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Synthesis of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes

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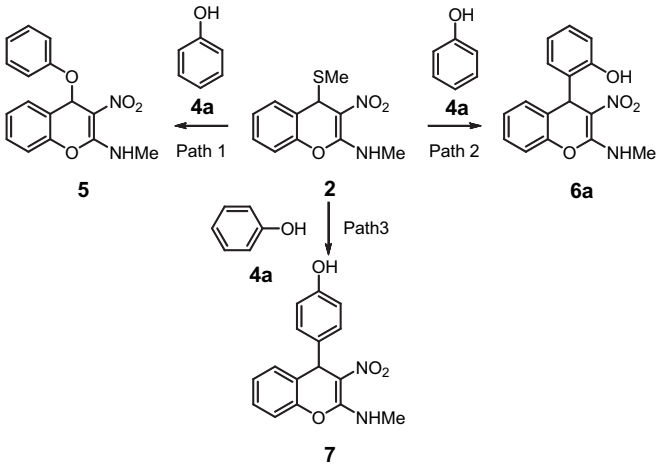
ABSTRACT

A combinatorial library of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes was synthesized in high yield by C4-SMe substitution in *N*-alkyl/phenyl 4-(methylthio)-3-nitro-4*H*-chromen-2-amines with a variety of phenols. The reaction always provided C2 substitution in the phenol ring, dictated by hydrogen bond interactions between the phenolic hydroxyl group and the nitro group in 3-nitro-4*H*-chromenes. Reduction of the nitro group with concomitant hydrolysis of the enamine in 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes with Zn, Ac_2O in AcOH furnished hybrid amino-acid lactone incorporating *ortho*-tyrosine and phenyl alanine moieties.

1. Introduction

The 4-aryl-4*H*-chromenes are potent apoptosis (controlled cell death) inducing agents.[1] Since cancer cells grow faster, apoptosis inducing agents act on cancer cells to restrict their abnormal cell division and thus act as anti-cancer drugs. 4-Aryl-4*H*-chromenes, e.g., **1** inhibit tubulin polymerization and in the process induce apoptosis.[2] In addition to being anti-cancer agents, a few 4-aryl-4*H*-chromenes, particularly those derived from 2-naphthol exhibit for antibacterial activity.[3] Generally, 4-aryl-4*H*-chromenes were synthesized by three-component condensation involving a phenol, an aromatic aldehyde and malononitrile. This method, however, is limited to electron rich phenols and electron poor aromatic aldehydes and is not suitable for the synthesis of 4-aryl-4*H*-chromenes emanating from electron poor phenols and electron rich aldehydes. We have recently disclosed a facile, high yielding and convenient synthesis of a combinatorial library of *N*-alkyl/aryl 4-(methylthio)-3-nitro-4*H*-chromen-2-amines like **2** from readily available nitroketene *N,S*-acetals and 2-hydoxybenzaldehydes.[4] We have also demonstrated that the C4 methylthio group (C4-SMe) in **2** is labile owing to electron donating ability of oxygen and availability of conjugation. C4-SMe in **2** can be replaced through S_N1 reaction pathway with nucleophiles like thiols or electron rich aromatic rings. For example, heating **2** with thiophenol provided *N*-methyl-3-nitro-4-(phenylthio)-4*H*-chromen-2-amine **3** in quantitative yield. In continuation of this work, we explored the possibility of replacing C4-SMe in **2** with phenols **4** to generate a combinatorial library of 4-aryl-4*H*-chromenes, e.g., **6a**. In this method there is a possibility of variation at three sites of 4-aryl-4*H*-chromenes namely chromene ring, C2-amine and C4-phenol.

Three pathways are possible in the reaction of C4-methylthio-4*H*-chromene **2** with phenol **4a** as shown in Scheme 1. Path 1 leads to ether **5** where S_N1 type substitution takes place on phenolic oxygen, similar to the reaction of **2** with thiophenol to provide thioether **3**. On the other hand, paths 2 and 3 furnish aromatic electrophilic substitution products of phenol **4a**, at *ortho* and *para* positions, leading to products **6a** and **7**, respectively. In reality and



Scheme 1. Three possible paths in the reaction of 4-methylthio-4*H*-chromene **2** with phenols **4**.

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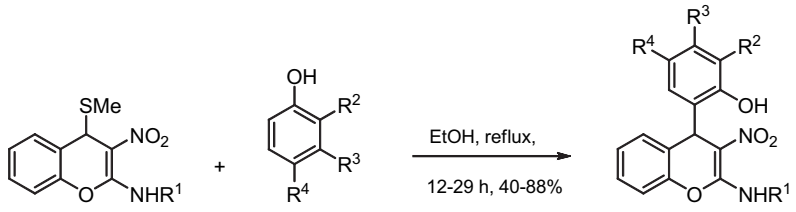


2a-d **4a-e** **6a-n**

2a: R^1 = Me;
2b: R^1 = *n*-Bu;
2c: R^1 = Ph;
2d: R^1 = Bn.

4a: $R^2 = R^3 = R^4$ = H;
4b: $R^2 = R^3$ = H, R^4 = Me;
4c: $R^2 = R^3$ = H, R^4 = Cl;
4d: $R^2 = R^4$ = H, R^3 = Me;
4e: R^2 = Me, $R^3 = R^4$ = H.

6a: R^1 = Me, $R^2 = R^3 = R^4$ = H;
6b: R^1 = Me, $R^2 = R^3$ = H, R^4 = Me;
6c: R^1 = Me, $R^2 = R^3$ = H, R^4 = Cl;
6d: R^1 = *n*-Bu, $R^2 = R^3 = R^4$ = H;
6e: R^1 = *n*-Bu, $R^2 = R^3$ = H, R^4 = Me;
6f: R^1 = *n*-Bu, $R^2 = R^3$ = H, R^4 = Cl;
6g: R^1 = Ph, $R^2 = R^3 = R^4$ = H;
6h: R^1 = Ph, $R^2 = R^3$ = H, R^4 = Me;
6i: R^1 = Ph, $R^2 = R^3$ = H, R^4 = Cl;
6j: R^1 = Bn, $R^2 = R^3 = R^4$ = H;
6k: R^1 = Bn, $R^2 = R^3$ = H, R^4 = Me;
6l: R^1 = Bn, $R^2 = R^3$ = H, R^4 = Cl;
6m: R^1 = Me, $R^2 = R^4$ = H, R^3 = Me;
6n: $R^1 = R^2$ = Me, $R^3 = R^4$ = H.

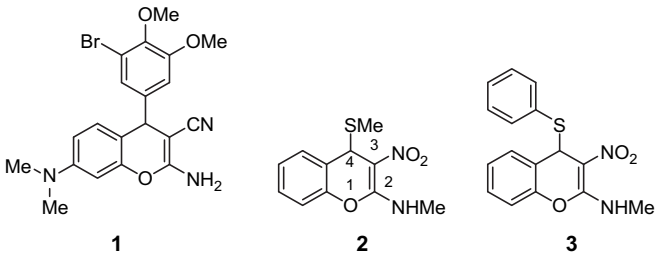
Scheme 2. Synthesis of a combinatorial library of 4-aryl-4*H*-chrmenes **6a**–**n**.

in contrast to the reaction of **2** with thiophenol, the reaction with phenol **4a** furnished the regioselective electrophilic aromatic ring substitution product **6a** exclusively (Scheme 2). There was no trace of O-substitution product **5** or *para*-substitution product **7**. We have now explored the scope of this reaction for the synthesis of a combinatorial library of 4-aryl-4*H*-chromenes. In addition, we have unmasked the enamine and nitro groups present in **6a** for the synthesis of the lactone of a non-natural hybrid amino acid incorporating phenyl alanine and *ortho*-tyrosine.

2. Results and discussion

When a mixture of 4*H*-chromene **2a** and phenol **4a** was heated to reflux in EtOH for 12 h, 2-(2-(methylamino)-3-nitro-4*H*-chromen-4-yl) phenol **6a** precipitated in quantitative yield. Simple filtration was sufficient to furnish the clean product. Although reaction was faster (2 h) in the presence of 1 equiv of NaOAc, the reaction was cleaner without it. Conducting the reaction in presence of NaH in THF or K_2CO_3 in CH_3COCH_3 or NaOMe in MeOH lowered the yield of **6a**. In all the cases, however, there was no trace of *para*-substitution product **7**. The assigned structure **6a** was established by analysis of ^{1}H and ^{13}C NMR spectra. The ^{1}H NMR spectrum displayed a characteristic singlet for C4-H at δ 5.4 ppm. In addition there was a doublet at δ 6.8 ppm for 1H—rather than for 2H—assignable to aromatic hydrogen next to phenolic hydroxyl group, which indicated that substitution had taken place on C2′ carbon *ortho* to phenolic hydroxyl. In the ^{13}C NMR spectrum six signals for the aromatic ring with phenolic hydroxyl group were discernable. This data also confirmed the substitution taking place at C2 rather than C4 of phenol **4a**. The ^{13}C NMR spectrum exhibited a quaternary carbon at 124.7 ppm. In comparison, the C2 quaternary carbon in 2-methylphenol occurs at 124.0 ppm. Further unequivocal confirmation of the structure came from single crystal X-ray structure determination of the acetyl derivative of 4*H*-chromene **6a** (Fig. 1; see Experimental section).[5]

Exclusive formation of **6a** can be traced to hydrogen bonding interaction of phenolic hydroxyl in **4a** with the nitro group in **2a**, which directs the substitution to take place at C2 position. Substitution on **2a** did not take place with anisole or with catechol dimethyl ether indicating the decisive role of the phenolic hydroxyl group in the formation of **6a**. We have conducted several experiments to find out if one-pot three-component condensation of 2-hydroxybenzldehyde, *N*-methyl-1-(methylthio)-2-nitroethenamine and phenol takes place to provide **6a** directly, that is, without isolating **2a**. All attempts, however, were mostly unsuccessful. In one case, under microwave irradiation for 2 min in a mono-mode microwave oven, the three-component domino condensation between 2-hydroxybenzldehyde, *N*-methyl-1-(methylthio)-2-nitroethenamine and phenol provided 51% yield of 4-aryl-4*H*-chromene **6a**. However, the reaction was not clean and purification required subjecting crude product to column chromatography. Even though the present procedure is a two-step process to 4-(2-hydroxyphenyl)-4*H*-chromene **6a** both the steps are high yielding and the products crystallize out of the reaction mixture in excellent yield, obliviating the need for column chromatographic purification.

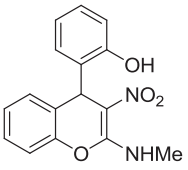
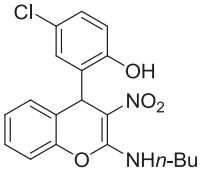
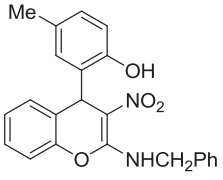
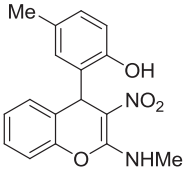
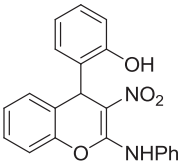
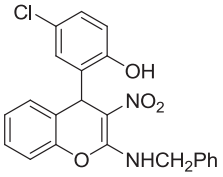
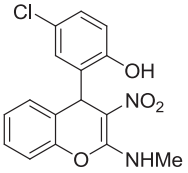
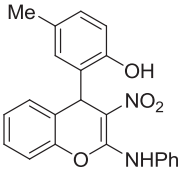
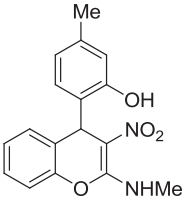
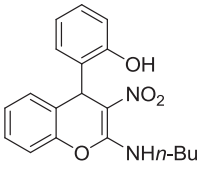
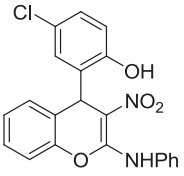
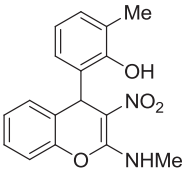
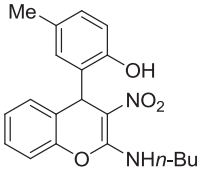
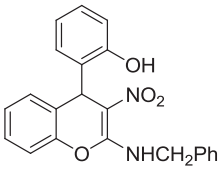


1 **2** **3**

Fig. 1. 4*H*-Chromenes **1**–**3**.

To test generality of above transformation, we subjected three phenols **4a**–**c** to reaction with four *N*-substituted 3-nitro-4*H*-chromenes **2a**–**d** to furnish 4-(2-hydroxyaryl)-4*H*-chromenes **6a**–**l** (Scheme 1 and Table 1). In each case, a single C2′ substituted regioisomer of **6** was obtained exclusively. We have, thus, prepared a combinatorial library of 12 4-aryl-3-nitro-4*H*-chromenes **6a**–**l** without any event. Electron donating (C4-Me, **4b**) or electron withdrawing (C4-Cl, **4c**) groups on phenol **4** did not affect outcome of the reaction in a perceptible manner. Other than three phenols **4a**–**c**, we subjected *ortho*-cresol **4d** and *meta*-cresol **4e** to reaction

Table 1
Combinatorial library of 4-aryl-3-nitro-4*H*-chromenes **6a**–**n** prepared from 4-methylsulfanyl-4*H*-chromenes **2a**–**d** and phenols **4a**–**e**

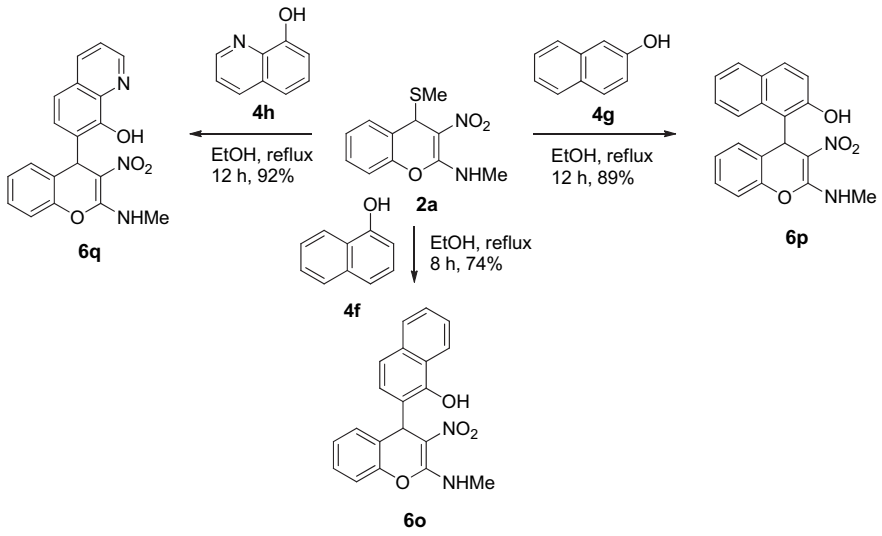
Entry	4-Aryl-3-nitro-4*H*-chromene	Entry	4-Aryl-3-nitro-4*H*-chromene	Entry	4-Aryl-3-nitro-4*H*-chromene
1.	 **6a** (12 h, 88%)	6.	 **6f** (13 h, 43%)	11.	 **6k** (16 h, 46%)
2.	 **6b** (19 h, 73%)	7.	 **6g** (14 h, 45%)	12.	 **6l** (22 h, 70%)
3.	 **6c** (29 h, 51%)	8.	 **6h** (14 h, 64%)	13.	 **6m** (16 h, 80%)
4.	 **6d** (12 h, 63%)	9.	 **6i** (16 h, 40%)	14.	 **6n** (16 h, 88%)
5.	 **6e** (12 h, 73%)	10.	 **6j** (12 h, 87%)		

with the parent 3-nitro-4*H*-chromenes **2a** to yield two isomeric 4-aryl-3-nitro-4*H*-chromenes **6m**–**n** in good yield.

Interestingly, some of the phenol substituted 4*H*-chromenes e.g., **6c** and **6m** exhibit atropisomerism due to restricted rotation around C4–C2′ single bond possibly due to strong hydrogen bonding stabilization between the hydroxyl and the nitro group of the chromene moiety. The operation of atropisomerism was evidenced by observation of two sets of equal intensity peaks in ^{1}H and ^{13}C spectra of 4*H*-chromenes.

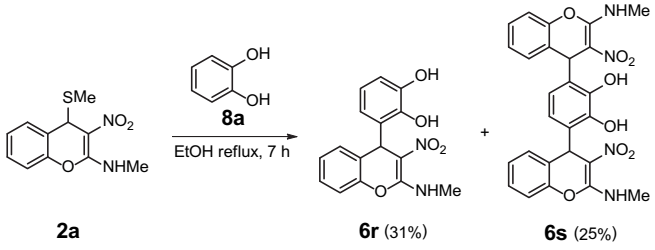
Parent 4*H*-chromene **2a** was subjected to substitution of C4-SMe with 1-naphthol **4f**, 2-naphthol **4g**, and 8-hydroxyquinoline **4h** in ethanol reflux to furnish 4-aryl-3-nitro-4*H*-chromenes **6o**–**q**, respectively, in very good yields (Scheme 3). In each case, only one regioselective C2′-substitution product was formed. The structure of 4-aryl-3-nitro-4*H*-chromenes **6o**–**q** was confirmed by HMBC correlations between C4-*H* and quaternary C2′ carbon, that is, the carbon next to aryl OH. It is interesting to note the regiochemical outcome of the reaction of **2a** with 1-naphthol **4f**. Aromatic electrophilic substitution on 1-naphthol **4f** takes place both at C2 and C4, generally yielding a mixture of products.[6] Isolation of a single regioisomer **6o**, however, shows that the substitution is highly influenced by hydrogen bonding interaction of phenolic OH in **4f** with NO_2 in **2a**.

After demonstrating facile aromatic substitution of phenols in their reaction with 4*H*-chromenes **2** to provide 4-aryl-4*H*-chromenes **6**, we turned our attention toward the synthesis of bis-chromenes by reaction of **2a** with 1,2-, 1,3- and 1,4-dihydroxybenzenes **8a**–**c**. The reaction of parent 4*H*-chromene **2a** (2.0 equiv), 1,2-dihydroxybenzene (catechol, 1.0 equiv) provided two products (Scheme 4). A major product (30%; higher R_f value in



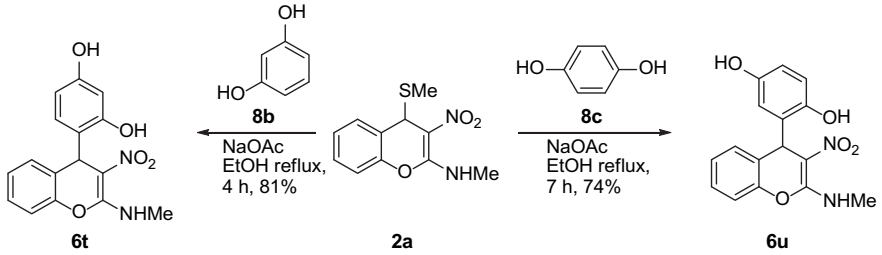
Scheme 3. Substitution of C4-SMe in **2a** with 1-napthol **4f**, 2-naphthol **4g** and 8-hydroxyquinoline **4h** to furnish 4-ayl-4*H*-chromenes **6o**–**q**.

silica gel TLC) is the mono-substitution product **6r** and the minor (25%) being bis-chromene **6s**. Formation of bis-chromene **6s** was confirmed on the basis of ESI-MS, which exhibited anticipated $M^{+}H$ signal at 519.1526. The ^{1}H and ^{13}C NMR spectra of **6s** matched well with 4-aryl-4*H*-chromene **6r**. Several attempts to increase yields of bis-chromene by changing reaction conditions like use of excess 4*H*-chromene **2a** or higher boiling solvents like isopropanol or using NaOAc did not help.



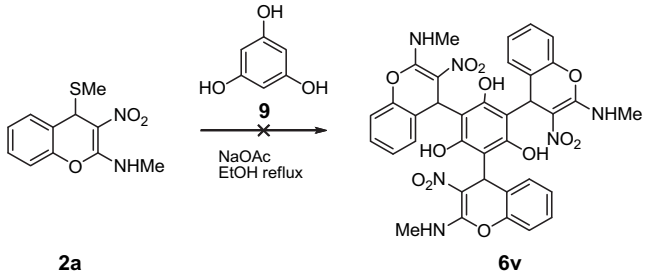
Scheme 4. Reaction of 1,2-dihydroxybenzene **8a** with **2a** to provide **6r** and **6s**.

Reaction of 1,3-dihydroxybenzene (resorcinol), 1,4-dihydroxybenzene (quinol) in presence or absence of NaOAc provided only a mono-substitution product **6t** and **6u**, respectively (Scheme 5). Even though TLC and ^{13}C NMR spectrum of the crude product indicated presence of bis-chromenes in minor quantities (less than 3%) they could not be purified and characterized.



Scheme 5. Synthesis of 4-aryl-4*H*-chromenes **6r**–**s** by the reaction of **2a** with 1,3-dihydroxybenzene **8b** and 1,4-dihydroxybenzene **8c**.

The reaction of 4*H*-chromene **2a** with 1,3,5-trihydroxybenzene (phloroglucinol) **9** did not yield desirable tris-4-aryl-4*H*-chromene **6v** (Scheme 6) but provided unintractable products in EtOH reflux with or without NaOAc.



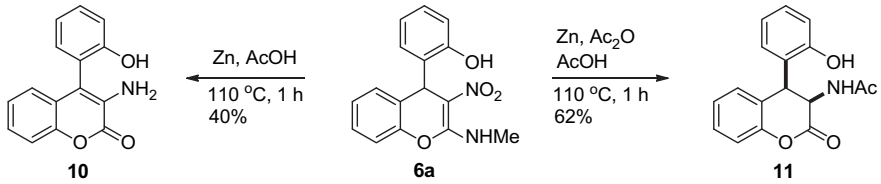
Scheme 6. Anticipated reaction of 1,3,5-trihydroxybenzene **9** with **2a**.

Attempted substation of C4-SMe in **2a** with marginally electron rich aromatic compounds like anisole, 1,3-dimethoxy benzene and *o*, *p*-directing chlorobenzene also did not provide substitution products, indicating that electron rich nature of aromatic ring and the hydrogen bonding interaction of OH with nitro group are required for the aromatic electrophilic substitution reaction.

2.1. Synthesis of non-natural hybrid amino acid 11

The 4*H*-chromene like **6a** has all the structural features of a masked amino acid. Reduction of the nitro group in **6a** to primary amine and hydrolysis of the enamine should reveal the amino acid having structural features of *ortho*-tyrosine lactone. *ortho*-Tyrosine lactone and other such non-essential amino acids possess enormous potential to be used as therapeutic agents.[7] As an example, levels of *ortho*-tyrosine lactone can indicate onset of diabetes or some diseases due to malfunctioning of kidneys.[8] Reduction of the nitro

group to amino with concomitant hydrolysis of the enamine in **6a** should deliver hybrid amino acid incorporating two units of *ortho*-tyrosine. After unsuccessfully screening several reducing agents like H_2/Pd/C, H_2/Pt, $LiAlH_4$, $NaBH_4$/$NiCl_2$ all of which have been used for reduction of the nitro group, we were gratified to find that Zn/AcOH delivered enamine **10** in good yield (Scheme 7). However, reduction with Zn/AcOH/Ac_2O system provided required protected hybrid amino-acid lactone **11** in good yield (Scheme 7).[9] From ^{13}C NMR spectrum we concluded both cis- and trans-isomers were formed in about 6:5 ratio. Interestingly, the cis-isomer **11** crystallized out during fractional crystallization and its structure was confirmed by single crystal X-ray analysis (Fig. 2; see Experimental section).



Scheme 7. Conversion of **6a** into hybrid amino-acid lactones **10** and **11**.

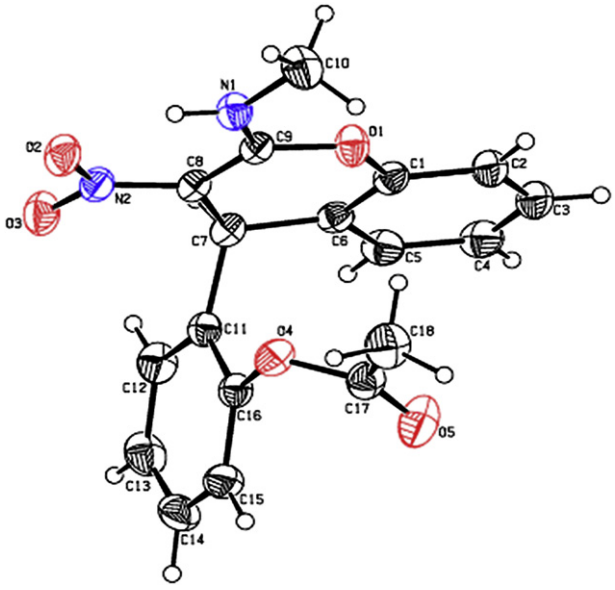


Fig. 2. The single crystal X-ray structure of 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenyl acetate. (deposited with CCDC; deposition No. 647163).

3. Conclusion

In conclusion, we have reported a facile synthesis of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes **6** from by C4-SMe substitution in 4*H*-chromene **2**. This effort leads to a combinatorial library of 4-(2-hydroxyaryl)-3-nitro-4*H*-chromenes with structural variations in phenol and *N*-alkyl groups. Reduction of the nitro group in 4-aryl-2-alkylamino-3-nitro-4*H*-chromene **6a** with Zn/AcOH favored the formation of enamine **10**. On the other hand, its reduction with Zn/Ac_2O/AcOH provided hybrid amino-acid lactone **11** incorporating phenyl alanine and *ortho*-tyrosine units.

4. Experimental section

4.1. General

All reagents and solvents were purchased from Sigma–Aldrich, E-Merck or SRL, India. The TLC was performed with silica gel-G (SRL, India) or silica gel GF-254 (E-Merck) using hexanes/ethyl acetate as eluent and the spots were visualized by short exposure to iodine vapor or UV light. Column chromatography was carried on silica gel (100–200 mesh, Acme Synthetic Chemicals, India) using increasing percentage of ethyl acetate in hexanes. Melting points were recorded using Gallenkamp melting point apparatus and were uncorrected. IR spectra were recorded as KBr pellets using Bomem MB104 spectrometer. UV spectra were recorded using Hitachi ratio-beam spectrometer. The ^1H NMR (500 MHz, 400 MHz, 300 MHz) and ^{13}C NMR (100 MHz or 75 MHz) and DEPT spectra were recorded in $CDCl_3$, DMSO-d_6 or $CDCl_3$/DMSO-d_6 (1:1) with Bruker 400 MHz, Bruker 300 MHz, JEOL 400 MHz with TMS (0 ppm) as internal standard. Mass spectra (HRMS) were recorded on HP MS-engine S989A (EI=Electron Impact, 70eV). Elemental analysis was carried out in NCL, Pune, India on a Perkin–Elmer 2400 Series II CHNS/O Elemental Analyzer.

4.2. Representative procedure for preparation of 4-(2-hydroxyaryl)-4*H*-chromenes. 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenol 6a

A solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and phenol **4a** (0.56 g, 5.9 mmol) in ethanol (15 mL) was heated to reflux for 12 h by which time the reaction was completed (TLC). The reaction mixture was cooled to room temperature and kept aside for 3 h. The compound that crystallized out was separated by filtration with the help of cold ethanol (5 mL) to yield title compound **6a** (0.52 g, 88%) as a colorless solid; mp >220 °C (EtOH); R_f (60% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 349 nm (log ε=3.9), 277 nm (log ε=3.5); ν_{max} 3184, 1644, 1600, 1469, 1349, 1249, 1062, 755, 704 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.46 (br q, J=5.1 Hz, 1H), 9.5 (s, 1H), 7.3–7.0 (m, 5H), 6.69 (t, J=7.2 Hz, 2H), 5.51 (s, 1H), 3.16 (d, J=5.1 Hz, 3H); δ_C (75 MHz, DMSO-d_6) 159.5 (C), 154.5 (C), 147.4 (C), 130.2 (C), 129.1 (CH), 129.0 (CH), 127.9 (CH), 127.7 (CH), 125.2 (CH), 124.7 (C), 118.8 (CH), 115.8 (CH), 115.6 (CH), 106.8 (C), 37.1 (CH), 28.0 (NHMe). Anal. Calcd for $C_{16}H_{14}N_2O_4$: C, 64.42; H, 4.73; N, 9.30; Found: C, 64.48; H, 4.84; N, 9.38.

4.2.1. 2-[2-(Methylamino)-3-nitro-4H-4-chromenyl]phenyl acetate. To a well stirred mixture of 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenol **6a** (0.5 g, 1.7 mmol) and Ac_2O (0.53 g, 0.5 mL, 5.2 mmol), pyridine (0.16 g, 0.02 mL, 0.2 mmol) was added at room temperature. The reaction mixture was stirred thoroughly for 16 h. Excess pyridine was quenched with 0.01N HCl (6 mL) and then extracted with dichloromethane (DCM; 30 mL). Separated organic layer was washed with water and brine solution. Evaporation of DCM afforded 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenyl acetate (57%) as a pale yellow solid. Single crystals were grown by slow evaporation of 20% DCM in hexanes; mp >200 °C (EtOH); R_f (80% hexanes/EtOAc) 0.6; UV (MeOH) λ_{max} 351 nm (log ε=4.8), 261 nm (log ε=4.5), 229 nm (log ε=4.7); ν_{max} 3202, 3059, 1767, 1648, 1609, 1478, 1402, 1368, 1211, 1059, 758 cm^{-1}; δ_H (300 MHz, $CDCl_3$/DMSO-d_6) 10.50 (br s, 1H), 7.45–6.80 (m, 8H), 5.53 (s, 1H), 3.27 (d, J=5.1 Hz, 3H), 2.48 (s, 3H); δ_C (75 MHz, $CDCl_3$/DMSO-d_6) 168.1 (C), 158.6 (C), 147.8 (C), 146.7 (C), 134.1 (C), 130.4 (CH), 129.2 (CH), 127.9 (CH), 127.4 (CH), 125.4 (CH), 125.2 (CH), 123.0 (CH), 122.7

(C), 115.3 (CH), 107.2 (CH), 37.4 (CH), 27.4 (Me), 20.4 (CH_3). Anal. Calcd for $C_{18}H_{16}N_2O_5$: C, 63.52; H, 4.74; N, 8.23. Found: C, 63.48; H, 4.82; N, 8.19.

4.2.2. 4-Methyl-2-[2-(methylamino)-3-nitro-4H-4-chromenyl]phenol ***6b***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and *p*-cresol **4b** (0.64 g, 5.9 mmol) in EtOH (10 mL) reflux for 19 h provided title compound **6b** (0.45 g, 73%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 349 nm (log ε=4.1), 277 nm (log ε=3.6); ν_{max} 3269, 1644, 1600, 1472, 1395, 1202, 1063, 812, 756, 701, 637 cm^{-1}; δ_H (300 MHz, $CDCl_3$/DMSO-d_6) 10.5 (br s, 1H), 9.35 (s, 1H), 7.3–6.5 (m, 7H), 5.48 (s, 1H), 3.2 (d, *J*=4.8 Hz, 3H), 2.19 (s, 3H); δ_C (75 MHz, $CDCl_3$: DMSO-d_6) 159.1 (C), 154.1 (C), 145.0 (C), 133.7 (C), 129.7 (CH), 128.6 (CH), 128.5 (CH), 127.7 (CH), 127.0 (CH), 123.9 (CH), 118.3 (CH), 115.2 (CH), 114.8 (CH), 106.7 (C), 36.7 (CH), 27.3 (NHMe), 19.9 (CH_3). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.38; H, 5.16; N, 8.97. Found: C, 65.33; H, 5.18; N, 8.88.

4.2.3. 4-Chloro-2-[2-(methylamino)-3-nitro-4H-4-chromenyl]phenol ***6c***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 1.9 mmol) and 4-chlorophenol **4c** (0.76 g, 5.9 mmol) in EtOH (10 mL) reflux for 29 h provided title compound **6c** (0.33 g, 51%) as yellow color crystals; mp 204–206 °C (EtOH); R_f (40% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 350 nm (log ε=3.8), 282 nm (log ε=3.4); ν_{max} 3228, 1734, 1646, 1601, 1476, 1400, 1337, 1231, 1061, 766, 655, 578 cm^{-1}; δ_H (300 MHz, $CDCl_3$/DMSO-d_6) 10.49 (br s, 1H), 9.67 and 9.46 (s, 1H), 7.3–6.68 (m, 7H), 5.53 and 5.49 (s, 1H), 3.23 (d, *J*=2.1 Hz, 3H); δ_C (75 MHz, $CDCl_3$/CCl_4/DMSO-d_6 6:3:1) 159.1 (C), 153.4 (C), 147.3 (C), 131.8 (C), 128.8 (CH), 128.4 (CH), 127.7 (CH), 127.0 (CH), 124.9 (CH), 123.7 (C), 122.4 (C), 117.0 (CH), 115.4 (CH), 106.3 (C), 37.0 (CH), 27.7 (NHMe). Anal. Calcd for $C_{16}H_{13}ClN_2O_4$: C, 57.75; H, 3.94; N, 8.42; Found: C, 57.69; H, 408; N, 8.34.

4.2.4. 2-[2-(Butylamino)-3-nitro-4H-4-chromenyl]phenol ***6d***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2b** (0.5 g, 1.7 mmol) and phenol **4a** (0.480 g, 5.1 mmol) in EtOH (10 mL) reflux for 12 h provided title compound **6d** (0.36 g, 63%) as yellow color crystals after recrystallization; mp 200 °C (EtOH); R_f (60% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 351 nm (log ε=4.3), 275 nm (log ε=4.0); ν_{max} 3460, 2955, 1637, 1600, 1458, 1417, 1350, 1248, 1065, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 10.79 (br s, 1H), 7.64 (s, 1H), 7.29–6.67 (m, 8H), 5.77 (s, 1H), 3.6 (m, 2H), 1.7 (pentet, *J*=7.2 Hz, 2H), 0.99 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, $CDCl_3$) 159.9 (C), 153.6 (C), 148.3 (C), 130.2 (C), 129.9 (CH), 129.2 (CH), 128.5 (CH), 128.4 (CH), 126.4 (CH), 125.0 (C), 121.2 (CH), 118.1 (CH), 115.7 (CH), 106.8 (C), 41.5 (CH_2), 35.5 (CH_2NH), 31.5 (CH_2), 20.0 (CH_2), 13.6 (CH_3). Anal. Calcd for $C_{19}H_20N_2O_4$: C, 67.05; H, 5.92; N, 8.23. Found: C, 67.05; H, 6.02; N, 8.20.

4.2.5. 2-[2-(Butylamino)-3-nitro-4H-4-chromenyl]-4-methylphenol ***6e***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2b** (0.5 g, 1.7 mmol) and *p*-cresol **4b** (0.55 g, 5.1 mmol) in EtOH (10 mL) reflux for 12 h provided title compound **6e** (0.44 g, 73%) as yellow color crystals; mp 158 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH): λ_{max} 351 nm (log ε=4.1), 277 nm (log ε=3.9); ν_{max} 3473, 3190, 2957, 2866, 1636, 1502, 1456, 1370, 1249, 1212, 1162, 1065, 941, 817, 755, 704 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.6 (s, 1H) 9.45 and 9.24 (s, 1H), 7.3–6.5 (m, 7H), 5.46–5.43 (s, 1H), 3.61 (br t, *J*=7.5 Hz, 2H), 2.17 and 2.13 (s, 3H), 1.65 (br pentet, *J*=7.5 Hz, 2H), 1.38 (br sextet, *J*=7.5 Hz, 2H), 0.94 (t, *J*=7.5 Hz, 3H); δ_C (75 MHz, DMSO-d_6) 159.2 and 159.1 (C), 154.6 and 152.3 (C), 147.4 and 145.5 (C), 134.3 (C), 130.0 and 129.8 (C), 129.4 and 129.0 (CH), 128.4 and 128.1 (CH), 127.9 and 127.7 (CH), 127.7 and 127.1 (CH), 125.2 (CH), 124.7 and 124.3 (C), 118.7 (CH), 115.7 and 115.5 (CH), 106.9 and 106.8 (C), 40.5 (CH_2NH), 37.4 and 37.2 (CH), 31.5 (CH_2), 20.3 and 20.2 (CH_3), 19.4 (CH_2), 13.6 (CH_3). Anal. Calcd for $C_{20}H_{22}N_2O_4$: C, 67.78; H, 6.26; N, 7.90. Found: C, 67.71; H, 6.34; N, 7.82.

4.2.6. 2-[2-(Butylamino)-3-nitro-4H-4-chromenyl]-4-chlorophenol ***6f***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2b** (0.5 g, 5.1 mmol) and 4-chlorophenol **4c** (0.66 g, 3.4 mmol) in EtOH (10 mL) reflux for 13 h furnished the title compound **6f** (0.27 g, 43%) as yellow color crystals; mp 200 °C (EtOH); R_f (60% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 349 nm (log ε=3.6), 282 nm (log ε=3.1); ν_{max} 3177, 1636, 1609, 1479, 1422, 1345, 1250, 1210, 1168, 1068, 828, 756, 668 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.62 (br s, 1H), 9.80 and 9.56 (s, 1H), 7.3–7.0 (m, 6H), 6.68 (br d, *J*=8.4 Hz, 1H), 5.47 and 5.45 (s, 1H), 3.61 (br q, *J*=7.0 Hz, 2H), 1.66 (pentet, *J*=7.2 Hz, 2H), 1.35 (septet, *J*=7.2 Hz, 2H), 0.94 (t, *J*=7.2 Hz, 3H); δ_C (75 MHz, DMSO-d_6) 159.0 (C), 153.7 (C), 147.5 (C), 131.9 (C), 129.0 (CH), 129.0 (CH), 128.2 (CH), 127.4 (CH), 125.2 (CH), 123.6 (C), 122.1 (C), 117.2 (CH), 115.7 (CH), 106.2 (C), 40.7 (CH_2), 37.6 (CH), 31.5 (CH_2), 19.4 (CH_2), 13.5 (CH_3). Anal. Calcd for $C_{19}H_{19}ClN_2O_4$: C, 60.88; H, 5.11; N, 7.47. Found: C, 60.93; H, 5.05; N, 7.42.

4.2.7. 2-(2-Anilino-3-nitro-4H-4-chromenyl)phenol ***6g***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2c** (0.5 g, 1.6 mmol) and phenol **4a** (0.449 g, 4.8 mmol) in EtOH (10 mL) reflux for 14 h provided the title compound **6g** (0.26 g, 45%) as a yellow color solid; mp >200 °C (EtOH); R_f (60% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 347 nm (log ε=3.0), 280 nm (log ε=3.5); ν_{max} 3209, 1636, 1575, 1458, 1417, 1352, 1205, 1168, 1068, 749 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 12.12 (s, 1H), 9.57 (s, 1H), 7.59–6.97 (m, 11H), 6.67 (br d, *J*=7.2 Hz, 2H), 5.58 (s, 1H); δ_C (75 MHz, DMSO-d_6) 156.9 (C), 154.7 (C), 147.3 (C), 135.3 (C), 129.6 (C), 129.5 (CH), 129.2 (2× CH), 129.1 (2× CH), 128.0 (CH), 127.9 (CH), 126.2 (CH), 124.5 (CH), 124.4 (C), 123.8 (2× CH), 118.8 (CH), 115.7 (CH), 108.2 (C), 37.4 (CH). Anal. Calcd for $C_{21}H_{16}N_2O_4$: C, 69.99; H, 4.48; N, 7.77. Found: C, 69.89; H, 4.52; N, 7.84.

4.2.8. 2-(2-Anilino-3-nitro-4H-4-chromenyl)-4-methylphenol ***6h***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2c** (0.5 g, 1.6 mmol) and *p*-cresol **4b** (0.52 g, 4.8 mmol) in EtOH (10 mL) reflux for 14 h provided the title compound **6h** (0.38 g, 64%) as yellow color crystals; mp 202–204 °C (EtOH); R_f (60% hexanes/EtOAc) 0.6; UV (MeOH) λ_{max} 367 nm (log ε=3.7), 261 nm (log ε=3.3); ν_{max} 3492, 1635, 1581, 1461, 1362, 1212, 1149, 1065, 742 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 12.16 (s, 1H), 9.57 and 9.34 (s, 1H), 7.5–6.6 (m, 12H), 5.53 and 5.51 (s, 1H), 2.16 (s, 3H); δ_C (75 MHz, DMSO-d_6) 157.0 and 156.9 (C), 154.7 and 152.4 (C), 147.2 and 145.4 (C), 135.3 and 134.6 (C), 129.8 and 129.6 (CH), 129.2 (2× CH), 129.1 and 129.0 (CH), 128.6 and 128.3 (CH), 128.0 (CH), 127.2 (C), 126.2 and 125.5 (CH), 124.4 (C), 124.0 (C), 123.7 (CH) 118.9 (CH), 115.7 (2× CH), 115.6 and 115.4 (CH), 108.3 (C), 37.6 and 37.4 (CH), 20.3 and 20.2 (CH_3). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.52; H, 4.71; N, 7.37.

4.2.9. 2-(2-Anilino-3-nitro-4H-4-chromenyl)-4-chlorophenol ***6i***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2c** (0.5 g, 1.6 mmol) and 4-chlorophenol **4c** (0.61 g, 4.8 mmol) in EtOH (10 mL) reflux for 16 h provided the title compound **6i** (0.25 g, 40%) as yellow color crystals; mp >200 °C (EtOH); R_f (60% hexanes/EtOAc) 0.6; UV (MeOH) λ_{max} 318 nm (log ε=4.2), 240 nm (log ε=4.0); ν_{max} 3209, 1635, 1579, 1483, 1417, 1347, 1161, 1068, 824, 755, 686 cm^{-1}; δ_H

(300 MHz, $CDCl_3$/DMSO-d_6 9:1) 12.3 (br s, 1H) 9.69 (br s, 1H), 7.9–6.7 (m, 12H), 5.56 (s, 1H); δ_C (75 MHz, $CDCl_3$: DMSO-d_6 5:1) 156.6 (C), 153.3 (C), 147.1 (C), 134.8 (C), 130.9 (C), 128.9 (2× CH), 127.7 (CH), 127.2 (CH), 125.9 (CH), 125.2 (CH), 123.2 (CH), 123.0 (CH), 122.9 (C), 122.5 (C), 116.9 (CH), 115.2 (CH), 107.7 (C), 37.4 (CH). Anal. Calcd for $C_{21}H_{15}ClN_2O_4$: C, 57.75; H, 3.94; N, 8.42. Found: C, 57.821; H, 3.87; N, 8.39.

4.2.10. 2-[2-(Benzylamino)-3-nitro-4H-4-chromenyl]phenol ***6j***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2d** (0.5 g, 1.5 mmol) and phenol **4a** (0.43 g, 4.6 mmol) in EtOH (10 mL) reflux for 12 h provided the title compound **6j** (0.5 g, 87%) as a yellow color solid; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 303 nm (log ε=4.6), 230 nm (log ε=4.3); ν_{max} 3569, 3215, 1634, 1601, 1471, 1368, 1212, 1168, 1056, 756, 698, 623 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.94 and 10.82 (s, 1H), 9.55 and 9.32 (s, 1H), 7.5–6.9 (m, 11H), 6.72 (t, *J*=5.2 Hz, 1H), 6.65 (d, *J*=9.0 Hz, 1H), 5.49 and 5.28 (s, 1H), 4.82 (br s, 2H); δ_C (75 MHz, $DMSO_6$) 158.9 and 158.5 (C), 156.2 and 154.6 (C), 147.4 (C), 134.8 and 138.1 (C), 130.0 (C), 129.2 and 129.1 (CH), 128.9 (CH), 128.7 (2× CH), 128.1 (CH), 127.9 and 127.8 (CH), 127.6 (2× CH), 127.4 (CH), 125.7 and 125.2 (CH), 124.7 (C), 118.8 (CH), 116.0 and 115.7 (CH), 115.6 and 115.2 (CH), 108.2 and 107.1 (C), 44.7 and 44.6 (CH_2), 37.2 (CH). Anal. Calcd for $C_{22}H_{18}N_2O_4$: C, 70.58; H, 4.85; N, 7.48. Found: C, 70.62; H, 4.77; N, 7.55.

4.2.11. 2-[2-(Benzylamino)-3-nitro-4H-4-chromenyl]-4-methylphenol ***6k***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2d** (0.5 g, 1.5 mmol) and *p*-cresol **4b** (0.49 g, 4.6 mmol) in EtOH (10 mL) reflux for 16 h provided the title compound **6k** (0.27 g, 46%) as yellow color crystals; mp 126 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 351 nm (log ε=3.7), 276 nm (log ε=3.2); ν_{max} 3592, 3178, 1631, 1606, 1462, 1370, 1205, 1063, 805, 753, 692, 521 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.91 (br s, 1H), 9.49 and 9.29 (s, 1H), 7.45–6.59 (m, 12H), 5.46 and 5.0 (s, 1H), 4.81 and 4.79 (br s, 2H), 2.14 and 2.10 (s, 3H); δ_C (75 MHz, DMSO-d_6) 159.0 (C), 154.6 and 152.2 (C), 147.3 and 145.4 (C), 138.2 (C), 134.4 (C) 130.0 and 129.9 (CH), 129.1 (CH), 128.6 (2× CH), 128.4 and 128.1 (CH), 127.9 and 127.7 (CH), 127.6 and 127.4 (2× CH), 127.1 (CH), 125.3 (CH), 124.9 (C), 124.3 (C), 118.8 and 115.7 (CH), 115.6 and 115.4 (CH), 107.2 and 107.1 (C), 44.5 (CH_2), 37.2 and 36.8 (CH), 20.3 and 20.2 (CH_3). Anal. Calcd for $C_{23}H_{20}N_2O_4$: C, 71.12; H, 5.19; N, 7.21. Found: C, 71.02; H, 5.11; N, 7.17.

4.2.12. 2-[2-(Benzylamino)-3-nitro-4H-4-chromenyl]-4-chlorophenol ***6l***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2d** (0.5 g, 1.5 mmol) and 4-chlorophenol **4c** (0.59 g, 4.6 mmol) in EtOH (10 mL) reflux for 22 h provided the title compound **6l** (0.44 g, 70%) as yellow color crystals; mp 190–192 °C (EtOH); R_f (60% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 303 nm (log ε=4.5), 237 nm (log ε=4.2); ν_{max} 3078, 1634, 1607, 1469, 1419, 1354, 1246, 1179, 1062, 819, 755, 686 cm^{-1}; δ_H (300 MHz, $CDCl_3$/DMSO-d_6) 10.9 (br s, 1H), 9.62 and 9.42 (s, 1H), 7.5–6.7 (m, 12H), 5.55 and 5.2 (s, 1H), 4.86 and 4.84 (s, 2H); δ_C (75 MHz, $CDCl_3$/DMSO-d_6 5:1) 158.7 (C), 153.3 (C), 147.2 (C), 137.3 (C), 131.4 (C), 128.8 (CH), 128.4 (2× CH), 127.7 (CH), 127.2 (3× CH), 127.1 (CH), 125.0 (CH), 123.6 (C), 122.5 (C), 118.7 (CH), 116.9 (CH), 115.6 and 115.3 (CH), 106.7 (C), 44.5 (CH), 37.1 (CH). Anal. Calcd for $C_{22}H_{17}ClN_2O_4$: C, 64.63; H, 4.19; N, 6.85. Found: C, 64.54; H, 4.21; N, 6.87.

4.2.13. 5-Methyl-2-[2-(methylamino)-3-nitro-4H-4-chromenyl]phenol ***6m***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and *m*-cresol **4d** (0.64 g, 5.9 mmol) in EtOH (10 mL) reflux 16 h provided the title compound **6m** (0.5 g, 80%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 351 nm (log ε=4.5), 273 nm (log ε=4.2); ν_{max} 3266, 1647, 1619, 1469, 1400, 1362, 1250, 1168, 1056, 943, 755 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 10.46 (s, 1H), 9.46 and 9.37 (s, 1H), 7.2–6.9 (m, 5H), 6.68 and 6.49 (s, 1H), 5.46 (s, 1H), 3.17 (s, 3H), 2.25 and 2.12 (s, 3H); δ_C (100 MHz, DMSO-*d*) 159.4, 159.3 (C), 154.4, 154.2 (C), 147.3, 147.1 (C), 137.6, 136.8 (C), 130.3, 128.9 (CH), 128.8, 128.5 (CH), 127.7, 127.5 (CH), 127.3, 125.9 (CH), 125.0, 124.8 (CH), 121.6, 119.3 (C), 118.7, 116.1 (C), 115.8, 115.6(CH), 115.5 (CH), 106.9 (C), 36.7 (CH), 27.8 (NHMe), 20.6, 20.3 (CH_3). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.28; H, 5.22; N, 9.07.

4.2.14. 2-Methyl-6-[2-(methylamino)-3-nitro-4H-4-chromenyl]phenol ***6n***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and *o*-cresol **4e** (0.64 g, 5.9 mmol) in EtOH (10 mL) reflux for 16 h provided the title compound **6n** (0.54 g, 88%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.5; UV (MeOH) λ_{max} 350 nm (log ε=5.9), 273 nm (log ε=4.0); ν_{max} 3472, 1645, 1614, 1460, 1369, 1268, 1187, 1087, 1031, 786, 586 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 10.42 (br s, 1H), 9.5 (s, 1H), 7.16–7.10 (m, 3H), 6.97 (m, 2H), 6.70–6.68 (m, 2H), 5.53 (s, 1H) 3.20 (s, 3H) 2.33 (s, 3H); δ_C (100 MHz, DMSO-d_6) 159.3 (C), 154.4 (C), 145.8 (C), 130.4 (C), 129.0 (CH), 128.8 (CH), 127.5 (CH), 126.4 (CH), 124.8 (CH), 124.6 (CH), 124.5 (CH), 118.8 (CH), 115.5 (CH), 106.9 (C), 36.9 (CH), 28.0 (NHMe), 15.4 (CH_3). Anal. Calcd for $C_{17}H_{16}N_2O_4$: C, 65.36; H, 5.16; N, 8.97. Found: C, 65.41; H, 5.06; N, 9.02.

4.2.15. 2-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-1-naphthol ***6o***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and 1-naphthol **4f** (0.86 g, 6.0 mmol) in EtOH (10 mL) on 8 h reflux provided the title compound **6o** (0.51 g, 74%) as a yellow color solid after recrystallization; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 352 nm (log ε=3.5), 279 nm (log ε=3.2), 227 nm (log ε=4.0); ν_{max} 3178, 1628, 1456, 1381, 1262, 1174, 1093, 1018, 955, 750, 692 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.53 (br q, *J*=4.8 Hz, 1H), 9.5 (s, 1H), 8.2 (d, *J*=8.1 Hz, 1H), 7.89 (d, *J*=7.8 Hz, 1H), 7.7–7.5 (m, 2H), 7.4–7.2 (m, 2H), 6.96 (t, *J*=7.5 Hz, 1H), 6.7–6.6 (m, 2H), 5.61 (s, 1H), 3.35 (d, *J*=4.8 Hz, 3H); δ_C (75 MHz, DMSO-d_6) 159.2 (C), 154.7 (C), 141.6 (C), 132.6 (C), 129.9 (C), 129.5 (CH), 127.8 (2× CH), 127.0 (CH), 126.7 (CH), 125.9 (CH), 124.6 (CH), 122.4 (C), 120.4 (CH), 119.6 (C), 118.9 (CH), 115.6 (CH), 107.0 (C), 37.6 (CH), 28.2 (Me). Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.84; H, 4.71; N, 7.97.

4.2.16. 1-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-2-naphthol ***6p***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and 2-naphthol **4g** (0.86 g, 6.0 mmol) in EtOH (10 mL) on 12 h reflux provided the title compound **6p** (0.61 g, 89%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 354 nm (log ε=3.9), 268 nm (log ε=3.2), 226 nm (log ε=4.1); ν_{max} 3234, 1644, 1596, 1456, 1396, 1274, 1212, 1174, 1062, 817, 755, 695 cm^{-1}; δ_H (400 MHz, DMSO-d_6) 10.39 (s, 1H), 9.58 (s, 1H), 8.31–8.29 (m, 1H), 7.90–7.88 (m, 2H), 7.50–7.36 (m, 4H), 6.93 (m, 1H), 6.69–6.62 (m, 2H), 6.0 (s, 1H), 3.22 (s, 3H); δ_C (100 MHz, DMSO-d_6) 158.7 (C), 154.6 (C), 145.6 (C), 131.2 (CH), 130.8 (C), 130.3 (C), 128.9 (CH), 128.4 (CH), 128.2 (C), 127.6 (CH), 127.0 (CH), 125.0 (CH), 123.5 (CH), 118.5 (CH), 117.1 (C), 116.3 (CH), 115.7 (CH), 107.8 (C), 34.9 (CH), 27.9 (Me). Anal. Calcd for $C_{20}H_{16}N_2O_4$: C, 68.96; H, 4.63; N, 8.04. Found: C, 68.85; H, 4.75; N, 7.92.

4.2.17. 7-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-8-quinolinol ***6q***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g,

2.0 mmol) and 8-quinolinol **4h** (0.863 g, 5.9 mmol) in EtOH (10 mL) on 12 h reflux provided the title compound **6q** (0.638 g, 92%) as yellow color crystals after recrystallization; mp >200 °C (EtOH); R_f (70% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 347 nm (log ε=3.9), 248 nm (log ε=4.3), 210 nm (log ε=4.0); ν_{max} 3200, 1638, 1607, 1463, 1400, 1356, 1212, 1168, 1062, 893, 824, 743, 680 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 10.51 (br q, J=5.1 Hz, 1H), 9.90 (br s, 1H), 8.25 (d, J=6.9 Hz, 1H), 8.81 (d, J=2.7 Hz, 1H), 7.5–7.0 (m, 7H), 5.86 (s, 1H), 3.28 (d, J=5.1 Hz, 3H); δ_C (75 MHz, DMSO-d_6) 159.3 (C), 149.6 (C), 148.2 (CH), 147.2 (C), 138.3 (C), 135.9 (CH), 129.0 (CH), 128.1 (CH), 127.8 (CH), 127.4 (C), 126.8 (C), 125.4 (CH), 124.4 (C), 121.5 (CH), 117.2 (CH), 116.0 (CH), 106.6 (C), 36.7 (CH), 28.1 (Me). Anal. Calcd for $C_{19}H_{15}N_3O_4$: C, 65.32; H, 4.33; N, 12.03. Found: C, 65.27; H, 4.38; N, 12.12.

4.2.18. 3-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-1,2-benzenediol ***6r***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and pyrocatechol **8a** (0.65 g, 5.9 mmol) in EtOH (10 mL) on 7 h reflux provided the title compound **6r** (0.192 g, 31%) as yellow color crystals after recrystallization; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 352 nm (log ε=4.1), 274 nm (log ε=3.6); ν_{max} 3478, 1644, 1612, 1460, 1402, 1368, 1281, 1212, 1168, 1062, 761 cm^{-1}; δ_H (300 MHz, DMSO-*d*6) 10.46 (br s, 1H), 9.49 (s, 1H), 7.4–6.4 (m, 7H), 5.97 and 5.50 (s, 1H), 3.2 (s, 3H); δ_C (75 MHz, DMSO-*d*6) 159.4 (C), 154.5 (C), 144.9 (C), 136.4 (C), 130.4 (C), 128.9 (CH), 127.5 (CH), 125.0 (CH), 126.0 (C), 118.8 (CH), 118.5 (CH), 115.6 (CH), 114.6 (CH), 106.9 (C), 37.1 (CH), 28.1 (Me). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.24; H, 4.53; N, 8.87.

4.2.19. 3,6-Di[2-(methylamino)-3-nitro-4H-4-chromenyl]-1,2-benzenediol ***6s***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and pyrocatechol **8a** (0.65 g, 5.9 mmol) in EtOH (10 mL) on 7 h reflux furnished the title compound **6s** (0.26 g, 25%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.2; UV (MeOH) λ_{max} 353 nm (log ε=4.0), 263 nm (log ε=3.5); ν_{max} 3202, 1644, 1464, 1368, 1249, 1212, 1172, 1062, 755 cm^{-1}; δ_H (300 MHz, DMSO-*d*6) 10.47 (br s, 1H), 9.43 (s, 1H), 9.34 9s, 1H0, 7.24–6.49 (m, 10H), 5.75, 5.52, and 5.43 (s, 2H), 3.23 and 3.18 (d, J=5.1 Hz, 3H); δ_C (DEPT-135, DMSO-*d*6) 129.1 (CH), 128.1 (CH), 127.5 (CH), 126.0 (CH), 125.3 (CH), 118.6 (CH), 115.6 (CH), 37.0 (CH), 28.0 (Me); HRMS (ESI^+): calcd for $C_{26}H_{22}N_4O_8$ (MH^+), 519.1517; found, (MH^+), 519.1521. Anal. Calcd for $C_{26}H_{22}N_4O_8$: C, 60.23; H, 4.28; N, 10.81. Found: C, 60.31; H, 4.17; N, 10.77.

4.2.20. 4-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-1,3-benzenediol ***6t***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (1.37 g, 5.4 mmol) and resorcinol **8b** (0.3 g, 2.7 mmol) in the presence of NaOAc (0.45 g, 5.4 mmol) using EtOH (10 mL) on 4 h reflux provided the title compound **6t** (0.231 g, 81%) as yellow color crystals after recrystallization; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 351 nm (log ε=4.2), 279 nm (log ε=3.3); ν_{max} 3272, 1646, 1475, 1375, 1237, 1055, 974, 866, 759 cm^{-1}; δ_H (500 MHz, DMSO-*d*6) 10.5 (br s, 1H), 9.09 (br s, 1H), 7.29–6.49 (m, 5H), 6.19 (s, 1H), 6.1 (d, J=9.0 Hz, 3H), 5.4 (s, 1H), 3.2 (d, J=4.5 Hz, 3H); δ_C (125 MHz, DMSO-*d*6) 160.1 (C), 157.4 (C), 147.8 (C), 131.0 (C), 129.7 (CH), 127.6 (CH), 125.8 (C), 125.3 (CH), 116.1 (C), 113.3 (CH), 107.9 (C), 107.35 (CH), 102.5 (CH), 36.9 (CH), 22.8 (Me). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.17; H, 4.37; N, 8.85.

4.2.21. 2-[2-(Methylamino)-3-nitro-4H-4-chromenyl]-1,4-benzenediol ***6u***. Following the representative procedure described previously for preparation of **6a**, a solution of 4*H*-chromene **2a** (0.5 g, 2.0 mmol) and hydroquinone **8c** (0.65 g, 5.9 mmol) in EtOH (10 mL) on 7 h reflux provided the title compound **6u** (0.46 g, 74%) as yellow color crystals; mp >200 °C (EtOH); R_f (50% hexanes/EtOAc) 0.4; UV (MeOH) λ_{max} 351 nm (log ε=4.5), 281 nm (log ε=4.2), 224 nm (log ε=4.5); ν_{max} 3522, 3159, 1649, 1612, 1481, 1312, 1249, 1193, 1070, 816, 754, 703, 648 cm^{-1}; δ_H (400 MHz, CCl_4/DMSO-d_6) 10.44–10.40 (m, 1H), 9.44 (s, 1H), 9.28 (s, 1H), 7.18–6.93 (m, 3H), 6.73–6.57 (m, 4H), 5.48 (s, 1H), 2.50–2.49 (m, 3H); δ_C (100 MHz, CCl_4:DMSO-d_6) 159.5 (C), 154.3 (C), 154.3 (C), 140.2 (C), 130.4 (C), 128.4 (CH), 127.3 (CH), 125.5 (C), 118.6 (CH), 116.3 (CH), 115.4 (CH), 114.5 (CH), 114.2 (CH), 106.8 (C), 36.7 (CH), 27.7 (Me). Anal. Calcd for $C_{16}H_{14}N_2O_5$: C, 61.14; H, 4.49; N, 8.91. Found: C, 61.05; H, 4.39; N, 9.01.

4.2.22. 3-Amino-4-(2-hydroxyphenyl)-2H-2-chromenone ***10***. A mixture of 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenol **6a** (0.5 g, 1.7 mmol) and zinc powder (1.58 g, 0.017 mol) in AcOH (9.4 g, 9 mL) medium was heated at 110 °C for 1 h by which time reduction was complete (TLC). Filtration of undissolved solids and removal of AcOH under reduced pressure followed by column chromatographic purification with EtOAc (20%–50%) in hexanes furnished the title compound **10** (0.17 g, 40%) as an orange color solid; mp 170 °C (EtOH); R_f (50% hexanes/EtOAc) 0.6; UV (MeOH) λ_{max} 326 nm (log ε=4.1), 284 nm (log ε=3.8), 243 nm (log ε=4.0); ν_{max} 3415, 3334, 1673, 1600, 1494, 1451, 1341, 1283, 1194, 1112, 841, 759, 598 cm^{-1}; δ_H (300 MHz, DMSO-d_6) 9.53 (br s, 1H), 7.37–7.10 (m, 5H), 7.04 (d, J=8.1 Hz, 1H), 6.97 (t, J=7.5 Hz, 2H), 6.83 (d, J=7.5 Hz, 1H), 4.90 (s, 2H); δ_C (75 MHz, DMSO-d_6) 158.6 (C), 154.9 (C), 147.6 (C), 130.8 (CH), 130.0 (C), 129.9 (CH), 125.8 (CH), 124.3 (CH), 123.9 (CH), 122.0 (CH), 119.8 (CH), 119.2 (CH), 117.6 (C), 116.5 (CH), 115.7 (CH); HRMS (ESI^+): calcd for $C_{15}H_{11}NO_3$ (MH^+), 254.0818, (MNa^+) 276.0637, (MK^+) 292.1722; found, (MH^+), 254.0817, (MNa^+), 276.0639, (MK^+) 292.1720 (Fig. 3).

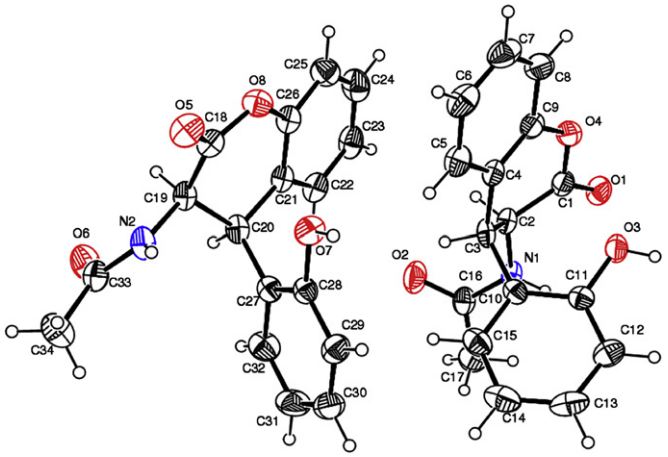


Fig. 3. Single crystal XRD structure of *N*1-[4-(2-hydroxyphenyl)-2-oxo-3, 4-dihydro-2*H*-3-chromenyl]acetamide **11** (deposited with CCDC; deposition No. 698176).

4.2.23. N1-[4-(2-Hydroxyphenyl)-2-oxo-3,4-dihydro-2H-3-chromenyl]acetamide ***11***. Following the above procedure, on heating a mixture of 2-[2-(methylamino)-3-nitro-4*H*-4-chromenyl]phenol **6a** (0.5 g, 1.7 mmol) and zinc dust (2.2 g, 34 mmol) in Ac_2O (9.72 g, 9 mL, 95 mmol) and AcOH (1.0 g, 1 mL, 17 mmol) for 1 h at 110 °C provided the title compound **11** (0.31 g, 62%) as a colorless solid; mp 192–194 °C (EtOH); R_f (20% hexanes/EtOAc) 0.5; ν_{max} 3316, 1763, 1650, 1532, 1369, 1225, 1143, 755 cm^{-1}; δ_H (300 MHz, $CDCl_3$) 9.5 (br s, 1H), 7.2–6.6 (m, 8H), 5.18 (d, J=6.8 Hz, 1H), 4.87 (d, J=6.8 Hz, 1H), 1.87 (s, 3H); δ_C (75 MHz, $CDCl_3$) 169.8 (C), 166.7 (C), 155.3 (C), 150.5 (C), 128.9 (CH), 128.3 (CH), 128.2 (CH), 124.8 (2× C), 124.3 (CH), 124.1 (CH), 118.9 (CH), 116.1 (CH), 115.3 (CH), 51.2 (CH),

38.8 (CH), 22.1 (CH_3). Anal. Calcd for $C_{17}H_{15}NO_4$: C, 68.68; H, 5.09; N, 4.71; Found: C, 68.71; H, 5.14; N, 4.69.

Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tet.2011.08.045.

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