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Rational design, synthesis of novel 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazole derivatives as an anti-angiogenesis and anti-cancer

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Abstract:

Based on earlier proven pharmacophore analogues of cancer a novel 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles (**13-16**) were rationally designed and synthesized. By the reaction of chromene-3-carboxylic acids (**10a-d**) with substituted acyl bromides in the presence of TEA followed by refluxing with NH_4OAc in toluene. The compounds **13-16** were screened *in vitro* for inhibition of KRAS/Wnt and their anti-angiogenesis property. Compound **16f** has been identified as a potent anti-angiogenesis molecule which can be considered as a new lead structure. Molecular docking analysis displayed higher binding affinity of **16f** with KRAS, Wnt and VEGF.

Keywords: Chromene-3-carboxylic acid, Imidazole, Anti-cancer activity, Anti-angiogenesis activity, Molecular docking analysis.

1.0 Introduction:

Several researchers are working to discover new drugs based on natural products to treat cancer but the success rate is very less due to toxicity issues as well as due to the inability of the compounds to act selectively on the cancer cell. Epidemiological studies have reported that diets rich in isoflavones particularly Soybeans and Soya products reduce the incidence of various cancers. *In vitro* and *in vivo* animal studies showed that isoflavones genistein (**1**) and diadzein (**2**)[1-8] are promising agents for cancer chemoprevention and inhibition of tumor progression. Isoflavones inhibit cell growth at concentrations greater than 20 μM. Inhibition of cell proliferation by isoflavones may involve interference with signaling via the epidermal growth factor receptor kinase, effects on cell cycle, capsase or transforming growth factor β signaling.

Tumor angiogenesis is a complex dynamic process necessary for the growth of all tumors.[9-12] Tumor cannot grow through a defined volume if it is not vascularized. Among the angiogenic factors secreted by the tumor cells, the Vascular Endothelial Growth Factor (VEGF) is one of the important. Most human cancer cells express elevated levels of VEGF and VEGF receptors on their surface. An anti-angiogenic drug impairs VEGF pathway and tumor vasculature by targeting VEGF (for eg: Bevacizumab[13] a monoclonal antibody) or their receptors. In the last two decades several small molecules are being evaluated as anti-angiogenicagents.[14] A few successfully derived natural product anticancer drugs include vincristine (acute lymphocytic leukemia),[15,16] taxol (ovarian cancer)[17] and etoposide (lung cancer).[18]

Synthetic analogs of the isoflavones, diadzein (**2**) and phenoxodiol (**3**) [19-23] showed strong apoptotic and anti-angiogenic activities in ovarian carcinoma *in vitro* and reduced tumor volume of ovarian xenografts*in vivo*. Phenoxodiol (**3**) is a dihydroxylated-3-arylchromene.

Synthetic heterocyclic compounds containing nitrogen and oxygen are commonly explored as anticancer agents with anti-angiogenesis as the mode of action.[4] These compounds are chromenes with an aryl imidazole substitution at 3-position of chromene. The imidazole moiety is present in a wide range of naturally occurring compounds. It is a common scaffold in many significant biomolecules, including biotin, histamine, the essential amino acid histidine, and the pilocarpine alkaloids.[24] The use of imidazole and their derivatives in chemical processes, especially in pharmaceuticals have increased, because of their ability to form hydrogen bond with the active site of several enzymes.[25] The incorporation of the imidazole nucleus is an important synthetic strategy in rational drug discovery.

We rationally designed and synthesized novel 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles (**13a-j; 14a, e-j; 15a, e-j; 16a-f**) that are structurally similar to the natural isoflavones and phenoxodiol and are considered potential anti-angiogenic agents. Molecular models enable us to build the three dimensional shape of small molecules and target. It allows us to check whether the shape of a potential lead is complementary to the shape of its target. It also allows us to calculate binding energy liberated when a molecule binds to active site. Molecular modelling has reduced need to synthesize every analogue of a lead compound. The synthesized compounds were characterized by the IR, NMR, Mass Spectrometric methods. Of those synthesized compounds, fourteen compounds were screened in the *Eli Lilly's Open Innovation Drug Discovery programme (OIDD)*. Therefore, this leads used competitive biological activity against cancer cell lines. Experimental procedures for angiogenesis assay, cellular imaging and Endothelial and nuclear staining were carried out.

2.0 Results and discussion

2.1 Chemistry:

1,3-Dimethoxybenzene **(5)** on regioselective lithiation with n-BuLi at 0 °C in THF/TMEDA gave 2-lithiated dimethoxybenzene which on treatment with DMF gave 2,6-dimethoxybenzaldehyde (**6**) [26], Selective mono demethylation with $AlCl_3$ gave 2-hydroxy-6-methoxybenzaldehyde (**8a**).[26,27] 2,4-Dihydroxybenzaldehyde (**7**) was prepared from resorcinol by Vilsmeier-Haackformylation.[28, 29] Compound-**7** on methylation with CH_3I gave **8b** (Scheme-1). 3-Methoxysalicylaldehyde (vanillin) and salicylaldehydes are commercially available. Treatment of the substituted salicylaldehydes (**8a-d),** with acrylonitrile and 1,4-diazabicyclo [2.2.2] octane (DABCO) as a catalyst in Baylis-Hillman reaction[30] afforded chromene-3-nitriles (**9a-d**), which in turn were hydrolyzed to chromene-3-carboxylic acids[31] (**10a-d**) (Scheme-2)**.** Chromene-3-carboxylic acids (**10a-d**) were reacted with substituted acyl bromides (**12a-j**) (Scheme-3) in the presence of TEA followed by refluxing with NH_4OAc in toluene gave 2-(substituted-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles[31] (**13-16**) (Scheme-4, 5, 6, & 7).

2.2 Biological activity

2.2.1 Anti-Cancer activity

Of the 29 chromenyl imidazoles synthesized in this study 14 compounds (**16a-f, 15h, 14f, h, j, 13f, g, i, j**) were selected for screening from OIDD chemo informatics filter. Compounds (**16a-f, 15h, 14f, h, j, 13f, g, i, j**) were subjected to *in vitro* primary screening in the KRAS-Wnt SL (Synthetic Lethal) in the basal viability of colon cancer cell lines (SW480, DLD-1, HCT116, GSK 3b in pretreated viability HCT116, HT-29, RKO, SW837, Colo320, SNU-C1) and the % inhibition (at 0.2, 2.0 and 20 μM) was calculated by IC_{50} values (summarized in Table-1). According to the IC_{50} values from their concentration-response curves

compounds **13g, 16a, 16e** and **16f** were found to be the potent inhibitors. Especially compound **16f** showed IC_{50} value in the range of 0.37-8.3 μM on the different cancer cell lines tested. The colorectal cancer cell line inhibitions depend on the nature of substituents on phenyl ring of imidazole nucleus and methoxy group of chromene nucleus. IC_{50} values were also determined for other three compounds in the basal TCF/TK Luciferase DLD-1 assay wherein **16f** showed IC_{50} = 4.731 μM (Table 2). It was observed that compounds possessingmethoxy group on 5th position of chromenenucleus demonstrated augmented cancer inhibitory activity, benzyloxy substitution was found more favorable towards cancer inhibition over other substitution.

2.2.2 Anti-angiogenic activity

The three compounds (**16a, 16e, 16f**) were screened for anti-angiogenesis activity and they exhibited greater than 50% inhibition of tube area at 10 μM in primary single point assay. These three were further screened at different concentrations to draw CRC (concentration response curves) and IC_{50} values (Table-3). Only the compound **16f** with benzyloxy substitution at 4th position of the phenyl ring and methoxy group on 5th position of chromene nucleus showed significant activity with IC_{50} of 0.89 μM (Fig.2), and the remaining two compounds showed IC_{50} values greater than 10 μM. The compounds lacking the benzyloxy substituent failed to exhibit significant antiangiogenic activity indicating the importance of benzyloxy group for binding to the receptor and the subsequent inhibitory activity. Thus, our studies resulted in a new lead molecule with potent anti-angiogenic activity better than the earlier synthesized compounds (isoflavone metabolite 6-methoxyequol; IC_{50} value with 3).[32] Novel 16f compound could be studied further to discover a new clinical and therapeutic agents useful in cancer chemotherapy.

Figure 2

2.3 Molecular Docking Studies

2.3.1. Binding of 16f to Human KRAS receptor

The Docking of compound **16f** in the binding site of Human KRAS receptor illustrated that the chromene and imidazole ring play a decisive role in inhibiting angiogenesis activity. The docking results showed hydrogen bonding interactions between chromene ring oxygen with i) amine group of Asn 26 with a bond distance 1.1 Å, ii) ND2 of Asn 26d = 2.5 Å and iii) His 27 d= 3.2 Å. Methoxy oxygen in the chromene ring also showed hydrogen bonding with His 27, d = 2.8 Å.Further hydrogen bonding interactions were also observed involving the two nitrogen atoms of imidazole ring with backbone carbonyl of Gln 25 (d = 2.6 Å and d = 2.3 Å) and Ile 24 (d = 3.4 Å). Chromene aromatic ring of **16f** was surrounded by Asn26, His 27, Gln 25 and Ile 24 amino acid residues (Fig-3&4).

Figure 3 & Figure 4

2.3.2. Binding of 16f to Wnt receptor

Docking of compound **16f** in the active site of Human Wnt receptor showed hydrogen bonding between nitrogen atom of imidazole ring with backbone carbonyl of Gln 25 CB (d=1.66 Å) and His 27 (d= 3.03 Å). Oxygen atom of chromene ring showed interactions with amine group of Tyr100 (1.905Å) (Fig-5&6).

Figure 5 & Figure 6

2.3.3. Binding of 16f to VEGF receptor

The **16f** in the active site of VEGF receptor showed two hydrogen bonding interacts between nitrogen atom of imidazole ring with Arg 82 (d= 2.37 Å and d= 2.05 Å). Further hydrogen

bonding interactionsfrom the oxygen atom of chromene ring and amine group of Arg 105 (d=1.93 Å) was observed (Fig-7 & 8).

Figure 7 & Figure 8

For the other chromenyl imidazoles now synthesized their docking studies did not show closer interactions with KRAS, Wnt and VEGF receptors.

3.0 Conclusion:

Several new 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles (**13-16**) were rationally designed, synthesized and subjected to *in vitro* primary anticancer screening against several cancer cell lines (SW480, DLD-1, HCT116, GSK 3b in pretreated viability HCT116, HT-29, RKO, SW837, Colo320 and SNU-C1). Among them four compounds (**13g, 16a, 16e** and **16f)** were subjected to basal TCF/TK Luciferase DLD-1assay. Results of in vitro cancer assay indicated that all the compounds showed considerable cancer inhibition. However, substitution of methoxy group on 5th position of chromene and 4th position of benzyloxy group on phenyl ring of imidazole was found to bemore favorable for cancer inhibition. Whereas compounds with no methoxy group at 5th position on chromene showed diminished cancer activity. Among all the screened compounds, **16f** was found to be the morepotent inhibitor of cancer with the highest selectivity. Further in anti-angiogenesis assay compound **16f** showed potent activity in inhibiting VGF_ADSC/CFC AngioTube area. Molecular docking analysis also exhibited higher binding affinity of **16f** with Kras, Wnt and VEGF ligands. Hence **16f** could be considered as a lead structure in the development of new series of anti-angiogenesis/anticancer agents.

4.0 Experimental section:

4.1. General experimental methods:

Unless otherwise specified, all solvents and reagents were obtained from commercial suppliers. Solvents were purified as per the procedures given in the ''*Text book of practical organic chemistry*'' by Vogel (6^{th} Edition). All reactions were performed under nitrogen atmosphere unless otherwise noted. Column chromatography was performed using Merck silica gel 60-120 mesh. ^{1}H NMR spectra were recorded on Bruker spectrometer at 400 MHz spectrometer, ^{13}C NMR spectra were acquired on 100.6 MHz with tetramethylsilane as internal standard, chemical shift (δ) are reported in ppm. (δ) Shift (multiplicity, coupling constant, proton count). Mass spectral analysis was accomplished using electro spray ionization (ESI) techniques.

4.2. Preparation of 1, 3-dimethoxybenzene (5):

To a stirred solution of resorcinol **4** (20 g, 0.18 mol) and acetone (200 ml) in an ice both was added K_2CO_3 (62.72 g, 0.45 mol) and methyl iodide (25.8 ml, 0.399 mol) drop wise over a period of 10 minutes. After addition, the solution was stirred for overnight at rt. After completion the reaction acetone was removed under reduced pressure. The crude was diluted with water and extracted two times with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography, eluting with ethyl acetate/pet-etherto give the title compound **5 (**22g, 87.69%). ^{1}H NMR ($CDCl_3$) δ: 3.78 (s, 6H, 2xOCH_3), 6.4 (t, J = 2.0 Hz, H_5), 6.5 (dd, J = 2.0 Hz, H_4), 6.52 (dd, J = 1.6 Hz, H_6), 7.2 (t, J = 2.0, H_2). ^{13}C NMR ($CDCl_3$) δ: 56.5 (2xO-C), 100.4 (C_2), 107.5 (C_4&C_6), 129.8 (C_5), 162.7 (C_1&C_3).

4.3. Preparation of 2,6-dimethoxybenzaldehyde (6):

A suitable RB flask was charged with 1,3-dimethoxybenzene (**5)** (21.5 g, 0.155 mol), N, N, N', N'– tetramethylethylenediamine (TMEDA, 27.6 ml, 0.176 mol) and dry THF (200 ml). At 0 °C, 1.6 M n-butyl lithium (116.77 ml, 0.186 mol) was added. The solution was stirred at 5 °C for 30 minutes and dry DMF (18.3 ml, 0.233 mol) was added slowly and maintained the temperature less than 10 °C (38 °C adiabatic temperature rise from the addition). The solution was continued for stirring for 2 hour and quenched with 4 M HCl under cold water and continued the stirring for 30 minutes at 5 to 15 °C. The reaction mixture was filtered and washed with water followed pet-ether successively to get compound **6** as off white solid (18.4 g, 71.15 %). ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, 6H, 2xOCH_3), 6.4 (t, J = 2.0 Hz, H_5), 6.58 (d, J = 2.0 Hz, 2H, H_3& H_5), 7.46 (t, J = 8.8 Hz, H_4), 10.51 (s, CHO). ^{13}C NMR ($CDCl_3$) δ: 56.06 (O-C), 103.8 (C_3&C_5), 114.3 (C_1), 135.9 (C_4), 162.2 (C_2&C_8), 189.4 (CHO).

4.4. Preparation of 2,4–Dihydroxybenzaldehyde (7):

To a well cooled (0–5 °C) solution of resorcinol (4) (20 g, 0.18 mol) in acetonitrile (200 ml), dry DMF (21.24 ml, 0.272 mol) and freshly distilled dry $POCl_3$ (25.34 ml, 0.272 mol) were added with constant stirring at 0–5 °C. The salt that separated was filtered and was washed with cold acetonitrile. To this salt, water was added and heated at 50 °C for 0.5 h and then cooled. The solid that separated was filtered, washed with cold water, and dried to give 2,4-dihydroxybenzaldehyde (**7)** (18 g, 72%)**.** ^{1}H NMR ($CDCl_3$) δ: 6.38 (d, J = 1.2 Hz, H_3), 6.5 (dd, J = 10.4, 2.0 Hz, H_5), 7.35 (d, J = 8.8 Hz, H_6), 9.64 (s, 2-OH), 10.1 (s, 4-OH), 11.42 (s, CHO). ^{13}C NMR ($CDCl_3$) δ: 102.8 (C_3), 109.2 (C_5), 114.5 (C_1), 135.8 (C_6), 164.3 (C_2), 165.8 (C_4), 194.0 (CHO).

4.5. Preparation of 2-hydroxy-6-methoxybenzaldehyde (8d):

To a RB flask with $AlCl_3$ (22.02 g, 0.165 mol) and dichloromethane (120 ml) cooled to -15 °C, solution of 2,6-dimethoxybenzaldehyde (**6**) (18 g, 0.108 mol) in dichloromethane (60 ml)

was slowly added while maintaining the temperature below 0 °C. The solution was slowly warmed to ambient temperature and allowed to stir for 6 hours. A solution of con.HCl in water was slowly added while maintaining the temperature below 25 °C, the dichloromethane was removed under vacuum distillation. The product was collected by filtration and washed with a solution of con.HCl and water. After drying compound **8d** was obtained (13 g, 78.9%). ^{1}H NMR ($CDCl_3$) δ: 3.89 (s, OCH_3), 6.37 (d, J = 8.4 Hz, H_3), 6.53 (d, J = 8.4 Hz, H_5), 7.42 (t, J = 8.4 Hz, H_4), 11.97 (s, CHO). ^{13}C NMR ($CDCl_3$) δ: 55.8 (O-C), 100.8 (C_5), 109.9 (C_3), 110.8 (C_1), 138.4 (C_4), 162.4 (C_6), 163.6 (C_2), 194.3 (CHO).

4.6. Preparation of 2-hydroxy-4-methoxybenzaldehyde (8c):

To a stirred solution of **7** (18 g, 0.13 mol) and acetone (150 ml) in an ice both was added K_2CO_3 (35.88 g, 0.26 mol) and methyl iodide (12.18 ml, 0.195 mol) drop wise over a period of 10 minutes. After addition, the solution was stirred for overnight at rt. After completion the reaction acetone was evaporated. The crude was diluted with water and extracted two times with ethyl acetate. The combined ethyl acetate extracts were dried (Na_2SO_4) and evaporated. The residue was purified by chromatography, eluting with ethyl acetate/pet-etherto give the title compound **8c** (13 g, 68.4%). ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, OCH_3), 6.42 (d, J = 2.0 Hz, H_3), 6.54 (dd, J = 8.4, 2.4 Hz, H_5), 7.42 (d, J = 8.4 Hz, H_6), 9.71 (s, OH), 11.49 (s, CHO). ^{13}C NMR ($CDCl_3$) δ: 56.0 (O-C), 103.0 (C_3), 108.0 (C_5), 114.0 (C_1), 135.9 (C_6), 162.0 (C_2), 164.2 (C_4), 194.0 (CHO).

4.7. General procedure for the synthesis of Substituted-2H-chromene-3-carbonitriles (9a-d): Substituted salicylaldehydes (1.0 mol) **(8a-d)** with excess of acrylonitrile in the presence of 1,4-diazabicyclo [2.2.2] octane (DABCO, 0.25 mol) as a catalyst was stirred at 80 °C for 10 h, undergo Baylis-Hillman reaction. The excess acrylonitrile was removed under reduced pressure, and then the reaction mixture was dissolved in ethyl acetate, washed with

1N NaOH followed by 1N HCl. The organic phase was dried over anhydrous Na_2SO_4, filter and the solvent was evaporated under vacuum and the residue was subjected to column chromatography using silica gel (60-120) to obtain the product substituted-2H-chromene-3-carbonitriles **9a-d**, in quantitative yield.

4.7.1.2H-chromene-3-carbonitrile (9a):

Yellow solid, yield 75 %. ^{1}H NMR ($CDCl_3$) δ: 4.8 (d, J = 1.2 Hz, O-CH_2), 6.86 (d, J = 8.0, H_8), 6.96 (td, J = 7.6, 0.8 Hz, H_6), 7.09 (dd, J = 7.6, 1.2 Hz, H_5), 7.153 (s, H_4), 7.25 (td, J = 8.0, 0.8 Hz, H_7). ^{13}C NMR ($CDCl_3$) δ: 71.4 (C_2), 109.0 (C_3), 114.2 (C_8), 115.7 (C_{4a}), 117.3 (CN), 121.4 (C_6), 126.5 (C_5), 128.4 (C_7), 141.8 (C_4), 157.5 (C_{8a}).

4.7.2. 8-Methoxy-2H-chromene-3-carbonitrile (9b):

Off white solid, yield 70 %. ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, OCH_3), 4.86 (d, J = 1.2 Hz, OCH_2), 6.74 (m, H_6), 6.93 (m, 2H, H_4& H_7), 7.17 (m, H_5). ^{13}C NMR ($CDCl_3$) δ: 55.5 (OCH_3), 64.4 (C_2), 105.4 (C_3), 113.5 (C_7), 115.9 (C_{4a}), 118.9 (C_5), 117.0 (CN), 125.2 (C_6), 138.7 (C_4), 154.9 (C_{8a}), 162.8 (C_8).

4.7.3. 7-Methoxy-2H-chromene-3-carbonitrile (9c):

Off white solid, yield 72 %. ^{1}H NMR ($CDCl_3$) δ: 3.8 (s, OCH_3), 4.7 (s, OCH_2), 6.42 (d, J = 2.0 Hz, H_8), 6.51 (dd, J = 8.4, 2.4 Hz, H_6), 7.02 (d, J = 8.8 Hz, H_5), 7.13 (s, H_4). ^{13}C NMR ($CDCl_3$) δ: 55.5 (OCH_3), 64.4 (C_2), 99.3 (C_8), 101.9 (C_6), 108.9 (C_{4a}), 113.4 (C_3), 117.0 (CN), 129.6 (C_5), 138.7 (C_4), 155.9 (C_{8a}), 163.4 (C_7).

4.7.4. 5-Methoxy-2H-chromene-3-carbonitrile (9d):

Off white solid, yield 70 %. ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, OCH_3), 4.74 (s, OCH_2), 6.48 (t, J = 8.0 Hz, 2H, H_6& H_8), 7.21 (t, J = 8.4 Hz, H_7), 7.53 (s, H_4). ^{13}C NMR ($CDCl_3$) δ: 55.8 (O-C),

63.9(C_2), 100.4 (C_6), 104.1 (C_8), 109.0 (C_{4a}), 110.3 (C_3), 117.0 (CN), 133.0 (C_7), 134.4 (C_4), 155.1 (C_5), 156.3 (C_{8a}).

4.8. General procedure for the synthesis of substituted-2H-chromene-3-carboxylic acid (10a-d): A mixture of 5-methoxy-2H-chromene-3-carbonitrile and 10 % sodium hydroxide was refluxed for 6 h. The reaction mixture was acidified with con.HCl and the separated product was washed with water and dried, recrystallization with ethanol to afford desired compounds.

4.8.1. 2H-chromene-3-carboxylicacid (10a):

Yellow solid, yield 90 %. ^{1}H NMR (DMSO-d_6) δ: 4.9 (d, *J* = 1.2 Hz, OCH_2), 6.8 (d, *J* = 8.0 Hz, H_8), 6.95 (td, *J* = 7.2, 7.6, 0.8, 1.2 Hz, H_6), 7.26 (td, *J* = 8.0, 7.6, 1.6, 1.2 Hz, H_7), 7.32 (dd, *J* = 7.6, 7.2, 1.6, 1.2 Hz, H_5), 7.45 (s, H_4), 12.86 (s, COOH). ^{13}C NMR (DMSO-d_6) δ: 63.5 (C_2), 115.0 (C_8), 120.7 (C_{4a}), 121.4 (C_6), 121.5 (C_5), 123.4 (C_7), 132.4 (C_3), 143.3 (C_4), 147.5 (C_{8a}), 165.4 (COOH).

4.8.2. 8-Methoxy-2H-chromene-3-carboxylicacid (10b):

Off white solid, yield 85 %. ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, OCH_3), 4.88 (s, OCH_2), 6.9 (m, 2H, H_6&H_7), 7.0 (dd, *J* = 7.2, 2.8 Hz, H_5), 7.42 (s, H_4), 12.8 (s, COOH). ^{13}C NMR (DMSO-d_6) δ: 55.6 (O-C), 63.9 (C_2), 115.0 (C_7), 120.7 (C_{4a}), 121.4 (C_5), 121.5 (C_6), 123.4 (C_3), 132.4 (C_4), 143.4 (C_{8a}), 147.5 (C_8), 165.5 (COOH).

4.8.3. 7-Methoxy-2H-chromene-3-carboxylicacid (10c):

Off white solid, yield 80 %. ^{1}H NMR (DMSO-d_6) δ: 3.7 (s, OCH_3), 4.89 (s, OCH_2), 6.45 (s, H_8), 6.55 (d, *J* = 8.8 Hz, H_6), 7.22 (d, *J* = 8.8 Hz, H_5), 7.4 (s, H_4), 12.69 (s, COOH). ^{13}C NMR (DMSO-d_6) δ: 55.3 (O-C), 64.2 (C_2), 101.2 (C_8), 107.9 (C_6), 113.9 (C_{4a}), 119.8 (C_5), 130.1 (C_3), 132.4 (C_4), 156.0 (C_{8a}), 162.3 (C_7), 165.6 (COOH).

4.8.4. 5-Methoxy-2H-chromene-3-carboxylicacid (10d):

Off white solid, yield 85 %. ^{1}H NMR (DMSO-d_6) δ: 3.82 (s, OCH_3), 4.83 (s, OCH_2), 6.47 (d, J = 8.4 Hz, H_6), 6.61 (d, J = 8.4 Hz, H_8), 7.23 (t, J = 8.4 Hz, H_7), 7.55 (s, H_4), 12.73 (s, COOH). ^{13}C NMR (DMSO-d_6) δ: 55.8 (O-C), 63.6 (C_2), 104.2 (C_6), 108.4 (C_8), 110.0 (C_{4a}), 121.3 (C_7), 127.0 (C_3), 132.3 (C_4), 155.1 (C_5), 156.4 (C_{8a}), 165.4 (COOH).

4.9. General procedure for the synthesis of 2-bromo-1-(substituted-phenyl)ethanone derivatives (12a-h): Following the literature method[33], to a stirred solution of acetophenone (5 g, 0.041 mol) in diethyl ether (30 ml) in an ice bath bromine (2.08 ml, 0.041 mol) in dichloromethane (30 ml) was added drop wise over 10-15 minutes. After addition, the solution stirred 2 hour at rt. The solvent evaporated under reduced pressure and triturated with pet-ether and kept in freeze for few hours, the separated solid was filtered to get the desired compounds **12a-h**.

4.9.1. 2-Bromo-1-phenylethanone (12a):

Off white solid, yield 85 %. ^{1}H NMR ($CDCl_3$) δ: 4.46 (s, CH_2), 7.5 (t, J = 8.0, 7.6 Hz, 2H, H_3&H_5), 7.61 (t, J = 7.2 Hz, H_4), 7.99 (d, J = 8.4 Hz, 2H, H_2& H_6). ^{13}C NMR ($CDCl_3$) δ: 30.9 (C-Br), 128.8 (C_2&C_6), 128.9 (C_3&C_5), 131.7 (C_4), 133.9 (C_1), 191.2 (C=O).

4.9.2. 2-Bromo-1-(4-chlorophenyl)ethanone (12b):

Brown solid, yield 70 %. ^{1}H NMR ($CDCl_3$) δ: 4.41 (s, CH_2), 7.34 (d, J = 8.8, 2H, H_3& H_5), 7.84 (d, J = 8.4, 2H, H_2& H_6). ^{13}C NMR ($CDCl_3$) δ: 30.5 (C-Br), 129.3 (C_3&C_5), 130.4 (C_2&C_6), 132.2 (C_1), 132.6 (C_4), 190.4 (C=O).

4.9.3. 2-Bromo-1-(2, 4-chlorophenyl)ethanone (12c):

Brown oil, yield 60 %. ^{1}H NMR ($CDCl_3$) δ: 4.25 (s, CH_2), 7.5 (s, H_3), 7.65 (m, 2H, H_5&H_6). ^{13}C NMR ($CDCl_3$) δ: 30.5 (C-Br), 126.9 (C_5), 130.4 (C_3), 132.0 (C_6), 132.8 (C_2), 133.2 (C_1), 142.1 (C_4), 190.4 (C=O).

4.9.4. 2-Bromo-1-(3-nitrophenyl)ethanone (12d):

Off white solid, yield 70 %. ^{1}H NMR ($CDCl_3$) δ: 4.48 (s, CH_2), 7.74 (t, J = 8.0 Hz, H_5), 8.33 (d, J = 8 Hz, H_6), 8.48 (d, J = 8.4 Hz, H_4), 8.81 (s, H_2). ^{13}C NMR ($CDCl_3$) δ: 30.8 (C-Br), 122.7 (C_2), 123.5 (C_4), 127.6 (C_5), 133.6 (C_6), 137.2 (C_1), 145.3 (C_3), 190.9 (C=O).

4.9.5. 2-Bromo-1-(4-bromophenyl)ethanone (12e):

Brown solid, yield 75 %. ^{1}H NMR ($CDCl_3$) δ: 4.41 (s, CH_2), 7.65 (d, J = 8.8 Hz, 2H, H_3&H_5), 7.85 (d, J = 8.4 Hz, 2H, H_2&H_6). ^{13}C NMR ($CDCl_3$) δ: 30.5 (C-Br), 129.3 (C_4), 130.2 (C_2&C_6), 132.2 (C_3&C_5), 132.3 (C_1), 190.2 (C=O).

4.9.6.1-(4-(Benzyloxy) phenyl)-2-bromoethanone (12f):

Off white solid, yield 65 %. ^{1}H NMR ($CDCl_3$) δ: 4.39 (s, CH_2-Br), 5.14 (s, Bn-CH_2), 7.03 (dd, J = 6.8, 2.0 Hz, 2H, H_3&H_5), 7.4 (m, 5H, $H_{1'-5'}$) 7.97 (dd, J = 6.8, 2.0 Hz, 2H, H_2&H_6). ^{13}C NMR ($CDCl_3$) δ: 30.5 (C-Br), 69.7 (Bn-CH_2), 114.2 (C_3&C_5), 127.1 ($C_{2'}$&$C_{6'}$), 127.4 (C_4), 127.7 ($C_{3'}$ &$C_{5'}$), 128.1 (C_1) 130.2 (C_2&C_6), 140.2 ($C_{1'}$), 166.4 (C_4), 190.3 (C=O).

4.9.7.2-Bromo-1-(4-fluorophenyl)ethanone(12g):

Off white solid, yield 85 %. ^{1}H NMR ($CDCl_3$) δ: 4.42 (s, CH_2), 7.17 (t, J = 8.8, 8.4 Hz, 2H, H_3&H_5), 8.03 (dd, J = 9.2, 5.6 Hz, 2H, H_2&H_6).^{13}C NMR ($CDCl_3$) δ: 30.5 (C-Br), 112.4 (C_3&C_5), 129.3 (C_2&C_6), 130.4 (C_1), 160.3 (C_4), 190.2 (C=O).

4.9.8. 2-Bromo-1-(4-methoxyphenyl)ethanone (12h):

Brown solid, yield 70 %.^{1}H NMR ($CDCl_3$) δ: 3.38 (s, O-CH_3), 4.4 (s, CH_2), 6.96 (d, *J* = 8.8 Hz, 2H, H_3&H_5), 7.97 (d, *J* = 8.8 Hz, 2H, H_2&H_6). ^{13}C NMR ($CDCl_3$) δ: 30.8 (C-Br), 55.5 (O-C), 114.3 (C_3&C_5), 128.2 (C_1), 131.3 (C_2&C_6), 164.1 (C_4), 189.9 (C=O).

4.9.9. 2-Bromo-1-(pyridin-3-yl)ethanone (12i):

Following the literature method[34], 3-acetyl pyridine (**11i**) (5 g, 0.04 mol) was added to 33% HBr/AcOH (50 ml) with stirring. Bromine (2.04 ml, 0.04 mol) was then added and the reaction mixture was heated to 60 °C for 2h. The solution was cooled to rt and diethyl ether (50 ml) was added. The separated solid was filtered, washed with diethyl ether and dried to give 2-bromo-1-(pyridin-3-yl) ethanone (**12i).** White solid 5.6 g, 70 %. ^{1}H NMR ($CDCl_3$) δ: 4.39 (s, CH_2), 7.9 (m, 3H, H_4, H_5&H_6), 9.13 (s, H_2). ^{13}C NMR ($CDCl_3$) δ: 31.5 (C-Br), 121.3 (C_5), 123.3 (C_1), 131.6 (C_6), 145.4 (C_4), 147.5 (C_2), 190.2 (C=O).

4.9.10. 2-Bromo-1-(thiophen-2-yl)ethanone (12j):

Following the literature method[35], a solution of bromine (1.98 ml, 0.039 mol) in dichloromethane (20 ml) was added drop wise to 2-acetylthiophene (**11j**) (5 g, 0.039 mol) in dichloromethane (30 ml) in 20 min. The reaction mixture was stirred at 25 °C for 2h and neutralized with a saturated solution of $NaHCO_3$. The organic layer was washed with water followed by brine and dried over Na_2SO_4, filtered. Removal of the solvent gives a residue which was purified by column chromatography (silica gel, ethyl acetate/pet-ether 5:95 as eluent). Yellow oil 6 g, 73.6%. ^{1}H NMR ($CDCl_3$) δ: 4.37 (s, CH_2), 7.17 (dd, *J* = 4.8, 4.0 Hz, H_4), 7.73 (dd, *J* = 3.6, 1.2 Hz, H_3), 8.81 (dd, *J* = 4.8, 1.2 Hz, H_5). ^{13}C NMR ($CDCl_3$) δ: 31.1 (C-Br), 128.6 (C_4), 133.7 (C_3), 135.4 (C_5), 140.7 (C_2), 184.4 (C=O).

4.10. General procedure for preparation of 2-(substituted -2H-chromen-3-yl)-5-aryl-1H-imidazoles (13-16):

To a mixture of substituted-2H-chromene-3-carboxylicacid (**10a-d**) (1.0 mol) and triethylamine (3.0 mol) in dichloromethane in an ice both was added acyl bromides (**12a-f)** (1.2 mol), the solution stirred overnight at rt. The reaction mixture was diluted with chloroform and washed with water and brine solution, successively, and dried over Na_2SO_4, after removal of the solvent under reduced pressure; the residue was washed with pet-ether and dried under vacuum. The residue was dissolved in toluene and treated with ammonium acetate (5.0 mol) under nitrogen atmosphere. The reaction mixture was refluxed for 12 hour and was monitored by TLC. The reaction mixture was quenched with saturated $NaHCO_3$. The product was extracted with ethyl acetate (2 times), and washed with water followed by brine solution, successively and dried over Na_2SO_4. After removal of the solvent under reduced pressure, the crude product was purified by column chromatography using petroleum ether/ethyl acetate.

4.10.1 .(2H-chromen-3-yl)-5-phenyl-1H-imidazole (13a):

Yellow solid; yield 50%; mp.165-170 °C; ^{1}H NMR ($CDCl_3$) δ: 5.29 (s, O-CH_2), 6.85 (t, *J* = 8.4, 9.2 Hz, H_6), 6.9 (d, *J* = 7.2 Hz, H_8), 7.03 (d, *J* = 7.2 Hz, H_5) 7.14 (t, *J* = 8.0, 7.6 Hz, H_7), 7.25 (s, $H_{4'}$), 7.29 (d, *J* = 7.2 Hz, 2H, $H_{2''}$& $H_{6''}$), 7.34 (s, H_4), 7.37 (t, *J* = 8.0, 2.8 Hz, 3H, $H_{3''}$, $H_{4''}$&$H_{5''}$), 7.69 (s, NH), ^{13}CNMR (DMSO-d_6) δ: 64.7 (C_2), 114.8 (C_8), 115.4 (C_{4a}), 118.6 ($C_{4'}$), 121.7 (C_6), 122.4 (C_5), 123.2 (C_7), 124.3 ($C_{2''}$& $C_{6''}$), 126.3 ($C_{4''}$), 127.0 ($C_{3''}$ &$C_{5''}$), 128.4 (C_4), 129.1 ($C_{1''}$), 134.3 ($C_{2'}$), 141.0 (C_3), 143.2 ($C_{5'}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3162 (N-H), 1578 (C=N); MS (ESI, m/z): 275.07.

4.10.2.5-(4-Chlorophenyl)-2-(2H-chromen-3-yl)-1H-imidazole (13b):

Brown solid; yield 45%; mp.180-185 °C; ^{1}H NMR ($CDCl_3$) δ: 5.33 (s, O-CH_2), 6.86 (s, $H_{4'}$), 6.91 (d, *J* = 8.0 Hz, H_8), 6.94 (td, *J* = 7.2, 7.6, 0.8, 1.2 Hz, H_6), 7.1 (dd, *J* = 7.6, 1.2 Hz, H_5), 7.19 (td, *J* = 8.0, 7.6, 1.6, 1.2 Hz, H_7), 7.28 (s, H_4), 7.38 (d, *J* = 8.0 Hz, 4H, $H_{2'}$, $H_{3'}$, $H_{5'}$&

$H_{6'}$), 7.71 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 64.7 (C_2), 115.4 (C_8), 115.5 (C_{4a}), 118.9 ($C_{4'}$), 121.7 (C_6), 122.3 (C_5), 125.9 (C_7), 127.1 ($C_{2''}$ & $C_{6''}$), 128.4 ($C_{3''}$& $C_{5''}$), 129.2 (C_4), 130.5 ($C_{1''}$), 133.2 ($C_{4''}$), 139.8 ($C_{2'}$ & C_3), 143.4 ($C_{5'}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3162 (N-H), 1577 (C=N);MS (ESI, m/z): 308.97, 310.98

4.10.3.5-(2, 4-Dichlorophenyl)-2-(2H-chromen-3-yl)-1H-imidazole (13c):

Yellow solid; yield 45%; mp.190-195 °C; ^{1}H NMR ($CDCl_3$) δ: 5.34 (s, OCH_2), 6.88 (s, $H_{4'}$), 6.91 (d, J = 9.2 Hz, H_8), 6.95 (t, J = 8.4 Hz, H_6), 7.12 (d, J = 8.8 Hz, 2H, H_5& $H_{3''}$), 7.2 (t, J = 7.6 Hz, H_7) 7.28 (s, 2H, H_4& $H_{5''}$), 7.34 (d, J = 10.4 Hz, $H_{2''}$), 7.47 (s, NH). ^{13}C NMR ($CDCl_3$) δ: 64.6 (C_2), 115.5 (C_8), 115.84 (C_{4a}), 118.9 ($C_{4'}$), 121.75 (C_6), 122.2 (C_5), 125.3 (C_7& $C_{5''}$), 127.1 ($C_{1''}$), 129.2 ($C_{4,}$), 130.5 ($C_{6''}$& $C_{3''}$), 133.1 (($C_{2''}$), 133.2 ($C_{4''}$), 139.8 (C_3&$C_{2'}$), 143.4 ($C_{5'}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3168 (N-H), 1581 (C=N); MS (ESI, m/z): 342.93, 344.95.

4.10.4.5-(4-Bromophenyl)-2-(2H-chromen-3-yl)-1H-imidazole (13e):

Pale yellow solid; yield 52%; mp.165-170 °C. ^{1}H NMR ($CDCl_3$) δ: 5.34 (s, OCH_2), 6.88 (m, 3H, H_8, H_6& $H_{4'}$), 7.11 (d, J = 7.6 Hz, H_5), 7.19 (t, J = 6.4 Hz, H_7), 7.39 (s, H_4), 7.54 (d, J = 15.6 Hz, 2H, $H_{2''}$&$H_{6''}$), 7.65 (d, J = 11.6 Hz, 2H, $H_{3''}$& $H_{5''}$). ^{13}C NMR (DMSO-d_6) δ: 64.7 (C_2), 115.5 (C_8), 118.9 (C_{4a}), 119.0 ($C_{4'}$), 121.7 (C_6), 122.3 (C_5), 123.0 ($C_{4''}$), 126.3 (C_7), 127.1 ($C_{2''}$& $C_{6''}$), 129.2 (C_4), 131.3 ($C_{1''}$), 133.6 ($C_{3''}$& $C_{5''}$), 139.8 (C_3&$C_{2'}$), 143.4 ($C_{5'}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3017 (N-H), 1576 (C=N); MS (ESI, m/z):354.94, 355.94.

4.10.5.5-(4-(Benzyloxy) phenyl)-2-(2H-chromen-3-yl)-1H-imidazole (13f):

Pale yellow solid; yield 45%; mp.170-175 °C. ^{1}H NMR (DMSO-d_6) δ: 5.12 (s, OCH_2), 5.48 (s, Bn-OCH_2), 6.9 (m, 3H, H_8, H_6& $H_{4'}$), 7.04 (d, J = 8.0 Hz, 2H, $H_{3''}$& $H_{5''}$), 7.23 (m, 2H, H_5& H_7), 7.41 (m, 6H, $H_{2'''-6'''}$& H_4), 7.7 (d, J = 8.4 Hz, 2H, $C_{2''}$& $C_{6''}$), 12.2 (s, NH). ^{13}C

NMR (DMSO-d_6) δ: 64.7 (C_2), 69.2 (Bn-O-C), 113.6 ($C_{3''}$& $C_{5''}$), 114.8 (C_8), 115.4 (C_{4a}), 118.3 ($C_{4'}$), 121.7 (C_6), 122.4 (C_5), 125.6 (C_7), 125.9 ($C_{1''}$), 126.9 ($C_{2'''}$& $C_{6'''}$), 127.3 ($C_{4'''}$), 127.7 ($C_{2''}$ & $C_{6''}$), 128.4 ($C_{3'''}$& $C_{5'''}$), 129.1 (C_4), 137.1 (C_3& $C_{2'}$), 140.9 ($C_{1'''}$), 142.9 ($C_{5'}$), 153.2 (C_{8a}), 157.1 ($C_{4''}$); IR (KBr, Cm^{-1}): 3061 (N-H), 1575 (C=N); MS (ESI, m/z): 381.06.

4.10.6.2-(2H-chromen-3-yl)-5-(4-fluorophenyl)-1H-imidazole (13g):

Pale yellow solid; yield 40%; mp.160-165 °C. ^{1}H NMR ($CDCl_3$) δ: 5.31 (d, *J* = 1.6Hz, 2H, OCH_2), 6.84 (s, H_4), 6.88 (d, *J* = 8 Hz, H_8), 6.92 (td, *J* = 8.0, 1.6, 7.2, 1.2 Hz, H_6), 7.09 (m, 5H, H_5, $H_{2''}$, $H_{3''}$, $H_{5''}$, $H_{6''}$), 7.17 (td, *J* = 7.6, 1.2, 8.0, 1.6 Hz, 1H,H_7), 7.31 (s,H_4), 7.7 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 64.7 (C_2), 114.6 (C_8), 115.1 (C_{4a}), 115.3 ($C_{3'''}$& $C_{5'''}$), 118.7 ($C_{4'}$), 121.7 (C_6), 122.3 (C_5), 126.1 (C_7), 126.2 ($C_{1''}$), 127.0 ($C_{2''}$& $C_{6''}$), 129.2 (C_4), 140.1 (C_3&$C_{2'}$), 143.2 ($C_{5'}$), 153.2 (C_{8a}), 159.7 ($C_{4''}$); IR (KBr, Cm^{-1}): 3116 (N-H), 1577 (C=N); MS (ESI, m/z): 293.07.

4.10.7. 2-(2H-chromen-3-yl)-5-(4-methoxyphenyl)-1H-imidazole (13h):

Light green solid; yield 42%; mp.150-155 °C. ^{1}H NMR ($CDCl_3$) δ: 3.88 (s, OCH_3) , 5.44 (s, OCH_2) , 6.84 (s, $H_{4'}$), 6.86 (d , *J* = 8 Hz, H_8), 6.93 (td, *J* = 7.2, 0.8, 7.6, 1.2Hz, H_6), 6.97 (d, *J* = 8.8 Hz, 2H, $H_{3''}$& $H_{5''}$), 7.16 (dd, *J* = 7.6, 2.0, 7.2, 1.6 Hz, H_5), 7.25 (td, *J* = 8.0, 1.6, 7.6, 1.2 Hz, H_7), 7.59 (s, H_4), 7.71 (s, NH), 7.92 (d, *J* = 8.8 Hz, $H_{2''}$&$H_{6''}$). ^{13}CNMR (DMSO-d_6) δ: 55.6 (C_2), 65.5 (O-C), 113.6 ($C_{3''}$&$C_{5''}$), 114.1 (C_8), 115.8 (C_{4a}), 120.6 ($C_{4'}$), 121.6 (C_6), 122.0 (C_5), 126.7 (C_7&$C_{1''}$), 129.4 ($C_{2''}$& $C_{6''}$), 130.1 (C_4), 140.5 (C_3& $C_{2'}$), 141.4 ($C_{5'}$), 150.6 (C_{8a}), 163.2 ($C_{4''}$); IR (KBr, Cm^{-1}): 3068 (N-H), 1573 (C=N); MS (ESI, m/z): 305.

4.10.8.3-(2-(2H-chromen-3-yl)-1H-imidazol-5-yl) pyridine (13i):

Brown solid; yield 45%; mp.265-270 °C. ^{1}H NMR (DMSO-d_6) δ: 5.23 (s, OCH_3), 6.76 (d, J = 8.0 Hz, H_8), 6.96 (t, *J* = 7.2 Hz, H_6), 7.17 (m, 3H, H_5, H_4& $H_{4'}$), 7.4 (t, *J* = 4.8 Hz, H_7), 7.96

(s, $H_{4''}$), 8.15 (dt, *J* = 2.0 Hz, $H_{5''}$), 8.42 (d, *J* = 3.6 Hz, $H_{6''}$), 9.03 (s, $H_{2''}$), 12.82 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 64.6 (C_2), 115.5 (C_8), 119.1 (C_{4a}), 121.7 ($C_{4'}$), 122.2 (C_6), 122.9 (C_5), 123.6 ($C_{5''}$), 127.1 (C_7), 128.1 (C_4), 128.8 ($C_{3''}$), 129.3 ($C_{4''}$), 131.3 (C_3), 143.9 ($C_{2'}$), 145.8 ($C_{6''}$& $C_{5'}$), 147.3 ($C_{2''}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3128 (N-H), 1573 (C=N); MS (ESI, m/z): 276.02 $([M+1]^+$.

4.10.9.2-(2H-chromen-3-yl)-5-(thiophen-2-yl)-1H-imidazole (13j):

Brown solid; yield 47%; mp.170-175 °C. ^{1}H NMR (DMSO-d_6) δ: 5.27 (d, *J* = 1.6 Hz, OCH_2), 6.84 (s, $H_{4'}$), 6.86 (t, *J* = 9.2 Hz, H_8), 6.9 (td, *J* = 7.2, 1.2 Hz, H_6), 7.04 (m, 2H, H_5& $H_{4''}$), 7.15(td, *J* = 8.0, 1.6, 7.6, 1.2Hz, H_7), 7.23 (dd, *J* = 4.8, 0.8, 5.2, 1.2 Hz, $H_{3''}$), 7.26 (s, H_4), 7.27 (d, *J* = 3.6 Hz, $H_{5''}$). ^{13}C NMR (DMSO-d_6) δ: 64.6 (C_2), 115.4 (C_8), 118.9 (C_{4a}), 121.7 ($C_{4'}$& C_6), 122.2 ($C_{5'}$), 122.8 (C_5& $C_{5''}$), 127.1 (C_7&$C_{3''}$), 127.6 (C_4& $C_{4''}$), 129.2 (C_3& $C_{2''}$), 14.1 ($C_{2'}$), 153.2 (C_{8a}); IR (KBr, Cm^{-1}): 3023 (N-H), 1578 (C=N); MS (ESI, m/z): 281.12 $([M+1]^+$, 282.16 $[M+2]^+$, 283.05 $[M+3]^+$.

4.10.10. 2-(8-Methoxy-2H-chromen-3-yl)-5-phenyl-1H-imidazole (14a):

White solid; yield 55%; mp.145-150 °C. ^{1}H NMR (DMSO-d_6) δ: 3.78 (s, OCH_3), 5.19 (s, OCH_2), 6.78 (dd, *J* = 6.8, 2.0, 7.2, 2.4 Hz, H_7), 6.9 (m, 2H, H_5& $H_{4'}$), 7.15 (s, H_4), 7.2 (t, *J* = 7.2, 7.6 Hz, H_6), 7.36 (t, *J* = 7.6, 8.0 Hz, 2H, $H_{3''}$&$H_{5''}$),7.44 (t, *J* = 7.6, 8.0 Hz, $H_{4''}$) 7.82 (d, *J* = 7.6 Hz, 2H, $H_{2''}$& $H_{6''}$), 12.69 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.6 (O-C), 64.6 (C_2), 112.8 (C_7), 114.8 (C_{4a}), 118.7 (C_5), 119.1 ($C_{4'}$), 121.4 (C_6), 122.3 ($C_{2''}$&$C_{6''}$), 126.2($C_{4''}$), 128.4 ($C_{3''}$& $C_{5''}$), 128.8 (C_4), 134.3 ($C_{1''}$), 141.0 (C_3& $C_{2'}$), 142.0 ($C_{5'}$), 143.2 (C_{8a}), 147.5 (C_8); IR (KBr, Cm^{-1}): 3119 (N-H), 1571 (C=N);MS (ESI, m/z): 305.06 $([M+H]^+$.

4.10.11.5-(4-Bromophenyl)-2-(8-methoxy-2H-chromen-3-yl)-1H-imidazole (14e):

Yellow solid; yield 55%; mp.155-160 °C. ^{1}H NMR ($CDCl_3$-d_6): δ 3.89 (s, 3H, OCH_3), 5.34 (s, 2H, OCH_2), 6.71 (d, *J* = 6.8 Hz, 1H, H_7), 6.83 (m, 3H, H_6, $H_{4'}$&H_5), 7.35 (s, 1H, H_4), 7.49 (d, *J* = 8.4 Hz, 2H, $H_{3''}$& $H_{5''}$), 7.6 (d, *J* = 8 Hz, 2H, $H_{2''}$& $H_{6''}$). ^{13}C NMR (DMSO-d_6) δ: 55.6 (O-C), 64.5 (C_2), 112.9 (C_7), 115.0 (C_{4a}), 119.1 (C_5), 120.7 ($C_{4'}$), 121.4 (C_6), 122.9 ($C_{4''}$), 126.3 (C_4), 128.7 ($C_{2''}$& $C_{6''}$), 131.3 ($C_{1''}$), 132.4 ($C_{3''}$&$C_{5''}$), 142.0 (C_3& $C_{2'}$), 143.5 ($C_{5'}$), 144.7 (C_{8a}), 147.5 (C_8); IR (KBr, Cm^{-1}): 3123 (N-H), 1576 (C=N); MS (ESI, m/z): 386.24 $[M+2]^+$.

4.10.12.5-(4-(Benzyloxy)phenyl)-2-(8-methoxy-2H-chromen-3-yl)-1H-imdazole (14f).

Pale green solid; yield 40%; mp.150-160 °C. ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, OCH_3), 5.12 (s, OCH_2), 5.16 (s, OCH_2), 6.82 (dd, *J* = 6.4, 2.0, 6.8, 2.4 Hz, H_7), 6.9 (m, 2H, H_6& H_5), 7.04 (d, *J* = 6.8 Hz, 2H, $H_{3''}$& $H_{5''}$), 7.16 (s, $H_{4'}$), 7.4 (m, 6H, H_4, Bn-5H), 7.72 (d, *J* = 8.4 Hz, 2H, $H_{2''}$& $H_{6''}$), 12.5 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (O-C), 65.1 (C_2), 69.7 (Bn-O-C), 113.3 (C_7), 115.4 ($C_{3''}$, $C_{5''}$& C_{4a}), 119.0 ($C_{4'}$), 119.5 (C_5), 121.9 (C_6), 123.6 ($C_{1''}$), 126.2 ($C_{2'''}$& $C_{6'''}$), 127.9 ($C_{4'''}$), 128.2 ($C_{2''}$& $C_{6''}$), 128.3 ($C_{3'''}$& $C_{5'''}$), 128.9 (C_4), 137.6 (C_3& $C_{2'}$), 142.5 ($C_{5'}$), 143.6 ($C_{1'''}$), 148.0 (C_8& C_{8a}), 157.7 ($C_{4''}$); IR (KBr, Cm^{-1}): 3082 (N-H), 1576 (C=N);MS (ESI, m/z): 411.04 $([M+1]^+$.

4.10.13.5-(4-Fluorophenyl)-2-(8-methoxy-2H-chromen-3-yl)-1H-imidazole (14g).

Pale green solid; yield 45%; mp.135-140 °C. ^{1}H NMR (CDCl3) δ: 3.9 (s, OCH_3), 5.36 (s, OCH_2), 6.72 (d, *J* = 7.2 Hz, H_7), 6.82 (d, *J* = 7.2 Hz, H_5), 6.88 (t, *J* = 7.2 Hz, H_6), 6.88 (s, $H_{4'}$), 7.08 (t, *J* = 8.4, 8.8 Hz, 2H, $H_{2''}$& $H_{6''}$), 7.3 (s, H_4), 7.7 (t, *J* = 8.8, 10.8, 2H, $H_{3''}$& $H_{6''}$). ^{13}C NMR (DMSO-d_6) δ: 55.6 (O-C), 64.5 (C_2), 112.9 (C_7), 115.2 (C_{4a}), 115.4 ($C_{3''}$ & $C_{5''}$), 118.9 (C_5), 119.1 ($C_{4'}$), 121.4 (C_6), 122.0 ($C_{1''}$), 126.2 ($C_{2''}$& $C_{6''}$), 126.2 (C_4), 142.0 (C_3& $C_{2'}$), 143.6 ($C_{5'}$), 147.5 (C_{8a}), 159.8 (C_8), 162.2 ($C_{4''}$); IR (KBr, Cm^{-1}): 3081 (N-H), 1579 (C=N); MS (ESI, m/z): 323.09 $[M+1]^+$.

4.10.14. 2-(8-Methoxy-2H-chromen-3-yl)-5-(4-methoxyphenyl)-1H-imidazole (14h).

Brown solid; yield 40%; mp.150-155 °C. ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, 2xOCH_3), 5.17 (s, OCH_2), 6.78 (dd, *J* = 6.0, 2.8 Hz, H_6), 6.89 (s, $H_{4'}$), 6.9 (d, *J* = 2.8 Hz, 2H, H_7& H_5), 6.96 (d, *J* = 8.0 Hz, 2H, $H_{3''}$& $H_{5''}$), 7.16 (s, H_4), 7.72 (d, *J* = 8.8 Hz, 2H, $H_{2''}$& $H_{6''}$), 12.61 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.5 (O-C), 56.1 (O-C), 65.1 (C_2), 113.2 (C_7), 114.5 ($C_{3''}$& $C_{5''}$), 118.9 (C_{4a}), 119.5 ($C_{4'}$& C_5), 121.9 (C_6), 123.6 ($C_{1''}$), 126.2 ($C_{2''}$& $C_{6''}$), 129.1 (C_4), 136.5 (C_3 & $C_{2'}$), 142.5 ($C_{5'}$), 143.6 (C_{8a}), 148.0 (C_8), 158.6 ($C_{4''}$); IR (KBr) Cm^{-1}: 3130 (N-H), 1575 (C=N); MS (ESI, m/z): 335.12 $[M+1]^+$.

4.10.15.3-(2-(8-Methoxy-2H-chromen-3-yl)-1H-imidazole-5-yl)pyridine(14i).

Brown solid; yield 40%; mp.225-230 °C. ^{1}H NMR (DMSO-d_6) δ: 3.78 (s, OCH_3), 5.19 (s, OCH_2), 6.8 (d, *J* = 6 Hz, H_7), 6.9 (m, 2H, H_5& H_6), 7.19 (s, $H_{4'}$), 7.41 (t, *J* = 4.8, 6.0 Hz, $H_{5''}$), 7.93 (s, H_4), 8.15 (d, *J* = 8.0 Hz, $H_{6''}$), 8.42 (d, *J* = 3.2 Hz, $H_{4''}$), 9.03 (s, $H_{2''}$), 12.82 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (O-C), 65.0 (C_2), 113.5 (C_7), 119.6 (C_{4a}), 119.8 (C_5), 121.9 ($C_{4'}$), 123.4 (C_6), 124.1 ($C_{5''}$), 128.0 (C_4), 133.0 ($C_{4''}$), 136.0 (C_3& $C_{2'}$), 131.8 ($C_{3''}$), 142.6 (C_5), 144.4 ($C_{6''}$), 146.3 (C_{8a}), 147.8 ($C_{2''}$), 148.0 (C_8); IR (KBr, Cm^{-1}): 3085 (N-H), 1581 (C=N); MS (ESI, m/z): 306.12 $[M+1]^+$.

4.10.16. 5-2-(8-Methoxy-2H-chromen-3-yl)-5-(thiophen-2-yl)-1H-imidazole (14j).

Pale green solid; yield 40%; mp.155-160 °C. ^{1}H NMR (DMSO-d_6) δ: 3.77 (s, OCH_3), 5.14 (s, OCH_2), 6.78 (dd, *J* = 6.4, 1.6, 6.8, 2.0 Hz, H_6), 6.91 (m, 2H, H_7& $H_{4'}$), 7.05 (dd, *J* = 4.8, 3.6 Hz, $H_{4''}$), 7.14 (s, H_4), 7.31 (d, *J* = 3.6 Hz, $H_{3''}$), 7.36 (d, *J* = 5.2 Hz, H_5), 7.67 (d, *J* = 1.6 Hz, $H_{5''}$), 12.7 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (O-C), 65.0 (C_2), 113.4 (C_7), 114.6 (C_{4a}), 119.6 (C_5& $C_{4'}$), 121.9 ($C_{6'}$), 122.0 ($C_{5'}$), 123.3 ($C_{5''}$), 123.5 ($C_{3''}$), 123.8 ($C_{4''}$), 128.1 (C_4),

137.0 ($C_{2''}$), 138.6 ($C_{2'}$), 142.5 (C_3), 143.5 (C_{8a}), 148.0 (C_8); IR (KBr, Cm^{-1}): 3086 (N-H), 1574 (C=N); MS (ESI, m/z): 311.01 $[M+1]^+$, 312.16 $[M+2]^+$, 313.06 $[M+3]^+$.

4.10.17. 2-(7-Methoxy-2-H-chromen-3-yl)-5-phenyl-1-H-imidazole (15a).

Yellow solid; yield50%; mp.155-160 °C. ^{1}H NMR ($CDCl_3$+DMSO-d_6) δ: 3.78 (s, OCH_3), 5.28 (s, OCH_2), 6.46 (s,H_8), 6.48 (d, *J* = 2.4 Hz, H_6), 6.81 (s, $H_{4'}$), 6.96 (d, *J* = 8.0 Hz, H_5), 7.27 (t, *J* = 7.6, 4.0 Hz, $H_{4''}$), 7.34 (s, H_4), 7.39 (t, *J* = 7.6 Hz, 2H,$H_{3''}$& $H_{5''}$), 7.69 (d, *J* = 7.2Hz, 2H, $H_{2''}$& $H_{6''}$),12.12 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.2 (O-C), 64.8 (C_2), 101.5 (C_8), 107.6 (C_6), 115.4 (C_{4a}), 118.7 ($C_{4'}$), 124.3 ($C_{2''}$& $C_{6''}$), 127.8 (C_5), 128.5 (C_4, $C_{3''}$& $C_{5''}$), 134.2 ($C_{1''}$), 138.7 ($C_{2'}$& C_3), 143.7 ($C_{5'}$), 154.5 (C_{8a}), 160.4 (C_7); IR (KBr, Cm^{-1}): 3000 (N-H), 1572 (C=N); MS (ESI, m/z): 305.06 $[M+1]^+$.

4.10.18.5-(4-Bromophenyl)-2-(7-methoxy-2-H-chromen-3-yl)-1-H-imidazole (15e).

Yellow solid; yield 45%; mp.175-180 °C. ^{1}H NMR ($CDCl_3$) δ: 3.79 (s, OCH_3), 5.27 (s, OCH_2), 6.47 (s, H_8), 6.5 (d, *J* = 2.0 Hz, H_6), 6.8 (s, $H_{4'}$), 6.98 (d, *J* = 8.4 Hz, H_5), 7.32 (s, H_4), 7.5 (d, *J* = 8.8 Hz, 2H, $H_{2''}$& $H_{6''}$), 7.6 (d, *J* = 7.6 Hz, 2H, $H_{3''}$& $H_{5''}$). ^{13}C NMR (DMSO-d_6) δ: 55.3 (O-C), 64.7 (C_2), 101.5 (C_8), 107.7 (C_6), 115.3 (C_{4a}), 118.9 ($C_{4'}$), 119.9 ($C_{4''}$), 126.2 (C_5, $C_{2''}$& $C_{6''}$), 127.9 (C_4, $C_{3''}$& $C_{5''}$), 131.3 ($C_{1''}$), 137.8 ($C_{2'}$& C_3), 143.9 ($C_{5'}$), 154.6 (C_{8a}), 160.5 (C_7); IR (KBr, Cm^{-1}): 3085 (N-H), 1570 (C=N); MS (ESI, m/z): 386$[M+2]^+$.

4.10.19.5-(4-(Benzyloxy)phenyl)-2-(7-methoxy-2-H-chromen-3-yl)-1-H-imidazole (15f).

Yellow solid; yield 45%; mp.320-330 °C. ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, OCH_3), 4.88 (s, OCH_2), 5.12 (s, OCH_2), 6.55 (d, *J* = 8.4, 2H, $H_{3''}$& $H_{5''}$), 7.11 (d, *J* = 8.4 Hz, H_6), 7.25 (d, *J* = 8.0 Hz, H_5), 7.41 (s, H_4), 7.44 (t, *J* = 7.6 Hz, 3H, $H_{3'''}$, $H_{4'''}$& $H_{5'''}$), 7.47 (d, *J* = 6.8 Hz, 2H, $H_{2''}$& $H_{6''}$), 7.72 (d, *J* = 8.4 Hz, 2H, $H_{2''}$& $H_{6''}$), 12.6 (s, NH).^{13}C NMR (DMSO-d_6) δ: 56.1 (O-C), 65.1 (C_2), 69.7 (Bn-O-C), 113.3 (C_8), 115.4 ($C_{3''}$, $C_{5''}$& C_{4a}), 119.0 ($C_{4'}$), 119.5 (C_5),

121.9 (C_6), 123.6 ($C_{1''}$), 126.2 ($C_{2'''}$& $C_{6'''}$), 127.9 ($C_{4'''}$), 128.2 ($C_{2''}$& $C_{6''}$), 128.3 ($C_{3'''}$& $C_{5'''}$), 128.9 (C_4), 137.6 (C_3& $C_{2'}$), 142.5 ($C_{5'}$), 143.6 ($C_{1'''}$), 148.0 (C_7& C_{8a}), 157.7 ($C_{4''}$); IR (KBr, Cm^{-1}): 3007 (N-H), 1597 (C=N);MS (ESI, m/z): 411.04 $[M+1]^+$.

4.10.20. 5-(4-Fluorophenyl)-2-(7-methoxy-2-H-chromen-3-yl)-1-H-imidazole (15g).

Yellow solid; yield 50%; mp.165-170 °C. ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, OCH_3), 5.17 (s, OCH_2), 6.49 (d, *J* = 2.4 Hz, H_8), 6.55 (dd, *J* = 8.0, 2.4, 8.4, 2.8 Hz, H_6), 7.1 (d, *J* = 8.4 Hz, H_5), 7.14 (s, $H_{4'}$), 7.2 (t, *J* = 6.8Hz, 2H, $H_{2''}$& $H_{6''}$), 7.73 (s, H_4), 7.83 (dd, *J* = 8.8, 8.0 Hz, 2H, $H_{2''}$& $H_{6''}$), 12.57 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.3 (O-C), 64.8 (C_2), 101.5 (C_8), 107.6 (C_6), 115.3 (C_{4a}), 118.8 ($C_{3''}$& $C_{5''}$), 120.0 ($C_{4'}$), 126.1 (C_5), 126.2 ($C_{1''}$), 127.8 (C_4, $C_{2''}$&$C_{6''}$), 139.2 ($C_{2'}$& C_3), 143.7 ($C_{5'}$), 154.5 (C_{8a}), 160.0 (C_4), 162.1 ($C_{4''}$); IR (KBr, Cm^{-1}): 3039 (N-H), 1572 (C=N); MS (ESI, m/z): 323 $[M+1]^+$.

4.10.21.2-(7-Methoxy-2-H-chromen-3-yl)-5-(4-methoxyphenyl)-1-H-imidazole (15h).

Brown solid; yield 45%; mp.135-140 °C. ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, OCH_3), 3.85 (s, OCH_3), 5.5 (s, OCH_2), 6.45 (m, 2H, $H_{3''}$& $H_{5''}$), 6.6 (s, $H_{8'}$), 6.9 (m, 3H, $H_{6'}$, $H_{4'}$), 7.45 (m, 1H,), 7.6 (m, H_5), 7.8 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.0 (O-C), 58.3 (O-C), 64.8 (C_2), 101.5 (C_8), 107.6 (C_6), 114.0 (C_{4a}), 115.3 ($C_{3''}$& $C_{5''}$), 119.9 ($C_{4'}$), 124.8 ($C_{1''}$), 125.7 (C_5), 127.8 ($C_{2''}$& $C_{6''}$), 128.5 (C_4), 139.5 ($C_{2'}$& C_3), 140.0 ($C_{5'}$), 154.5 (C_{8a}), 160.3 ($C_{4''}$), 160.4 (C_7); IR (KBr, Cm^{-1}): 3003 (N-H), 1570 (C=N); MS (ESI, m/z): 334.96 $[M+1]^+$.

4.10.22.3-(2-(7-Methoxy-2-H-chromen-3-yl)-1-H-imidazol-5-yl)pyridine(15i).

Brown solid; yield 50%; mp.240-245 °C. ^{1}H NMR (DMSO-d_6) δ: 3.78 (s, OCH_3), 5.2 (s, OCH_2), 6.8 (d, *J* = 6.0 Hz, H_8), 6.85 (m, 2H, H_5& H_6), 7.19 (s, $H_{4'}$), 7.4 (t, *J* = 6.0 Hz, $H_{5'''}$), 7.95 (s, H_4), 8.15 (d, *J* = 8 Hz, $H_{6''}$), 8.45 (d, *J* = 3.2 Hz, $H_{4''}$), 9.1 (s, $H_{2''}$), 12.8 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (O-C), 65.0 (C_2), 113.5 (C_8), 119.6(C_{4a}), 119.8 (C_5), 121.9 ($C_{4'}$),

123.4 (C_6), 124.1 ($C_{5''}$), 128.0 (C_4), 133.0 ($C_{4''}$), 136.0 (C_3& $C_{2'}$), 131.8 ($C_{3''}$), 142.6 (C_5), 144.4 ($C_{6''}$), 146.3 (C_{8a}), 147.8 ($C_{2''}$), 148.0 (C_7); IR (KBr, Cm^{-1}): 3085 (N-H), 1581 (C=N); MS (ESI, m/z): 306 ($[M+1]^+$.

4.10.23. 2-(7-Methoxy-2-H-chromen-3-yl)-5-(thiophen-2-yl)-1-H-imidazole (15j).

Brown solid; yield 40%; mp.120-124 °C. ^{1}H NMR (DMSO-d_6) δ: 3.75 (s, OCH_3), 5.14 (s, OCH_2), 6.49 (s, $H_{4'}$), 6.54 (dd, *J* = 8.4, 2.4 Hz, H_8), 7.04 (t, *J* = 4.0, 4.4 Hz, $H_{4''}$), 7.09 (s, H_4), 7.12 (d, *J* = 4.8 Hz, H_6), 7.29 (d, *J* = 2.8 Hz, $H_{3''}$), 7.35 (d, *J* = 4.8 Hz, H_5), 7.63 (d, *J* = 1.6 Hz, $H_{5''}$),12.6 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.2 (O-C), 64.7 (C_2), 101.5 (C_8), 107.7 (C_6), 113.7 (C_{4a}), 119.0 ($C_{4'}$), 121.3 ($C_{5'}$), 123.2 ($C_{5''}$), 127.5 (C_5& $C_{3''}$), 127.9 ($C_{4''}$), 136.3 (C_3), 138.3 ($C_{2''}$), 143.3 ($C_{2'}$), 154.5 (C_{8a}), 160.4 (C_7); IR (KBr, Cm^{-1}): 3111 (N-H), 1604 (C=N); MS (ESI, m/z): 311.01 $[M+1]^+$, 312.16 $[M+2]^+$, 313.06 $[M+3]^+$.

4.10.24. 2-(5-Methoxy-2H-chromen-3-yl)-5-phenyl-1H-imidazole (16a).

White solid; yield 60%; mp.165-170 °C. ^{1}H NMR ($CDCl_3$) δ: 3.86 (s, OCH_3), 5.28 (s, OCH_2), 6.47 (d, *J* = 8.4 Hz, H_8), 6.54 (d, *J* = 8.4 Hz, H_6), 7.1 (t, *J* = 8.4 Hz, H_7), 7.17 (s, $H_{4'}$), 7.26 (s, H_4), 7.28 (d, *J* = 7.2 Hz, 2H, $H_{2''}$& $H_{6''}$), 7.38 (dd, *J* = 8.0, 15.4 Hz, 3H, $H_{3'''}$, $H_{4'''}$& $H_{5'''}$), 7.69 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (OCH_3), 64.8 (C_2), 104.6 (C_8), 108.9 (C_6), 112.1 (C_{4a}), 114.1 ($C_{4'}$), 121.6 ($C_{2''}$& $C_{6''}$), 124.8 ($C_{4''}$), 129.7 ($C_{1''}$), 128.9 (C_7, $C_{3''}$& $C_{5''}$), 134.8 (C_3& $C_{2'}$), 144.2 ($C_{5'}$), 154.4 (C_{8a}), 155.8 (C_5); IR (KBr, Cm^{-1}): 3134 (N-H), 1584 (C=N); MS (ESI, m/z): 305.13 $[M+1]^+$.

4.10.25. 5-(4-Chlorophenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole (16b).

Yellow solid; yield 60%; mp.170-174 °C. ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, OCH_3), 5.27 (s, OCH_2), 6.47 (d, *J* = 8.4 Hz, H_8), 6.54 (d, *J* = 8.0 Hz, H_6), 7.11 (t, *J* = 8.4, 8.0 Hz, H_7), 7.16 (s, $H_{4'}$), 7.26 (s, H_4), 7.33 (m, 4H, $H_{2''}$, $H_{3''}$, $H_{5''}$& $H_{6''}$), 7.7 (s, NH). ^{13}C NMR (DMSO-d_6) δ:

55.7 (OCH_3), 64.8 (C_2), 103.6 (C_8), 108.9 (C_6), 111.6 (C_{4a}), 114.9 ($C_{4'}$), 126.1 ($C_{2''}$& $C_{6''}$), 128.8 (C_4, $C_{3''}$& $C_{5''}$), 129.7 ($C_{1''}$& C_7), 132.5 ($C_{4''}$), 132.6 (C_3& $C_{2'}$), 144.8 ($C_{5'}$), 154.7 (C_{8a}), 155.6 (C_5); IR (KBr, Cm^{-1}): 3015 (N-H), 1582 (C=N); MS (ESI, m/z): 339.08 $[M+1]^+$, 341.11 $[M+2]^+$.

4.10.26. 5-(2,4-Dichlorophenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole (16c).

Off white solid; yield 55%; mp.190-195 °C. ^{1}HNMR ($CDCl_3$) δ: 3.87(s, OCH_3), 5.27 (s, OCH_2), 6.48 (d, J = 7.6 Hz, H_8), 6.55 (d, J = 8.0 Hz, H_6), 7.12 (t, J = 8.4, 8.0 Hz, H_7), 7.18 (s, $H_{4'}$), 7.26 (s, H_4), 7.29 (d, J = 2.0 Hz, $H_{5''}$), 7.32 (d, J = 2.0 Hz, $H_{3''}$), 7.44 (d, J = 2.0 Hz, $H_{6''}$), 7.71 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 56.1 (OCH_3), 64.7 (C_2), 104.7 (C_8), 108.9 (C_6), 114.9 ($C_{4'}$), 127.8 ($C_{1''}$& C_4), 129.8 (C_7), 130.1 ($C_{6''}$), 130.7 ($C_{3''}$), 130.8 ($C_{2''}$), 131.4 ($C_{4''}$), 136.4 (C_3& $C_{2'}$), 143.8 ($C_{5'}$), 154.5 (C_{8a}), 155.9 (C_5); IR (KBr, Cm^{-1}): 3013 (N-H), 1583 (C=N); MS (ESI, m/z): 373.06 $[M+1]^+$, 375.02 $[M+2]^+$.

4.10.27. 2-(5-Methoxy-2H-chromen-3-yl)-5-(3-nitrophenyl)-1H-imidazole (16d).

Orange solid; yield 55%; mp.245-250 °C. ^{1}H NMR (DMSO-d_6) δ: 3.86 (s, OCH_3), 5.18 (s, OCH_2), 6.52 (d, J = 8.0 Hz, H_8), 6.64 (d, J = 8.0 Hz, H_6), 7.14 (t, J = 8.4, 8.0 Hz, H_7) 7.44 (s, H_4), 7.66 (t, J = 8.0 Hz, $H_{5''}$), 8.03 (s, $H_{4'}$), 8.05 (d, J = 7.2 Hz, $H_{6''}$), 8.25 (d, J = 7.6 Hz, $H_{4''}$),8.6 (s, $H_{2''}$),12.9 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.6 (OCH_3), 64.2 (C_2), 104.2 (C_8), 108.4 (C_6), 111.4 (C_{4a}), 114.3 ($C_{4'}$), 118.2 ($C_{2''}$), 120.6 ($C_{4''}$), 120.8 ($C_{5''}$), 129.5 (C_7& C_4), 130.0 ($C_{6''}$), 130.4 ($C_{1''}$), 136.1 ($C_{2'}$), 138.6 (C_3), 142.2 ($C_{5'}$), 148.3 ($C_{3''}$), 153.9 (C_{8a}), 155.9 (C_5); IR (KBr, Cm^{-1}): 3092 (N-H), 1580 (C=N); MS (ESI, m/z): 350.1 $[M+1]^+$.

4.10.28. 5-(4-Bromophenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole (16e).

Off white solid; yield 60%; mp.195-200 °C. ^{1}H NMR ($CDCl_3$) δ: 3.85 (s, OCH_3), 5.26 (s, OCH_2), 6.47 (d, J = 8.4 Hz, H_8), 6.54 (d, J = 8.0 Hz, H_6), 7.11 (t, J = 8.4, 8.0 Hz, H_7), 7.17 (s,

H4$_{'}$), 7.33 (s, H_4), 7.49 (d, J = 8.0 Hz, 4H, $H_{2''}$, $H_{3''}$, $H_{5''}$& $H_{6''}$), 7.62 (s, NH). ^{13}C NMR (DMSO-d_6) δ: 55.7 (OCH_3), 64.8 (C_2), 103.6 (C_8), 109.0 (C_6), 111.6 (C_{4a}), 114.9 ($C_{4'}$), 120.6 ($C_{4''}$), 126.4 (C_4, $C_{2''}$& $C_{6''}$), 129.8 (C_7& $C_{1''}$), 131.8 ($C_{3''}$& $C_{5''}$), 137.0 ($C_{2'}$& C_3), 144.8 ($C_{5'}$), 155.6 (C_{8a}), 154.7 (C_5); IR (KBr, Cm^{-1}): 3135 (N-H), 1583 (C=N); MS (ESI, m/z): 385.02 $[M+1]^+$, 386.02 $[M+2]^+$.

4.10.29. 5-(4-(Benzyloxy)phenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole (16f).

Pale green solid; yield 54%; mp.175-180 °C. ^{1}H NMR ($CDCl_3$) δ: 3.86(s, OCH_3), 5.09 (s, OCH_2), 5.27 (d, J = 0.8 Hz, Bn-OCH_2), 6.47 (d, J = 8.4 Hz, H_8), 6.54 (d, J = 8.0Hz, H_6), 7.02 (d, J = 8.8 Hz, 2H, $H_{3''}$& $H_{5''}$) 7.1 (t, J = 8.4 Hz, H_7), 7.14 (s, H_4), 7.25 (s, H_4), 7.34 (d, J = 7.2 Hz, 2H, $H_{2'''}$& $H_{6'''}$), 7.39 (t, J = 6.8, 7.6 Hz, 3H, $H_{3'''}$, $H_{4'''}$& $H_{5'''}$), 7.44 (d, J = 7.2 Hz, $H_{2''}$& $H_{6''}$), 7.6 (s, NH). ^{13}C NMR ($CDCl_3$); δ 55.6 (OCH3), 64.9 (C_2), 70.1 (Bn-O-C), 103.6 (C_8), 108.9 (C_6), 111.7 (C_{4a}), 114.3 ($C_{3''}$& $C_{5''}$), 115.2 ($C_{4'}$), 120.7 ($C_{1''}$), 126.2 ($C_{2'''}$& $C_{6'''}$), 127.5 ($C_{4'''}$), 128.0 ($C_{2''}$& $C_{6''}$), 128.6 (C_4, $C_{3'''}$& $C_{5'''}$), 129.5 (C_7), 136.9 (C_3& $C_{2'}$), 143.7 ($C_{5'}$), 144.3 ($C_{1'''}$), 154.7 (C_{8a}), 155.6 (C_5), 158.1 ($C_{4''}$); IR (KBr, Cm^{-1}): 3072 (N-H), 1580 (C=N); MS (ESI, m/z): 411.14 $[M+1]^+$.

5.0 Biological Assay[36]:

5.1 Angiogenesis Assay:

Human clonal endothelial colony forming cells (ECFC, Engenator) were cultured in EGM-2MV media containing 10% FBS (EGM-2MV+FBS). ECFCs were expanded to passage 7, rapidly frozen and stored in liquid N_2 until further use. Human adipose derived stem cells (ADSC, Zen Bio) were derived from pooled donor samples, cultured in EGM-2MV+FBS, rapidly frozen and stored over liquid N_2 until further use.On day1, ECFCs were quickly thawed, diluted into pre-warmed EGM-2 media containing 10% FBS (EGM-2+FBS), and incubated for 24 hours. ECFCs were washed with PBS, trypsinized and

replated withEGM-2+FBS for 48 hours. On third day, ADSCs were quickly thawed and diluted into pre-warmed EGM-2MV+FBS. The ADSCs were collected by centrifugation and suspended in Optimized Media (TCS Cell works). ADSCs (5000/well) were added to a 384 well Cell Bind plate (Corning), incubated at room temperature for 5 minutes, and then placed in a CO_2 incubator overnight. On fourth day, ECFC cultures from Day 2 were washed with PBS, trypsinized and resuspendedwithEGM-2+FBS. Cells were collected by centrifugation, suspended in Optimized Media and passed through a sterile 23 gauge needle. ECFCs (500 /well) were overlaid onto the ADSC feeder layer from Day 3 and returned to the CO_2 incubator. After 2 hours, rhVEGF (10 ng/ml; R&D Systems) and compounds at the indicated concentrations were added (0.5% (v/v) DMSO final) and incubated for 96 hours. Maximum and minimum responses correspond to rhVEGF +0.5% (v/v) DMSO orrhVEGF + 500 nMsutent (Sunitinib), respectively.

5.2 Endothelial and Nuclear Staining:

Co-cultures were fixed with 3.7% formaldehyde-PBS for 20 minutes, treated with 0.1% TX-100-PBS for 20 minutes, washed twice with PBS, and incubated with 63 ng/ml mouse Anti-Human CD31 antibody (BD Pharmigen, 550389) in PBS containing 1% BSA at 4°C overnight. Following PBS wash, samples were then incubated with 3ug/ml Alexa 488 goat secondary antibody in PBS for 1 hr and then washed twice with PBS before staining cellular DNA with Hoechst stain (2 ug/ml).

***5.3 Cellular Imaging*:**

Fixed and stained ECFC-ADSC co-cultures were analyzed with an Array Scan VTI (Thermo Scientific) using a 5x objective and collecting 4, non-adjacent frames per well; nuclei and CD31 were visualized using the XF93-Hoechst and XF93-Alexa-488 dichroic mirror emission filter pairs, respectively. Endothelial tube features were determined with the Cellomics Tube Formation V3 application by analysis of the CD31 channel. Relative cell

death in the ECFC-ADSC co-culture was measured by loss of valid nuclear objects as determined by the Target Activation V3 applications.

6.0 Molecular Docking Studies:

With a view to find a correlation between the anti-angiogenesis activity of 5-(substituted aryl)-2-(5methoxy-2H-chromen-3-yl)-1H-imidazoles (**16a-f, 15h, 14f, h, j, 13f, g, I, j**)and theirbinding with target proteins viz; KRAS, Wnt and VEGF,the docking studies were carried out employing AutoDocksoftware.[37,38] The receptor-ligand interactions and the corresponding interaction energies were identified after the docking studies.

Since Human KRAS protein is a target in anti-angiogenesis[39-43]**,** we have selected the crystal structure of Human KRASreceptor protein with PDB ID: (4EPX.pdb) from protein data bank.[44] Docking studies were performed with fourteen molecules (**16a-f, 15h, 14f, h, j, 13f, g, i, j**) to investigate the receptor interactions. All the fourteen molecules were constructed using the tools of SYBYL software2 and the structures were minimized using 500 steps of steepest descent followed by 500 steps of conjugate gradient methods and structure was stabilized at 1100 steps. Later binding / catalytic sites of protein 4EPX.pdb were identified using biopolymer module of the SYBYL-X (Tripos) software.

Further, the molecules were loaded into the AutoDock software[45], and converted into pdb structures by applying the charge assigning methodof Kolman and Gasteiger Huckle and saved into a pdbqt form. Later, polar atoms are added to protein and protein structure was kept in grid N-dimension (Grid sizes for receptor X = 11.393, Y = 1.498, Z = 9.595; ligand X = 40, Y = 36, Z = 38) for fourteen molecules. Virtual screening studies were performed using AutoDock 4.0 software to predict interactions based on Genetic and Lamarckian

algorithms.[46] Docking was performed and 140 results were generated on the basis of their energy values. The results were put in the chronological order and analyzed.

Similarly the above procedure was also applied to perform the docking studies for the Wnt receptor PDB ID: (3FOA.pdb)[47] and PDB ID: Vegf (2VPF.pdb)[48]

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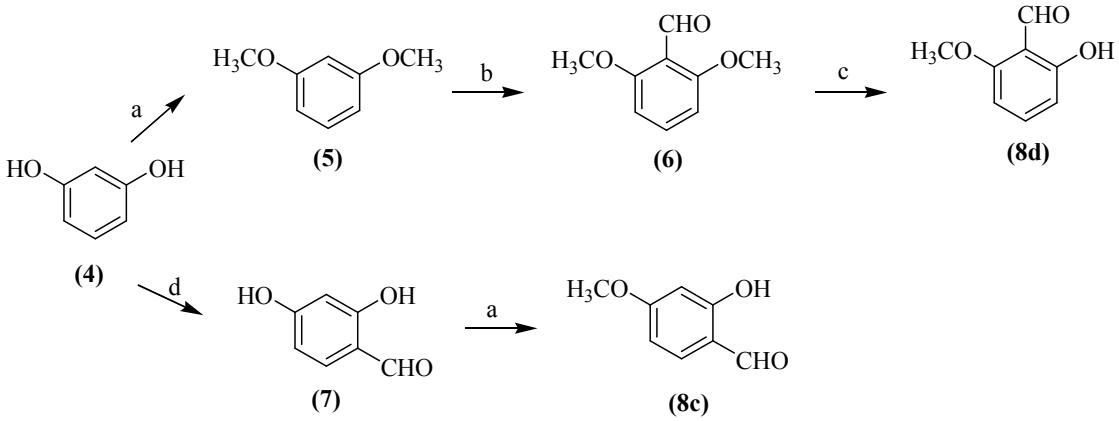
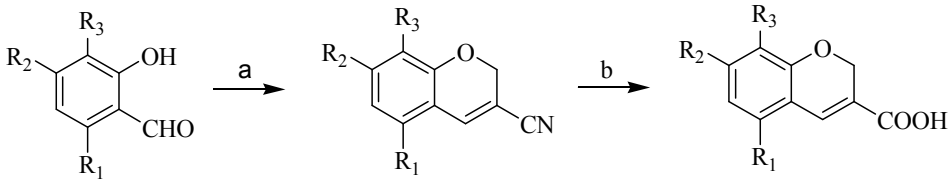
Scheme 1: Synthesis of substituted salicylaldehydes



Reagents and Conditions: (a) MeI, K_2CO_3, acetone, rt, 12h; (b) n-BuLi, TEMDA, dry DMF, dry THF, 0 to 5 ^{0}C; (c) $AlCl_3$, DCM, -15 ^{0}C, rt, 6h; (d) DMF, $POCl_3$, acetonitrile.

Scheme 2: Synthesis of substituted chromene-3-carboxylic acids (**10a-d**)



8a) $R_{1\text{-}3}$= H

8b) R_3=OCH_3, $R_{1,\,2}$ = H

8c) R_2=OCH_3, $R_{1,\,3}$ = H

8d) R_1=OCH_3, $R_{2,3}$ = H

9a) $R_{1\text{-}3}$= H

9b) R_3=OCH_3, $R_{1,\,2}$ = H

9c) R_2=OCH_3, $R_{1,\,3}$ = H

9d) R_1=OCH_3, $R_{2,3}$ = H

10a) $R_{1\text{-}3}$= H

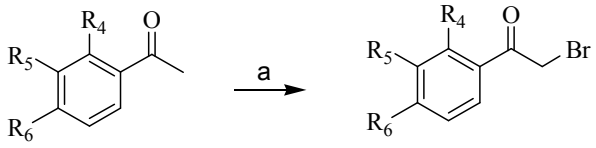
10b) R_3=OCH_3, $R_{1,\,2}$ = H

10c) R_2=OCH_3, $R_{1,\,3}$ = H

10d) R_1=OCH_3, $R_{2,3}$ = H

Reagents and conditions: (a) Acrylonitrile, DABCO, reflux, 10h; (b) NaOH, H_2O, reflux, 6h.

Scheme 3a: Synthesis of Substituted phenacyl bromides (**12a-h**)



11a) R_{4-6} = H

11b) R_{4-5} = H, R_6 = Cl

11c) R_5 = H, $R_{4,6}$ = Cl

11d) $R_{4,6}$ = H, R_5 = NO_2

11e) $R_{4,5}$ = H, R_6= Br

11f) $R_{4,5}$ = H, R_6= OBn

11g) $R_{4,5}$ = H, R_6 = F

11h) $R_{4,5}$ = H, R_6 = OMe

12a) R_{4-6} = H

12b) R_{4-5} = H, R_6 = Cl

12c) R_5 = H, $R_{4,6}$ = Cl

12d) $R_{4,6}$ = H, R_5 = NO_2

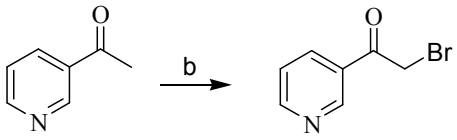
12e) $R_{4,5}$ = H, R_6= Br

12f) $R_{4,5}$ = H, R_6= OBn

12g) $R_{4,5}$ = H, R_6 = F

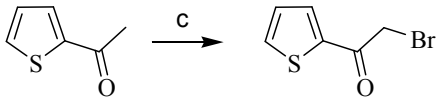
12h) $R_{4,5}$ = H, R_6 = OMe

Scheme 3b: Synthesis of 2-bromo-1-(pyridin-3-yl)ethanone (**12i**)



(**11i**) (**12 i**)

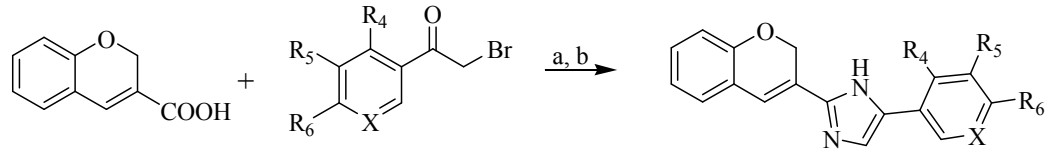
Scheme 3c: Synthesis of 2-bromo-1-(thiophen-2-yl)ethanone (**12j**)



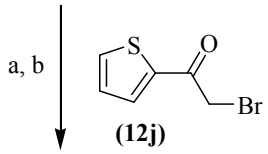
(**11j**) (**12j**)

Reagents and conditions: (a) Bromine, diethyl ether, DCM, 0 ^{0}C to rt, 2h; (b) Bromine, 33%HBr in acetic acid, 0 to 60 ^{0}C, 2h; (c) Bromine, DCM, rt, 2h.

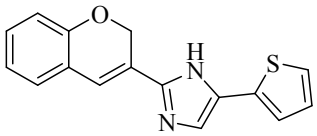
Scheme4: Synthesis of 2-(2H-chromen-3-yl)-5-aryl-1*H*-imidazoles (**13a-c, e-j**):



(**10a**)



(**12j**)



(**13j**)

12a) R_{4-6} = H, X=C

12b) R_{4-5} = H, R_6 = Cl , X=C

12c) R_5 = H, $R_{4,6}$ = Cl, X=C

12e) $R_{4,5}$ = H, R_6= Br, X=C

12f) $R_{4,5}$ = H, R_6= OBn, X=C

12g) $R_{4,5}$ = H, R_6 = F, X=C

12h) $R_{4,5}$ = H, R_6 = OMe, X=C

12i) R_{4-6} = H, X=N

13a) R_{4-6} = H, X=C

13b) R_{4-5} = H, R_6 = Cl, X=C

13c) R_5 = H, $R_{4,6}$ = Cl, X=C

13e) $R_{4,5}$ = H, R_6= Br, X=C

13f) $R_{4,5}$ = H, R_6= OBn, X=C

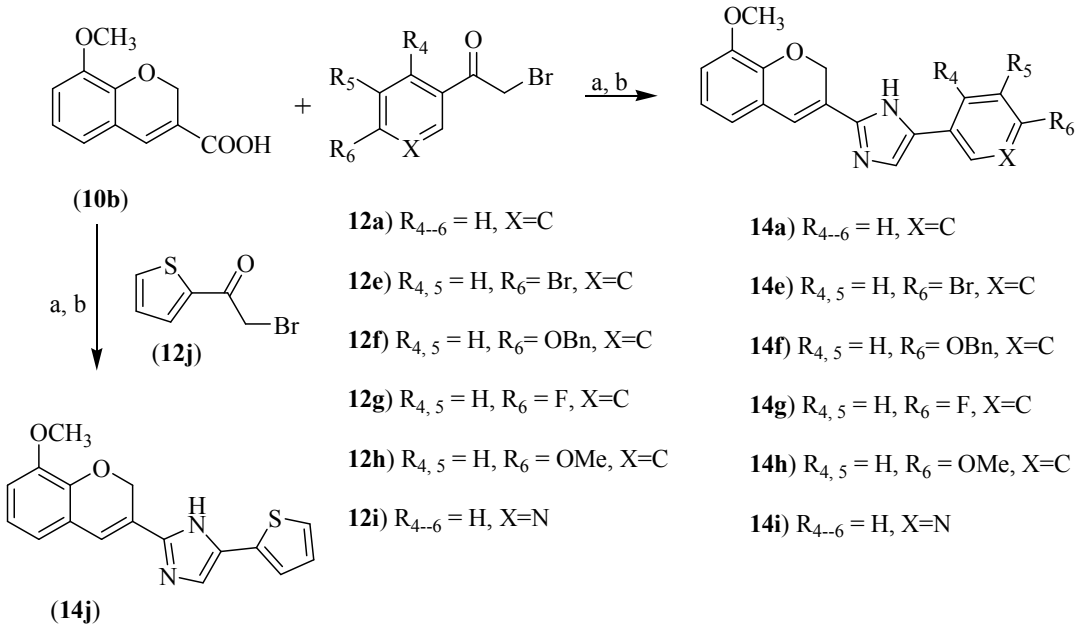
13g) $R_{4,5}$ = H, R_6 = F, X=C

13h) $R_{4,5}$ = H, R_6 = OMe, X=C

13i) R_{4-6} = H, X=N

Reagents and conditions: (a) TEA, DCM, RT, 12h; (b) NH_4OAc, toluene, reflux,12h.

Scheme 5: Synthesis of 2-(8-methoxy-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles (**14a, e-j**)



12a) R_{4-6} = H, X=C

12e) $R_{4,5}$ = H, R_6= Br, X=C

12f) $R_{4,5}$ = H, R_6= OBn, X=C

12g) $R_{4,5}$ = H, R_6 = F, X=C

12h) $R_{4,5}$ = H, R_6 = OMe, X=C

12i) R_{4-6} = H, X=N

14a) R_{4-6} = H, X=C

14e) $R_{4,5}$ = H, R_6= Br, X=C

14f) $R_{4,5}$ = H, R_6= OBn, X=C

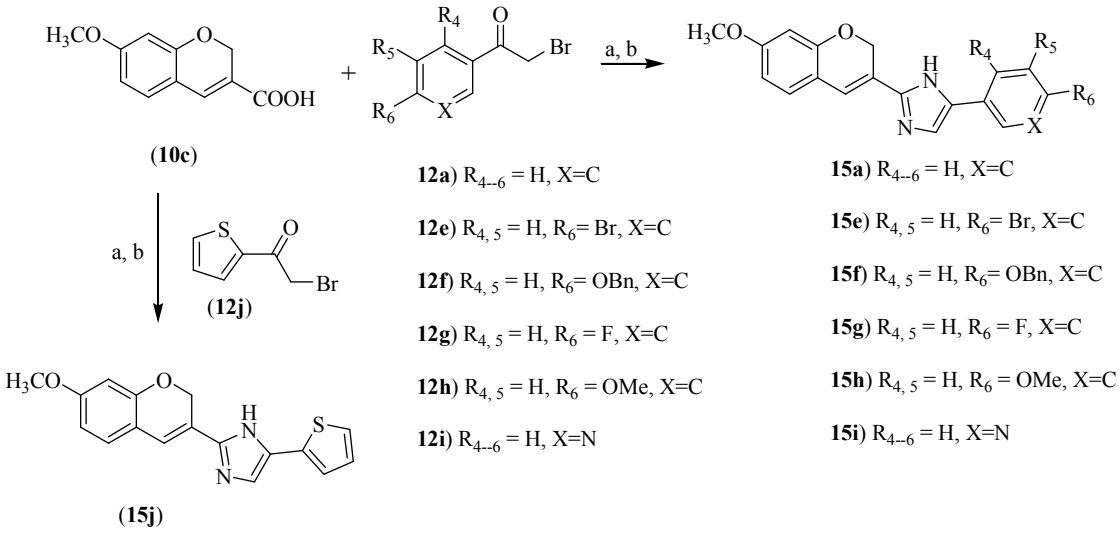
14g) $R_{4,5}$ = H, R_6 = F, X=C

14h) $R_{4,5}$ = H, R_6 = OMe, X=C

14i) R_{4-6} = H, X=N

Reagents and conditions: (a) TEA, DCM, RT, 12h; (b) NH_4OAc, toluene, reflux, 12h

Scheme6: Synthesis of 2-(7-methoxy-2-H-chromen-3-yl)-5-aryl-1-H-imidazoles (**15a, e-j**)



12a) R_{4-6} = H, X=C

12e) $R_{4,5}$ = H, R_6= Br, X=C

12f) $R_{4,5}$ = H, R_6= OBn, X=C

12g) $R_{4,5}$ = H, R_6 = F, X=C

12h) $R_{4,5}$ = H, R_6 = OMe, X=C

12i) R_{4-6} = H, X=N

15a) R_{4-6} = H, X=C

15e) $R_{4,5}$ = H, R_6= Br, X=C

15f) $R_{4,5}$ = H, R_6= OBn, X=C

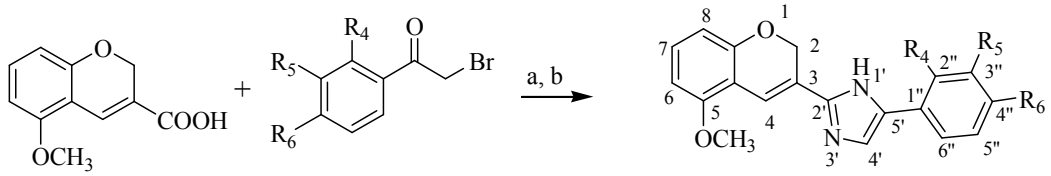
15g) $R_{4,5}$ = H, R_6 = F, X=C

15h) $R_{4,5}$ = H, R_6 = OMe, X=C

15i) R_{4-6} = H, X=N

Reagents and conditions: (a) TEA, DCM, rt,12h; (b) NH_4OAc, toluene, reflux, 12h.

Schemes 7: Synthesis of 2-(5-methoxy-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazole**s (16a-f)**



(**10d**)

12a) R_{4--6} = H

12b) R_{4--5} = H, R_6 = Cl

12c) R_5 = H, $R_{4,6}$ = Cl

12d) $R_{4,6}$ = H, R_5 = NO_2

12e) $R_{4,5}$ = H, R_6= Br

12f) $R_{4,5}$ = H, R_6= OBn

16a) R_{4--6} = H

16b) R_{4--5} = H, R_6 = Cl

16c) R_5 =H, $R_{4,6}$ = Cl

16d) $R_{4,6}$ = H, R_5 = NO_2

16e) $R_{4,5}$ = H, R_6 = Br

16f) $R_{4,5}$ = H, R_6 = OBn

Reagents and conditions: (a) TEA, DCM, rt, 12h; (b)NH_4OAc, toluene, reflux, 12h.

Figure captions

Figure1: Structures of isoflavone based anti-angiogenesis molecules, genistein(**1**) and diadzein (**2**)and phenoxodiol(**3**)

Figure2: Anti-angiogenesis activity of compound **16f**

Figure3: H-bonding interactions between amino acid residues at active site of Human KRAS target and the compound **16f**

Figure4: Surface representation of KRAS receptor and ligand complex**16f**

Figure5: H-bonding interactions between amino acid residues at active site of Wnt target and the compound **16f**

Figure 6: Surface representation of Wnt receptor and ligand complex**16f**

Figure 7: H-bonding interactions between amino acid residues at active site of VEGF target and the compound **16f**

Figure8: Surface representation of VEGF receptor and ligand complex **16f**

Table Captions

Table 1: Synthetic Lethal Primary SP Assay: IC_{50} of novel 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles **(13-16)** on K-RAS/WNT expression and the basal viability of cancer cells in different colon cancer cell lines.

Table 2: Wnt Reporter Assay: IC_{50}based on Luciferase Reporter activity of 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles **(13g, 16a, e, f)**

Table 3: Anti-Angiogenesis Assay: Anti-angiogenic, Cell Cycle effectsinfluenced by5-(4-(Benzyloxy)phenyl)-2-(5-methoxy-2H-chromen-3-yl)-1H-imidazole**(16f)** on CRC cell lines and ADSC/ECFC co-culture cell lines.

Scheme Captions

Scheme 1: Synthesis of substituted salicylaldehydes

Scheme 2: Synthesis of substituted chromene-3-carboxylic acids (**10a-d**)

Scheme 3a: Synthesis of Substituted phenacyl bromides (**12a-h**)

Scheme 3b: Synthesis of 2-bromo-1-(pyridin-3-yl)ethanone (**12i**)

Scheme 3c: Synthesis of 2-bromo-1-(thiophen-2-yl)ethanone (**12j**)

Scheme4: Synthesis of 2-(2H-chromen-3-yl)-5-aryl-1*H*-imidazoles (**13a-c, e-j**)

Scheme 5: Synthesis of 2-(8-methoxy-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazoles (**14a, e-j**)

Scheme6: Synthesis of 2-(7-methoxy-2-H-chromen-3-yl)-5-aryl-1-H-imidazoles (**15a, e-j**)

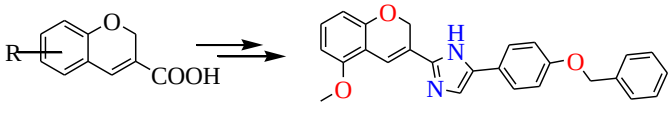
Schemes 7: Synthesis of 2-(5-methoxy-2*H*-chromen-3-yl)-5-aryl-1*H*-imidazole**s (16a-f)**

Rational design, synthesis of novel 2-(substituted 2*H*-chromen-3-yl)-5-aryl-1*H*-imidazole derivatives as an anti-angiogenesis and anticancer

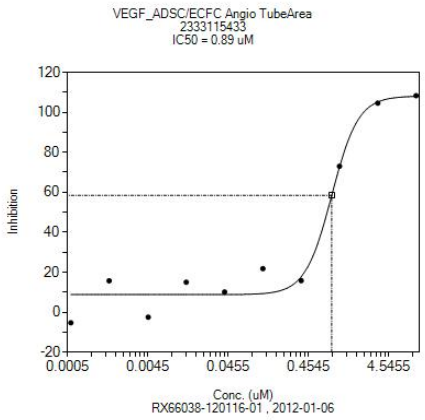
GopinathGudipudi[1], Sagurthi S. R[2], ShyamPerugu3, G. Achaiah[4]and David Krupadanam.G.L[1]*.

Graphical Abstract

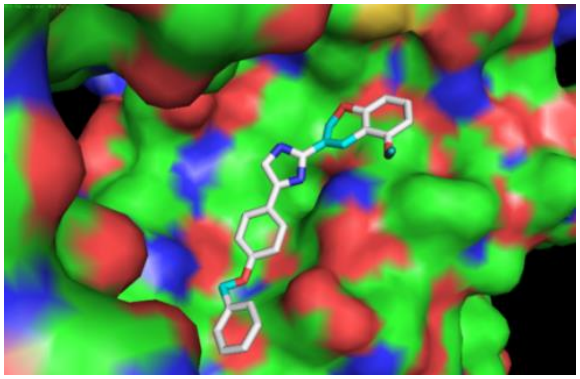
Anti-cancer and Anti-angiogenesis activity of 16f ligand



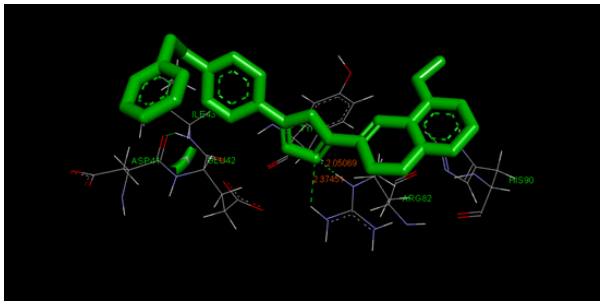
16f ligand



Assay



Docking figure



Anti-cancer and Anti-angiogenesis activity of 16f