4-Aryl-4*H*-Chromene-3-Carbonitrile Derivates: Synthesis and Preliminary Anti-Breast Cancer Studies

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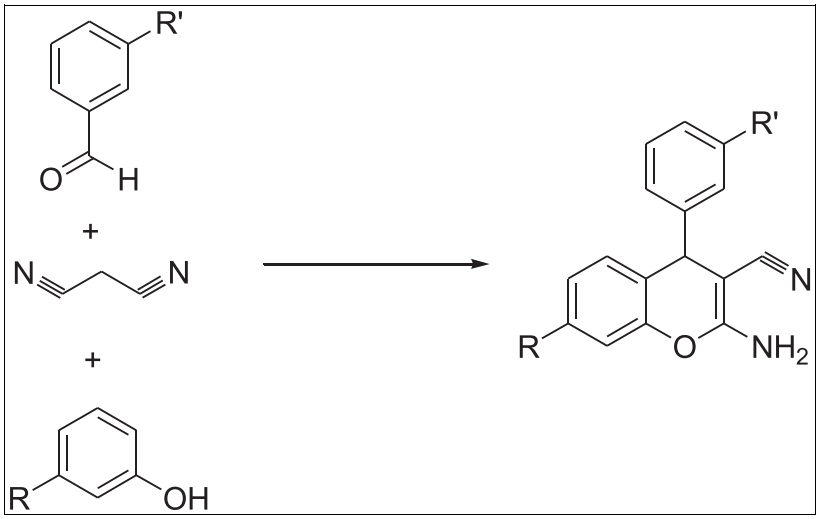


A series of new 4-aryl-4*H*-chromene-3-carbonitrile derivatives were obtained by one-pot synthesis using substituted benzaldehydes, malononitrile, and substituted phenols. All the synthesized compounds (**1a–e**) were screened *in vitro* for antioxidant and anticancer activities. Compounds **1c–e** showed significant antioxidant activity in nitric oxide free radical scavenging method while compounds **1c** and **1e** showed significant activity in hydrogen peroxide free radical scavenging method. The other compounds showed significant to moderate activities in both the methods in comparison with ascorbic acid and butylated hydroxytoluene as standards. Compounds **1c–e** exhibited good anticancer activity, using Michigan Cancer Foundation-7 (MCF-7) cell line, compared with those of other synthesized compounds.

INTRODUCTION

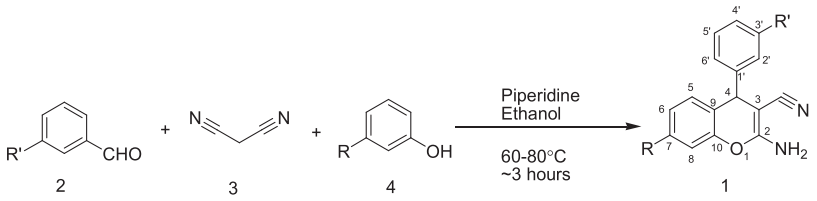
Chromene and its derivatives are widely present in plants/fruits that possess a broad range of biological activity [1,2] and identified as one of the potential anticancer agent [3,4]. Among different types of chromene systems, 2-amino-4*H*-chromenes are of particular utility as they belongs to privileged medicinal scaffolds serving for generation of small-molecule ligands with highly pronounced anticoagulant, diuretic, spasmolytic, antianaphylactic, antimicrobial, antiviral, mutagenicity, and antiproliferative activities [5–11]. Several procedures for the synthesis of 2-amino-4*H*-pyrans have been described [12–16]. Many catalysts such as piperidine [17], morpholine [18], cetyltrimethylammonium chloride [19], triethylbenzylammonium chloride [20] and alumina [21] have been used for this reaction, but all these methods require a long duration and suffer from lack of general applicability. A multi-component reaction finds special place in synthetic strategy for rapid and efficient library generation. This article describes a simple and efficient one-pot synthesis of chromene derivatives (Scheme 1) followed by the results of preliminary *in vitro* screening for anticancer activities.

CHEMISTRY

In a previous study [2], it was shown that *in silico* target profiling was able to identify the targets at which a chemical library of biological molecules should be tested, leading to the identification of new molecules for tubulin, estrogen receptor, and Tumor necrosis factors (TNF)-α receptor containing a chromene scaffold. The synthetic pathway to obtain compounds namely 4-Aryl-4*H*-chromene-3-carbonitrile derivates **1** is outlined in Scheme 1.

One-pot synthesis of 4-aryl-4*H*-chromenes **1a–e** was performed by using malononitrile **3**, substituted benzaldehydes **2**, and substituted phenols **4**. The reaction mixture was heated at 60–80°C for 3 h in ethanol using catalytic quantities

Scheme 1. Synthesis of compounds **1a–e.**



of piperidine. The completion of reaction was monitored using thin-layer chromatography (TLC); precipitate formed was filtered and washed with cold ethanol–water mixture. The crude product was crystallized from ethanol to get corresponding chromene analogue in good yield (Table 1). The compounds **1a–e** were characterized by ^{1}H-NMR, ^{13}C-NMR, IR, and mass spectra, and the data were found to be in good agreement with the proposed structures. All the phenols employed in the present work are 3-substituted which could in principle cyclise through position 2 or 6. The regioselective cyclisation at position 6 is most likely due to the hindrance at position 2 of the 3-substituted phenols.

Table 1

One-pot synthesis of malonitrile, substituted benzaldehyde, and substituted phenol for the preparation of 4-Aryl-4*H*-chromene-3-carbonitrile derivatives **1**[a].

Product **1**[b]	*R* and *R′*	Yield[c] (%)	Mp (°C)
a	OH and Br	85	108–110
b	OH and F	80	176–178
c	OCH_3 and Br	70	115–116
d	OCH_3 and Cl	70	162–164
e	OCH_3 and F	73	134–136

[a]All reactions were run with corresponding substituted phenol, aldehyde, and malononitrile in ethanolic medium
[b]As per Scheme 1.
[c]The yield of the reaction is based on substituted phenol.

The plausible mechanism of one-pot synthesis involves three steps, namely Knoevenagel condensation, Michael addition followed by intramolecular cyclisation of the Michael adduct, as shown in Scheme 2.

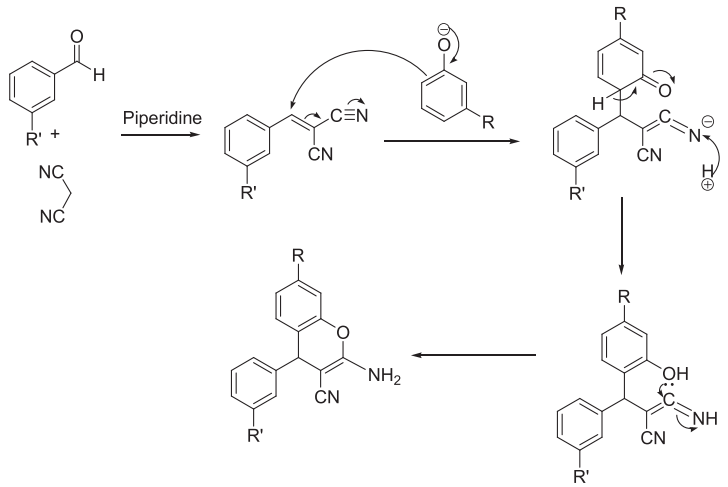
RESULTS AND DISCUSSION

Biological study. ***Antioxidant studies.*** The main feature of an antioxidant was its ability to trap free radicals. These free radicals may oxidize nucleic acids, proteins, lipids, or DNA and can initiate degenerative disease. Antioxidant compounds scavenge free radicals such as peroxide, hydroperoxide, or lipid peroxyl and thus inhibit the oxidative mechanisms. In this study, *in vitro* antioxidant activity of all the synthesized compounds was assessed by nitric oxide and hydrogen peroxide free radical scavenging methods using ascorbic acid and butylated hydroxytoluene as references.

The nitric oxide scavenging method is based on the generation of nitric oxide (NO) from sodium nitroprusside. The NO generated reacts with oxygen to produce nitrite ions, which are frequently inhibited by antioxidants or nitric oxide scavengers. The quantity of NO generated will be less when sodium nitroprusside is incubated in the presence of antioxidants such as chromenes, which are used in this study. The excess NO is estimated through Griess reagent.

Excess concentration of nitric oxide implicates cytotoxic effects observed in various disorders such as cancer,

Scheme 2. Plausible mechanism of the reaction.



Alzheimer's, arthritis, and tissue damage. The nitric oxide free radical can react with superoxide to form the peroxynitrite anion, which is a potential oxidant that can decompose to produce hydroxyl radicals and nitric oxide radicals.

The results presented in Table 2 reveal that 4-aryl-4*H*-chromene-3-carbonitrile analogues exhibit effective antioxidant activity compared with references. Out of these compounds, **1c–e** were found to be potent than other molecules. The IC_{50} values of **1e** (IC_{50} 30.0 μg/mL) exhibited higher nitric oxide scavenging activity when compared with other molecules and standard ascorbic acid (IC_{50} = 20.6 μg/mL). The compounds **1a** and **1b** show moderate to good inhibition activity compared with the standard.

Scavenging of hydrogen peroxide by compounds **1a–e** may be attributed to their radical scavenging activity, by which they can donate electrons to H_2O_2, thus reducing it to water. The analysis revealed that all the compounds exhibited significant antioxidant properties (Table 3). From the results of hydrogen peroxide scavenging activity, it is observed that maximum scavenging activity was exhibited by **1c** (IC_{50} = 26.8 μg/mL) and **1e** (IC_{50} = 24.2 μg/mL) when compared with standard ascorbic acid (IC_{50} = 24.8 μg/mL). Hydrogen peroxide is highly important because of its ability to penetrate biological membranes and may oxidize a number of compounds. Hydrogen peroxide molecule gets converted into singlet oxygen (O_2) and hydroxy radicals, which is a powerful oxidizing agent. Although H_2O_2 itself is not very reactive, it can sometimes be toxic to a cell because it may give rise to hydroxyl radicals in the cells.

Cytotoxicity studies [22]. The *in vitro* anticancer screening of all the prepared compounds was carried out by 3-[4,5-dimethylthiazol-2-yl]-2,5 diphenyl tetrazolium bromide (MTT) assay in MCF-7 cell lines. The MTT assay is based on the hypothesis that living cells reduce tetrazolium due to the presence of mitochondrial Succinate dehydrogenase (SDH), which is absent in the metabolically inactive dead cells. This assay therefore depends on both the number of viable cells present and mitochondrial activity per cell.

Compounds **1a–e** were evaluated for their *in vitro* cytotoxicity toward human estrogen receptor-positive breast adenocarcinoma MCF-7 cell line. Cytotoxic activity was evaluated by using the standard MTT assay, after exposure of cells to the tested compounds for 72 h (Table 4). Concentration of test drug needed to inhibit cell growth of 50% (CTC_{50}) is obtained from the dose–response curves for MCF-7 cell line. All the compounds were screened for their cytotoxicity at different concentrations of 1000, 500, 250, 125, and 62.5 μg/mL. It is evident from results that all the tested compounds displayed potent to moderate growth inhibitory activity against MCF-7 cell line. The

Table 2

Nitric oxide scavenging activity.

	Percentage inhibition ± SEM (μg/mL)				
Compound code	10	20	30	40	50
1a	29.60 ± 0.1822	42.06 ± 0.0431	53.47 ± 0.1288	66.61 ± 0.1111	75.37 ± 0.1866
1b	22.80 ± 0.0897	35.56 ± 0.0777	48.30 ± 0.2364	59.36 ± 0.1026	68.25 ± 0.1680
1c	30.30 ± 0.2000	46.18 ± 0.1400	59.41 ± 0.1324	67.42 ± 0.0637	76.67 ± 0.0944
1d	28.51 ± 0.1468	45.41 ± 0.1415	54.28 ± 0.1888	68.63 ± 0.1415	74.68 ± 0.1095
1e	25.45 ± 0.0775	39.38 ± 0.1035	48.61 ± 0.1142	61.57 ± 0.1111	70.65 ± 0.1184
BHT	31.75 ± 0.1444	38.55 ± 0.0888	49.65 ± 0.0466	58.40 ± 0.4800	66.28 ± 0.0644
Ascorbic acid	34.77 ± 0.0533	50.53 ± 0.0555	68.47 ± 0.0666	77.82 ± 0.0466	89.55 ± 0.1755

SEM, standard error of the mean; BHT, butylated hydroxytoluene.

Table 3

Hydrogen peroxide scavenging activity.

	Percentage inhibition ± SEM (μg/mL)				
Compound code	10	20	30	40	50
1a	29.35 ± 0.1900	44.55 ± 0.0497	56.37 ± 0.1706	68.35 ± 0.1417	76.46 ± 0.1835
1b	23.64 ± 0.0622	37.26 ± 0.0755	49.14 ± 0.0586	60.83 ± 0.0533	70.84 ± 0.0444
1c	26.44 ± 0.0764	41.75 ± 0.0422	53.61 ± 0.2142	66.45 ± 0.0564	74.55 ± 0.0471
1d	28.21 ± 0.0464	43.65 ± 0.0484	54.57 ± 0.0846	67.33 ± 0.0555	75.47 ± 0.0826
1e	27.26 ± 0.0511	46.46 ± 0.0820	55.45 ± 0.0888	63.69 ± 0.0697	74.83 ± 0.0833
BHT	29.85 ± 0.0822	37.86 ± 0.0533	48.44 ± 0.0768	59.35 ± 0.0888	68.14 ± 0.0806
Ascorbic acid	26.89 ± 0.0488	41.25 ± 0.0622	56.76 ± 0.2333	68.83 ± 0.0377	86.72 ± 0.0666

SEM, standard error of the mean; BHT, butylated hydroxytoluene.

Table 4

Percentage inhibition of the compounds on MCF-7 cell lines.

Compounds	Test concentrations (μg/mL)	Percentage cytotoxicity	CTC_{50} (μg/mL)
1a	1000	88.16 ± 0.3	
	500	86.44 ± 0.5	
	250	82.12 ± 0.6	62.67 ± 0.30
	125	74.96 ± 0.4	
	62.5	50.50 ± 0.3	
1b	1000	77.43 ± 0.3	
	500	75.12 ± 0.5	
	250	58.58 ± 0.4	118.00 ± 2.00
	125	52.99 ± 0.3	
	62.5	34.64 ± 0.6	
1c	1000	89.31 ± 0.2	
	500	87.02 ± 0.4	
	250	75.93 ± 0.3	<62.5
	125	73.50 ± 0.2	
	62.5	71.75 ± 0.3	
1d	1000	87.95 ± 0.2	
	500	79.36 ± 0.3	
	250	78.04 ± 0.4	<62.5
	125	73.61 ± 0.3	
	62.5	71.10 ± 0.3	
1e	1000	87.88 ± 0.4	
	500	85.91 ± 0.2	
	250	77.65 ± 0.5	<62.5
	125	75.54 ± 0.4	
	62.5	55.19 ± 0.5	

analogues **1c**, **1d**, and **1e** were found to be more potent, when compared with others, against MCF-7 cell lines with CTC_{50} less than 62.5 μg/mL.

The results highlighted that the presence of electron-donating methoxy group at position 7 increases the cytotoxic activity. Besides, presence of halogen at position 3′ imparted the cytotoxic effect in the compounds. Our findings are in agreement with other research groups who emphasized the importance of halogen substitution at 3′ position on chromene derivatives [23–25]. The compounds **1a** and **1b** have demonstrated anticancer activity with CTC_{50} values of 62.67 and 118.00 μg/mL, which are found to be less active than other compounds.

CONCLUSION

We described a convenient route to the synthesis of 4-aryl-4*H*-chromenes in good yields. From the biological screening, it was observed that the presence of electron-donating methoxy groups at position 7 and electronegative halogens at position 3′ of 4-aryl-4*H*-chromene moiety improves the antioxidant and anticancer activity of the compounds. Molecules **1c**, **1d**, and **1e** showed good antioxidant and anticancer activities compared with other compounds of the present study. Cytotoxic effects of these compounds indicate that they are good candidates for further pharmacological studies toward discovering effective chemotherapeutic agents for the treatment of human cancer diseases.

EXPERIMENTAL

Chemistry. ***General.*** All the chemicals used for the reactions were purchased from Sigma-Aldrich (Bangalore, India) or Loba Chemie Pvt Ltd. (Mumbai, India) unless otherwise indicated. All the reactions were performed under nitrogen/argon atmosphere. The reactions were monitored by TLC, carried out on Silica gel G60 with detection by UV or staining in an iodine chamber. NMR (^1H and ^{13}C) spectra were recorded on a Bruker AXS (400 MHz) instrument. IR spectra were recorded on Shimadzu Fourier transform infrared spectrophotometer. Melting points were measured with Roy Capillary melting point apparatus using open capillary tubes and are uncorrected. Mass data were obtained by using Waters 2695–3100 LC/MS equipped with an electrospray ionization (ESI) source.

General procedure for the synthesis of compounds (1a–e). Two drops of piperidine were added to a mixture of substituted benzaldehyde (1 mmol), malononitrile (1 mmol), and substituted phenol (1 mmol) in ethanol (3 mL) at room temperature. The reaction mixture was heated to 60–80 °C and stirred for 3 h. The reaction was monitored by TLC (hexane : ethyl acetate = 7:3); after the completion of reaction, cooled to room temperature, the precipitate formed was filtered and washed with cold ethanol containing trace of water. The crude product was re-crystallized from ethanol to obtain the desired molecules **1a–e**.

2-Amino-3-cyano-4-(3′-bromophenyl)-7-hydroxy-4H-chromene (1a). White crystalline solid. IR (KBr, ν_{max}, cm^{-1}): 3444 (–OH), 3348 and 3585 (NH_2), 3070 (arom. –CH), 2191 (CN), 1510 (C=C), 1311 (C–N), 572 (C–Br). ^1H-NMR (DMSO-d_6, 400 MHz): δ_H 9.78 (s, 1H, OH), 7.41 (d, J = 8 Hz, 1H, H-4′), 7.34 (s, 1H, H-2′), 7.28 (t, J = 8 Hz, 1H, H5′), 7.18 (d, J = 8 Hz, 1H, H-6′), 6.99 (s, 2H, –NH_2), 6.82 (d, J = 8.4 Hz, 1H, H–Ar), 6.50 (dd, J = 2.4, 8.8 Hz, 1H, H–Ar), 6.41 (d, J = 2.4 Hz, 1H, H–Ar), 4.67 (s, 1H, H-4). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ_C 160.33, 157.28, 149.09, 148.79, 130.90, 129.94, 129.87, 129.57, 126.56, 121.80, 120.43, 112.94, 112.51, 102.24, 55.99, 45.60. MS (ESI): 365 (M + Na), 343 (M + H).

2-Amino-3-cyano-(3′-fluorophenyl)-7-hydroxy-4H-chromene (1b). Yellow crystalline solid. IR (KBr, ν_{max}, cm^{-1}): 3442 (O–H), 3375 and 3217 (NH_2), 3088 (arom. –CH), 2193 (CN), 1500 (C=C), 1313 (C–N), 1047 (C–F str.). ^1H-NMR (DMSO-d_6, 400 MHz): δ_H 9.74 (s, 1H, OH), 7.06–6.96 (m, 4H, o-, m-, & p- to F), 6.93 (s, 2H, NH_2), 6.83–6.41 (m, 3H, Ar–H), 4.69 (s, 1H, H-4). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ_C 163.43, 160.34, 157.23, 149.27, 148.81,

130.61, 130.52, 123.44, 120.45, 114.09, 113.34, 113.05, 112.45, 102.02, 55.99, 45.66; MS (ESI): 283 (M + H).

2-Amino-3-cyano-(3′-bromophenyl)-7-methoxy-4H-chromene (1c). Yellow crystalline solid. IR (KBr, ν_{max}, cm^{-1}): 3423 and 3360 (NH_2), 3064 (arom. –CH), 2193 (CN), 1506 (C=C), 1290 (C–N), 1147 (C–O), 580 (C–Br). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ_H 7.43 (d, J = 7.6 Hz, 1H, H-4′), 7.36 (s, 1H, H-2′), 7.29 (t, J = 8 Hz, 1H, H-5′), 7.19 (d, J = 7.6 Hz, 1H, H-6′), 7.01 (s, 2H, NH_2), 6.95 (d, J = 8.4 Hz, 1H, Ar–H), 6.68 (dd, J = 8.4 Hz, 1H, Ar–H), 6.57 (d, J = 2.4 Hz, 1H, Ar–H), 4.74 (s, 1H, H-4), 3.73 (s, 3H, OCH_3). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ_C 160.28, 159.04, 149.09, 148.89, 133.07, 130.94, 129.96, 129.66, 126.56, 121.84, 120.33, 114.61, 111.43, 100.98, 55.57, 55.37, 45.53. MS (ESI): 379 (M + Na), 357 (M + H), 201 (M + 2Na).

2-Amino-3-cyano-(3′-chlorophenyl)-7-methoxy-4H-chromene (1d). Yellow crystalline solid. IR (KBr, ν_{max}, cm^{-1}): 3441 and 3370 (NH_2), 3053 (arom. –CH str.), 2191 (CN), 1506 (C=C), 1294 (CN), 1128 (C–O), 785 (C–Cl). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ_H 7.35 (d, J = 7.6 Hz, 1H, H-4′), 7.29 (s, 1H, H-2′), 7.22 (t, J = 8 Hz, 1H, H-5′), 7.15 (d, J = 8 Hz, 1H, H-6′), 7.0 (s, 2H, NH_2), 6.95 (d, J = 8.8 Hz, 1H, Ar–H), 6.68 (dd, J = 2.4, 8.4 Hz, 1H, Ar–H), 6.57 (d, J = 2.4 Hz, 1H, Ar–H), 4.75 (s, 1H, H-4), 3.74 (s, 3H, OCH_3). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ_C 160.29, 159.04, 148.88, 148.63, 133.15, 130.62, 129.93, 127.10, 126.76, 126.16, 120.32, 114.61, 111.42, 100.98, 55.57, 55.37, 45.50. MS (ESI): 313 $(M + H)^+$.

2-Amino-3-cyano-(3′-fluorophenyl)-7-methoxy-4H-chromene (1e). Pinkish yellow crystalline solid. IR (KBr, ν_{max}, cm^{-1}): 3437 and 3382 (NH_2), 3053 (arom. –CH str.), 2189 (CN), 1455 (C=C), 1296 (C–N), 1126 (C–O), 1045 (CF). ^{1}H-NMR (DMSO-d_6, 400 MHz): δ_H 7.07–6.95 (m, 4H, o-, m-, & p- to F), 6.99 (s, 2H, NH_2), 6.69–6.56 (m, 3H, Ar–H), 4.75 (s, 1H, H-4), 3.74 (s, 3H, $–OCH_3$). ^{13}C-NMR (DMSO-d_6, 400 MHz): δ_C 163.44, 161.01, 160.29, 159.02, 149.00, 148.88, 130.68, 129.91, 123.46, 120.35, 114.70, 113.43, 111.36, 100.96, 55.60, 55.40, 45.67. MS (ESI): 295 (M – H).

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REFERENCES AND NOTES

[1] Filipe, A.; Marta, C.; Marián, C.; José, B.; Elisabet, G.-P.; Fernanda, P.; Jordi, M.; María, I. L. Eur J Med Chem 2012, 54, 303.

[2] Nancy, T.; Subin, M. Z. Int J Pharm Sci Rev Res 2013, 22, 50.

[3] Shiva Kumar, K.; Rambabu, D.; Bagineni, P.; Mohammad, M.; Rama Krishna, G.; Basaveswara Rao, M. V. Org Biomol Chem 2012, 10, 4774.

[4] Manal Kandeel, M.; Aliaa Kamal, M.; Eman Abdelall, K. A.; Heba Elshemy, A. H. Eur J Med Chem 2013, 59, 183.

[5] Safari, J.; Banitaba, S. H.; Khalili, S. D. J. Mol Catal A: Chem 2011, 335, 46.

[6] Li, Y. L.; Chen, H.; Shi, C. L.; Shi, D. Q.; Ji, S. J. J Comb Chem 2010, 12, 231.

[7] Shi, D. Q.; Chen, J.; Zhuang, Q. Y.; Hu, W. W. J Chem Res 2003, 30, 674.

[8] Patchett, A. A.; Nargund, R. P. Annu Rep Med Chem 2000, 35, 289.

[9] Bonsignore, L.; Loy, G.; Secci, D.; Calignano, A. Eur J Med Chem 1993, 28, 517.

[10] Bhat, M. A.; Siddiqui, N.; Khan, S. A. Acta Pol Pharm 2008, 65, 235.

[11] Skommer, J.; Wlodkowic, D.; Matto, M.; Eray, M. Pelkonen J Leukemia Res 2006, 30, 322.

[12] Gourdeau, H.; Leblond, L.; Hamelin, B.; Desputeau, C.; Dong, K.; Kianicka, I.; Custeau, D.; Bourdeau, C.; Geerts, L.; Cai, S.; Drewe, X. J.; Labrecque, D.; Kasibhatla, S.; Tseng, B. Mol Cancer Ther 2004, 3, 1375.

[13] Cheng, J. F.; Akira, I.; Yoshinori, O.; Thomas, A.; Alex, N. Bioorg Med Chem Lett 2003, 13, 3647.

[14] Kabalka, G. W.; Venkataiah, B.; Das, B. C. Synlett 2004, 2004, 2194.

[15] Makarem, S.; Mohammadi, A. A.; Fakhari, A. R. Tetrahedron Lett 2008, 49, 7194.

[16] Shaabani, A.; Ghadari, R.; Ghasemi, S.; Pedarpour, M.; Rezayan, A. H.; Sarvary, A. W.; Ng, S. J. Comb Chem 2009, 11, 956.

[17] Chetan, B. S.; Nimesh, M. S.; Manish, P. P.; Ranjan, G. P. J Serb Chem Soc 2012, 77, 1.

[18] Ruth, D.; David, S. C. B.; Vanida, C.; Rohan, A. D.; Naresh, K. Bioorg Med Chem 2012, 20, 1527.

[19] Bhagya, B.; Ramakrishna, A. NUJHS 2012, 2, 2.

[20] Odedire, O. O.; Olaleye, M. T.; Adekunle, A. S.; Ehigie, L. O.; Olabinri, P. F. Research Journal of Biological Sciences 2010, 5, 102.

[21] Serhat, K.; Sait, C.; Semra, T.; Okkes, Y.; Ismail, T. Chemistry Journal 2012, 2, 9.

[22] Francis, D.; Rita, L. J Immunol Methods 1986, 89, 271.

[23] Abdou, I. M.; Saleh, A. M.; Zohdi, H. F. Molecules 2004, 9, 109.

[24] Mortimer, C. G.; Wells, G.; Crochard, J. P.; Stone, E. L.; Bradshaw, T. D.; Stevens, M. F. G.; Westwell, A. D. J Med Chem 2006, 49, 179.

[25] Sathianarayanan, Amrutha B Chittethu, Asha Jose, Ranganathan Balasubramanian; Saranya T. S.; Asha Asokan Manakadan; Prasanna Ramani 2015, Design and Synthesis of Isatin Semicarbazone Derivatives Against Mammary Carcinoma Cells, Medicinal Chemistry Research, Accepted.