), 6.39 (s, 1H), 6.47-6.50 (m, 3H), 6.85 (s, 2H), 6.85 (d, $J=8.5$ Hz, 1H), 9.69 (s, 1H), ^{13}C NMR (300 MHz DMSO- d_6); δ_c 56.25, 56.37, 60.37, 102.60, 105.01, 112.79, 113.97, 121.18, 130.33, 136.61, 142.44, 149.12, 157.51, 160.80.

2-Amino-4-(2,3-dichlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4j

IR: (KBr cm^{-1}) 3406 (OH), 3342, 3266 (NH_2), 3035 (CH-Ar), 2928 (CH-Aliphatic), 2195 (CN), 1643 (C=C) 1461 (C=C), 1154 (C-C), 1109 (C-O-C), 1342 (C-N), ^1H NMR (500 MHz DMSO - d_6): δ_H 5.21 (s, 1H), 6.41 (d, $J=20.5$ Hz, 1H), 6.42-6.49 (m, 1H), 6.72 (d, $J=8.5$ Hz, 1H), 6.99 (s, 2H), 7.17 (d, $J=7.5$ Hz, 1H), 7.31-7.34 (m, 1H), 7.51 (d, $J=8$ Hz, 1H), 9.80 (s, 1H), ^{13}C NMR (500 MHz DMSO d_6), δ_c 54, 102.75, 112.36, 113.05, 120.67, 129.09, 129.62, 129.67, 130.03, 130.45, 149.50, 157.96, 161.00.

2-Amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4k

IR: (KBr cm^{-1}) 3464 (OH), 3340, 3243 (NH_2), 3063 (CH-Ar), 2928 (CH-Aliphatic), 2192 (CN), 1639 (C=C) 1458 (C=C), 1155 (C-C), 1110 (C-O-C), 1344 (C-N), ^1H NMR (500 MHz DMSO - d_6): δ_H 6.41 (d, 1H, $J=2$ Hz, H-Ar), 6.48-6.50 (dd, 1H, $J=2$, 6.5 Hz, H-Ar), 6.77 (d, 1H, $J=8.5$ Hz, H-Ar), 6.91 (s, 2H, NH_2), 7.18 (d, 2H, $J=8.5$ Hz, H-Ar), 7.35 (d, 2H, $J=8.5$ Hz, H-Ar), 9.72 (s, 1H, OH), ^{13}C NMR (500 MHz DMSO d_6), δ_c 56.35, 102.71, 112.95, 113.67, 120.97, 129.03, 129.75, 130.36, 131.71, 145.76, 149.30, 157.69, 160.72.

2-Amino-4-(2-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4l

IR: (KBr cm^{-1}) 3421 (OH), 3337, 3220 (NH_2), 3070 (CH-Ar), 2922 (CH-Aliphatic), 2193 (CN), 1653 (C=C) 1461 (C=C), 1110 (C-O-C), 1301 (C-N), ^1H NMR (500 MHz DMSO - d_6): δ_H 6.42 (d, 1H, $J=1.5$ Hz, H-Ar), 6.47-6.49 (dd, 1H, $J=2.5$, 6 Hz, H-Ar), 6.73 (d, 1H, $J=8.5$ Hz, H-Ar), 6.92 (s, 2H, NH_2), 7.179-7.19 (t, 1H, $J=7$ Hz, H-Ar), 7.21-7.24 (q, 1H, $J=1.5$, 6 Hz, H-Ar), 7.28-7.31 (t, 1H, $J=7.5$ Hz, Ar-CH), 7.40 (d, 1H, 7.45 Hz, Ar-H), 9.74 (s, 1H, OH), ^{13}C NMR (500 MHz DMSO d_6), δ_c 55.37, 102.72, 112.96, 112.97, 120.76, 128.28, 129.00, 129.71, 130.18, 131.24, 132.30, 143.31, 149.48, 157.80, 160.98.

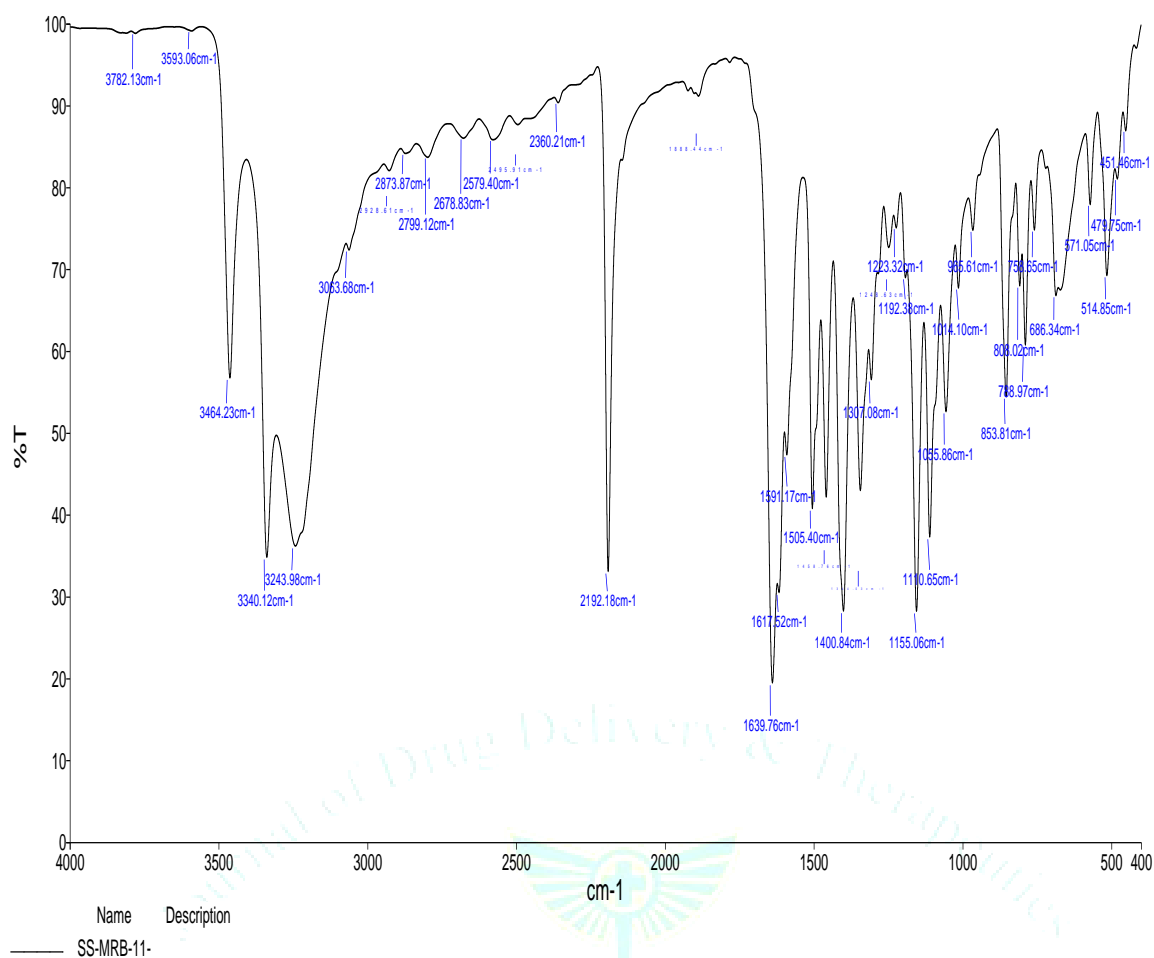


Figure 4: IR-Spectrum of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4k

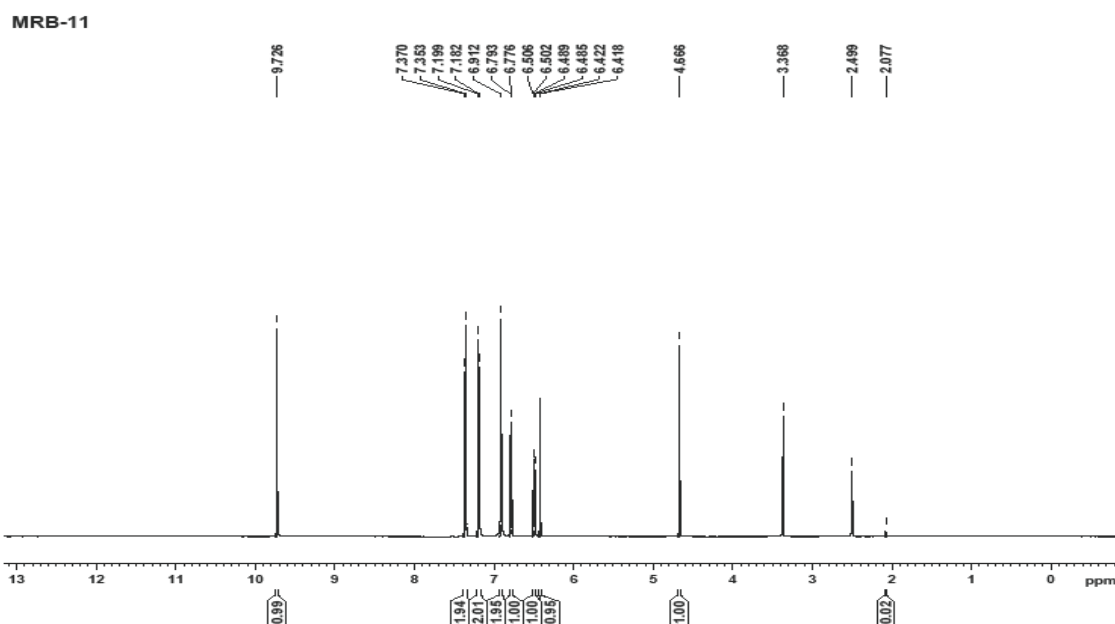


Figure 5: ¹H NMR-Spectrum of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4H-chromene-3-carbonitrile 4k

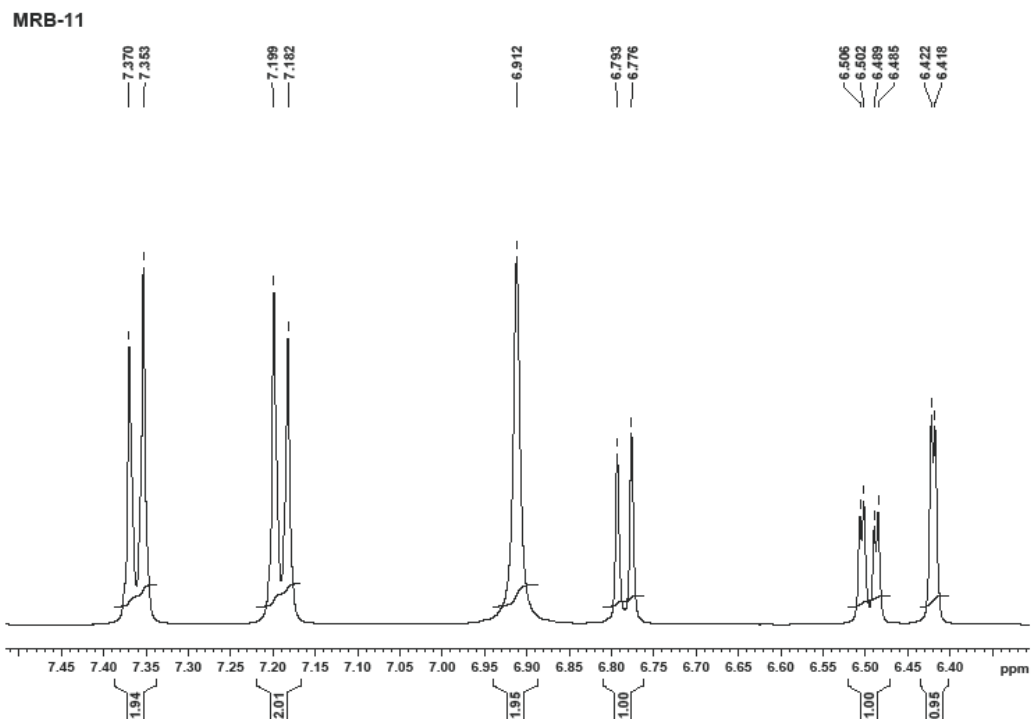


Figure 5a: ^1H NMR-Spectrum of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4*H*-chromene-3-carbonitrile 4k

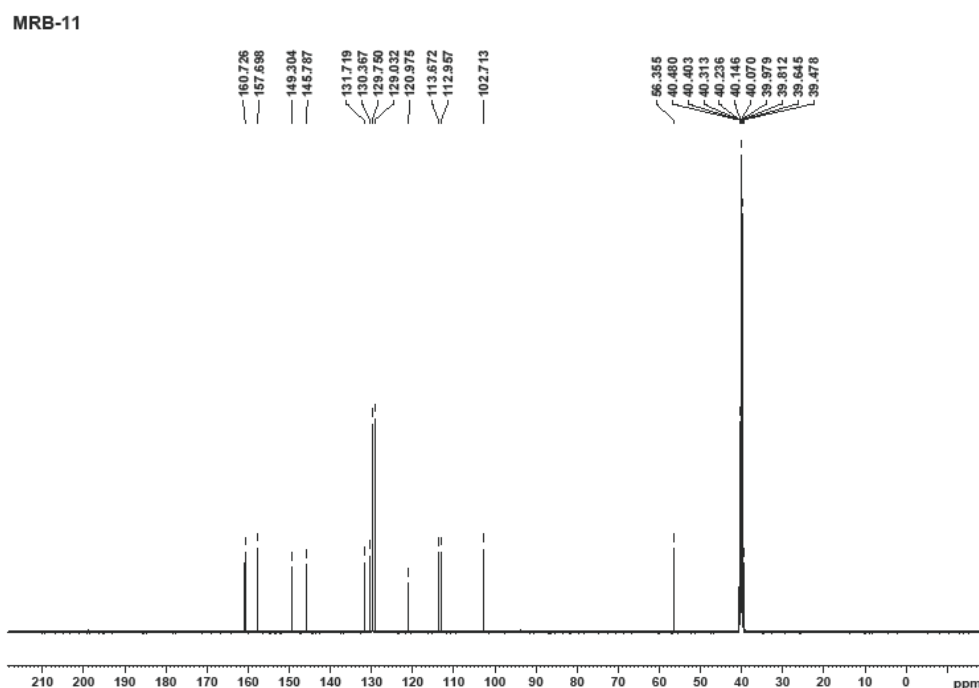


Figure 6: ^{13}C NMR-Spectrum of 2-amino-4-(4-chlorophenyl)-7-hydroxy-4*H*-chromene-3-carbonitrile 4k

CONCLUSION

In this work, cascade reaction has been carried out for the synthesis of 2-amino-3-cyanobenzopyrans 4k from malononitrile, aryl aldehyde and resorcinol in methanol, ethanol, acetone and water solvents using K_2CO_3 or Na_2CO_3

as base. Nevertheless, the use of water was successful for this reaction. Under the found conditions, the high yield for the products were achieved at short reaction time in aqueous medium. The structure of the products were confirmed by IR, ^1H , ^{13}C NMR spectra and X-ray diffraction study.

REFERENCES

- [1] Kathrotiya HG, Patel MP, Microwave-assisted synthesis of 30-indolyl substituted 4H-chromenes catalyzed by DMAP and their antimicrobial activity, *Medicinal Chemistry Research*, 2012; 21:3406–3416.
- [2] Thomas N, Zachariah SM, In Silico drug design and analysis of 4-Phenyl-4H-chromene derivatives as anticancer and anti-inflammatory agents, *International Journal of Pharmaceutical Sciences Review and Research*, 2013; 22:50–54.
- [3] Magedov IV, Manpadi M, Evdokimov NM, Elias EM, Rozhkova E, Ogasawara MA, Bettale JD, Przheval'skii NM, Rogelj S, Kornienko A, Antiproliferative and apoptosis inducing properties of pyrano[3,2-c]pyridones accessible by a one-step multicomponent synthesis, *Bioorganic & Medicinal Chemistry Letters*, 2007; 17:3872–3876.
- [4] Singh OM, Devi NS, Thokchom DS, Sharma GJ, Novel 3-alkanoyl/aroyle/heteroaryl-2H-chromene-2-thiones: synthesis and evaluation of their antioxidant activities, *European Journal of Medicinal Chemistry*, 2010; 45:2250–2257.
- [5] Bhat M, Siddiqui N, Khan S, Synthesis of novel 3-(4-acetyl-5H/methyl-5-substituted phenyl-4,5-dihydro-1,3,4-oxadiazol-2-yl)-2H-chromen-2-ones as potential anticonvulsant agents, *Acta poloniae pharmaceutica*, 2008; 65:235–239.
- [6] Nimesh RK, Dhaval DH, Prashant TM, Saurabh KP, Synthesis and evaluation of in vitro antitubercular activity and antimicrobial activity of some novel 4H-chromeno[2,3-d]pyrimidine via 2-amino-4-phenyl-4H-chromene-3-carbonitriles, *Medicinal Chemistry Research*, 2011; 20:854–864.
- [7] Nareshkumar J, Jiayi X, Ramesh MK, Fuyong D, Guo JZ, Emmanuel P, Identification and structure–activity relationships of chromene-derived selective estrogen receptor modulators for treatment of postmenopausal symptoms, *Journal of Medicinal Chemistry*, 2009; 52: 7544–7569.
- [8] Cheng JF, Ishikawa A, Ono Y, Arrhenius T, Nadzan A, Novel chromene derivatives as TNF- α inhibitors, *Bioorganic & Medicinal Chemistry Letters*, 2003; 13:3647–3650.
- [9] Birch KA, Heath WF, Hermeling RN, Johnston CM, Stramm L, Dell C, Smith C, Williamson JR, Reifel-Miller A, LY290181, an inhibitor of diabetes induced vascular dysfunction, blocks protein kinase C-stimulated transcriptional activation through inhibition of transcription factor binding to a phorbol response element, *Diabetes*, 1996; 45:642–650.
- [10] Joulain D, Tabacchi R, Two volatile beta-chromenes from *Wisteria sinensis* flowers, *Phytochemistry*, 1994; 37:1769–1770.
- [11] Nolan KA, Zhao H, Faulder PF, Frenkel AD, Timson DJ, Siegel D, Ross D, Burke Jr T R, Stratford IJ, Bryce RA, Coumarin-based inhibitors of human NAD(P)H: quinone oxidoreductase-1. Identification, structure–activity, off-target effects and in vitro human pancreatic cancer toxicity, *Journal of Medicinal Chemistry*, 2007; 50:6316–6325.
- [12] Doshi JM, Tian D, Xing C, Structure– activity relationship studies of ethyl 2-amino-6-bromo-4-(1-cyano-2-ethoxy-2-oxoethyl)-4 H-chromene-3-carboxylate (HA 14-1), an antagonist for antiapoptotic Bcl-2 proteins to overcome drug resistance in cancer, *Journal of Medicinal Chemistry*, 2006; 49(26):7731–7739.
- [13] Kemnitzer W, Drewe J, Jiang S, Zhang H, Crogan-Grundy C, Labreque D, Bubenick M, Attardo G, Denis R, Lamothe S, Gourdeau H, Tseng B, Kasibhatla S, Cai SX, Discovery of 4-Aryl-4H-chromenes as a New Series of Apoptosis Inducers Using a Cell- and Caspase-Based High Throughput Screening Assay. 4. Structure–Activity Relationships of N-Alkyl Substituted Pyrrole Fused at the 7,8-Positions, *Journal of Medicinal Chemistry*, 2008; 51(3):417–423.
- [14] Stolle, T. Szuppa, S. E. S. Leonhardt and B. Ondruschka, Ball milling in organic synthesis: a. solutions and challenges, *Chemical Society of Review*, 2011; 40: 2317–2329; (b) G. W. Wang, Mechanochemistry of fullerenes and related materials, *Chemical Society of Review*, 2013; 42: 7668–7700; (c) R. B. Nasir-Baig and R. S. Varma, Stereo- and regio-selective one-pot synthesis of triazole-based unnatural amino acids and β -amino triazole *Journal of communication*, 2012;41: 1559 -1584.
- [15] J. G. Hernández and E. Juaristi, Asymmetric Aldol Reaction Organocatalyzed by (S)- Proline-Containing Dipeptides: Improved Stereoinduction under Solvent-Free Conditions *Journal of Organic Chemistry* .2011; 76: 5, 1464-1467; (b) T. Chatterjee, D. Saha and B. C. Ranu, Solvent-free transesterification in a ball-mill over alumina surface, *Tetrahedron Letters*; 2012: 53, 4142-4144; (c) M. Nüchter, B. Ondruschka, W. Bonrath and A. Gum, Microwave assisted synthesis – a critical technology overview , *Journal of Green Chemistry*, 2004;6:128-141. (d) J. Mokhtari, M. R. Naimi-Jamal, H. Hamzeali, M. G. Dekamin and G. Kaupp, Kneading ball-milling and stoichiometric melts for the quantitative derivatization of carbonyl compounds with gas-solid recovery, *sustainable chemistry*,2009;2: 248-254. (e) M. R. Naimi-Jamal, J. Mokhtari, M. G. Dekamin and G. Kaupp, Sodium Tetraalkoxyborates: Intermediates for the Quantitative Reduction of Aldehydes and Ketones to Alcohols through Ball Milling with NaBH_4 *European Journal of Organic Chemistry* .,2009, 3567-3572